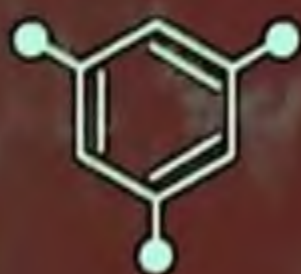


PHARMACOLOGY

TEXTBOOK

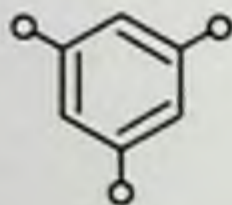
Edited by
G.Z. Sufianova



ФАРМАКОЛОГИЯ

УЧЕБНИК

Под редакцией
Г.З. Суфиановой



Министерство науки и высшего образования РФ

Рекомендовано Координационным советом по области
образования «Здравоохранение и медицинские науки» в качестве
учебника для использования в образовательных учреждениях, реализующих
основные профессиональные образовательные программы высшего
образования специалитета по направлениям подготовки и специальностям
«Лечебное дело», 31.05.02 «Педиатрия», 33.05.01 «Фармация»

Регистрационный номер рецензии 1712 от 18 ноября 2021 года



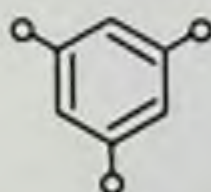
Москва
ИЗДАТЕЛЬСКАЯ ГРУППА
«ГЗОТАР-Медиа»
2023

Pharmacology

TEXTBOOK

EDITED BY G. Z. SUFIANOVA

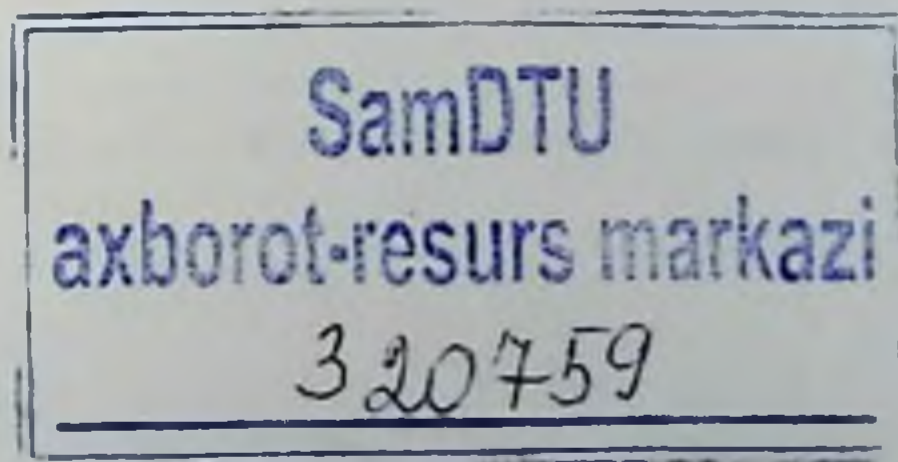
TRANSLATED FROM RUSSIAN LANGUAGE



Ministry of Science and Higher Education of the Russian Federation

Recommended by the Coordinating Council for the field of education "Health and Medical Sciences"
as a textbook for use in educational institutions implementing basic higher education
professional specialists's degree programmes in the following specialties:
31.05.01 "Medicine", 31.05.02 "Pediatrics", 33.05.01 "Pharmaceutics"

Registration number of the review 1712 from November 18, 2023



Tyumen, 2023

УДК 615.2/.3(075.8)-111
ББК 52.81я73-1
S91

S91 **Pharmacology: textbook / edited by G. Z. Sufianova — Tyumen: Print-Service LLC, 2023. — 523 p.**

ISBN 978-5-600-03764-9(англ.)

ISBN 978-5-9704-7084-8(рус.)

This textbook was prepared by professors from the Department of Pharmacology at the Federal State Budget Educational Institution of Higher Education (FSBEI HE), Tyumen State Medical University of the Ministry of Health of Russia. It is an integrated and comprehensive guide developed specifically for medical students that complies with all the requirements of the Russian "Federal State Educational Standards" for higher education programs.

This textbook covers a wide range of topics, from the basic principles of pharmacology, pharmacokinetics and pharmacodynamics to an in-depth analysis of different drug classes. Each of these chapters goes into great detail about the development, mechanisms of action, indications and contraindications, adverse reactions, dosing, and use of specific drugs. The text is accompanied by illustrations and diagrams, making it easier to understand complex concepts. This textbook is a reliable and up-to-date source of knowledge that will help students to better understand pharmacology, the principles of drug action and the rationale behind the use of specific drugs.

УДК 615.2/.3(075.8)-111
ББК 52.81я73-1

First published in Russian under the title:
Pharmacology : textbook / edited by G.Z. Sufianova. - Moscow : GEOTAR-Media, 2023. - 560 pp.

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Moscow, Publishing Group "GEOTAR-Media" 2023

ISBN 978-5-600-03764-9(англ.)
ISBN 978-5-9704-7084-8(рус.)

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LIST OF ABBREVIATIONS AND DESIGNATIONS

•	— trade name of the medicinal drug product and/or pharmaceutical substance
•	— medicinal drug product currently not approved in the Russian Federation
AAs	— adrenergic agonists
ABA	— adrenergic blocking agents
AC	— adenylyl cyclase
ACE	— angiotensin converting enzyme
ACh	— acetylcholine
ALT	— alanine aminotransferase
AP	— action potential
AR	— adrenergic receptors
AST	— Aspartate aminotransferase
AT	— angiotensin
ATP	— adenosine triphosphate
AV	— atrioventricular
BBB	— blood-brain barrier
BP	— blood pressure
CAD	— coronary artery disease
cAMP	— cyclic adenosine monophosphate
cGMP	— cyclic guanosine monophosphate
ChB	— cholinergic blockers
CHF	— congestive heart failure
ChM	— cholinergic mimetics
ChR	— cholinergic receptors
CNS	— central nervous system
COMT	— catechol-O-methyl transferase
COPD	— chronic obstructive pulmonary disease
COX	— cyclooxygenase
CysLT-R	— cysteinyl leukotriene receptors
duodenum	— duodenum
DNA	— deoxyribonucleic acid
DS	— drug substance
ERP	— effective refractory period
GABA	— γ -aminobutyric acid
GC	— guanylate cyclase
GCs	— glucocorticoids/steroids
GIT	— gastrointestinal tract
GP IIb/IIIa	— glycoprotein IIb/IIIa
Hypertension	— arterial hypertension
HIV	— human immunodeficiency virus
HR	— heart rate
ICP	— intracranial pressure

IFN	—	interferons
IOP	—	intraocular pressure
IU	—	international unit
MAO	—	monoamine oxidase
MPDP	—	medicinal drug product
MRSA	—	methicillin-resistant <i>Staphylococcus aureus</i>
OPs	—	organophosphorus compounds
PABA	—	para-aminobenzoic acid
PDEase	—	phosphodiesterase
PG	—	prostaglandins
PPI	—	proton pump inhibitors
RAAS	—	renin-angiotensin-aldosterone system
RNA	—	ribonucleic acid
SA	—	sinoatrial
TPVR	—	total peripheral vascular resistance
TTS	—	transdermal therapeutic system
TXA ₂	—	thromboxane A ₂
U	—	unit of activity
UT	—	urinary tract

1. BASIC CONCEPTS OF PHARMACOLOGY

BASICS OF PHARMACOLOGY

Pharmacology (derived from Greek *pharmakon* — “medicine” and *logos* — “word, doctrine”) is the study of the interactions that occur between a living organism and chemicals.

Pharmacology examines the drug products (DPs) used to treat and prevent various diseases and pathologies. One of the most important tasks of pharmacology is to discover new, safe and effective DPs.

Pharmacology is closely related to various fields of experimental and applied medicine. It greatly influenced the development of many other biomedical disciplines, especially physiology and biochemistry. For example, autonomic substances have helped us better understand the mechanisms of synaptic transmission, which occur with the participation of mediators. The discovery of substances that selectively block certain enzymes or accelerate their synthesis has facilitated the development of enzymology. Many complex functions of the central nervous system (CNS) can now be studied thanks to neurotropic agents.

- ▶ In experimental practice, the main value of pharmacological substances is that they provide ample opportunity to control various biochemical and physiological processes and analyze the underlying mechanisms.
- ▶ Agents that inhibit and excite the central and peripheral nervous systems, increase and lower blood pressure (BP), stimulate cardiac activity and respiration, regulate hematopoiesis, blood clotting, and metabolic processes are widely used in medicine. Antimicrobial and antiparasitic agents used to treat and prevent infections also play an important role.

Progress in pharmacology has affected the development of several clinical disciplines:

- ▶ The advent of general and local anesthetics, muscle relaxants, ganglionic blockers and other DPs have contributed to the success of surgery.
- ▶ The discovery of psychotropic agents led to a new phase in the development of psychiatry.
- ▶ The isolation and synthesis of hormonal substances has significantly changed the treatment outcomes of patients with endocrine diseases.

- ▶ Effective treatment of bacterial infections became possible only after antimicrobials were discovered.
- ▶ Organ transplantation was made possible mainly through the development of immunosuppressive agents.

Because pharmacotherapy is crucial for the practice of medicine, knowledge of pharmacology is essential for pharmacists and physicians of all specialties.

History of pharmacology

For many thousands of years, the discovery, production, and use of DPs (usually of plant origin) was carried out empirically. In the 9th century, the Arabs made the first attempt to systematize and standardize preparations used in that era. To this end, special books were created, which were a prototype for the modern pharmacopoeia. In Europe, the first printed pharmacopoeia was published in Italy in the 15th century. Pharmacopoeias then appeared in Britain (17th century), France (17th century), Russia (18th century), and the USA (19th century). The isolation of purified alkaloids (morphine, quinine, etc.) and the first synthesis of organic matter (urea) in the early 19th century were a significant step forward. The introduction of animal experiments into pharmacology research in the early 19th century was an important event. In 1849, P. Buchheim, a professor at the University of Dorpat (Tartu in Estonia), set up the world's first experimental pharmacology laboratory in his own apartment. Pharmacology as an independent science was formed in the middle of the 19th century.

Development of pharmaceutical science in Russia

In ancient Russia, the main advisers in the use of DPs were wanderers and znakhars (traditional healers). Monks actively collected information about medicinal herbs. The first manuscripts on pharmaceutical science by herbalists started to appear. The first pharmacy opened in Moscow in 1581. The Aptekarsky Prikaz (Pharmacy Department), which regulated the medical affairs in the country, was established in Moscow in the early 17th century. To standardize the manufacture and quality of DPs, the first State Pharmacopoeia was published in 1778 in Latin and in 1866 in Russian.

The first Russian handbook of pharmaceutical science was published in 1783 by Prof. N. M. Maksimovich-Ambodik, an obstetrician-gynecologist in St. Petersburg.

The largest medical research center in Russia was the Medical and Surgical Academy in St. Petersburg. O. V. Zabelin organized a special pharmacological laboratory at the Academy. A number of experimental works were carried out here: Prof. E. V. Pelikan studied the mechanism of action of curare and Strophanthus.

A. P. Nelyubin studied Caucasian mineral waters and wrote a three-volume manual entitled "Pharmacography, or Chemical and Medical Prescriptions for the Preparation and Use of the Latest Medicines".

I. P. Pavlov was the head of the experimental laboratory at the Botkin Clinic in St. Petersburg and also the Department of Pharmacology at the Military Medical Academy. Physiological methods created by Pavlov made it possible to study the therapeutic effect of cardiac glycosides (lily of the valley, adonis) on the heart and

blood circulation, and the effect of alkaloids (pilocarpine, nicotine, atropine, morphine), acids, alkalis and amines on digestion. The mechanism of action of ethanol, bromides, and caffeine on the CNS was first discovered using the conditioned reflex method. For this research, Pavlov was awarded the Nobel Prize in Physiology or Medicine in 1904.

N. P. Kravkov introduced isolated organ methods into experimental practice. Together with surgeon S. P. Fedorov, Kravkov carried out intravenous anesthesia with hedonal in the clinic. He was the first to study the effects of DPs on the endocrine system.

The students of N. P. Kravkov, S. V. Anichkov and V. V. Zakusov conducted fundamental studies of drugs regulating CNS functions.

M. D. Mashkovsky developed many original drugs (neuroleptics, antidepressants, psychostimulants, muscle relaxants, etc.) and wrote the popular reference book "Medicines".

A. S. Saratikov suggested using camphor preparations, psychostimulants and adaptogens, hepatotropic agents, interferon (IFN) inducers in clinical practice.

General understanding of drug products

A DP is one or more drug substances (DS) used to treat or prevent diseases. A DS is an individual chemical compound used as a DP. A dosage form is a pharmaceutical form of the DP that is convenient for administration (solid, liquid, semi-solid).

International nonproprietary names are important characteristics of DPs. They are in the public domain and are assigned by the World Health Organization. Commercial trade names are given to finished single- or multi-component products available in specific doses and dosage forms. Commercial names are a property of the manufacturer.

DPs are discovered using the following approaches:

I. Chemical synthesis: DPs are produced mainly through chemical synthesis.

A. Streamlined synthesis

1. Reproduction of biogenic substances [epinephrine (Adrenaline*), norepinephrine (Noradrenaline*)]
2. Creation of antimetabolites [para-aminobenzoic acid (PABA) and sulfonamides]
3. Modification of compounds with known biological activity (carbonic anhydrase inhibitors and thiazide diuretics)
4. Studying the structure of the substrate with which the DP interacts (X-ray analysis was improved, and spectroscopy based on nuclear magnetic resonance was developed. The latter method was revolutionary, since it made it possible to establish the three-dimensional structure of substances in a solution, i.e., in the non-crystalline state)
5. Combining fragments of two compounds that have the desired properties
6. Synthesis based on how substances are transformed chemically in the body (prodrugs; agents affecting the biotransformation mechanisms of substances: enalapril, phenobarbital).

B. Empirical methods

1. Serendipity

2. Screening

Trial and error is at the core of the empirical way of creating drug substances. Some drugs were introduced into medical practice as a result of accidental discoveries (prontosil). Others were found through screening: pharmacologists use a set of bioassays to identify a certain pharmacological activity in chemical compounds, then select the most active of these chemical compounds, then compare their pharmacological effect and toxicity with existing DPs (used as a reference).

II. Production of drug products from raw materials and isolation of individual substances:

- 1) of animal origin

- 2) of plant origin

- 3) of mineral origin.

Hormones, galenic and novel galenic agents, and minerals have been produced this way.

III. Isolation of drug substances that are products of vital activity of fungi and microorganisms, biotechnology (cell and gene engineering).

Biotechnology is a discipline that studies the use of living organisms, their systems, or the products of their vital functions to solve technological problems, and the possibility of creating living organisms with the desired properties by gene engineering. Biotechnology uses biological systems and biological processes on an industrial scale. Microorganisms, cell, plant and animal tissue cultures are usually used. Semi-synthetic antibiotics, insulin, and steroid hormones are synthesized this way.

Basic principles and testing methods for new drug products

A Good Practice standard guides each step in the life cycle of a DP. Standards ensure the DPs are safe and effective.

Preclinical studies are conducted on laboratory animals (intact animals and human disease models in animals), in cell culture and in organoids. These studies must provide reliable, evidence-based data and follow the principles of humane care and use of laboratory animals.

The following experimental methods are used:

- ▶ Screening consists of standard methods to evaluate the activity of chemical compounds in comparison with that of known DPs; however, the screening output is low: on average, 5,000–10,000 compounds per DP are screened before progressing to clinical trials).
- ▶ In-depth study of the mechanism of action using physiological, biochemical, biophysical, morpho-histochemical, electron microscopy and molecular biology methods.
- ▶ Pharmacokinetic studies
- ▶ Acute and chronic toxicity studies
- ▶ Specific toxicity studies (immunotoxicity, allergizing, mutagenic, carcinogenic, embryotoxic, teratogenic, fetotoxic effects, ability to cause drug dependence).

Clinical trials of new drug products include four phases, which are conducted by comparing the effect of reference products in a given pharmacological group or a placebo.

A placebo (derived from Latin placebo - "I shall give pleasure") is a dosage form that does not contain the DP, but has the same appearance, smell, and taste as the DP. Patients in the experimental and control groups should have the same age, type and stage of the disease, initial background treatment. Groups are formed by assigning patients randomly (randomization).

The clinical trial process uses single-blind and double-blind methods.

- ▶ In a single-blind study, the DP and placebo are alternated in a sequence unknown to the patient. Only the investigator knows when the patient is taking a placebo.
- ▶ In the double-blind method, neither the patient nor the investigator know who is taking the placebo. Only the study sponsor knows which treatment is assigned.

Reliability of the data obtained by different methods (clinical, instrumental, laboratory and morphological) should be confirmed statistically.

Clinical trial phases:

- ▶ Phase I: based on the results of preclinical efficacy and safety studies, the effect of a DP is studied in healthy volunteers (5–10 people) to establish the optimal doses that produce the desired effect.
- ▶ Phase II: the efficacy and safety of a DP are studied in a comparative setting (placebo, reference product) in a limited number of patients (100–200) who have the disease for which the DP is intended; its therapeutic dose range is determined, and any side effects are documented.
- ▶ Phase III: a clinical (randomized, controlled) trial on a large patient population (up to several thousands of patients). The efficacy (including double-blind placebo-controlled trials) and safety of DPs are thoroughly studied. If the results of the study are positive, study materials are submitted to the regulatory authority that approves it for registration and then releases the product for clinical use.
- ▶ Phase IV: starts while the DP is being evaluated for registration and continues after it is launched to the market. It aims to solve additional issues associated with DP usage, expand its therapeutic indications, provide doctors with an opportunity to gain experience with its use, and position the DP on the pharmaceutical market.

Post-marketing surveillance: collection and analysis of product safety reports, safety overviews based on the product's use in tens of thousands of patients, survival analysis.

The creation of a new DP is an extremely expensive, complex and time-consuming process. Only 1 out of 10,000 studied candidate DS progresses to registration and becomes a DP. Data collection on the DP being studied takes 8–15 years.

GENERAL PHARMACOLOGY CONCEPTS

General pharmacology studies general patterns of pharmacokinetics and pharmacodynamics.

Pharmacokinetics (derived from Greek *pharmakon* — "medicine" and *kinetikos* - "setting in motion") is a branch of pharmacology that studies:

- ▶ Absorption

- ▶ Distribution
- ▶ Deposition
- ▶ Metabolism
- ▶ Elimination of the DS.
- ▶ Pharmacodynamics (derived from Greek *pharmakon* — “medicine” and *dynamikos* — “power”) is a branch of pharmacology that studies:
 - ▶ Biological (pharmacological) effects
 - ▶ Localization and type of action
 - ▶ Mechanism of action of the DS.

Pharmacokinetics

Absorption is an active physiological process in which various substances move from the place of administration through biological membranes into blood, lymph, tissue fluids, etc.

Several substances (such as acetylsalicylic acid, barbiturates and other weak electrolytes that are acidic) are partially absorbed from the stomach.

The vast majority of DPs are mostly absorbed in the small intestine.

Absorption mechanisms

1. Passive diffusion through the cell membrane, determined by the concentration gradient. Lipophilic (non-polar) substances (digitoxin, phenobarbital) are absorbed this way. In simple diffusion, DPs are dissolved in the lipid bilayer of membranes, which is the most common mechanism.
2. Facilitated diffusion through the cell membrane involves transport systems that function without energy input. Hydrophilic (polar) substances [dextrose (Glucose*), strophanthus K] are absorbed this way.
3. Filtration through membrane pores: diffusion of water, hydrophilic compounds (urea), some ions (Cl^-), glucose.
4. Active transport—a “biological pump”. Cell membranes have systems (special carriers) that allow it to transport a substance against a concentration gradient and with energy input [iodine is known to enter thyroid follicles against a 50-fold concentration gradient; norepinephrine (Noradrenaline*) undergoes neuronal uptake against a 200-fold gradient]. Active transport provides absorption of hydrophilic polar molecules, a number of inorganic ions, sugars, amino acids (vitamin B12, iron, corticosteroid hormones).
5. Pinocytosis. The cell membrane will invaginate to form a bubble (vacuole), which is filled with fluid and the trapped substances (high molecular weight polypeptides, fatty acids, fat-soluble vitamins). The vacuole can migrate along the cytoplasm to the opposite side of the cell, where the contents are released outwards by exocytosis.

Routes of administration

Enteral routes

1. Oral route. This is the easiest, most comfortable route for the patient. It does not require sterilization or the participation of any medical personnel. The effect

appears within 15–40 minutes; the dose is 2–3 times higher than parenteral administration. However, the oral route has several limitations:

- DPs can be inactivated by hydrochloric acid in the stomach (benzylpenicillin, erythromycin, adrenaline), proteases (insulin), colonic bacterial enzymes (digoxin) and can form non-absorbable products when they interact with mucin (ChB) and bile;
 - Highly polar compounds (streptomycin) are not absorbed from the gastrointestinal tract;
 - Food usually slows down the absorption of DPs, because the pH of digestive juices changes after a meal and intestinal peristalsis accelerates; the exception is fat-soluble compounds (vitamins);
 - DPs form non-absorbed complexes with food components, e.g., tetracycline antibiotics bind to Ca^{2+} and iron ions, while alkaloids are precipitated by tannins in tea, coffee, and fruit juices (it is recommended to take most DPs 30–40 minutes before a meal or 1.5–2.0 hours after a meal, weak bases with alkaline mineral water, sodium hydrogen carbonate solution);
 - Some DPs have an irritating effect on the stomach and intestines (nonsteroidal anti-inflammatory drugs), thus such products should be taken after meals;
 - DPs undergo first-pass metabolism—inactivation by mucosal enzymes in the small intestine and liver before entering the arterial bloodstream [propranolol (Anaprilin[®]), nitroglycerin, verapamil];
 - Oral administration is not possible in patients with intestinal resection, malabsorption syndrome (impaired absorption), severe digestive and cardiovascular system diseases, who are vomiting or unconscious, or in young children.
2. Sublingual (dissolving under the tongue) and buccal (dissolving inside the cheek) routes. Dissolution in the oral cavity allows the DPs to rapidly enter the superior vena cava, with no effect of digestive juices and liver enzymes. Only lipid-soluble DPs, such as nitroglycerin, clonidine (Clopheline[®]), nifedipine, are taken sublingually.
 3. Rectal route. Suppositories, enemas (platyphylline, Microlax[®]) are administered by this route: 50% of the dose is absorbed from the rectum into the inferior vena cava, bypassing the liver, while 50% enters the portal vein and is partially inactivated in the liver. Limitations of the rectal administration route are that the rectal mucosa is highly sensitive to irritants (risk of proctitis), small absorption surface, short contact time of DPs with the mucosa, small volume of solutions used for enemas (50–100 mL).

Parenteral routes

1. Subcutaneous injection. Sterile, isotonic aqueous and lipid DP solutions are administered as 1–2 mL doses [adrenaline, camphor, neostigmine methylsulfate (Proserin[®])]. The solutions have physiological pH values. Products should have no irritant effect or cause vasospasm. The pharmacological effect occurs 15–20 minutes after injection. Silicone depository containers can be implanted subcutaneously [levonorgestrel contraceptive (Norplant[®]), testosterone products].
2. Intramuscular injection. Sterile isotonic aqueous and lipid solutions are administered by this route. The maximum volume of an intramuscular injection is 10 mL. The

effect of most DPs develops faster than when injected subcutaneously because muscles have an abundant blood supply. When lipid solutions are injected into the muscles, a depot of DPs is formed, which ensures their prolonged release into the blood and thereby, their prolonged effect [nandrolone (Retabolil[®]), hexestrol].

3. Intravenous injection. Sterile aqueous solutions [noradrenaline, suxamethonium iodide (Dithylin-Darnitsa[®])] are administered by this route. Hypertonic solutions may be administered by this route. The effect is 5–10 times stronger than that of the products administered orally, and its onset quicker.
4. Intraarterial injection. Only sterile isotonic aqueous solutions of MPs are injected into arteries, cancellous bone, subarachnoid and epidural spaces. Antibiotics, X-ray contrast agents, and antineoplastic agents in high concentrations are injected into the arteries supplying blood to the affected organs. Arterial access is a surgical procedure involving the creation of an arteriovenous graft.
5. Intraosseous route. This route of administration provides the same onset of action as intravenous injections. Intrasternal administration is used when intravenous administration is not possible. Local anesthetics (lidocaine) are injected into the cancellous bone of the heel during lower leg surgery.
6. Intrathecal route. Local anesthetics for spinal anesthesia, narcotic analgesics for pain, antibiotics for meningitis are injected into the subarachnoid or epidural space of the spinal cord. Injection is performed at the lower thoracic/upper lumbar vertebrae using an atraumatic needle less than 0.4 mm in diameter with a cone-shaped tip.
7. Inhalation route. Inhalation produces a quick DP effect due to the large contact area of alveoli and capillaries. Anesthetics—volatile liquids and gases—are administered by inhalation; aerosol bronchodilators, glucocorticoids, and antibiotics can also be inhaled to get a local effect. The complexity of dosing DPs for inhalation, their irritant effect on the lungs, the risk of medical personnel being exposed to propellants, and the possibility of exposure to allergens should be taken into account. Aerosols with extra-fine particles can be sprayed with a nebulizer (derived from the Latin nebula — “mist”). This quickly delivers a therapeutic dose of the product in an aerosol form and is suitable for use from the first months of a child’s life. To prevent the resorptive effect of DPs, poorly absorbed hydrophilic compounds (ipratropium bromide) or substances that undergo extensive pre-systemic elimination (salbutamol, beclomethasone) are used.
8. Cutaneous route. DPs can be used in the form of ointments, gels, pastes, solutions, emulsions, and suspensions. Barriers to absorption of lipid-soluble DPs into the blood should be taken into account, especially in cases of skin damage, inflammation, in children and elderly people (by the age of 60, all skin layers become thin, the number of capillaries decreases, microcirculation disorders in the form of stasis and microthrombosis occur). Transdermal Therapeutic Systems (TTS) are a route of administration for lipophilic DPs into the systemic bloodstream through intact skin. The DP is contained in a reservoir in the form of a suspension or gel; the rate of absorption is controlled by the permeability of the microporous polymer membrane or by diffusion from the polymer matrix. The amount of the active substance entering the body can be controlled by the area and design of the adhesive system. The action is more effective due to uniform release of the dose into the bloodstream, and side effects are reduced. TTSs containing fentanyl (treatment of chronic pain syndromes),

17- β -estradiol (during menopause), rivastigmine (treatment of Alzheimer's disease) are currently used in medical practice.

9. Intranasal administration. A DS is injected into the nasal cavity in the form of drops or special sprays. Intranasal absorption can be affected by mucosal blood flow, mucus viscosity, pH, humidity, temperature, etc. Some peptide hormones (desmopressin) are administered this way.

10. Intraperitoneal administration. DPs are injected between the parietal and visceral sheets of the peritoneum (e.g., antibiotics during abdominal surgery).

Other methods of administration: intrapleural (antitubercular agents), intra-articular (hydrocortisone), in the body and lumen of an organ (oxytocin), etc.

Absorption depends on:

- ▶ Functional state of the intestinal mucosa
- ▶ pH of the medium
- ▶ Gastrointestinal motility
- ▶ Composition of gastrointestinal contents
- ▶ Dosage form of the DP
- ▶ Physicochemical properties of the DP
- ▶ Route of administration of the DP (absorption rate, onset of action, degree of absorption, duration of action of the DS, severity of effect)
- ▶ Blood flow rate at the injection site.

Bioavailability

Bioavailability is the portion of the product dose that reaches the systemic bloodstream in an unchanged form and as metabolites formed as a result of first-pass metabolism (expressed as a percentage):

- ▶ up to 30% — low
- ▶ 30–60% — medium
- ▶ more than 60% — high.

Examples of bioavailability of various DPs are provided in Table 1.1.

Table 1.1. Bioavailability (F) of various drug products by route of administration

Drug product	F for different routes of administration, %	
	Oral	Sublingual
Nitroglycerin	<10	100
Isosorbide dinitrate	22	60
Morphine	20–25	100

First-pass elimination

- ▶ Some DPs, despite being easily absorbed through the intestinal mucosa cells, appear in the systemic bloodstream in small amounts (10–20% of the administered dose). This is due to their high liver first-pass metabolism.
- ▶ In liver disease, first-pass elimination is reduced, and bioavailability is increased, resulting in a higher incidence of toxic reactions.

DPs with a high degree of first-pass elimination:

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- ▶ Calcium antagonists (verapamil)
- ▶ Lipophilic β -adrenergic blocking agents (β -ABAs) (propranolol, metoprolol)
- ▶ Nitrate (nitroglycerin).

Distribution

After entering the systemic bloodstream, DPs are distributed to various organs and tissues. The rate and pattern of distribution depend on the following factors.

1. Lipid solubility of DPs: lipophilic products are rapidly distributed [long-acting β_2 -adrenergic agonists (AAs)], as they penetrate well into the extra- and intracellular spaces. Water- and lipid-insoluble molecules can be absorbed only when they are able to pass through pores in the cell membranes or through transport systems.

2. Binding of DS to plasma and tissue proteins:

- ▶ Many DS have a physical and chemical affinity for various plasma proteins (albumin, lipoprotein, γ -globulin, etc.)
- ▶ Binding of DS with plasma proteins decreases their concentration in the tissues and at the site of action, since only free (unbound) product can pass through membranes.
- ▶ The DS, which is in a complex with the target protein, no longer has a pharmacological activity.

Free and bound fractions of DPs are in a state of dynamic equilibrium (Fig. 1.1):

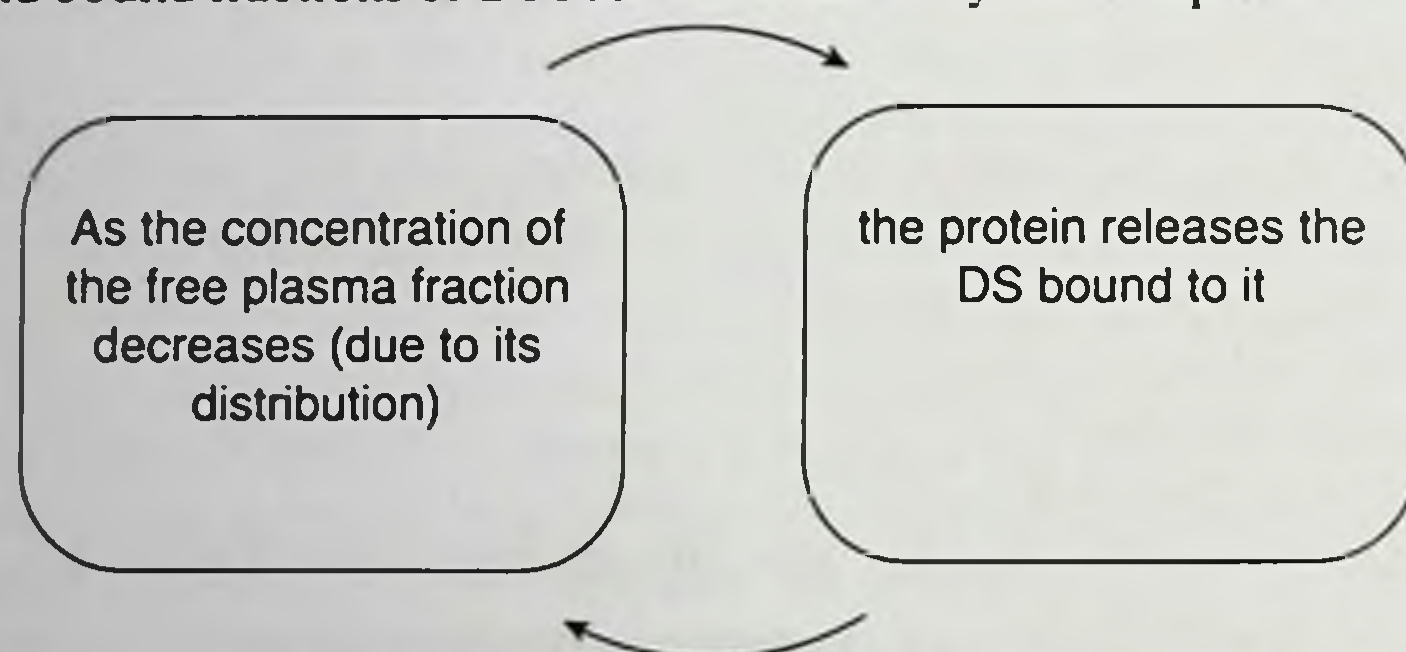


Fig. 1.1. Dynamic equilibrium between the free and bound fractions of a drug substance

- ▶ Plasma protein binding more than 90% — high: the effect is gradual, elimination is slow (digitoxin)
- ▶ Plasma protein binding less than 50% — low: the effect is rapid, elimination is high (strophanthus K).

3. Regional blood flow intensity

In the first minutes after absorption, most of the DS goes to highly vascularized organs, where the perfusion rate is more than 1.0 mL/min (kidneys, lungs, thyroid, adrenal glands) and then to organs with a perfusion rate of 0.1–1.0 mL/min (liver, heart, brain, spleen). The drug saturation is lower where the perfusion rate is less than 0.1 mL/min (adipose tissue, muscle, bone tissue, skin and mucous membranes).

The hemodynamic state is a determining factor in drug distribution. Impaired hemodynamics change the kinetics (Fig. 1.2).

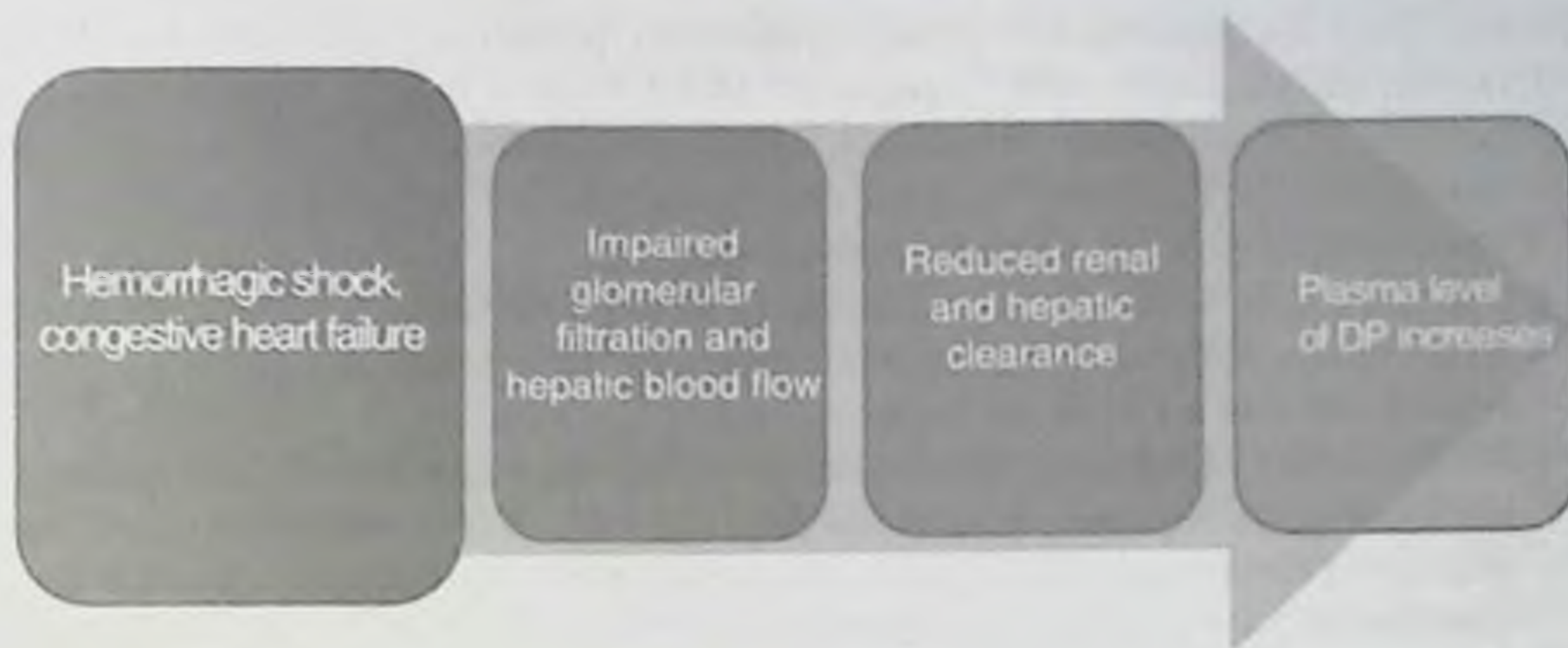


Fig. 1.2. An example of how the hemodynamic state affects the duration of action of a drug product: the duration of action of sodium thiopental increases during shock

Biological barriers:

- ▶ Blood-brain barrier (BBB)
- ▶ Placental barrier
- ▶ Blood-ocular barrier
- ▶ Blood-testis barrier

Blood-brain barrier

The BBB is a physiological barrier between the blood system and the CNS (endothelium has no pores, no pinocytosis, presence of glial elements on the outer surface of the endothelium).

Diffusion from the blood to the brain is limited due to the BBB's morphofunctional properties: polar molecules poorly diffuse through it while non-polar molecules easily diffuse through it. BBB permeability depends on the person's age: it is very high in the first weeks of life and very low in older age. Permeability increases with the osmotic pressure in brain vessels and BP, exposure to radiation and microwaves, inflammatory mediators (histamine, bradykinin), various pathological conditions (brain injury, brain ischemia, Alzheimer's disease, encephalitis, meningitis, etc.). For example, diphenhydramine (Dimedrol®), pefloxacin, rifampicin easily penetrate the BBB.

Targeted DS transport to the brain is ensured by using nanoparticles (10 to 1000 nm in size) prepared from biodegradable polymers that are slightly water-soluble and compatible with human tissues. The substance of interest can be incorporated into nanoparticles, bound to them covalently, or adsorbed on their surface. Nanoparticles are capable of transporting peptide and protein compounds (nerve growth factor, chloroquine) through the BBB.

Placental barrier

This is a complex transport system separating the mother's blood circulation from that of the fetus. It consists of a monolayer of cells (syncytiotrophoblasts), whose apical membrane is in contact with the maternal blood and whose basal membrane is in contact with the fetal blood. Lipophilic substances can diffuse passively and are

removed from the placenta by special transporters, primarily ATP-dependent (ATP - adenosine triphosphate), ABC transporter (ATP-binding cassette transporters) and P-glycoprotein (rifampicin, verapamil). Hydrophilic substances diffuse across the placenta differently, either by transport proteins or (rarely) pinocytosis.

The permeability of the placental barrier increases:

- ▶ From week 32 of pregnancy, since the placenta is thinning
- ▶ In toxemia, hypoxia, bleeding, endocrine disorders, etc.

Negative effect of a DP on the fetus

- ▶ Teratogenicity (impaired organogenesis — fetal development under the influence of teratogenic factors — certain physical, chemical (including DPs) and biological agents contribute to the development of morphological anomalies and malformations) — phenytoin, cyclophosphamide, tetracycline, carbamazepine.
- ▶ Embryotoxicity (ability of a DS to cause death or malignant changes in the embryo when the DS is administered before week 12 of pregnancy) — captopril, enalapril, misoprostol, furosemide, estrogens.
- ▶ Fetotoxicity (ability of a DS to cause death or malignant changes in a mature fetus after week 12) - acetylsalicylic acid (Aspirin*), indomethacin, propranolol (Anaprilin*).

Blood-ocular barrier

This is a barrier between capillary blood and intraocular fluid in the eye chamber. Lipid-soluble products [propranolol (Anaprilin*)] easily penetrate the refractive media of the eye.

Blood-testis barrier

This is a set of structures located between the lumen of blood capillaries and seminiferous tubules. It controls the flow of substances from the blood into the lumen of the convoluted tubule to the seminiferous epithelium, which prevents the development of an autoimmune process against surface antigens of sperm cells, retains a specific hormonal environment with high levels of testosterone within the seminiferous tubules necessary for differentiation of germ cells, helps to protect germ cells from the damaging effects of mutagenic factors. This barrier has a protective mechanism in the form of ATP-dependent transport proteins that limit the penetration of some lipophilic drug substances (cyclosporine).

Deposition

Drugs are transported to cell receptors and excretory organs in the form of depots with blood proteins. Weak acids (furosemide, acetylsalicylic acid, phenobarbital) bind to albumin, while weak bases (morphine, atropine, lidocaine) bind to acidic glycoproteins and lipoproteins.

Adsorption to proteins is reversible and occurs according to the complementarity principle involving hydrogen, ionic, dipole forces of interaction; alkylation of proteins is rare. Reactions with blood proteins turn water-soluble DPs into lipophilic ones. The elimination half-life of a DP complex with blood proteins is only 20 ms.

Lipid-soluble DPs are deposited in adipose tissue. For example, after intravenous injection of the anesthetic sodium thiopental, it quickly enters the brain and causes anesthesia, but after 20–25 minutes, most of it is detected in skeletal muscles and fat depots. Thiopental slowly re-enters the blood and brain from the depot, thus causing depression and drowsiness in the postanesthesia period. Polar compounds can accumulate in connective and bone tissues (tetracyclines).

Biotransformation

This is a complex series of physicochemical and biological transformations in which DPs form polar water-soluble substances (metabolites), which are more easily eliminated from the body (Fig. 1.3). In most cases, drug metabolites are less biologically active and less toxic than the parent compounds. However, biotransformation of some substances leads to the formation of metabolites that are more active than the substances originally administered into the body [enalapril (an antihypertensive agent) undergoes biotransformation to form an active metabolite, enalaprilat]. This can occur in the liver, kidneys, intestinal mucosa, lungs, skin, muscles, and other organs.

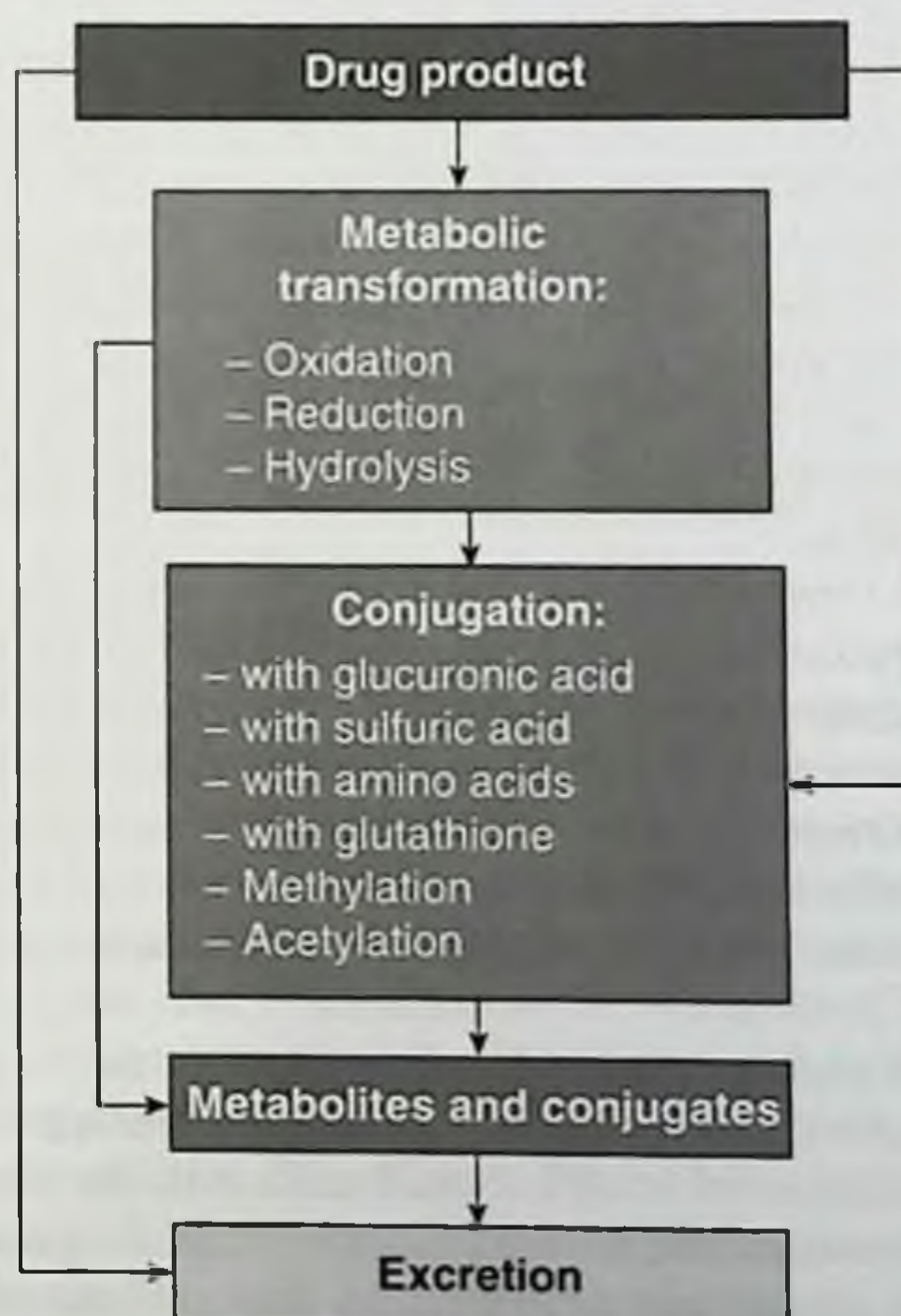


Fig. 1.3. Drug biotransformation pathways in the body (D. A. Kharkevich, 2021)

- ▶ Most DPs undergo biotransformation in the body.
- ▶ Generally, highly hydrophilic ionized compounds are excreted unchanged.

- ▶ Among lipophilic substances, the exception is inhalational anesthetics, most of which do not react chemically in the body and are eliminated by the lungs unchanged.
- ▶ The biotransformation of DPs involves many enzymes, the most critical being hepatic microsomal enzymes (located in the endoplasmic reticulum). They metabolize exogenous lipophilic compounds by converting them into more hydrophilic compounds.
- ▶ Non-microsomal enzymes at various locations (liver, intestine, other tissues, and plasma) are essential, especially for the biotransformation of hydrophilic substances.

There are two main types of drug transformation: metabolic transformation and conjugation.

1. Metabolic transformation is the transformation of substances by oxidation, reduction, and hydrolysis.

- Oxidation occurs primarily through microsomal mixed-function oxidases involving nicotinamide adenine dinucleotide phosphate, oxygen, and cytochrome P450 [imipramine (imisin), ephedrine, chlorpromazine (Aminasin*), histamine, codeine].
- Some drug products [chloral hydrate, chloramphenicol (Levomycetin*), nitrazepam, etc.] are subjected to reduction. This occurs through a system of nitro- and azoreductases and other enzymes.
- DPs are hydrolyzed mainly by non-microsomal enzymes (esterases, amidases, phosphatases) in plasma and tissues. Ether, amide, and phosphate bonds in the DP's molecules are broken by the addition of water. Esters [procaine (Novocaine*), atropine, acetylcholine, suxamethonium iodide (Dithylin-Darnitsa*), acetylsalicylic acid] and amides [procainamide (Novocainamide*)] undergo hydrolysis.

2. Conjugation is a biosynthetic process in which certain chemical groups (acetyl, methyl) or molecules of endogenous compounds (glucuronic or sulfuric acids, glutathione, glycine, etc.) are added to a DP or its metabolites.

These reactions occur thanks to the involvement of hepatic enzymes (glucuronyl transferase, sulfotransferase, transacylase, methyltransferase, glutathionyl transferase, etc.) and other tissue (intestinal walls, lungs, kidneys) enzymes. These enzymes are found in the endoplasmic reticulum of hepatocytes (microsomal enzymes) or in the cytosolic fraction.

- ▶ Conjugation with glucuronic acid (mediated by the microsomal enzyme uridine diphosphate-glucuronyl transferase) — morphine, oxazepam.
- ▶ Sulfation, i.e., addition of a sulfuric acid residue to the substrate (mediated by the cytosolic enzyme, sulfotransferase) — minoxidil, isoprenaline.
- ▶ Conjugation with glutathione (mediated by the cytosolic enzyme, glutathione-S-transferase) — paracetamol.
- ▶ Methylation of substances such as histamine and catecholamines; acetylation of sulfonamides, etc.

Conjugation is either the only way a DS is transformed or it can occur after a metabolic transformation. During metabolic transformation and conjugation, substances are converted into more polar and more water-soluble metabolites and

conjugates. They can be transformed further chemically, if necessary, which also contributes to their elimination from the body. The kidneys excrete hydrophilic compounds; lipophilic compounds are to a large extent subjected to reverse absorption (reabsorption) in the renal tubules. As a result of metabolic transformation and conjugation, DPs usually lose their biological activity. These processes limit a drug's effect over time.

In liver disease accompanied by a decrease in the activity of microsomal enzymes, the effect duration of certain substances increases. Inhibitors of various enzymes, both microsomal and non-microsomal [anticholinesterase agents, monoamine oxidase (MAO) inhibitors, etc.] prolong the effects of products that are inactivated by these enzymes. At the same time, some compounds increase or decrease the rate of synthesis of hepatic microsomal enzymes (Table 1.2).

Table 1.2. Inducers and inhibitors of hepatic microsomal enzymes

Inducers	Inhibitors
• Phenobarbital • Rifampicin • Phenytoin (Diphenin*) • Ethanol • Diazepam • Diphenhydramine (Dimedrol*) • Carbamazepine • Nicotine	• Chloramphenicol (Levomycetin*) • Erythromycin • Clarithromycin • Amiodarone • Indomethacin • Cimetidine • Ketoconazole • Ciprofloxacin

When DS are used concomitantly with inducers or inhibitors of hepatic enzymes involved in the metabolism of these DS, the prescribed DS dose must be adjusted. The dose should also be adjusted when inducers or inhibitors are discontinued.

Elimination pathways for drug products

- ▶ DPs, their metabolites and conjugates are mainly excreted with urine and bile.
- ▶ In the kidneys, low molecular weight compounds dissolved in plasma (not bound to proteins) are filtered through the membranes of the glomerular capillaries and capsules. Active secretion of substances into the proximal tubules by transport systems plays an essential role. Organic acids and bases are excreted in this way: penicillins, salicylates, sulfanilamides, histamines, thiazides, etc. Some lipophilic compounds can get from the blood into the lumen of tubules (proximal and distal) by simple diffusion across their walls.

The main processes affecting DS excretion by the kidneys are as follows.

- ▶ The excretion of DS largely depends on their reabsorption (reverse absorption) in the renal tubules (Fig. 1.4). Lipophilic non-polar compounds that penetrate easily through biological membranes are reabsorbed mainly by simple diffusion. Polar compounds are poorly reabsorbed from the renal tubules. Thus, the urine's pH is important for the excretion of weak acids and bases. Alkaline urine increases the excretion of acidic compounds, while acidic urine increases the excretion of bases. The reabsorption of certain endogenous substances (amino acids, glucose, uric acid) involves active transport.

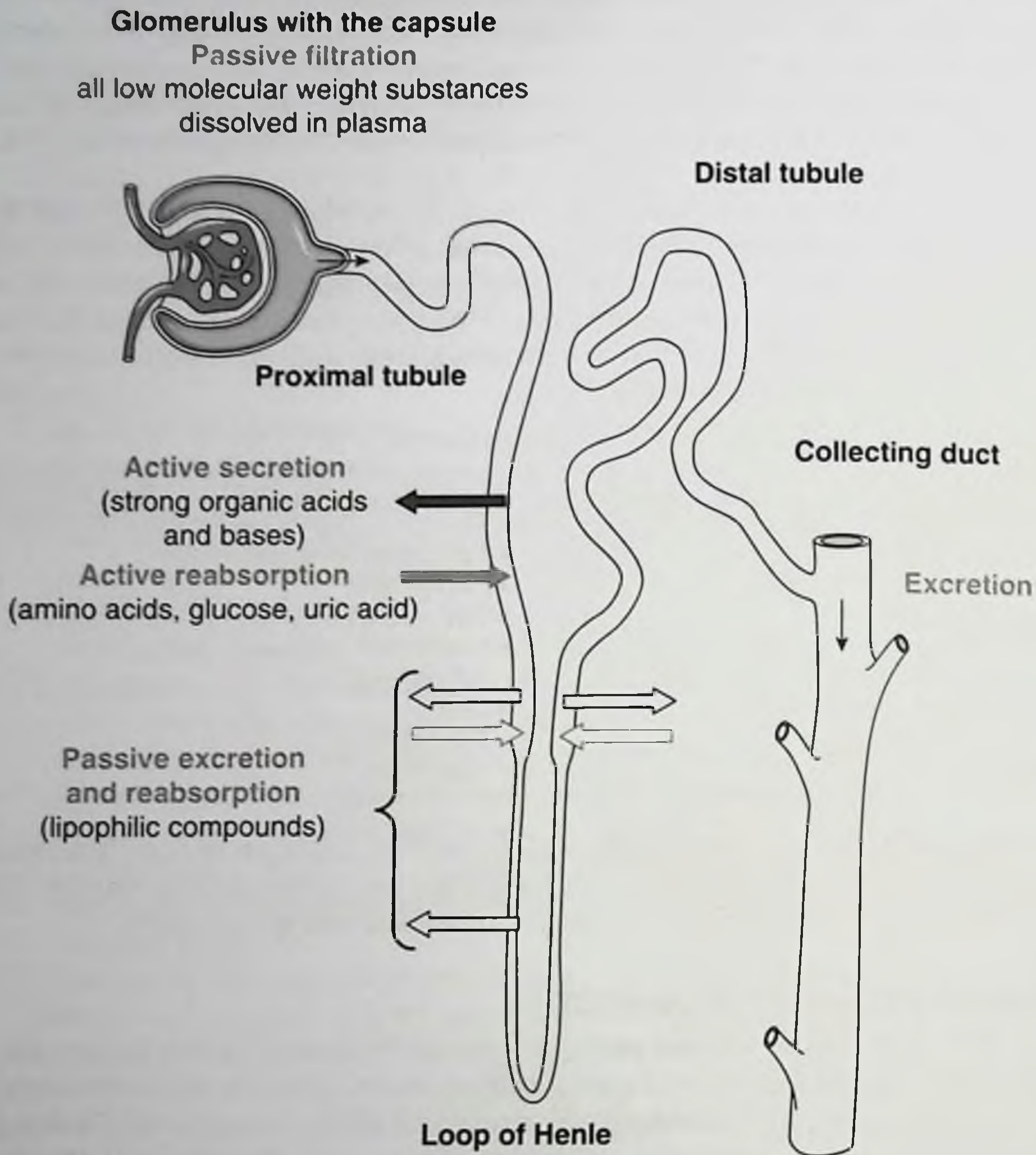


Fig. 1.4. tubular reabsorption of drug products in the kidneys

- ▶ Certain products [tetracyclines, penicillins, phenytoin (Diphenin[®]), colchicine, etc.], and especially their transformation products, are excreted with bile in significant amounts into the intestine, at which point they are partially eliminated with feces or can be reabsorbed and subsequently re-excreted in the intestine (so-called enterohepatic circulation or hepatic recirculation) (morphine, chloramphenicol, ethinyl estradiol). DS reach hepatocytes through the hepatic sinusoidal endothelium by passive diffusion (lipophilic substances) or by transport proteins; polar DS and endogenous substances (leukotrienes, bilirubin) are taken up by hepatocytes through facilitated diffusion or by secondary active transport.

- ▶ Gaseous and many volatile substances (inhalational anesthetics) are mainly eliminated by the lungs.
- ▶ Individual products are secreted by salivary glands (iodides), sweat glands (antileprotic agent ditopha), gastric glands (nicotine), intestinal glands (weak organic acids), and lacrimal glands (rifampicin).
- ▶ During lactation, the mammary glands secrete many substances that the nursing mother takes in [sleeping pills, painkillers, ethanol (Ethyl Alcohol*), nicotine, etc.]. Thus, caution is required when prescribing DPs to the mother, because they can enter the baby's body through breast milk and cause adverse effects to the baby.

Quantitative characterization of drug elimination

- ▶ The elimination rate constant (coefficient) is the removal rate of the substance from the body (expressed as a percentage) (digitoxin 7%, strophanthus K 40%).
- ▶ The elimination half-life ($T_{1/2}$) is the time during which the plasma level of the substance decreases by half of the initial concentration (50%) (digitoxin 168–192 h, strophanthus K 20–24 h).
- ▶ Systemic clearance (total clearance is the sum of renal and extrarenal clearance) is the rate of DS elimination from blood plasma per unit of time.

Clearance of drug products

Clearance is the volume of body fluids released from a DS as a result of biotransformation and excretion (calculated in mL/min/kg):

$$Cl = \text{elimination rate} / C \text{ (DS plasma level)}$$

The relative organ clearance is equal to the elimination rate in the organ (kidneys, liver, etc.) divided by the DS level, which together form the total systemic clearance (Cl).

Clearance can be determined relative to:

- ▶ Blood
- ▶ Plasma
- ▶ Plasma level of unbound substance.

Renal clearance is the DS clearance determined by urinary excretion.

The following factors affect renal clearance:

- ▶ Decreased renal blood flow
- ▶ Glomerular filtration
- ▶ Maximum rate of secretion and reabsorption
- ▶ Urine volume
- ▶ Fraction of DS not bound to plasma proteins.

Renal clearance depends on the physicochemical properties of the DS:

- ▶ Polar MPs are not reabsorbed, non-polar MPs are reabsorbed
- ▶ Ionic MPs are secreted, non-ionic MPs are not secreted.

The glomerular filtration rate (mL/min) and renal tubular reabsorption (%) are determined using the plasma and urine clearance of endogenous creatinine, taking into account the volume of fluid excreted (per unit of time).

Hepatic clearance is elimination of the DS by biotransformation of the initial substance into one or more metabolites and further excretion with bile.

Factors affecting hepatic clearance:

- ▶ Hepatic blood flow rate
- ▶ Maximum rate of excretion or metabolic transformations
- ▶ Unbound fraction.

Factors altering DS clearance:

- ▶ Drug interaction at the level of renal secretion, biochemical transformation, and enzyme induction phenomena
- ▶ Kidney diseases: blood flow disorders, acute and chronic kidney failure. Pharmacokinetic studies in patients with renal impairment have shown that the clearance of many DPs (meropenem, amikacin) correlates with creatinine clearance. The dose must be adjusted in these patients.
- ▶ Older age: pharmacokinetic studies in the elderly have also revealed a decrease in the clearance of some DPs (e.g., meropenem) that correlates with age-related decrease in creatinine clearance.
- ▶ Hepatic diseases: alcoholic liver disease, primary biliary cholangitis, hepatitis. In patients with elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activity (exceeding 3 times the upper limit of normal), dose adjustment or product discontinuation is required.
- ▶ Diseases of the gastrointestinal tract and endocrine organs
- ▶ Individual intolerance [e.g., lack of acetylation enzymes leads to intolerance of acetylsalicylic acid (Aspirin[®])]
- ▶ Elimination rate of DPs with a high hepatic extraction coefficient depends on the rate of their delivery to the liver via blood rather than on the liver's ability to eliminate these substances (diltiazem, lidocaine, morphine, propranolol, simvastatin).

Pharmacodynamics

Pharmacodynamics includes the concepts of pharmacological effects, localization of action and DS modes of action. It consists of primary and secondary pharmacological reactions. The primary pharmacological reaction is an interaction with cell receptors—biomacromolecules genetically determined to interact with biologically active substances, including DPs. Interaction with cell receptors is necessary for the development of a secondary pharmacological reaction such as changes in metabolism or cell and organ functions.

Pharmacological effects are changes in the function of organs and body systems caused by a DS, such as increased heart rate, decreased blood pressure, decreased body temperature, etc. Some pharmacological effects are useful, like a DS used in medical practice (main or therapeutic effects), while others are undesirable (side effects).

For many DS, the sites of their predominant action in the body (i.e., location of action) are known: some DS act mainly on certain structures of the brain (anti-Parkinsonian, antipsychotic agents), others act mainly on the heart (cardiac glycosides). The location of the DS action is determined not only at the systemic and organ levels, but also at the cellular and molecular levels: e.g., cardiac glycosides act

on the organ level (heart), cellular level (cardiomyocytes), and molecular level (Na^+/K^+ -ATPase in cardiomyocyte membranes).

The mode of action is how a DS causes pharmacological effects.

Drug targets are biological substrates with which a DS interact:

- ▶ Receptors
- ▶ Ion channels
- ▶ Enzymes
- ▶ Transport systems
- ▶ Genes.

Receptors are active groups of cell membrane macromolecules with which a DS interacts. They are selectively sensitive to certain endogenous chemical compounds (mediators). When substances (ligands) interact with receptors, the conformation of the receptor's proteins changes, which leads to a chain of biochemical reactions in the cell and further development of certain effects at the tissue, organ and system levels (pharmacological effects, if the ligand is a DS). Receptors are targets for both endogenous ligands and exogenous biologically active substances (including DS). Receptors that account for the effect of substances are called specific. They can be located in the cell membrane (membrane receptors) or inside the cells, in the cytoplasm or nucleus (intracellular receptors).

There are four types of receptors: three membrane and one intracellular.

Membrane receptors

1. Receptors that directly control ion channel function consist of several transmembrane subunits and form the ion channel. This type of receptor includes N-cholinergic receptors (ChR), GABA receptors (GABA, γ -aminobutyric acid), and glutamate receptors (Fig. 1.5).
2. Receptors coupled with the effector through the system of "G-protein plus secondary transmitter" or "G-protein coupled ion channels" (Fig. 1.6). One receptor is usually coupled with several proteins, and each protein can simultaneously interact with several enzyme molecules or several ion channels. This interaction results in amplification (enhancement) of the DS's effect. Such receptors are available for many hormones and mediators (muscarinic cholinergic receptors [MChR], adrenoreceptors [AR], histamine receptors, opioid receptors, etc.).
3. Enzyme-linked receptors (catalytic receptors) that directly control the function of the effector enzyme (Fig. 1.7). They are directly linked to tyrosine kinase and regulate protein phosphorylation. Insulin receptors, certain growth factor receptors, and cytokine receptors are arranged according to this principle.

Intracellular receptors control deoxyribonucleic acid (DNA) transcription (Fig. 1.8). Unlike membrane receptors, these are intracellular receptors (soluble cytosolic or nuclear proteins). Steroid and thyroid hormones, vitamins A and D interact with such receptors.

Osmotic diuretics, blood substitutes, complexing agents have a non-receptor-mediated mechanism of action.

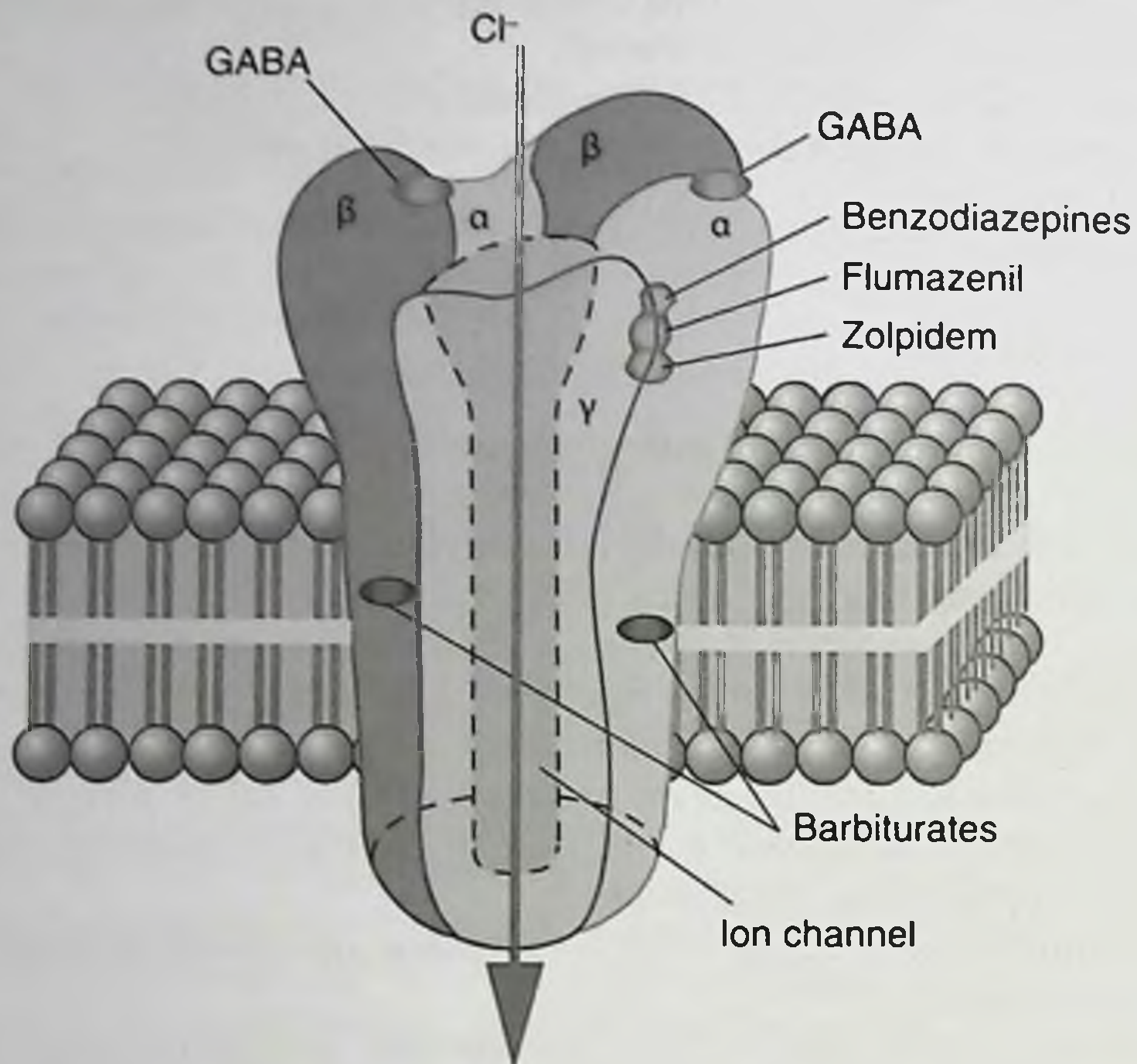


Fig 1.5. GABA_A-receptor structure (Katzung B.G., 2018)

Intermediate links of the receptor and effect.

- ▶ Regulatory G-proteins: Gq, Gi, Gs etc.
- ▶ Enzymes: adenylyl cyclase (AC), guanylate cyclase (GC), Phospholipase C, phosphodiesterase (PDEase) etc.
- ▶ Secondary transmitter: cyclic adenosine monophosphate (cAMP); cyclic guanosine monophosphate (cGMP); inositol trisphosphate (InsP3); diacylglycerol (DAG), Ca²⁺ ions, etc.

DPs have an affinity (derived from Latin *affinis* — “related”) and intrinsic activity for receptors. Affinity is the ability to form a complex with receptors. Intrinsic activity is aimed at creating an active stereoconformation (the effect of the drug molecule’s orientation in space relative to the receptor) and triggering a cellular response. Depending on their affinity and the presence of intrinsic activity, DPs can be divided into two groups:

- ▶ Agonists (derived from Greek *αγωνιστής* (*agōnistēs*), “participant”, “competitor”) or mimetics (derived from Greek *mimeomai*, “to mimic”) are substances with moderate affinity and high intrinsic activity: full agonists cause the maximum possible cellular response and have the maximum intrinsic activity (acetylcholine, morphine, fentanyl); partial agonists cause a less significant cellular response and have no maximum intrinsic activity (buprenorphine).

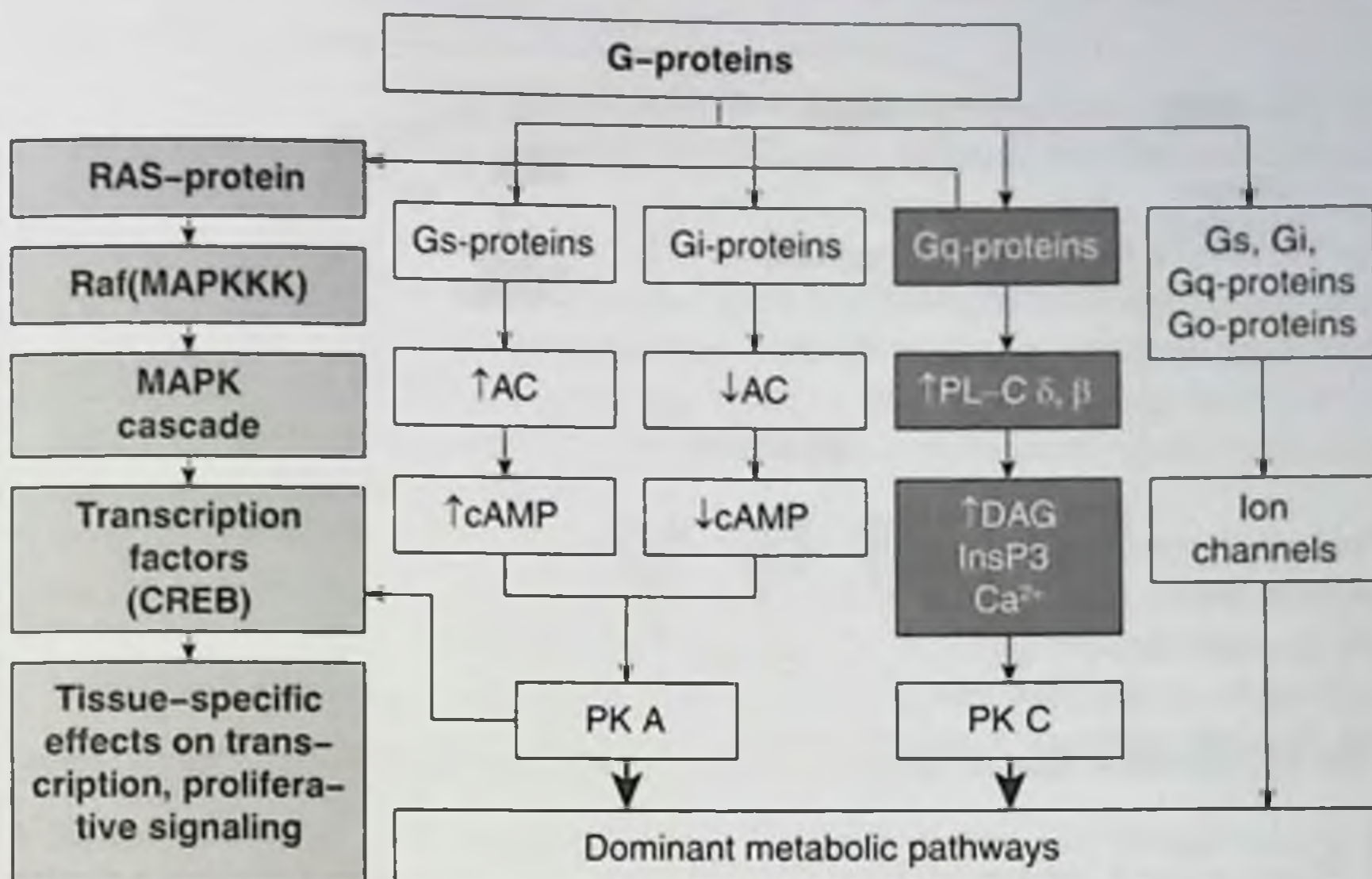


Fig. 1.6. Metabolic and proliferative signaling pathways controlled by G-protein coupled receptors: AC — adenylyl cyclase; cAMP — cyclic adenosine monophosphate; PK A — protein kinase A; PK C — protein kinase C; PL-C — phospholipase C; DAG — diacylglycerol; InsP3 — inositol trisphosphate

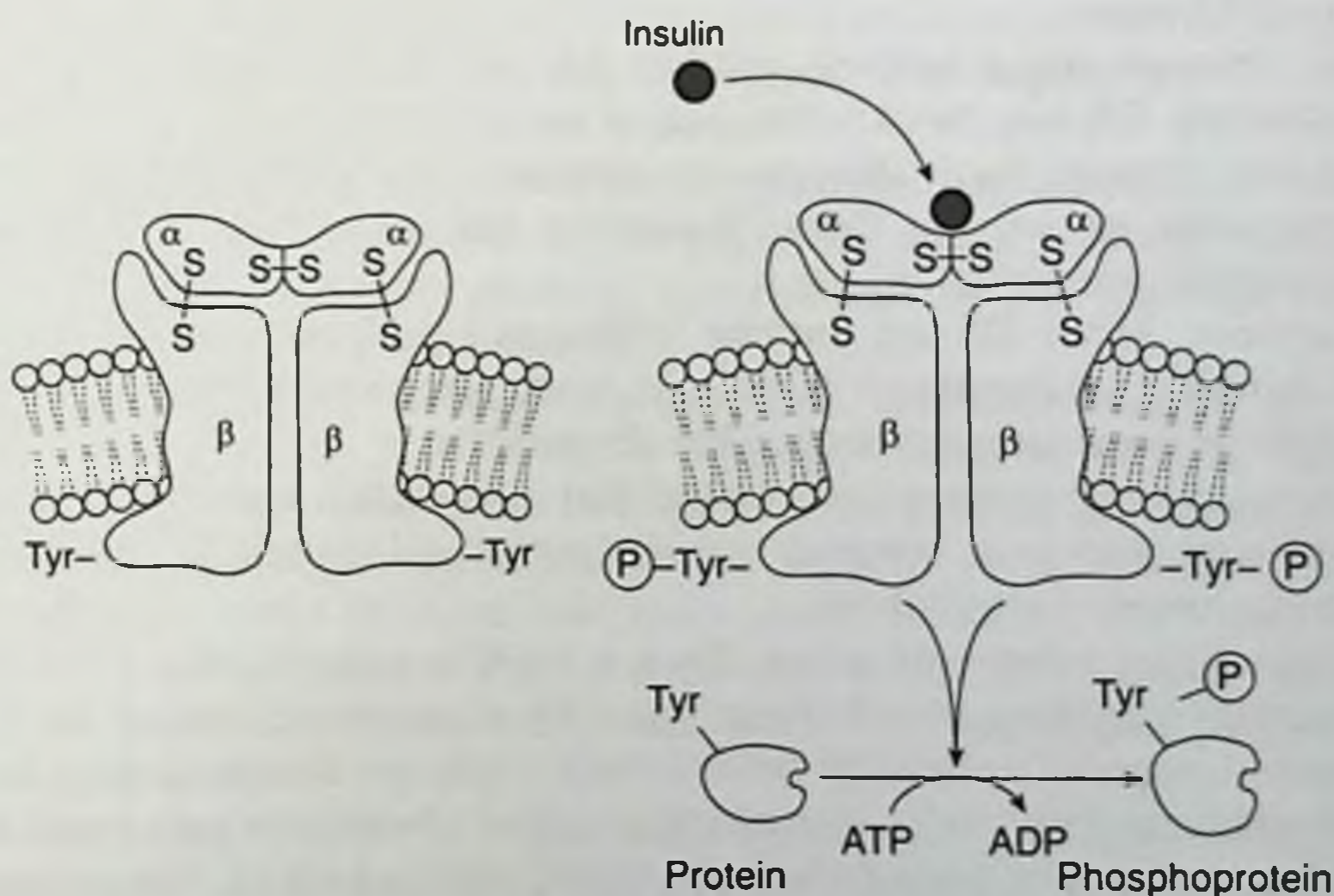


Fig. 1.7. Insulin receptor (tyrosine kinase activation): ATP — adenosine triphosphate; ADP — adenosine diphosphate; Tyr — tyrosine

- Antagonists (derived from Greek ἀνταγωνιστής, *antagonistēs*, “adversary, competitor”, which comes from anti, “against”, and agōn, “struggle”) or receptor blockers are substances with high affinity but no intrinsic activity.

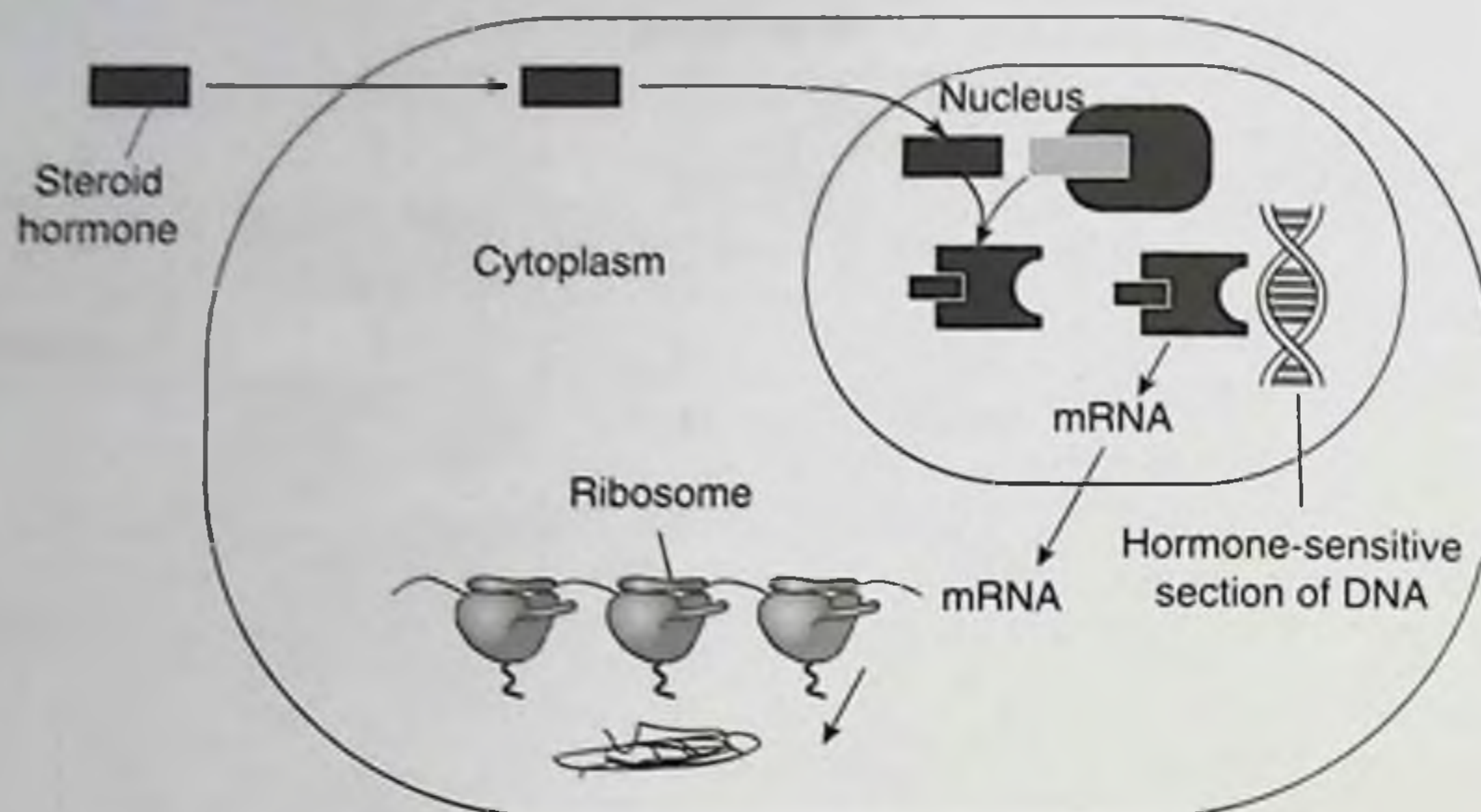


Fig. 1.8. Interaction between steroid hormones and intracellular receptors (E. S. Severin, 2015)

They quench receptors from the action of endogenous ligands and prevent the development of a cellular response by enhancing the effects of other, unblocked receptors.

Agonist and antagonist properties may be combined in pharmacodynamics; for example, agonist–antagonists activate some receptors and block others (pentazocine, nalbuphine).

Other DS targets:

- ▶ Ion channels that selectively conduct Na^+ , Ca^{2+} , K^+ [regulated by an action potential]. DS may block voltage-gated ion channels and thus disrupt the flow of ions through them (lidocaine, procainamide, carbamazepine, nifedipine, verapamil) or activate them, facilitating the movement of ionic currents (minoxidil, diazoxide).
- ▶ Enzymes. Many DS are enzyme inhibitors [antidepressant MAO inhibitor: nialamide, cyclooxygenase (COX) inhibitor: paracetamol, acetylcholinesterase inhibitor: neostigmine methylsulfate (Proserin[®])].
- ▶ Transport systems (transport proteins) that carry certain molecules or ions across cell membranes (e.g., blocking norepinephrine and serotonin reuptake with the antidepressant amitriptyline).
- ▶ Genes. Using selectively acting DS, it is possible to have a direct effect on the function of certain genes. In cases where the expression of certain genes will be blocked, a special technology called antisense oligonucleotides is used. The latter are relatively short chains of nucleotides (15–25 bases) that are complementary to the nucleic acid region where the target gene is located. The expression of this gene is suppressed by an interaction with the antisense oligonucleotide. This principle of action is relevant for the treatment of viral, tumor and other diseases. An example of this group of drug products is vitriven[®] (fomivirsen[®]), which is used topically for retinitis pigmentosa caused by cytomegalovirus infection. Drugs of this type have been developed for the treatment of myeloid leukemia and other blood diseases.

Types of drug effects

- ▶ Local effects are effects of the DP at the place of its application (reduction of pain and temperature sensitivity under the influence of local anesthetics: lidocaine, novocaine).
- ▶ Resorptive effects (derived from Latin *resorbeo* — “absorb”) are effects of the DP after absorption into the blood and penetration through the blood-tissue barriers (analgesia during the use of anesthetics, narcotic and non-narcotic analgesics).
- ▶ Direct (primary) effects are a change in organ function resulting from the DP's direct influence on this organ's cells (cardiac glycosides have a positive inotropic effect; diuretics increase diuresis).
- ▶ Indirect (secondary) effects are a change in organ or cell function due to the action on other organs and cells functionally related to the first (cardiac glycosides have a diuretic effect because they increase myocardial contractility, improve blood flow in the kidneys, increase urine filtration and formation). A particular type of indirect action is reflexive — a change in organ function through direct stimulation of sensory nerve endings.
- ▶ Reflexive effects due to excitation of exteroceptors are produced by skin irritants of interoceptors — expectorants, emetics, choleretics, laxatives, vascular chemoreceptors — analeptics, skeletal muscle proprioceptors — muscle relaxants.
- ▶ Reversible effects are due to the weak physicochemical bonds established with the receptors, which is typical of most DPs [neostigmine methylsulfate (Proserin[®]), galantamine].
- ▶ Irreversible effects result from the formation of covalent bonds with receptors or enzymes, typical of few products [acetylsalicylic acid (Aspirin[®])].
- ▶ Main effect — therapeutic effects of DPs.
- ▶ Side effects — adverse effects of DPs. The pharmacological effects of a DP may be main effects or side effects, depending on the disease. Adverse reactions are observed with many drug products (acetylsalicylic acid — ulcerogenic effect, gentamicin — hearing impairment).
- ▶ Selective action is the effect of a drug product on the functions of only certain organs and systems. It is caused to a greater extent by selective binding to receptors, and to a lesser extent by selective accumulation in organs and tissues. When taken orally, magnesium sulfate, without being absorbed from the intestine, increases peristalsis and has a choleretic effect. When administered parenterally, magnesium ions depress the CNS. Inhalational anesthetics create a concentration in the brain that is 1.5–2.0 times higher than the blood concentration.
- ▶ Nonselective action: β -AB — propranolol (Anaprilin[®]), M-CB — atropine.
- ▶ Central effect is a direct effect of a DS on the CNS (sleeping pills, antidepressants, anxiolytics, etc.).
- ▶ Peripheral effect is an effect of a DS on the peripheral nervous system or on organs and tissues (muscle relaxants).

Drug effects depend on the chemical structure

For all groups of products, the relationship of the chemical structure and activity has been established. The number and arrangement of atoms in the molecule are of great importance (Fig. 1.9). For example, adding fluorine to a glucocorticoid molecule increases its anti-inflammatory activity. The activity of geometric isomers, enantiomers, and stereoisomers differs significantly. Thus, for most DPs, left-handed isomers are more active than right-handed isomers (the alkaloid hyoscyamine, which is an active L-isomer, partially transforms into an inactive D-isomer during isolation from the plant, therefore a mixture of the two isomers [atropine] is 2 times less active than hyoscyamine). In addition, the DP's physical and chemical properties are directly related to its chemical structure (e.g., ionization, dissociation, solubility), on which the bioavailability, absorption, ability to pass through cell membranes and biological barriers depend, are also important for the intensity of the DP's effects. The lipophilicity of substances determines their ability to penetrate through the BBB and influence the CNS.

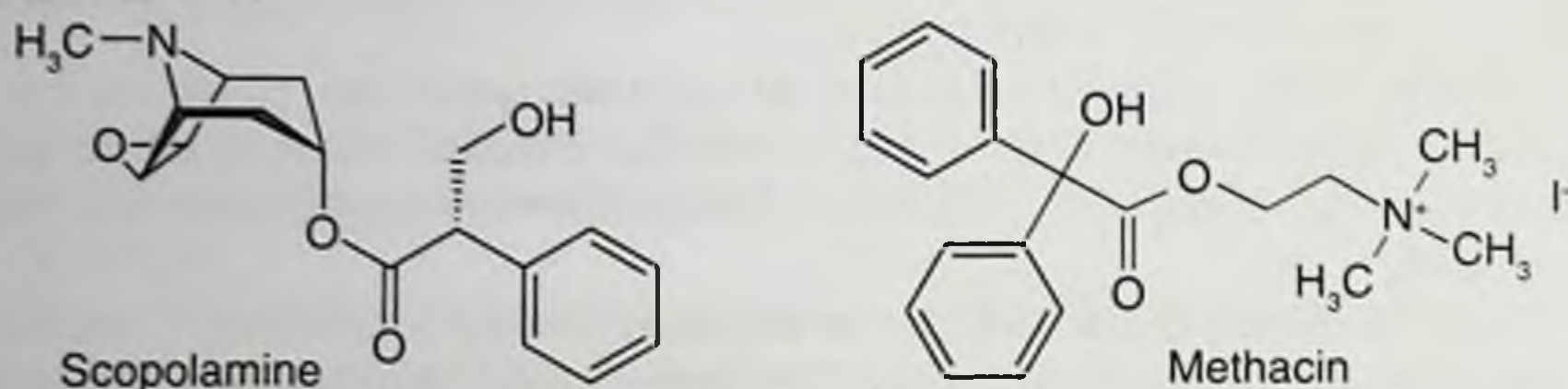


Fig. 1.9. A drug's effect depends on its chemical structure: Scopolamine*, a non-selective M-ChB, contains a tertiary nitrogen atom, thus easily penetrates tissues and through the blood-brain barrier (predominantly central effects). Metocinium iodide (Methacin*), a non-selective M-ChB, contains a quaternary nitrogen atom, thus penetrates poorly into tissues and through the blood-brain barrier (predominantly peripheral effects). Low molecular weight lipophilic molecules can easily cross the blood-brain barrier by passive diffusion, but many lipophilic molecules (quaternary ammonium compounds) are rather quickly removed from endothelial cells by transmembrane proteins, such as P-glycoproteins, which function as an adenosine triphosphate-dependent pump, preventing their penetration and accumulation in brain tissues.

Importance of individual characteristics for the intensity of a drug's effects

Age

Age-related changes in the effect of DS are particularly evident in newborns and patients over 60 years of age.

Newborns are more sensitive to some substances affecting the CNS (in particular, morphine, neostigmine), so children are prescribed smaller doses than adults, and some DS are contraindicated. Levomycetin is very toxic for them, and can even cause death, since the activity of many hepatic enzymes required for detoxification is lower in newborns (conjugation of its toxic metabolite is slow).

Young children should not be prescribed a DS that increases the secretion of glands (bronchial, nasal mucosa, etc.), which can disrupt the breathing process and cause respiratory organ pathology.

In persons over 60 years of age, the activity of some microsomal enzymes, hepatic blood flow, liver weight, and renal function decreases, resulting in a reduced rate of

metabolism and excretion for many DS. For example, doses of CNS depressants (sleeping pills, narcotic analgesics), cardiac glycosides, and diuretics should be reduced by half of those recommended for middle-aged persons.

Sex

There are some sex differences in DS metabolism and sensitivity to certain pharmacological effects.

Males:

- ▶ Activity of microsomal enzymes is higher than in women because the synthesis of these enzymes is stimulated by male sex hormones. Substances such as ethanol, estrogens, benzodiazepines, and salicylates are metabolized faster in men
- ▶ Clearance of paracetamol is faster
- ▶ Less sensitive to certain substances (nicotine, strychnine).

Females:

- ▶ Arrhythmogenic effect of antiarrhythmic agents is more frequent
- ▶ Analgesic effect of morphine occurs in smaller doses than in males
- ▶ Bioavailability of verapamil is higher
- ▶ Oxidation of diazepam is faster.

Genetic factors

There are significant differences in a person's sensitivity to a DS due to genetic factors:

- ▶ Glucose-6-phosphate dehydrogenase deficiency in red blood cells can lead to acute hemolysis (nitrofurantoin, furazolidone, sulfonamides)
- ▶ Atypical pseudocholinesterase (butyrylcholinesterase) deficiency can lead to prolonged apnea [suxamethonium iodide (Dithylin-Darnitsa*)]
- ▶ Acetyltransferase deficiency can lead to a high incidence of side effects (polyneuritis when using isoniazid)
- ▶ Catalase deficiency (acatalasia) leads to a high sensitivity to alcohol [low oxidation rate of ethanol (Ethyl Alcohol*)].

General health

The effect of DPs may depend on a person's health, particularly on the disease for which they are indicated. For example, antipyretics reduce body temperature only when a person has a fever; they have no effect in normothermia. The higher the sympathetic tone, the greater the antihypertensive effect of ganglionic blockers. Hyperthyroidism increases myocardial sensitivity to adrenaline. Diseases accompanied by impaired renal or hepatic function alter the biotransformation and excretion of DS accordingly. Other parameters—protein binding, bioavailability, distribution—may also change. Drug pharmacokinetics vary during pregnancy and with obesity.

Pregnancy

The following should be considered when prescribing a DS during pregnancy:

- ▶ Absorption in the stomach of products with low hydrophilicity is reduced
- ▶ Intestinal absorption of products increases due to decreased peristalsis rate and increased transit time in the small intestine
- ▶ Circulating blood volume increases, the activity of liver enzymes, the distribution volume and the elimination rate of DPs change

- ▶ Drug excretion into the amniotic fluid and the fetus is taken into account, and this leads to a decrease in the blood level of DPs in pregnant women
- ▶ From week 15 to week 2 after delivery, plasma protein binding of DPs decreases and the free fraction in blood increases
- ▶ Methyltransferase and glucuronyl transferase activity decreases
- ▶ Glomerular filtration and reabsorption increase.

Lactation

The following must be taken into account:

- ▶ Lipophilic DS are easily excreted by the mammary glands into the breast milk and can enter the baby's body
- ▶ Drugs that are weak bases penetrate into breast milk very easily and accumulate in it (breast milk is slightly acidic: pH 6.5–7.0) (the concentration of erythromycin in milk is 6–7 times higher than in blood plasma)
- ▶ Drugs that are weak acids are excreted into breast milk in smaller quantities, usually accounting for 2–5 times the plasma level.

Environmental factors

Food: eating cruciferous vegetables induces hepatic microsomal enzymes and thereby stimulates metabolism, while eating grapefruit suppresses metabolism.

Alcohol:

- ▶ A single dose of alcohol reduces the degradation rate of various DS in the liver, which leads to an increase in $T_{1/2}$ and consequently, their effect (benzodiazepines, barbiturates)
- ▶ Increases the effect of synthetic antimicrobials and indirect anticoagulants
- ▶ In combination with metronidazole, chloramphenicol, furazolidone may have an antabuse effect.

Nicotine increases the metabolic rate of propranolol (Anaprilin*), aminazine, diazepam.

Biorhythms

Diurnal rhythms are important for physiological functions. The sleep-wake cycle has a significant effect on the activity of the nervous system and endocrine glands. In turn, this is reflected in the body's sensitivity to various substances. Studying how a pharmacological effect depends on diurnal periodicity is one of the main tasks of a branch of pharmacology called "chronopharmacology".

During substitution therapy with steroid hormones from the glucocorticoids (GC) group, it is logical to prescribe them in the first half of the day (morning hours), because the acrophase of GCs released by endocrine glands falls on this time of day. The pain-relieving (depressing) effect of the narcotic analgesic, morphine, is more pronounced in the afternoon.

Drug substance doses

The dose is the amount of a DS per intake. It is expressed as the amount of a DS per 1 kg of body weight or per 1 m² of body surface area, which enables more precise dosing of the product. The activity of a DS is judged by the dose amount that gives an effect of a certain magnitude.

- ▶ Single (for uptake) (captopril in hypertensive crisis)

- ▶ Daily (Promedol in postoperative pain)
- ▶ Course (antibacterial agents: amoxiclav in urinary tract infections)
- ▶ Loading — saturating (sulfonamides)
- ▶ Therapeutic (minimum, medium, highest [maximum])
- ▶ Toxic (doses that cause toxic effects — drug poisoning)
- ▶ Lethal (doses leading to a lethal outcome)
- ▶ Maintenance (vitamin B₁₂ in hyperchromic anemia).

Therapeutic doses

The lowest therapeutic dose or minimum effective dose (MED) is the minimum dose that produces the desired therapeutic effect. It is usually 2–3 times less than the median therapeutic dose.

The median therapeutic dose is the dose of a drug product that produces an optimal therapeutic effect in a significant number of patients.

The highest (maximum) therapeutic dose (single and daily):

- ▶ Is the maximum tolerated dose (MTD) beyond which toxic effects may occur
- ▶ Does not reach the minimum toxic dose and is taken conventionally as the highest allowable dose.

The therapeutic window (therapeutic range, safety margin) is the range from the MED to the MTD.

The therapeutic index is the ratio of the average lethal dose LD₅₀ to the average effective dose ED₅₀ of the product (risk/benefit ratio). ED₅₀ is a dose that causes an effect equal to 50% of the maximum effect. The lower ED₅₀, the higher the activity of the DS.

The greater the therapeutic index, the greater the DP's therapeutic window. For example, the therapeutic index of benzylpenicillin (Benzylpenicillin sodium salt*) approaches 100, and the therapeutic index of digitoxin is about 1.5–2.0.

Sodium oxybate (an anesthetic) will be used as an example of a dose-dependent effect:

- ▶ In small doses, it has an analgesic and sedative effect
- ▶ In medium doses, it has an anticonvulsant and a hypnotic effect
- ▶ In high doses, it has an anesthetic effect.

Coadministration of drug products

Synergism (derived from Greek synergos — “working together”) is the combination of two or more DS whose resulting pharmacological effect exceeds that of each DS taken separately. A distinction is made between summated and potentiated synergism:

Summated synergism, or addition (derived from Latin additio — “addition”): the combined effect is equal to the arithmetic sum of the effects of the combined products. It is typical of DPs targeting the same receptors, cells, organs (e.g., synergism of general anesthetics for inhalational anesthesia, paracetamol and ibuprofen in chronic pain). Potentiated synergism or superaddition: the combined effect exceeds the arithmetic sum of effects of the combined products.

Potentiated synergism is the results of multiple pharmacokinetic and pharmacodynamic mechanisms:

- ▶ Change in absorption — by narrowing the blood vessels, an AA prevents the absorption of local anesthetics into blood, thereby increasing their local analgesic effect
- ▶ Displacement of DPs from binding to blood proteins — the anti-inflammatory DPs phenylbutazone (Butadion*) and indomethacin release anticoagulants and glibenclamide (a blood sugar-lowering drug) from binding to albumin, which increases the risk of bleeding and hypoglycemia
- ▶ Increased membrane permeability — insulin facilitates the penetration of glucose and K^+ ions through the cell membrane
- ▶ Metabolic inhibition — anticholinesterase agents prolong and enhance the effect of endogenous acetylcholine
- ▶ Effect of DPs on various regulatory and synergistic receptors — potentiated anesthesia with the use of muscle relaxants, tranquilizers, analgesics.

Antagonism (derived from Greek *ἀντι* — prefix with the meaning of the opposite, *agon* — “struggle”) is an interaction of drug products that weaken or eliminate their pharmacological properties.

Types of antagonism

1. Physical — reduction of absorption into the blood and resorptive action:
 - Adsorbents prevent absorption of many products taken orally; saline laxatives, by increasing the osmotic pressure in the intestinal lumen, delay absorption of products dissolved in intestinal juice.
 - Metal ions (Ca^{2+} , Mg^{+} , etc.) form non-absorbable complexes with tetracycline, levomycetin, sulfonamides, acetylsalicylic acid, phenylbutazone (Butadion*).
2. Chemical — chemical interaction of drug products in the blood with the formation of inactive products. Chemical antagonists are potassium permanganate, sodium thiosulfate, unithiol, a donator of sulfhydryl groups, complexing agents (EDTA disodium salt), and other antidotes used to treat poisoning.
3. Direct functional — develops when a DS has an opposite effect on the same functional elements (receptors, enzymes, etc.). For example, β -AR stimulators and blockers, MChR stimulators and blockers.
4. Indirect functional — develops when a DS has an opposite effect on the function of any organ, and their action is based on different mechanisms. For example, aceclidine increases smooth muscle tone by stimulating MChR and papaverine decreases smooth muscle tone due to its direct myotropic effect.

Repeated dosing of a drug substance

Cumulation (derived from Latin *cumulatio* — “increase, piling up”) of the DS itself (material cumulation) or its effects (functional cumulation) in the body.

Types

1. Material cumulation increases the DS content in the blood and/or tissues after each subsequent administration compared to the previous one. It occurs when lipophilic products with low hepatic and/or renal clearance and long elimination half-life are taken. In clinical practice, cumulation of phenobarbital, bromides, digitalis cardiac glycosides, indirect anticoagulants, etc. should be considered. Cumulation can be both positive and negative. Positive cumulation is associated

with prolongation of the DP's effect and consequently reducing the frequency of intake, e.g., patients with severe congestive heart failure can avoid taking cardiac glycosides at night. Negative cumulation brings a risk of intoxication because the repeated dose of the product is added to the amount retained from the previous intake.

2. Functional cumulation means an increase in the effect of a repeated dose of the DS in the absence of any increase in its blood and/or tissue levels. For example, in alcoholism, increasing changes in CNS function can lead to delirium; lead poisoning causing paralysis of the medulla oblongata, which occurs after the poison is eliminated from the body.

Tolerance (habituation) is a decrease in a DP's efficacy when administered repeated at the same dose. The dose must be increased to restore the therapeutic effect e.g., a 5–10 mg/day dose of the tranquilizer diazepam (Sibazon*) usually has an anxiolytic effect but up to 1000 mg/day is needed in addiction.

Tolerance can be congenital or acquired. Congenital (hereditary) tolerance is caused by enzymopathy. For example, a mutation in the aldehyde dehydrogenase gene impairs the metabolism of ethanol (Ethyl Alcohol*) and acetaldehyde, the oxidation product of ethanol is not oxidized to acetic acid. Accumulation of acetaldehyde is accompanied by toxic effects, which may reduce the desire to drink alcohol.

Tachyphylaxis (derived from Greek *tachys* — 'fast', *phylaxis* — "vigilance, protection") is rapid (within a few minutes/hours) addiction to a DS.

Tachyphylaxis is most often caused by depletion of mediator reserves in synaptic terminals. Ephedrine, an indirect AA, displaces norepinephrine from vesicles in adrenergic synapses and inhibits its neuronal uptake.

Addiction (drug dependence) is an irresistible urge to take a substance again, e.g., repeated use of psychoactive drugs with a narcotic effect to achieve euphoria (derived from Greek *eu* — "good", *phero* — "tolerate") or reduce the mental and/or physical discomfort resulting from drug withdrawal. In drug addiction, physical and psychological dependency develops.

At the stage of psychological dependence, drug withdrawal causes mental disorders (depression, irritability, aggression, insomnia, fear, prostration).

In physical dependence, drug discontinuation or initiation of its antagonists is accompanied by an abstinence syndrome (derived from Latin *abstinentia* — "self-restraint"), a complex of psychopathological, neurological, somatic and autonomic disorders with signs of a rebound effect (functional disorders opposite to those caused by the drug).

Sensitization is an increase in the body's sensitivity to a DS, which, when used repeatedly, forms complexes with blood plasma proteins that acquire antigenic properties under certain conditions (allergic reactions during the use of benzylpenicillin).

Idiosyncrasy is altered sensitivity to some DS due to a genetic deficiency, for example, the hemolytic effect of some antimalarials (quinine, primaquine, chloroquine) due to congenital glucose-6-phosphate dehydrogenase deficiency in red blood cells results in the formation of quinone that causes hemolysis of red blood cells.

Carcinogenicity is the ability of a DP to cause malignant tumors (combined hormonal contraceptives — gestodene and ethinyl estradiol).

Mutagenicity is the ability of a substance to cause persistent damage to the germ cell and its genetic apparatus, which manifests itself as a change in the genotype of the offspring (cytostatics, barbiturates).

MAIN TYPES OF DRUG THERAPY

- ▶ Causal therapy aims to eliminate the cause of the disease: the use of antimicrobial, antiviral and antiparasitic agents for infectious diseases, antidotes for poisoning.
- ▶ Pathogenetic therapy targets the pathogenetic mechanisms of a disease: prescription of antihypertensives for arterial hypertension (hypertension), cardiac glycosides for heart failure, anti-inflammatory agents for rheumatic diseases, psychotropic agents for treatment of mental disorders.
- ▶ Symptomatic therapy eliminates or alleviates the individual manifestations of a disease: the use of analgesics and antipyretics.
- ▶ Replacement therapy replenishes insufficient amounts of natural metabolites in the body: the use of vitamins, hormones, enzymes, iodized salts, fluorine, iron, calcium.
- ▶ Preventive therapy is carried out to prevent a disease. The following can be used: antiseptics, antivirals, vitamins, vaccinations.

TREATMENT OF ACUTE DRUG POISONING

Principle of detoxification

1. Delay absorption of the toxic substance into the blood (gastric lavage, flushing of mucous membranes, skin; use of sorbents, emetics, laxatives).
2. Remove the toxic substance from the body:
 - Forced diuresis
 - Peritoneal dialysis
 - Plasmapheresis
 - Hemodialysis and hemoadsorption (artificial kidney)
 - Blood transfusion
 - Hyperbaric oxygenation.
3. Eliminate the effects of the absorbed toxic substance with the help of antidotes — drug substances used for specific treatment:
 - Antidotes that bind toxic substances and facilitate their elimination from the body
 - Pharmacological antagonists.
4. Symptomatic treatments to restore vital functions.

2. DRUGS AFFECTING CHOLINERGIC SYNAPSES

Acetylcholine (ACh) was first discovered by H. Dale in 1915, who described its effects on heart tissue. In 1921, O. Loewi confirmed that ACh is a neurotransmitter and called it Vagusstoff (German for “vagus substance”) because it was obtained from the vagus nerve. In 1936, both scientists were awarded the Nobel Prize in physiology or medicine “for their discoveries relating to chemical transmission of nerve impulses”. In 1946, S. V. Anichkov and M. A. Grebenkina suggested dividing cholinergic receptors into two classes: muscarinic and nicotinic. This division is now universally accepted.

Basic anatomy and physiology of the parasympathetic nervous system

Excitation of the parasympathetic nervous system is transmitted through ACh.

Stimulating the parasympathetic nervous system results in trophotropic effects (from the Greek *trophe*, meaning “nourishment”, and *tropos*, meaning “turn”). These effects contribute to energy conservation and are most prominent when the body is at rest (activation of digestive processes, suppression of heart function) (Fig. 2.1).

Cholinergic synapse functions

ACh is synthesized in the cytoplasm of cholinergic nerve endings from choline and acetyl coenzyme A (of mitochondrial origin), catalyzed by the cytoplasmic enzyme choline acetyltransferase (Fig. 2.2 [1]). ACh is then deposited in synaptic vesicles. A presynaptic action potential (AP) results in the release of the contents of several hundred vesicles into the synaptic cleft. ACh binds to specific receptors in the postsynaptic membrane (Fig. 2.2), which increases its permeability to Na^+ , K^+ , and Ca^{2+} ions and results in an excitatory postsynaptic potential. The action of ACh is limited by its hydrolysis by the enzyme acetylcholinesterase (a hydrolytic enzyme in the esterase family) (Fig. 2.2 [2]; Fig. 2.3). Choline fragments of molecules are transported back to the cytosol (Fig. 2.2 [3]). New ACh molecules are synthesized with the help of transferases and then transported back to the vesicles.

Hydrolysis of acetylcholine

The cholinesterase surface that is in direct contact with each mediator molecule has two sites: anionic and esteratic (Fig. 2.3). The anionic site includes the carboxyl group of a glutamic acid residue and the esteratic site includes the imidazole ring of a histidine residue and the hydroxyl group of a serine residue.

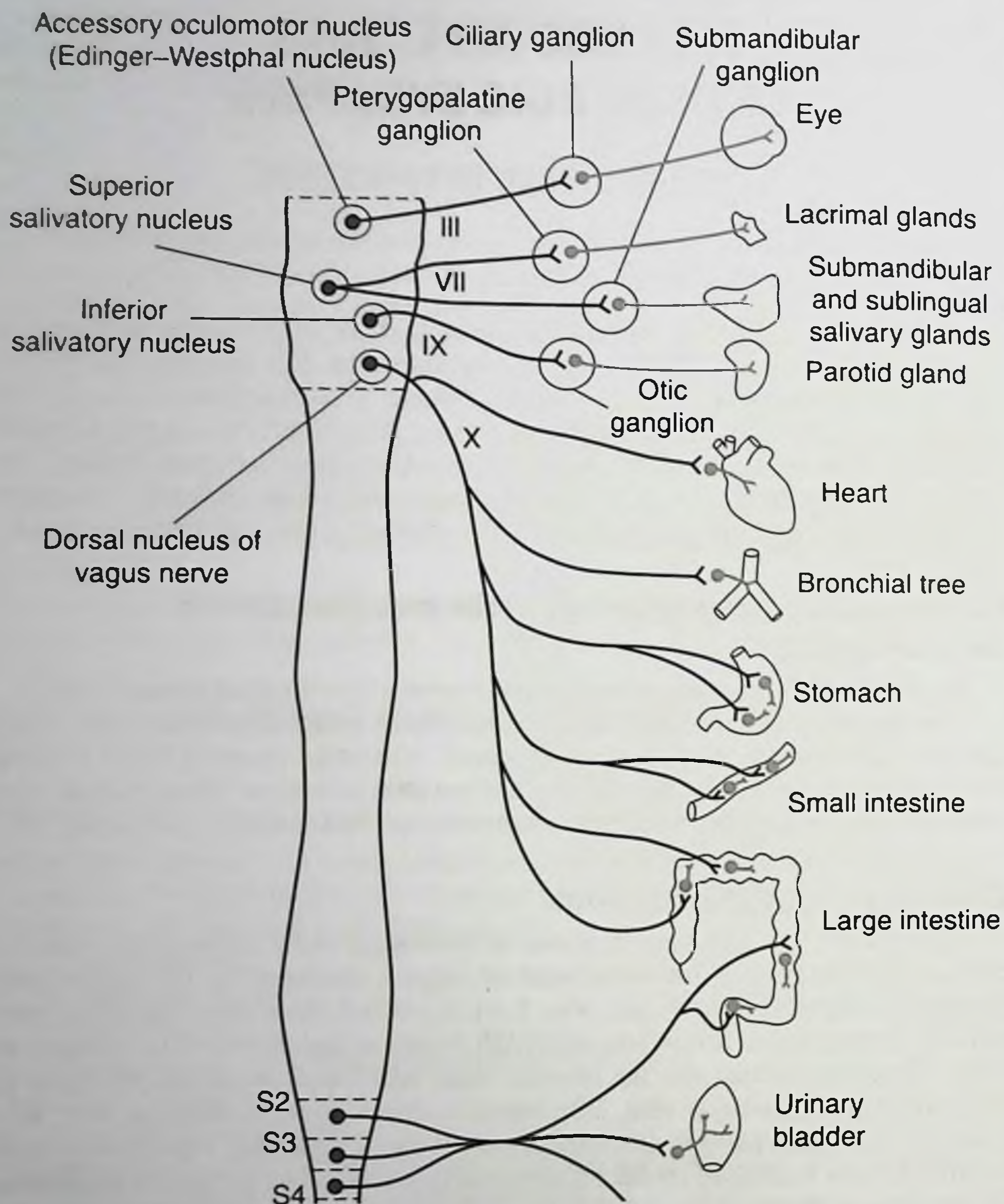


Fig. 2.1. Structure of the parasympathetic division of the autonomic nervous system (Saveliev S. V., 2008)

The positively charged nitrogen atom (cationic head) of ACh guides its orientation on the cholinesterase's surface. The anionic site attracts the cationic head of ACh, forms electrostatic bonds and promotes the convergence of its ether group with the esteratic site. Once the ether bond is broken, ACh is split into two parts: a choline part and an acetic part. The acetic acid residue remains attached to the esteratic site, and acetylated cholinesterase is formed. The complex is fragile and undergoes spontaneous hydrolysis.

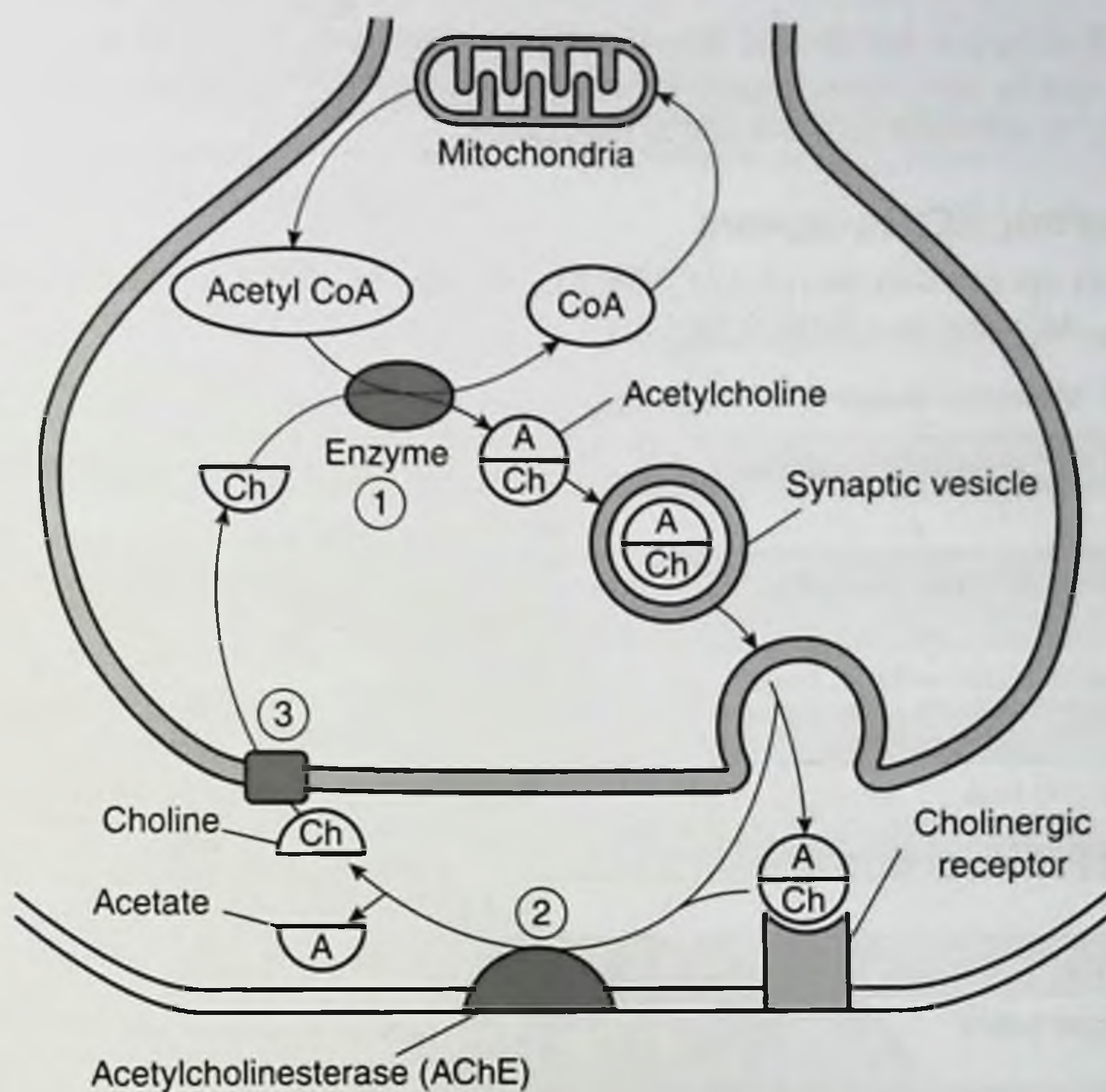


Fig. 2.2. Cholinergic synapse (original image taken from <https://ib.bioninja.com.au/>). A — acetate; Ch — choline; Acetyl CoA — acetyl coenzyme A; AChE — acetylcholinesterase (see text for details)

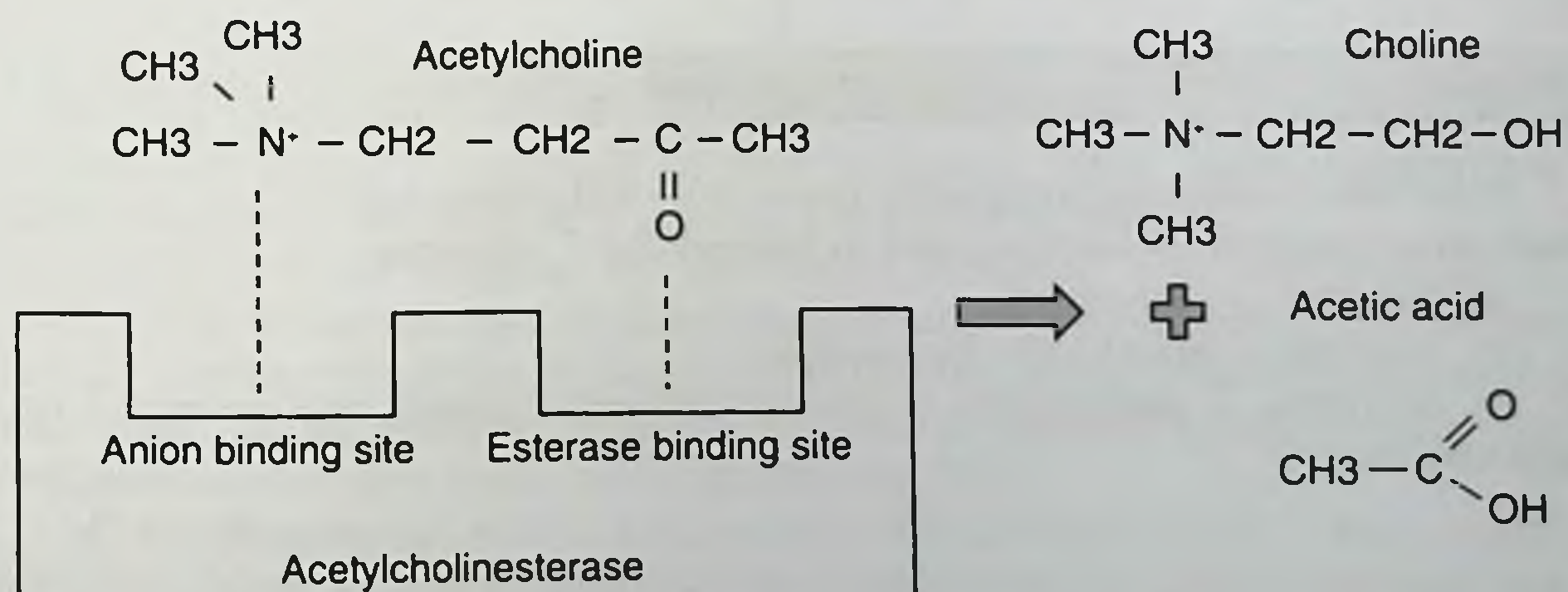


Fig 2.3. Hydrolysis of acetylcholine

Types and subtypes of cholinergic receptors

ACh receptors are divided into two types: muscarinic ACh receptors (mAChRs) are excited by muscarine; nicotinic acetylcholine receptors (nAChRs) are excited by nicotine at low doses and blocked at high doses.

Muscarinic ACh receptors

There are five subtypes of mAChRs: M_1 , M_2 , M_3 , M_4 , M_5 . The most studied are the M_1 , M_2 , M_3 subtypes (Table 2.1).

Table 2.1. Muscarinic receptors

Preferential localization	Effects caused by stimulation
M_1 receptor	
Gastric enterochromaffin-like cells	Release of histamine, which stimulates secretion of HCl by gastric parietal cells
CNS: cerebral cortex, midbrain, trunk	Excitation
M_2 receptor	
Sinoatrial (SA) node	Reduced excitation frequency — reduced HR
Atrioventricular (AV) node	Reduced conduction — AV block
Atrium	Reduced contractile activity
M_3 receptor	
Iris sphincter muscle	Shrinking, constriction of the pupil (miosis), intraocular pressure (IOP) reduction
Ciliary muscle	Contraction, spasm of accommodation (the eye focuses on a near object)
Smooth muscles of the bronchi, stomach, intestines, gallbladder and bile ducts, bladder, uterus	Contraction
Exocrine glands	Increased secretory function

mAChRs contain one polypeptide chain, 440–540 amino acid residues in length, with an extracellular N-terminus and an intracellular C-terminus.

M_1 receptors — postsynaptic

M_2 receptors — presynaptic, postsynaptic

M_3 receptors — postsynaptic innervated and extrasynaptic non-innervated (in endotheliocytes)

Stimulation of presynaptic M_2 receptors and extrasynaptic non-innervated M_3 receptors

- ▶ M_2 receptors — reduced ACh release
- ▶ M_3 receptors (located in the membrane of vascular endothelial cells) — increased synthesis and release of nitric oxide (NO), relaxation of vascular smooth muscles, decreased vascular tone (Fig. 2.4).

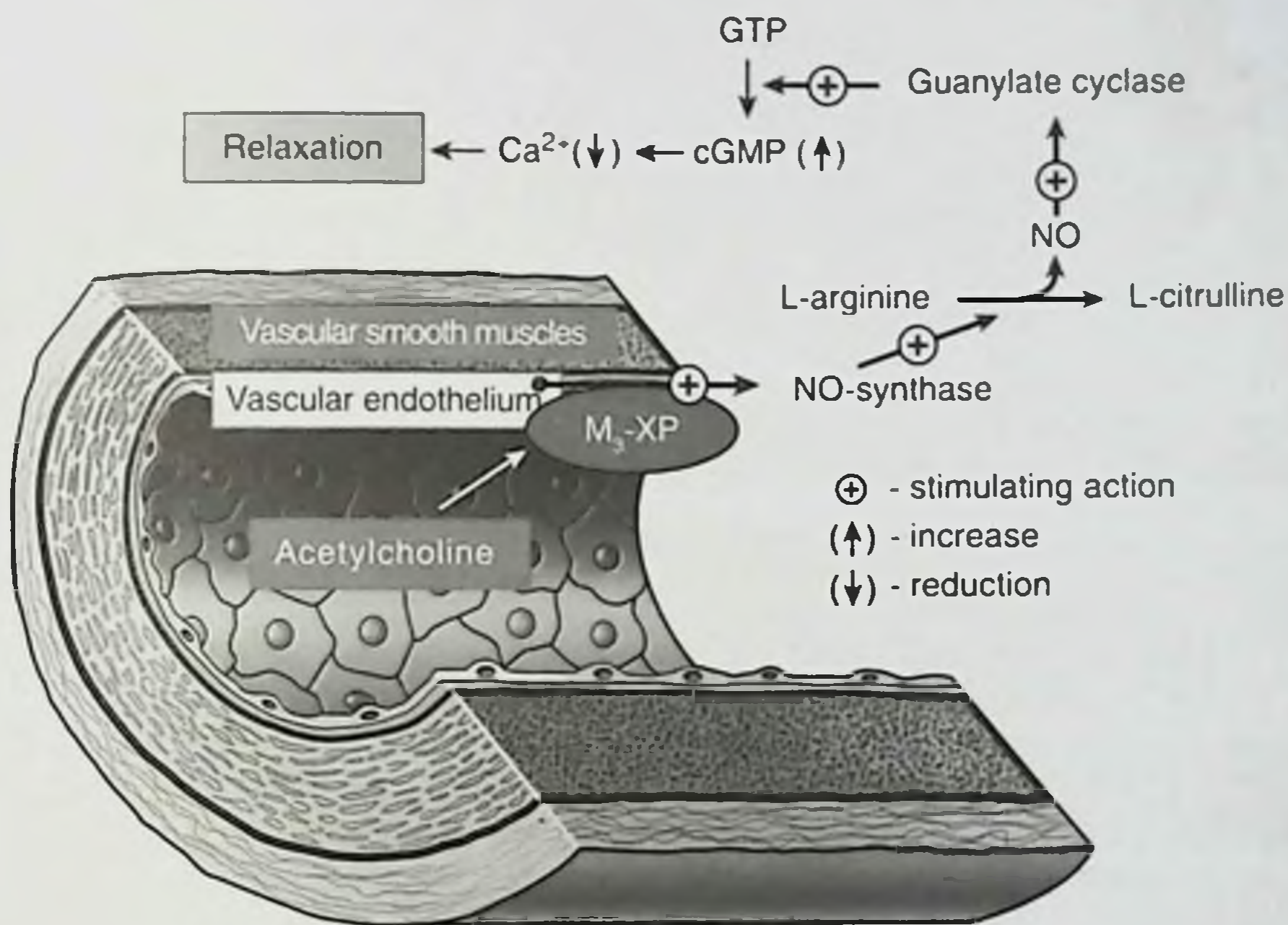


Fig. 2.4. Effects of acetylcholine on vascular smooth muscles

Mechanisms of Muscarinic receptor stimulation

mAChRs are slow G-protein-coupled receptors, where signal transmission through the membrane involves G proteins and second messengers.

The M_1 and M_3 receptors are functionally connected with phospholipase C, which catalyzes the cleavage of phosphatidylinositol 4,5-bisphosphate (PIP₂) into inositol trisphosphate (IP₃) and diacylglycerol (DAG). Inositol trisphosphate releases Ca^{2+} from the sarcoplasmic reticulum, resulting in increased smooth muscle tone and increased secretion from exocrine glands (Fig. 2.5).

M_2 receptors interact with G_i proteins to inhibit adenylate cyclase, which inhibits cAMP synthesis, disrupts phosphorylation of cardiomyocyte calcium channels, and decreases Ca^{2+} influx into cardiomyocytes. In addition, K^+ channels are activated, K^+ is released from the cells, and the membrane becomes hyperpolarized. The entry of Ca^{2+} ions into cardiomyocytes through voltage-gated channels is reduced, which

also contributes to the development of inhibitory effects (Fig. 2.6). Automatism and conductivity are reduced.

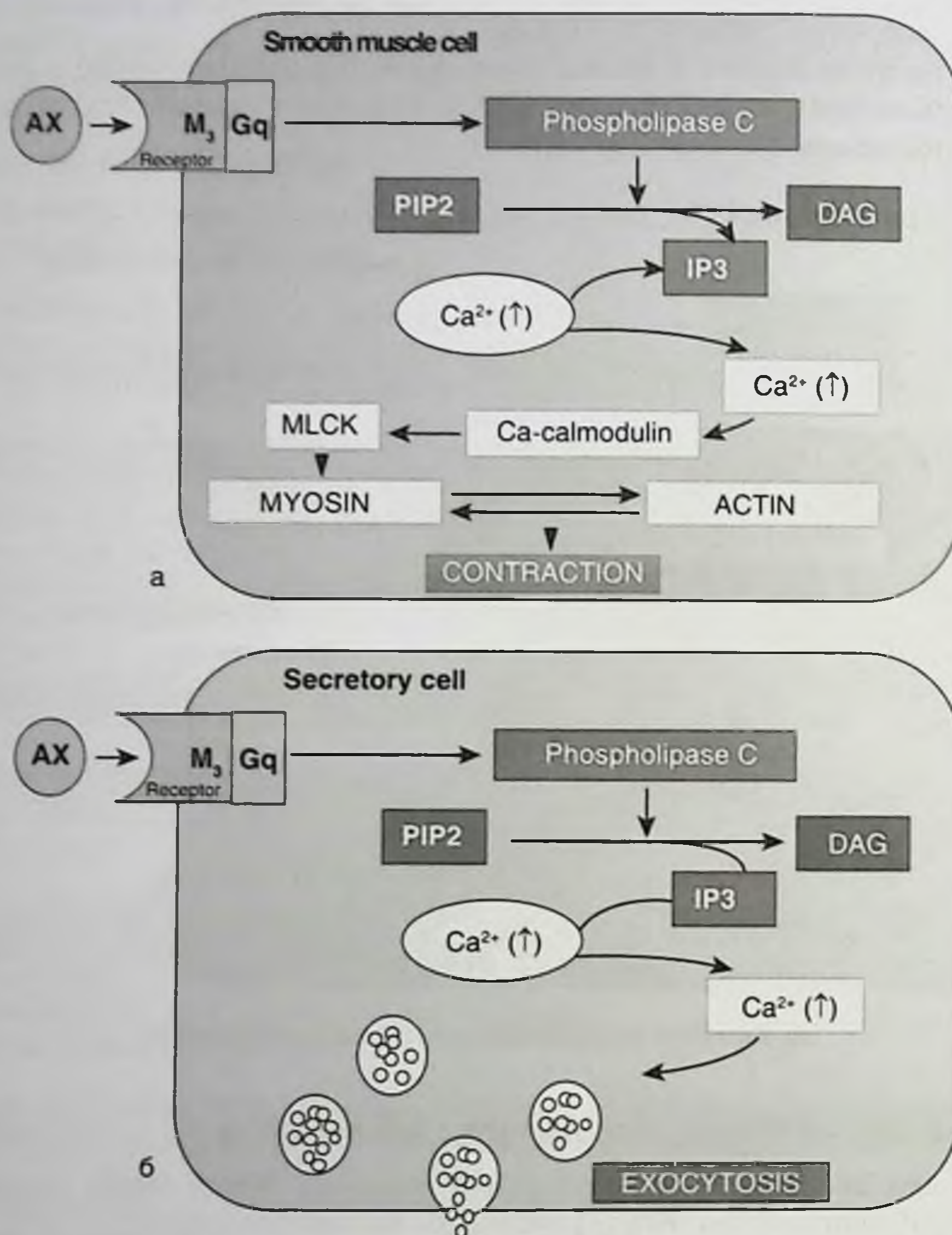


Fig. 2.5. Effects of acetylcholine (AX) on smooth muscle cells (a) and exocrine gland cells (b) (MLCK — myosin light-chain kinase)

Nicotinic ACh receptors

Nicotinic receptors are glycoproteins divided into neuronal (N_n) and muscular (N_m) subtypes. N_m receptors include five protein subunits (α , α , β , γ , δ) which surround the sodium channel. N_n receptors are composed of α and β subunits of various subtypes (Table 2.2).

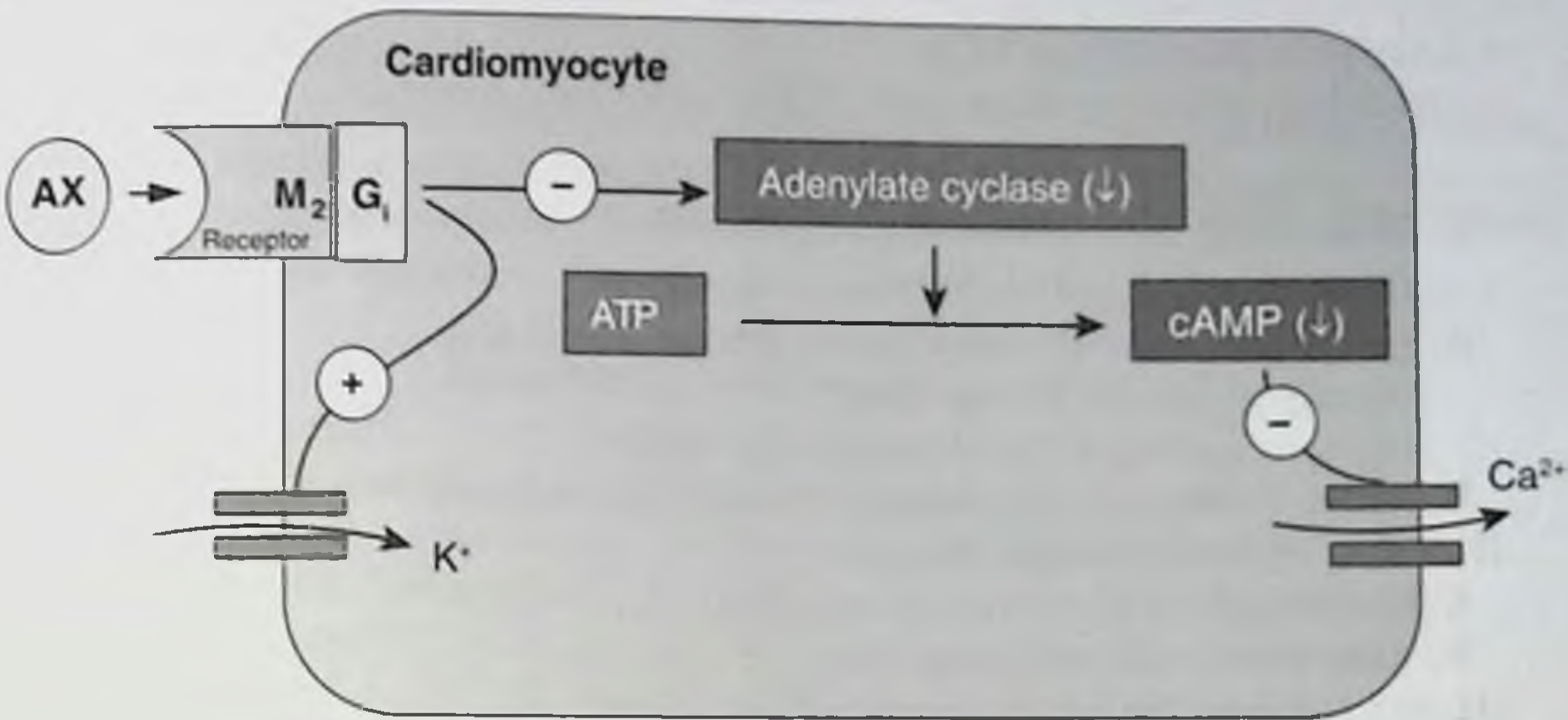


Fig. 2.6. Effects of acetylcholine (AX) on cardiomyocytes

Table 2.2. Nicotinic receptors

Preferential localization	Effects caused by stimulation
N_n receptor	
Neurons of sympathetic and parasympathetic ganglia	Excitation
Chromaffin cells of the adrenal medulla	Adrenaline secretion
Carotid bodies	Reflex excitation of respiratory and vasomotor centers
CNS: medulla oblongata, neurohypophysis, hippocampus, cortex, Renshaw cells	Facilitation of excitation transmission
N_m receptor	
Skeletal muscle endplate	Contraction

Mechanisms of Nicotinic receptor stimulation

nAChRs are fast transmembrane receptors directly linked with ion channels (ionotropic).

When two ACh molecules bind to the α subunit of the receptor, sodium channels open. Na^+ ions enter the cell, which triggers depolarization of the postsynaptic membrane and excitation of the effector cells.

Pharmacological effect of excitation transmission in cholinergic synapses

- ▶ ACh synthesis
- ▶ Mediator release
- ▶ Interaction of ACh and AChR

- ▶ Enzymatic hydrolysis of ACh
- ▶ Uptake of choline resulting from ACh hydrolysis by presynaptic terminals

Drugs affecting the cholinergic system

- I. Acting on both M and N cholinergic receptors
 - A. Enhance cholinergic transmission (cholinomimetics):
 - direct-acting (AChR agonists)
 - indirect-acting or anticholinesterase drugs
 - B. Inhibit cholinergic transmission (cholinergic blockers)
- II. Acting on M cholinergic receptors
 - A. Muscarinic cholinomimetics (agonists)
 - B. Muscarinic receptor antagonists
- III. Acting on N cholinergic receptors
 - A. Nicotinic cholinomimetics (agonists)
 - B. Nicotinic receptor antagonists:
 - ganglionic blockers
 - muscle relaxants

CHOLINOMIMETICS

Cholinomimetics (from the Greek *mimetikos*, meaning “imitative”) are drugs of different chemical structure that cause effects similar to the excitation effects of cholinergic nerve fibers or ACh.

They are divided into direct-acting (AChR agonists) and indirect-acting (cholinesterase inhibitors).

Classification

- I. Affecting both M and N ACh receptors
 1. Direct-acting (AChR agonists)
 - Quaternary
 - Acetylcholine
 - Carbacholine[®] [excluded from the Russian State Register of Medicinal Products. Carbachol [Miochol] is used in ophthalmic practice]
 2. Indirect-acting (anticholinesterase drugs)
 - A. Reversible
 - Tertiary
 - ◊ Physostigmine salicylate[®] (excluded from the Russian State Register of Medicinal Products)
 - ◊ Galantamine (Galantamine hydrobromide⁺, Nivalin⁺, Reminyl⁺)
 - ◊ Rivastigmine (Exelon⁺)
 - ◊ Donepezil (Aricept[®], Alzepil⁺)
 - Quaternary
 - ◊ Neostigmine methyl sulfate (Proserine⁺)
 - ◊ Pyridostigmine bromide (Kalymin⁺)
 - ◊ Distigmine bromide (Ubretid⁺)

B. Irreversible

- Armin[®] [excluded from the Russian State Register of Medicinal Products, currently being investigated to understand the toxicological significance of organophosphorus compounds (OPs)].

II. Muscarinic agonists

- Tertiary
 - ◊ Pilocarpine (pilocarpine hydrochloride[•])
 - ◊ Aceclidine[•]

III. Nicotinic agonists

- Tertiary
 - ◊ Lobeline (Lobesyl[®])
 - ◊ Anabesine[•]
- Secondary
 - ◊ Cytisine (Cytiton[®], Tabex[•])

Direct-acting AChR agonists

Direct-acting cholinomimetics, similarly to ACh, directly stimulate AChRs.

Acetylcholine is not used as a drug because the presence of an ester bond makes it sensitive to cholinesterase, limiting its duration of action. It is used in experimental physiology and pharmacology (as a chloride) and is obtained by synthesis.

- ▶ Ester of choline and acetic acid. Quaternary ammonium base. Rapidly broken down by blood cholinesterase, has a brief duration of action (Fig. 2.3).
- ▶ Ineffective when taken orally and easily hydrolyzed. Poorly penetrates the BBB.

Effects are dose-dependent: acts on mAChRs at doses of 0.1–0.5 µg/kg, causing activation of the parasympathetic system; acts on mAChRs and nAChRs at doses of 2–5 µg/kg. Selective activation of nAChRs is only possible after blockade of mAChRs.

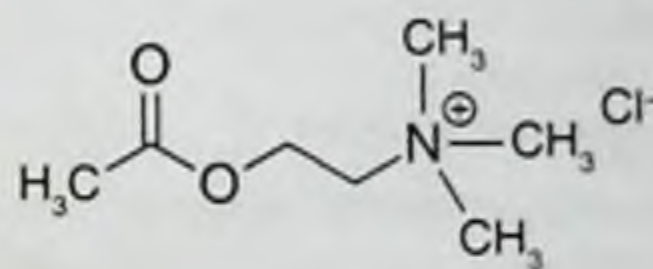


Fig. 2.7. 2-(Acetyloxy)-N,N,N-trimethylethanaminium chloride

Pharmacological effects

Local

- Pupil constriction (miosis) is associated with mAChR excitation at the iris sphincter muscle (*m. sphincter pupillae*) and its contraction (Fig. 2.8).
- IOP reduction. When the pupil constricts, the iris narrows, the anterior chamber angle (between the iris and cornea) opens, and the outflow of intraocular fluid through the spaces of iridocorneal angle into the Schlemm's canal increases.
- Spasm of accommodation: contraction of the ciliary muscle (*m. ciliaris*) results in relaxation of the ciliary zonule and an increase in the lens curvature. The eye focuses on a near object.

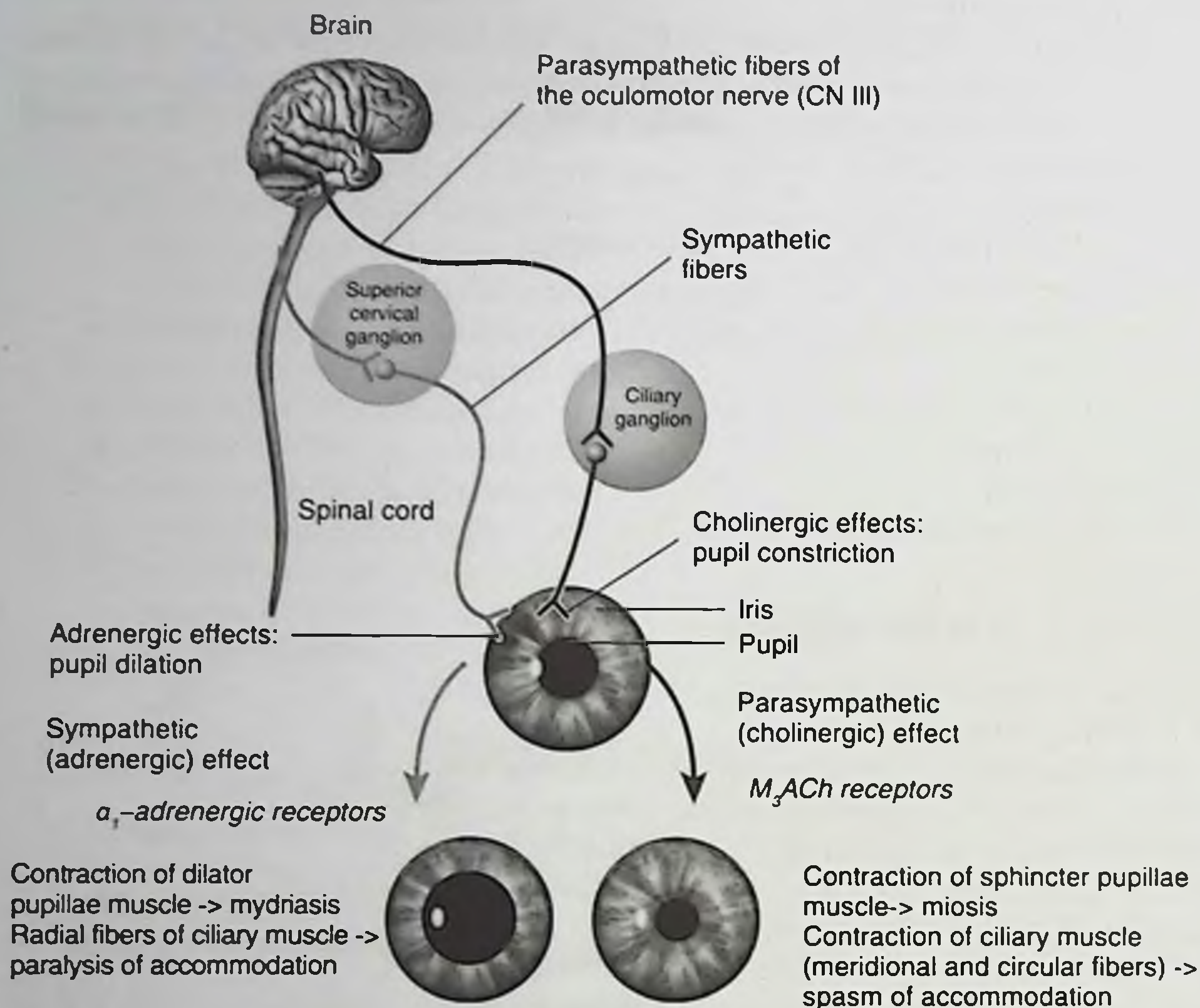
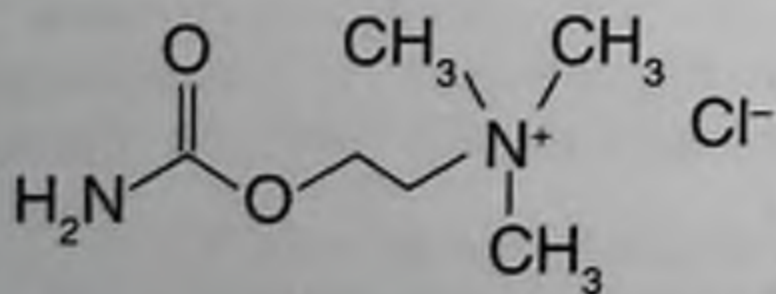


Fig 2.8. Innervation of the iris: effects of sympathetic and parasympathetic nervous system activation (Saladin K.S., 2003)

Systemic

A. Muscarine-like: bradycardia, vasodilation, decreased BP, increased tone and contractility of smooth muscles of the bronchi, GI tract, myometrium, gallbladder and urinary bladder, increased secretion from exocrine glands (digestive, lacrimal, bronchial and sweat glands).

B. Nicotine-like: facilitation of neuromuscular transmission (increased tone and contractility of skeletal muscles), reflex excitation of the respiratory center — stimulation of the carotid bodies. The stimulatory effect of ACh on nAChRs of the autonomic ganglia is masked by its M-cholinomimetic action.



Carbacholine[®]

This drug product is excluded from the Russian State Register of Medicinal Products. Carbachol (Miochol) is used in ophthalmic practice.

Fig. 2.9. 2-[(Aminocarbonyl)oxy]-N,N,N-trimethylethanaminium chloride (H₂N-COOH), its chemical structure and

pharmacological properties are close to those of ACh. It is more active and has prolonged action due to the replacement of the acetyl group by the carbamyl group: the molecule is resistant to the action of hydrolyzing enzymes. When it is used topically, miosis develops in 15–20 min and lasts 4–8 hours, IOP starts decreasing in 20–30 minutes and reaches peak values in 2 hours. When it is administered intraocularly, the action occurs in 2–5 minutes and lasts 24 hours.

► Metabolized to choline, excreted by the kidneys. For topical administration.

Therapeutic indications: glaucoma, ophthalmic surgery (cataract extraction)

Side effects: burning sensation in the eye, conjunctival hyperemia, headache

Contraindications: allergic reactions

Indirect cholinomimetics (anticholinesterase drugs)

Indirect cholinomimetics (anticholinesterase drugs) non-selectively enhance cholinergic transmission by inhibiting acetylcholinesterase, which increases the residence time of ACh in the synaptic cleft.

Mechanism of action: As a result of acetylcholinesterase inhibition in cholinergic synapses, ACh is not hydrolyzed; it accumulates, thereby enhancing the response to ACh released from the presynaptic terminals.

At the molecular level, acetylcholinesterase inhibitors bind either to the anionic site, the esteratic site, or both. Depending on the chemical structure, the bond between the inhibitor and the active site of cholinesterase may be short-lived, i.e. reversible, or stable phosphorylation of cholinesterase occurs and the enzyme activity is restored only by the synthesis of new molecules, resulting in an irreversible bond.

Reversible anticholinesterases: neostigmine methylsulfate, pyridostigmine bromide, distigmine, rivastigmine are esters of carbamic acid, i.e. carbamates. These drugs, similarly to ACh, bind to both the anionic and esteratic sites of acetylcholinesterase and undergo hydrolysis, with acetylcholinesterase becoming covalently bound to the carbamyl group (through the hydroxyl group of the serine residue) in its esteratic site. Hydrolysis of this stronger bond occurs more slowly, 30 minutes to several hours, which determines the duration of action of carbamates. Galantamine (Galantamine hydrobromide*), donepezil have a high affinity for the enzyme, bind to the anionic site of acetylcholinesterase through weak electrostatic and hydrogen bonds (non-covalent).

Irreversible anticholinesterases have the chemical structure of OPs. They inhibit acetylcholinesterase due to the formation of covalent bonds between the phosphorus residue and the serine hydroxyl group at the esteratic site. These bonds are strong and are hydrolyzed very slowly (over hundreds of hours), thus OPs inhibit acetylcholinesterase irreversibly (Fig. 2.10).

Pharmacological effects

- Miosis, IOP reduction, spasm of accommodation
- Bradycardia, slower AV conduction
- Increased bronchial tone, gastrointestinal tone and motility, tone and contractile activity of the bladder and myometrium
- Increased secretion from exocrine glands

- Facilitation of neuromuscular transmission
- Increased skeletal muscle tone

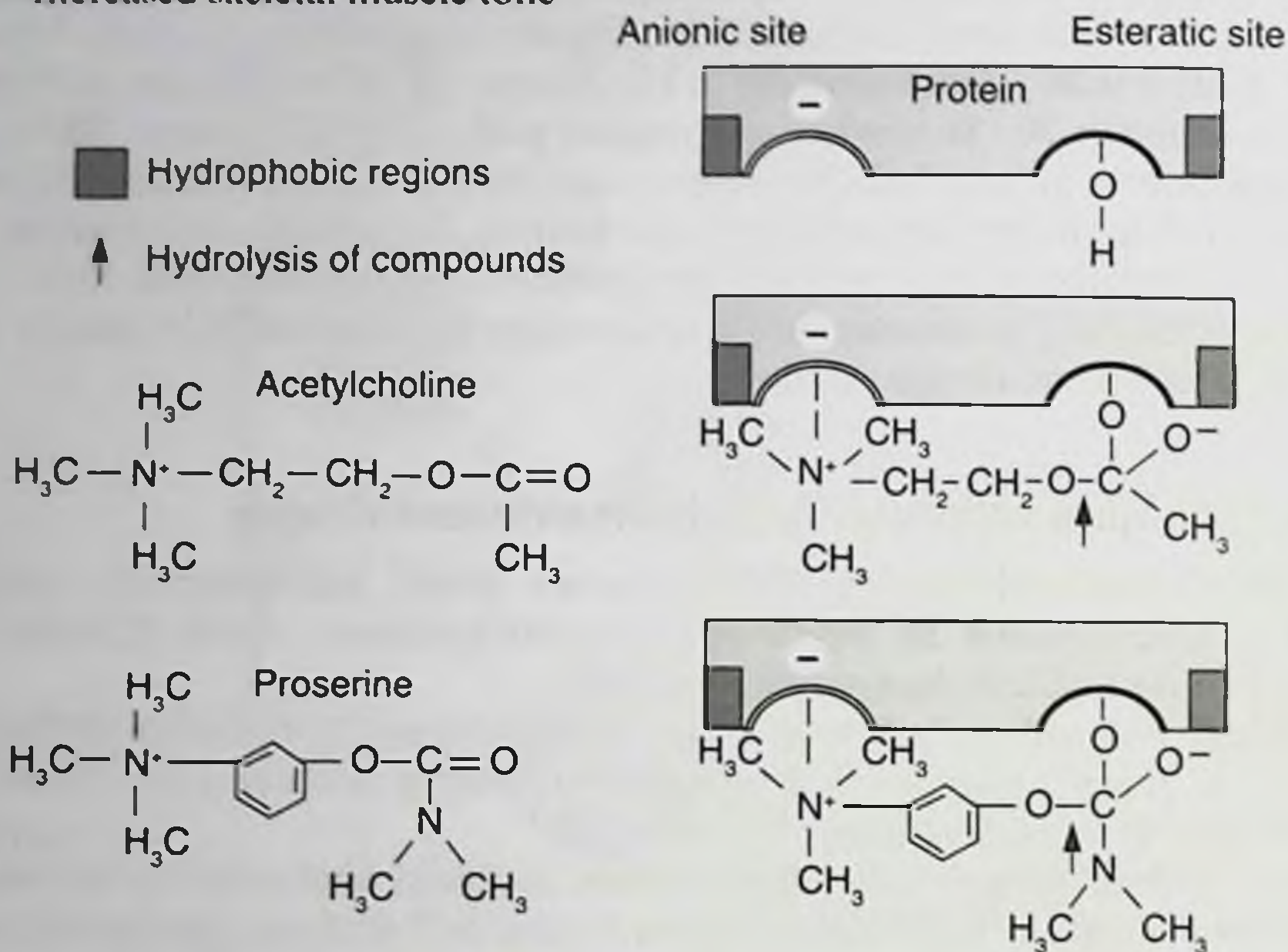


Fig. 2.10. Mechanism of action of anticholinesterase drugs (Kharkevich D. A., 2021)*

Therapeutic indications: **glaucoma** — except galantamine (Galantamine hydrobromide*, causes irritation and conjunctival edema); intestinal and bladder atony; myasthenia gravis, paresis, paralysis; CNS disorders (Alzheimer's disease, cerebral palsy, sequelae resulting from encephalitis, meningitis, stroke, brain injury) — tertiary amines; intoxication with muscarinic receptor antagonists (MRAs), psychotropic agents; overdose with non-depolarizing muscle relaxants.

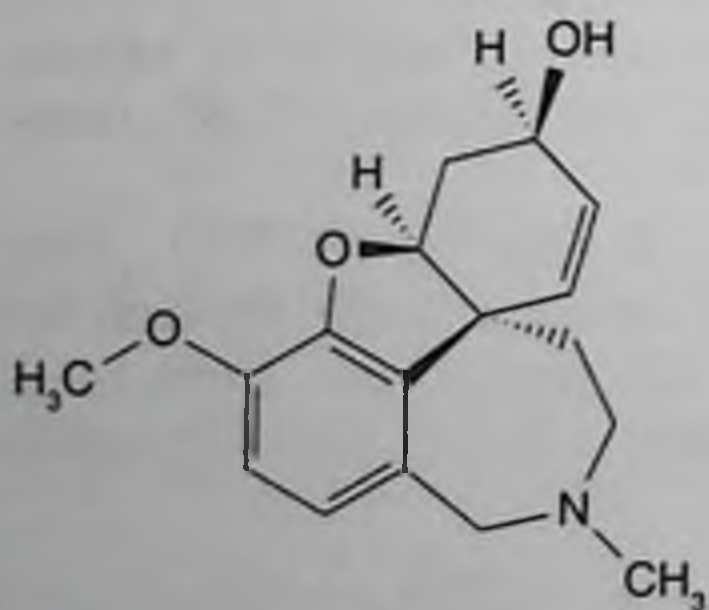


Fig. 2.11. (4aS,6R,8aS)-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol (as a hydrobromide)

Side effects: bradycardia, AV blocks, BP reduction, hypersalivation, bronchospasm, increased GI peristalsis, nausea, vomiting, diarrhea, frequent urination, spasm of accommodation, dizziness

Contraindications: bradycardia, AV block, chronic obstructive pulmonary disease (COPD), bronchial asthma, stomach and duodenal ulcers, intestinal colic, cholelithiasis and urolithiasis, epilepsy, hyperkinesia, pregnancy, breastfeeding

Specifics of individual products

Galantamine (Galantamine hydrobromide*, Nivalin*, Reminyl*)

► Alkaloid isolated from the bulbs and flowers of *Galanthus caucasicus* (Caucasian snowdrop),

Woronow's snowdrop. Tertiary amine; crosses the BBB. Reversible. Bioavailability: about 90%.

- ▶ Metabolized in the liver by cytochrome P450 enzymes, mainly through demethylation by CYP2D6 and CYP3A4 isoenzymes (5–6%), with its metabolites (epigalantamine and galantaminone) found in the plasma and urine; $T_{1/2}$: 7–8 hours; predominantly excreted in the urine. For subcutaneous, intramuscular, intravenous administration.

Donepezil (Aricept[®], Alzepil[®])

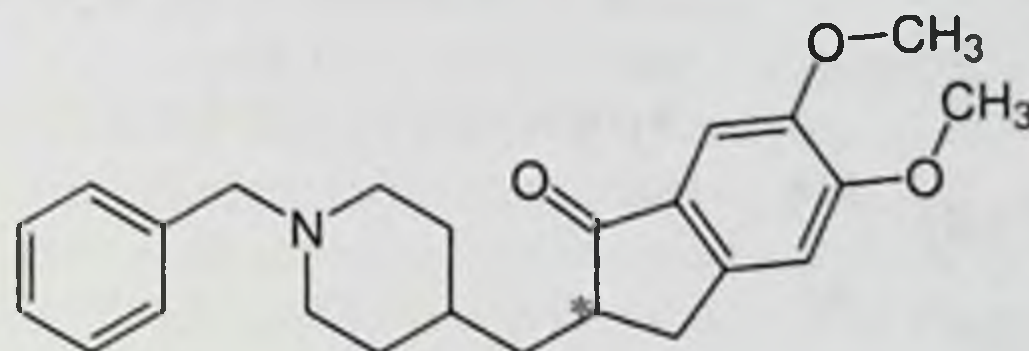


Fig. 2.12. 2,3-Dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one (as a hydrochloride)

- ▶ Tertiary amine, crosses the BBB. Selectively and reversibly inhibits acetylcholinesterase in the brain.
- ▶ Bioavailability: absolute, metabolized in the liver, $T_{1/2}$: 70 hours, 79% excreted in the urine, 21% excreted in the bile. For oral administration.

Therapeutic indications: dementia (Alzheimer's disease, Pick's disease, etc.)

Rivastigmine (Exelon[®])

- ▶ Tertiary amine; crosses the BBB. Selective and reversible carbamate inhibitor of acetylcholinesterase and butyrylcholinesterase in the brain. Rapidly and completely absorbed following oral administration, bioavailability: 30–40%. Absorption from TTS is slow.

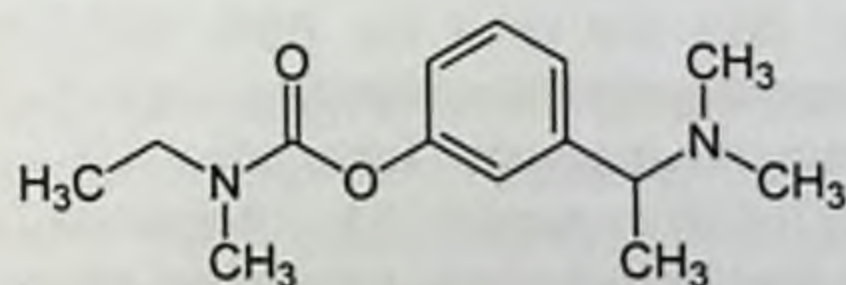


Fig. 2.13. 3-[(1S)-1-(Dimethylamino)ethyl]phenylethylmethylcarbamate

- ▶ Metabolized in the liver via esterase-mediated hydrolysis (biotransformation with involvement of cytochrome P450 isoenzymes is minimal), $T_{1/2}$: 1 hour for oral administration and 3–4 hours for transdermal administration. Primarily excreted in the urine as metabolites, less than 1% excreted in the bile. For oral, external (TTS) use.

Therapeutic indications: dementia (Alzheimer's disease, Pick's disease, etc.)

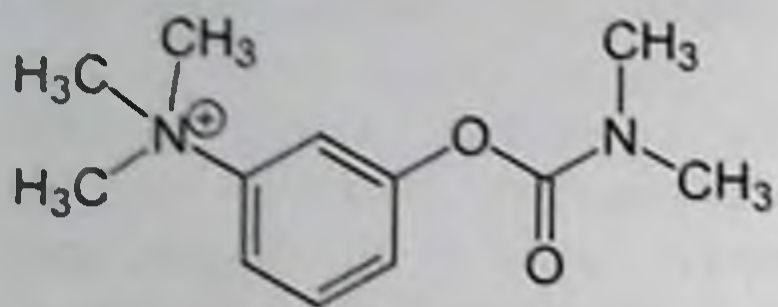


Fig. 2.14. 3-(((Dimethylamino(carbonyl)oxy)-N,N,N-trimethylbenzenaminium methyl sulfate

Neostigmine methyl sulfate (Proserine⁺)

- ▶ Quaternary amine, does not cross the BBB. Exhibits potent, rapid onset, short action. Bioavailability: 1–2%.
- ▶ Metabolized in the liver to form inactive metabolites. $T_{1/2}$: 42–60 min, short duration of action (2–4 hours). Excreted in the urine as unchanged drug (about 50%) and metabolites. For subcutaneous, intramuscular, intravenous, topical administration.

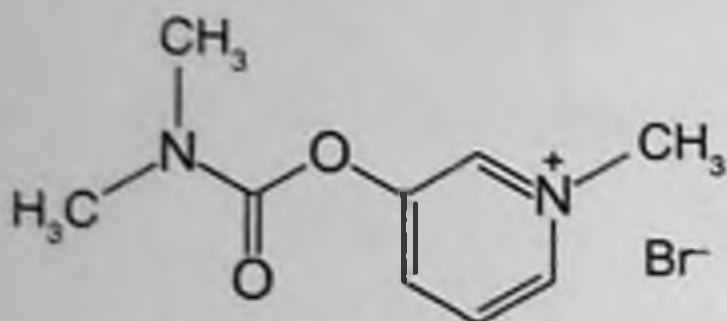


Fig. 2.15. 3-[[[(Dimethylamino)carbonyl]oxy]-1-methylpyridinium bromide

Pyridostigmine bromide (Kalymin⁺)

- ▶ Quaternary amine, does not cross the BBB. Less active than Proserine, used at higher doses, longer-acting (6 hours). Bioavailability: 8–20%.
- ▶ Metabolized in the liver to form 3-hydroxy-N-methylpyridine, $T_{1/2}$: 1.5–2.5 hours, excreted in the urine. For oral, subcutaneous, intramuscular, intravenous administration.

Distigmine bromide (Ubretid⁺)

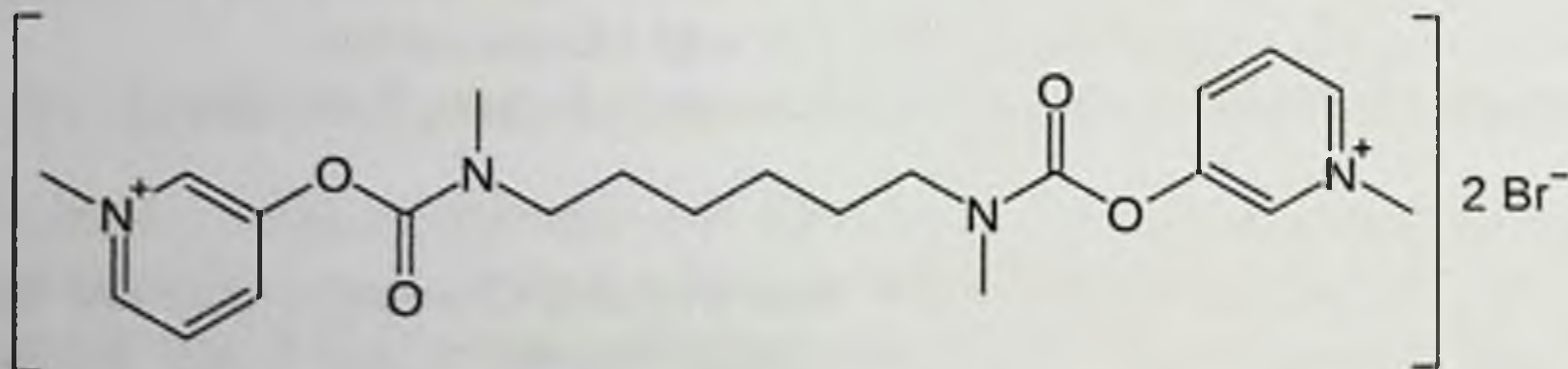


Fig. 2.16. 3,3'-[1,6-Hexanediylbis[(methylimino)carbonyl]oxy]bis[1-methylpyridinium] dibromide

- ▶ Quaternary amine, does not cross the BBB, reversible. Longer-acting and more potent than neostigmine methylsulfate since the chemical structure has two quaternary ammonium groups. Takes effect 1.0–1.5 hours following oral administration, reaches its maximum in 8–10 hours and lasts 20 hours.
- ▶ Metabolized in the liver by hydrolysis, metabolites are excreted in the urine. For oral, intramuscular administration.

Armin[®]

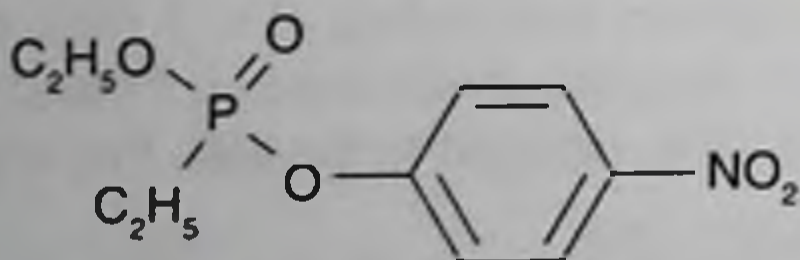


Fig. 2.17. Ethyl 4-nitrophenyl ethylphosphonate

This DP is excluded from the Russian State Register of Medicinal Products.

- ▶ Belongs to the class of organic phosphoric acid esters (OPs).
- ▶ Reversibly inhibits the esteratic site of acetylcholinesterase.

Toxicological significance of organophosphorus compounds

OPs are high-molecular-weight esters of phosphoric acid (phosphoric, pyrophosphoric, phosphorous, phosphonic, phosphinic, thiophosphoric and dithiophosphoric, thiophosphorous) and their sulfur and nitrogen derivatives (Fig. 2.18).

OPs were first synthesized in 1820. In 1847, several phosphines were synthesized by French scientist L. J. Thénard. OPs were extensively researched by L. Michaelis in 1903–1915 (Germany) and by A. E. Arbuzov in 1906 (Russia). In 1932, the toxic effects of OPs were first described by German scientists W. Lange and G. von Krüger. In 1937, G. Schrader discovered the insecticidal properties of parathion, paraoxon, schradan, etc. Sarin, tabun, soman synthesized by him were adopted as chemical warfare agents. Nowadays they are used as nerve agents, insecticides, polymer stabilizers, engine oil antioxidants, and fire retardants.

OP poisoning is acute intoxication that occurs due to respiratory, transdermal, or oral exposure to OPs. These highly lipophilic substances are rapidly absorbed and mainly accumulate in the liver, brain, cardiac and skeletal muscles, kidneys, adipose tissue. They are excreted in breast milk, urine, bile. The clinical presentation of poisoning only slightly depends on the route of exposure to OPs.

Mechanism of OP poisoning: The esteratic site binds to the phosphoric acid residue firmly, resulting in the formation of a hydrolysis-resistant compound unable to react with ACh molecules. Cholinesterase inhibition by OPs includes two phases: it is reversible during the first phase while the second phase occurs only after a certain period of time has elapsed. The transition from reversible to irreversible inhibition is gradual and depends on the temperature, structure, and concentration of the inhibitor.

Symptoms of acute poisoning with OP compounds

Stage I — excitation (mild intoxication): anxiety (fear, aggression); dizziness, headache; miosis, reduced visual acuity; nausea, vomiting, abdominal cramps, excessive sweating, hypersalivation, lacrimation, bronchorrhea; moderate tachycardia and increased BP.

Stage II — hyperkinesis with convulsions (moderate and severe intoxication): psychomotor agitation persists; lethargy, sopor, coma may develop; myoclonic hyperkinesis (myofibrillation), thoracic muscle rigidity with decreased thoracic excursion; marked miosis, absence of pupillary light reactivity; bradycardia; BP increased to 250/160 mmHg; extreme sweating, salivation and bronchorrhea; tenesmus, involuntary loose stools; frequent urination.

Stage III — paralysis (extremely severe intoxication): deep coma with extremely weak reflexes or complete areflexia; skeletal striated muscle paralysis; extreme miosis; hypersalivation, bronchorrhea, excessive sweating; predominant central respiratory disorders (shallow breathing, Cheyne–Stokes respiration, possible respiratory

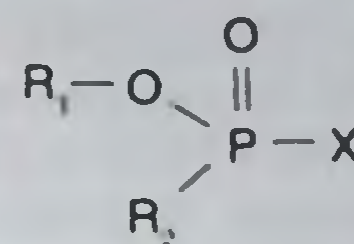


Fig. 2.18. Structure of organophosphorus compounds:
P — phosphorus atom, R₁ and R₂ — organic radicals, X — halogen (Cl, F), or CN-group, or benzene derivative (nitrophenol)

paralysis), exotoxic shock (due to inconsistency between the circulating blood volume and the vascular bed volume, disorganized microcirculation, redistribution of blood); marked bradycardia ($HR < 20$ bpm) or tachycardia ($HR > 120$ bpm), drop in blood pressure including collapse.

Supportive measures in the event of OP poisoning

- ▶ If skin and mucous membranes are exposed to OPs, wipe off with dry cotton wool, wash with 5–6% sodium bicarbonate solution and warm soapy water.
- ▶ If OPs are ingested, perform gastric lavage, give enterosorbents (activated charcoal, etc.) and saline laxatives (magnesium sulfate).
- ▶ Accelerate the excretion of substances from the body through forced diuresis (furosemide), hemodialysis, hemoadsorption, peritoneal dialysis.
- ▶ Antidotes:
 - Intravenous atropine (2–4 mL 0.1% solution) — MRA, competitive muscarinic receptor antagonist (inhibits mAChRs, preventing the action of ACh accumulated in nerve synapses). It is administered until signs of atropinization occur: pupil dilation, dry skin, tachycardia, end of salivation and bronchorrhea. This condition is maintained by repeated administration of atropine (maintenance dose) to create a persistent blockade of M-cholinoreactive systems for the time necessary to break down and remove the poison.
 - Cholinesterase reactivators, i.e. substances capable of dephosphorylating acetylcholinesterase blocked by OPs and restoring enzyme activity. 1 mL (50 mg) of dipyrroxime[®] solution should be administered intramuscularly or intravenously, repeatedly if necessary.

Cholinesterase reactivators

Classification

- ▶ Tertiary: Diethyxime^{*}
- ▶ Quaternary: trimedoxime bromide (Dipyrroxime[®])

Mechanism of action: Due to the presence of an oxime group ($-NOH$) in cholinesterase reactivators, the phosphoester bonds between the OP molecule and the esteratic site are broken. This restores the enzyme's activity, and the signs of OP intoxication subside or disappear completely (Fig. 2.19).

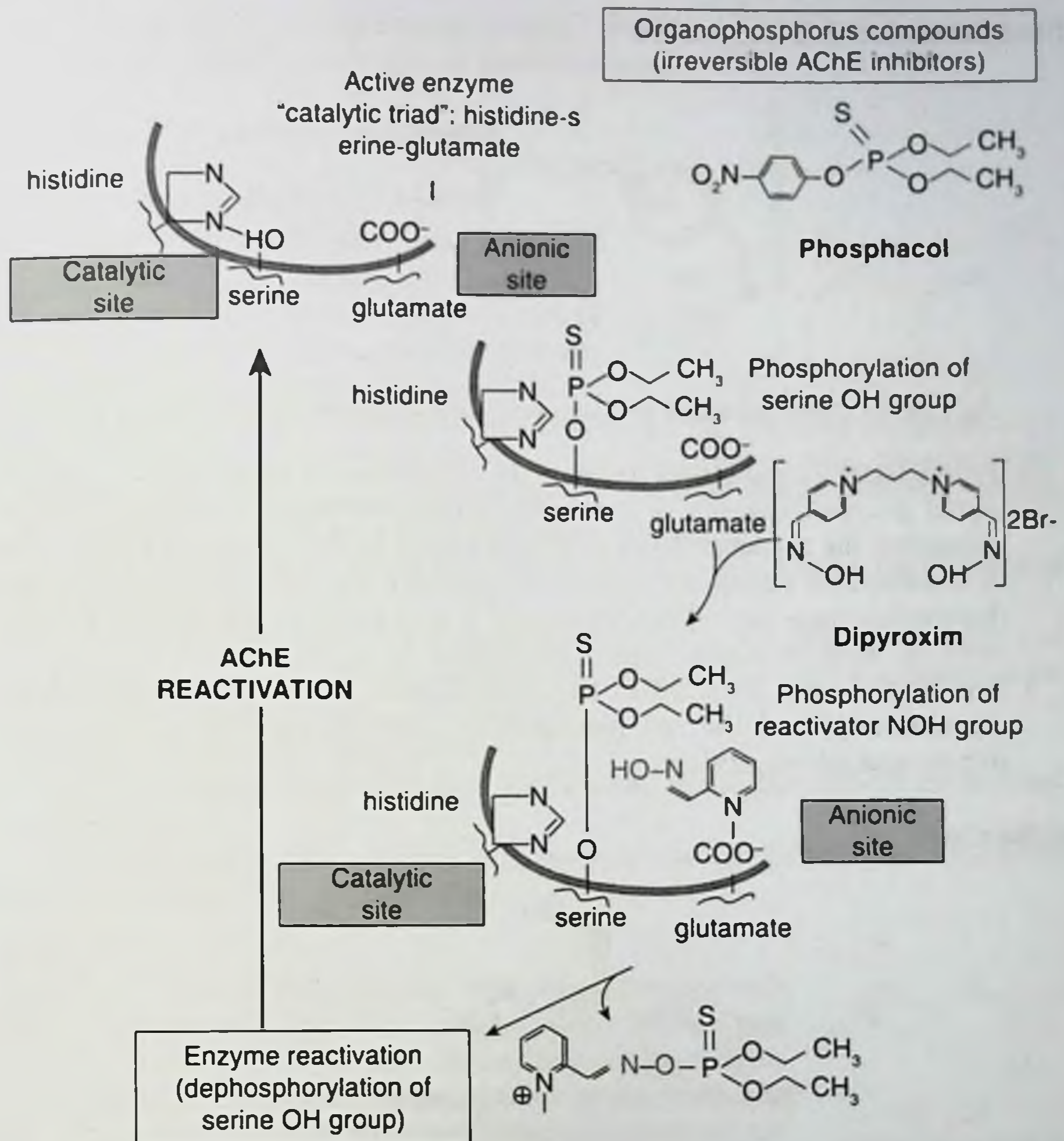


Fig. 2.19. Mechanism of action of cholinesterase reactivators (Rang H.P. et al., 2012)
AChE — acetylcholinesterase

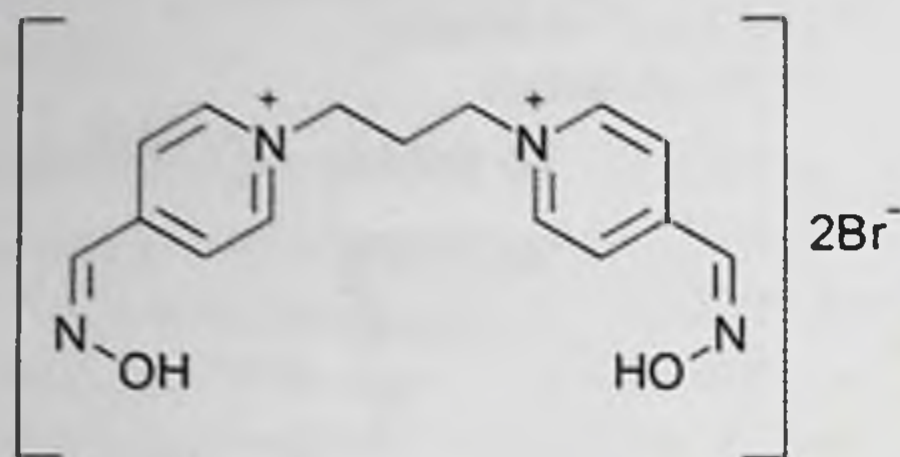
Trimedoxime bromide (Diproxime[®])

Fig. 2.20. 1,1'-1,1'-Trimethylene-bis-(4-oximinomethyl-pyridinium bromide)monohydrate

- ▶ Symmetrical bisquaternary ammonium compound, contains two $>\text{C}=\text{N}-\text{OH}$ oxime groups. Nitrogen of the oxime group is a strong nucleophilic agent, surpassing the nucleophilicity of phosphorus. For this reason, the oxime part of trimedoxime establishes a covalent bond with the OP's phosphorus site and dephosphorylates the active enzyme site. It is an ionized compound. It does not cross the BBB, placenta; excreted into breast milk.
- ▶ $T_{1/2}$: 15–20 days. Excreted in the urine (2% in the bile when administered intravenously) and through hemodialysis. For subcutaneous, intramuscular, intravenous administration.

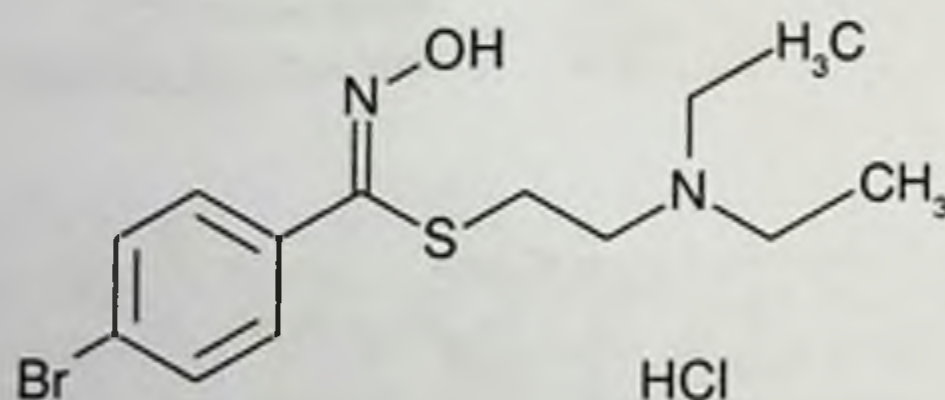
Diethyxime⁺

Fig. 2.21. 4-Bromo-N-hydroxybenzenecarboximidothioate 2-(diethylamino)ethylester

- ▶ Structurally similar to ACh. Crosses the BBB. Exhibits mild cholinolytic action.
- ▶ For intramuscular administration.

Muscarinic agonists

Substances that directly stimulate mAChRs located in the cell membranes of effector organs and tissues receiving parasympathetic innervation.

Pharmacological effects

- ▶ Miosis. IOP reduction, spasm of accommodation
- ▶ Bradycardia, AV block

- ▶ Increased secretion from exocrine glands
- ▶ Increased smooth muscle tone of internal organs

Specifics of individual products

Pilocarpine (pilocarpine hydrochloride*)

- ▶ Alkaloid extracted from the leaves of jaborandi (*Pilocarpus pennatifolius*), native to South America. Compound of methylimidazole and ethylfuranone. Obtained by synthesis. Tertiary amine, penetrates the CNS. Nonpolar, lipophilic. Highly toxic, mainly used topically in ophthalmic dosage forms. Essentially not absorbed in the conjunctival sac and has no significant systemic action. IOP reduction occurs in 10–30 min, the duration of action is 4–6 hours.

- ▶ Partially penetrates the plasma and is inactivated by hydrolysis in the serum and liver. Eye $T_{1/2}$: 1.5–2.5 hours, plasma $T_{1/2}$: 30 min. For topical administration (eye drops, films, ointments).

Therapeutic indications: glaucoma

Side effects: eye pain, reduced vision, lacrimation, rhinorrhea, superficial keratitis, allergic reactions

Contraindications: iritis, iridocyclitis, uveitis, retinal detachment (including history thereof), less than 18 years of age

Aceclidine

Synthetic tertiary base, crosses the BBB. Easily absorbed with different routes of administration, including when instilled into the conjunctival sac. Less toxic than pilocarpine (used for systemic action), has a more pronounced activating effect on smooth muscle tone of the GI tract, urinary and biliary tracts, and potent myotic action. For subcutaneous, topical (eye drops) administration.

Therapeutic indications: treatment of postoperative atony of the GI tract and urinary bladder; glaucoma

Side effects: hypersalivation, diarrhea, smooth muscle spasm, conjunctival irritation

Contraindications: bronchial asthma, coronary artery disease (CAD), GI bleeding, epilepsy, hyperkinesia, inflammation in the abdomen, pregnancy

Muscarinic poisoning

Muscarinic syndrome: hypersalivation, bronchorrhea, excessive sweating, bradycardia, AV block, hypotension, bronchospasm, miosis, visual impairment, increased intestinal peristalsis, diarrhea, nausea, vomiting, abdominal pain

Supportive measures:

- ▶ Gastric lavage with room temperature water

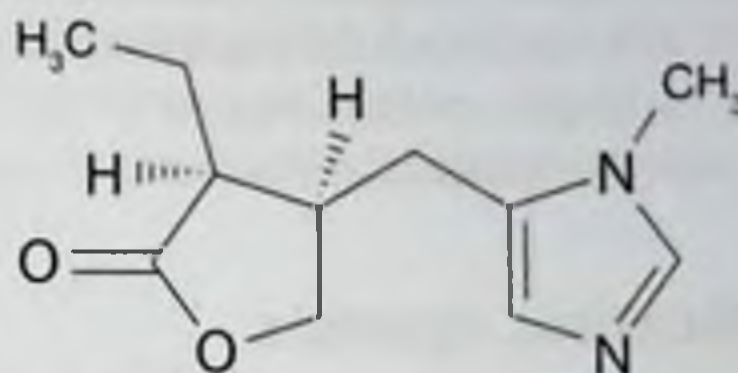


Fig. 2.22. (3S-cis)-3-Ethyl-4-[(1-methyl-1H-imidazole-5-yl)methyl]-2(3H)-furanone (as a hydrochloride or nitrate)

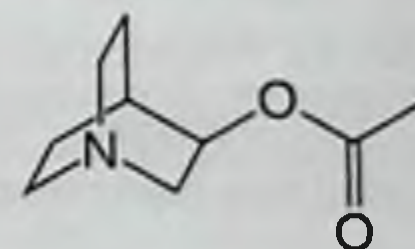


Fig. 2.23. 3-Acetoxyquinuclidine (as a salicylate or hydrochloride)

- ▶ Enterosorbents (activated charcoal, etc.)
- ▶ Saline laxatives (magnesium sulfate)
- ▶ Antidotes: atropine (Atropine sulfate*) — MRA, competitive muscarinic receptor antagonist (inhibits mAChRs, preventing the action of ACh accumulated in nerve synapses). Administered intravenously, with repeated intramuscular or intravenous dosing if necessary
- ▶ Supplemental oxygen
- ▶ Symptomatic treatment

Nicotinic agonists

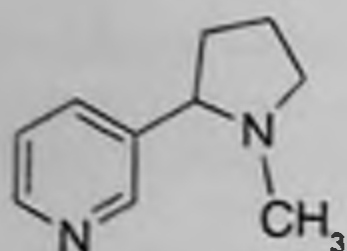


Fig. 2.24. (S)-3-(1-Methyl-2-pyrrolidinyl) pyridine

Nicotinic agonists are drugs that act directly by stimulating nAChRs. They predominantly affect the neuronal (N_n) nicotinic receptor subtype.

Nicotine is not a drug product; it is used in experimental pharmacology.

- ▶ Alkaloid found in tobacco leaves (*Nicotiana tabacum* and *Nicotiana rustica*). Acts on both peripheral and central nAChRs. nAChRs of the autonomic ganglia are especially sensitive to nicotine. Readily absorbed through the mucous membranes. Easily penetrates the BBB. Excreted into breast milk.
- ▶ Primarily metabolized in the liver. Major metabolites: cotinine and trans-3-hydroxycotinine. $T_{1/2}$: 2–3 hours. Metabolism products and small amounts of the alkaloid are excreted in the urine as unchanged substance.

Exerts biphasic action: stimulates nAChRs at low doses and inhibits nAChRs at high doses (Table 2.3).

Table 2.3. Peripheral actions of nicotine in the body

Location	Low doses	High doses
Carotid body chemoreceptors	Stimulates (reflex excitation of the respiratory and vasomotor centers)	Inhibits
Adrenal chromaffin cells	Excites (increases adrenaline secretion)	Inhibits
Neuromuscular junction	Facilitates transmission of nerve impulses	Inhibits transmission of nerve impulses
Cardiovascular system	Increased BP and tachycardia due to increased adrenaline release by chromaffin cells, stimulation of the vasomotor center. Bradycardia may develop with the onset of action due to stimulation of nAChRs of the parasympathetic ganglia.	
GI tract	Increases intestinal motility	Decreases intestinal motility
Salivary and bronchial glands	Increases secretory function	Inhibits secretory function

Central actions:

- ▶ Increases the release of dopamine, serotonin, ACh, noradrenaline, β -endorphins
- ▶ Reduces follicle stimulating hormone, prolactin levels
- ▶ Increases the secretion of antidiuretic hormone, adrenocorticotrophic hormone

Medical and social aspects of smoking

Tobacco smoking is extremely common worldwide and is one of the leading risk factors for socially significant diseases. The link between nicotine use and chronic diseases leading to premature death has been well established. Smoking a single cigarette causes the smoker to inhale about 3 mg of nicotine (the lethal dose is 60 mg). Nicotine addiction develops very fast, faster than heroin addiction. The urge to use tobacco (nicotine addiction) is associated with the excitatory effect of nicotine on nAChRs of the CNS.

Chronic smoking results in:

- ▶ COPD, pneumonia, emphysema
- ▶ gastritis, stomach and duodenal ulcers
- ▶ CAD, hypertension, peripheral vascular disease, aortic aneurysms
- ▶ cancer of the mouth, throat, vocal cords, lungs, pancreas, kidneys and urinary bladder, large intestine
- ▶ osteoporosis
- ▶ cataracts
- ▶ leukemia.

Tobacco smoke contains additional harmful substances that are irritating and carcinogenic (benzene, formaldehyde, acetaldehyde, 1,3-butadiene, aromatic amines, polycyclic aromatic hydrocarbons).

Smokers experience distress when they quit smoking. This is why many of them cannot quit, despite realizing how their smoking habit negatively affects their health.

Smoking cessation drugs

Cytisine, lobeline, and anabasine, an alkaloid of *Anabasis aphylla* that acts similarly to them, are used as smoking cessation aids. Their pharmacological properties are similar to those of nicotine. They reduce the urge to use nicotine and alleviate the discomfort and distress associated with smoking cessation.

Pharmaceutical forms:

- ▶ tablets: cytisine (Tabex[®]), lobeline (Lobesyl[®]), anabasine
- ▶ chewing gums: anabasine
- ▶ films: cytisine, anabasine — sublingual, transbuccal
- ▶ patches (TTS): cytisine

The mechanism of action consists of nAChR activation.

Effects:

- ▶ Changes the sensations associated with smoking
- ▶ Reduces the urge to smoke
- ▶ Alleviates the symptoms of withdrawal

Acute nicotine poisoning

Clinical manifestations: hypersalivation, nausea, vomiting, diarrhea, bradycardia changing to tachycardia, increased BP, tachypnea changing to bradypnea, pupils become constricted, then dilated.

Supportive measures:

- ▶ Mechanical ventilation, since death occurs due to respiratory failure
- ▶ There is no specific antidote
- ▶ Symptomatic treatment

Specifics of individual products

Lobeline

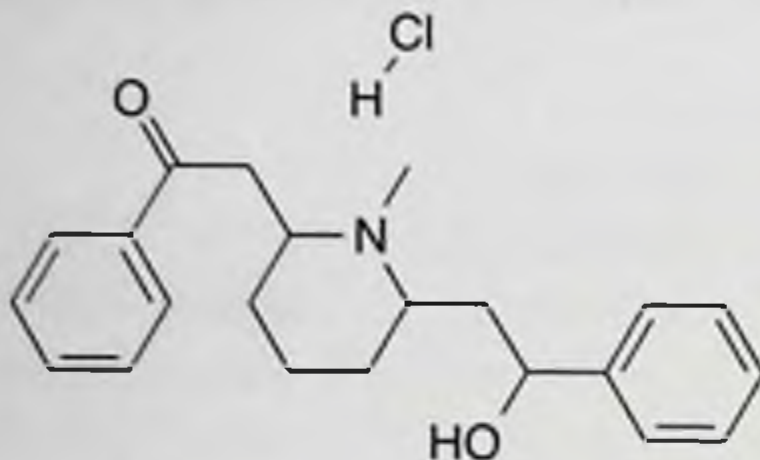


Fig. 2.25. 1-1-Methyl-2-benzoylmethyl-6-(2-oxy-2-phenylethyl)piperidine hydrochloride

Alkaloid of *Lobelia inflata*, tertiary amine

Cytisine

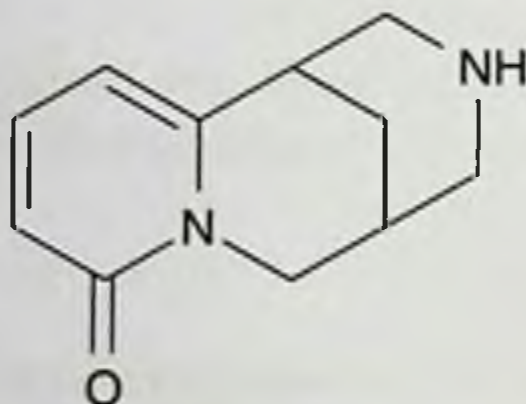


Fig. 2.26. (1R)-1,2,3,4,5,6-Hexahydro-1,5-methano-8H-pyrido[1,2-a][1,5]diazocin-8-one

Alkaloid of *Cytisus* (*Cytisus laburnum*) and tapered false lupin (*Thermopsis lanceolata*), secondary amine

Lobeline and cytisine penetrate the CNS. Their action is short-term, only lasting 2–5 min. They are administered intravenously for respiratory depression in patients with preserved reflex excitability. For this reason, they are not used for poisoning with substances that reduce the excitability of the respiratory center (sleeping pills, narcotic analgesics). Intramuscular or subcutaneous administration requires 10–20 times higher doses than intravenous administration.

Lobeline, activating the vagal nucleus in the medulla oblongata, causes bradycardia and hypotension. In the second phase of action, BP increases due to stimulation of the sympathetic ganglia and the adrenal medulla. Cytisine only exhibits pressor action.

Side effects: weakness, irritability, dizziness, nausea, vomiting, epigastric pain

Contraindications: exacerbation of stomach and duodenal ulcers, decompensation of cardiovascular disease

CHOLINERGIC BLOCKERS

Cholinergic blockers are drugs that prevent or stop the interaction of ACh with AChRs.

Grouping of drugs

- I. Muscarinic receptor antagonists
 1. Non-selective
 2. Selective (M_1)
 3. Relatively selective (preferential for bronchial M_2)
- II. Nicotinic receptor antagonists
 1. Ganglionic blockers (selective N_N receptor blocker)
 2. Peripheral muscle relaxants (N_M receptor blocker)
 - A. Non-depolarizing:
 - short-acting (10 min)
 - intermediate-acting (20–30 min)
 - long-acting (> 30 min)
 - B. Depolarizing:
 - short-acting (5–10 min)
 - C. Anticholinergics

Muscarinic receptor antagonists

Classification

1. Non-selective
 - A. Tertiary: atropine (Atropine sulfate*), scopolamine, platyphylline (Platyphylline hydrotartrate*), homatropine hydrobromide, tropicamide (Mydriacyl*)
 - B. Quaternary: metocinium iodide (Methacin*)
2. Selective
 - A. Tertiary: pirenzepine (Gastrozepin*, gastril[®]).
3. Relatively selective (predominantly bronchial M_2 receptors)
 - A. Quaternary: ipratropium bromide (Atrovent*), tiotropium bromide (Spiriva*)

Atropine is a typical representative of this class. This is why muscarinic antagonists are called atropine-like drugs.

Mechanism of action: By blocking mAChRs, these drugs prevent their interaction with ACh and suppress the parasympathetic nervous system

Pharmacological effects

- ▶ Mydriasis, increased IOP, paralysis of accommodation
- ▶ Increased HR, facilitation of AV conduction
- ▶ Decreased smooth muscle tone of the bronchi, urinary bladder, GI tone and motility
- ▶ Decreased secretion from exocrine glands: lacrimal, salivary, nasopharyngeal, bronchial, digestive

Therapeutic indications

- ▶ Renal colic and biliary colic, pylorospasm

- ▶ Stomach and duodenal ulcers, hyperacid gastritis, erosive esophagitis, reflux esophagitis, Zollinger-Ellison syndrome — for selective M1 blockers
- ▶ Prophylaxis and treatment of bronchial asthma, COPD — for relatively selective M3 blockers
- ▶ Bradycardia, AV block
- ▶ Premedication
- ▶ Overdose with muscarinic agonists or anticholinesterase drugs
- ▶ Diagnostic procedures in ophthalmology (examination of the fundus, selection of lenses), inflammatory eye diseases (iritis, iridocyclitis, etc.)
- ▶ Vestibular disorders (prevention of nausea and vomiting in motion sickness, Ménière's disease) — scopolamine hydrobromide⁶²

Side effects

- ▶ Tachyarrhythmias (sinus tachycardia, ventricular tachycardia, ventricular fibrillation)
- ▶ Mydriasis (photophobia), increased IOP, visual impairment (paralysis of accommodation)
- ▶ Dry skin and mucous membranes, dysarthria, dysphagia, xerostomia
- ▶ Obstipation, urinary retention

Contraindications: tachyarrhythmias, glaucoma, hepatic and/or renal impairment, intestinal atony, paralytic ileus, bladder atony, prostate hyperplasia

Specifics of individual products

Atropine (Atropine sulfate*)

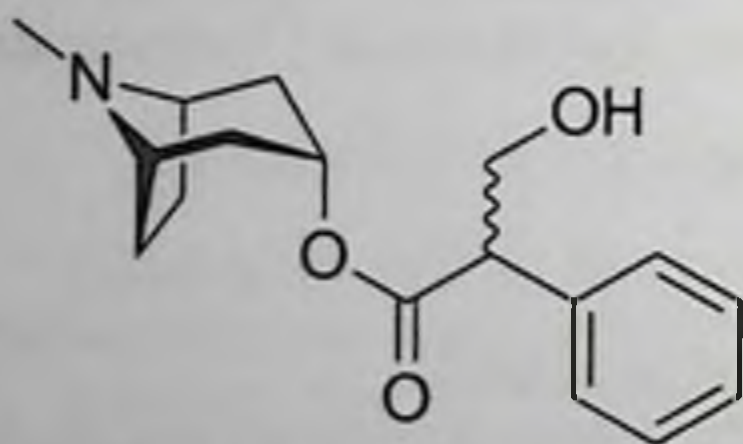


Fig. 2.27. Endo- α -(hydroxymethyl) benzeneacetic acid (8-methyl-8-azabicyclo[3.2.1] oct-3-yl ester (and as a sulfate)

- ▶ Alkaloid found in plants of the family Solanaceae: berries and roots of deadly nightshade (*Atropa belladonna*), seeds of jimsonweed (*Datura stramonium*), leaves and roots of henbanes (genus *Hyoscyamus*). Non-selective, tertiary, crosses the BBB. Duration of action: 4–6 hours. When administered topically, mydriasis lasts 7 days or more, paralysis of accommodation lasts 3–4 days. Bioavailability: 25%.

- ▶ Metabolized in the liver by enzymatic hydrolysis to tropine and tropic acid. $T_{1/2}$: 2 hours; excreted in the urine, with about 60% excreted

as unchanged drug and the remaining part excreted as products of hydrolysis and conjugation. For topical (eye drops, ointments, films), subcutaneous, intravenous, intramuscular administration.

Pharmacological effects

Local action

- ▶ Pupil dilation (mydriasis): eliminates the stimulatory effects of parasympathetic innervation on the iris sphincter muscle, which then relaxes; the iris dilator muscle contracts.

- ▶ Increase in IOP: when pupil is dilated, closes the anterior chamber angle, making it difficult to drain the intraocular fluid.
- ▶ Paralysis of accommodation (artificial hyperopia or cycloplegia): eliminates the stimulatory effects of parasympathetic innervation on the ciliary muscle, the muscle relaxes, the suspensory ligaments stretch, and the curvature of the lens decreases — the eye focuses on a distant object.

Systemic action

- ▶ Increased HR, improvement of AV conduction
- ▶ Decreased smooth muscle tone of the bronchi, stomach, intestines, bile ducts, urinary bladder
- ▶ Decreased secretion of the lacrimal, salivary, nasopharyngeal, bronchial, digestive glands
- ▶ Decreased release of histamine by the enterochromaffin cells of the stomach and elimination of its stimulatory effects on the parietal cells producing HCl, decreased secretion of hydrochloric acid

Acute atropine poisoning

Symptoms

Phase one — excitation phase:

- ▶ excitation of the CNS: disorientation, hallucinations, delusions
- ▶ mydriasis, photophobia, paralysis of accommodation, diplopia
- ▶ marked tachycardia (HR reaches 160–190 beats per minute), ventricular extrasystoles, moderate hypertension
- ▶ xerostomia, dysphagia, dysarthria, urinary and fecal retention
- ▶ hyperthermia due to impaired sweating and decreased heat loss; compensatory increase in cutaneous microcirculation (hyperemia of the face, neck, chest).

Phase two — depression phase: loss of consciousness (coma) and circulatory collapse. Respiratory failure and cardiovascular arrest result in death (lethal dose for adults: 100 mg).

Supportive measures

- ▶ Gastric lavage with potassium permanganate solution (0.1%), activated charcoal, saline laxatives
- ▶ Antidote: subcutaneous Proserine, repeatedly if necessary (facilitates ACh accumulation)
- ▶ Forced diuresis, hemoabsorption
- ▶ Symptomatic treatment

Scopolamine

- ▶ Alkaloid found in deadly nightshade, henbanes, jimsonweed, scopolia. Its chemical structure is similar to atropine (ester of scopine and tropic acid). Tertiary amine, crosses the BBB. Exerts depressive action on the CNS, particularly on the basal ganglia and nuclei of the vestibular nerve, which

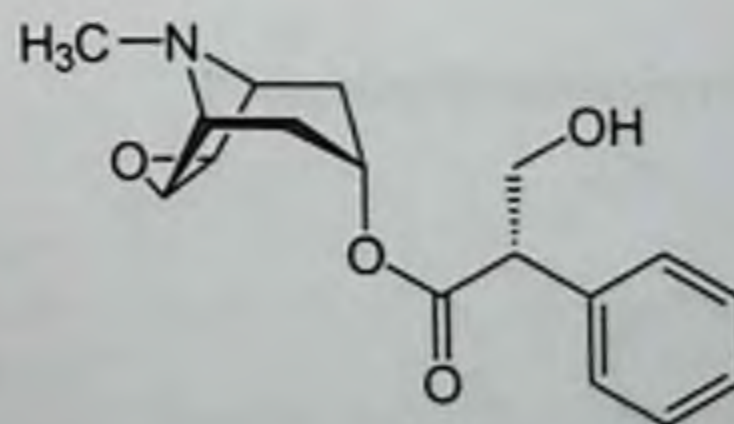


Fig. 2.28. (1*R*,2*R*,4*S*,7*S*,9*S*)-9-methyl-3-oxa-9-azatricyclo[3.3.1.0^{2,4}]non-7-yl-(-)-(S)-3-hydroxy-2-phenylpropionate

results in sedative, antiemetic effects, and eliminates the cholinergic effects on the extrapyramidal system. Has more pronounced effects on the eye and secretion from exocrine glands than atropine.

- ▶ Metabolized in the liver, $T_{1/2}$: 1.0–1.2 hours, excreted in the urine (with 4–5% excreted as unchanged drug). For subcutaneous, intramuscular, intravenous, topical (eye drops) administration 1–2 times daily, TTS — applied for 72 hours.

Platyllylline (Platyllylline hydrotartrate*)

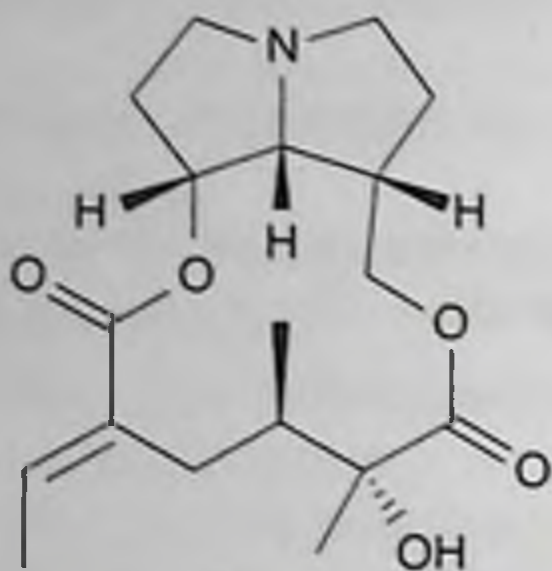


Fig. 2.29. 3-Ethylidene-6-hydroxy-5,6-dimethylperhydro-1,8-dioxacyclododeca [2,3,4-gh] pyrrolizin-2,7-dione (as a hydrotartrate)

- ▶ Alkaloid of large-leaved ragwort (*Senecio platyllyllus*). Tertiary amine, crosses the BBB. Inferior ability to block mAChRs than atropine. Exhibits direct myotropic antispasmodic, i.e. papaverine-like, action. Decreases smooth muscle tone in the internal organs and blood vessels (moderately lowers BP). Inhibits secretion from endocrine glands to a lesser extent than atropine, has lesser and shorter effects on accommodation.

- ▶ Metabolized in the liver. Undergoes hydrolysis to form platynecine and platynecic acid. Excreted in the urine and bile. For oral

administration 2–3 times daily, subcutaneous administration 1–2 times daily, rectal, topical (eye drops) administration.

Homatropine hydrobromide

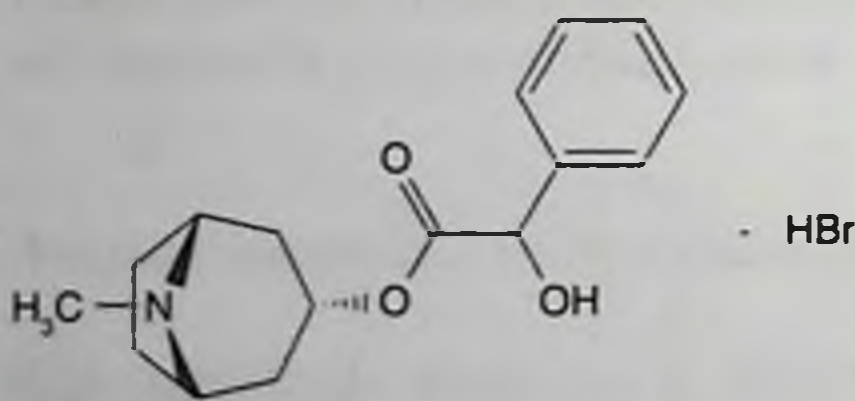


Fig. 2.30. α -Hydroxybenzeneacetic acid endo-($\pm$)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester hydrobromide

Semi-synthetic tertiary amine, mandelic acid tropine ester hydrobromide. Lower activity and shorter duration of action on the eye compared with atropine. Mydriasis occurs rapidly and lasts 10–20 hours. Used in ophthalmic practice for the examination of the fundus and prophylaxis of synechia in uveitis and iritis, etc. For topical administration (eye drops).

Tropicamide (Mydriacyl*)

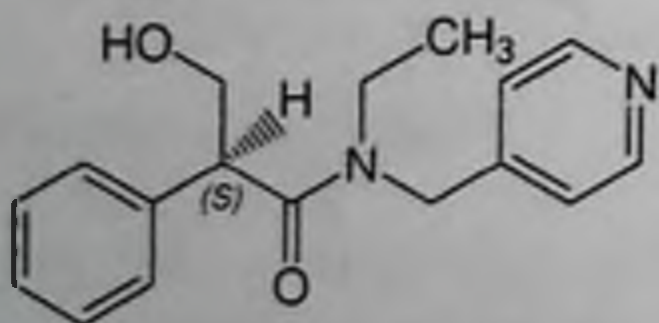


Fig. 2.31. (2-Hydroxyethyl) trimethylammonium iodide benzilate

Tertiary amine. Mydriasis occurs in 5–10 minutes and reaches its maximum in 20–45 minutes. Maximal pupil dilation lasts 1 hour; recovery occurs in 6 hours, with the pupil returning to its original size. Has lesser effects on IOP compared with atropine. Used in ophthalmology for diagnostic purposes as a component of combination therapy

for inflammatory eye diseases and in the postoperative period for synechia prophylaxis. For topical administration (eye drops).

Metocinium iodide (Methacin*)

Synthetic quaternary ammonium compound. Does not cross the BBB. Affects peripheral AChRs to a greater extent than atropine. Has a more pronounced bronchodilating effect, inhibits the secretion of the salivary and bronchial glands to a greater extent than atropine. Compared with atropine, has milder effects on the eye, causes pupil dilation, paralysis of accommodation, and increased IOP to a lesser extent (the pupil diameter can be monitored during the procedure). For oral administration 2–3 times daily, for subcutaneous, intramuscular, intravenous administration.

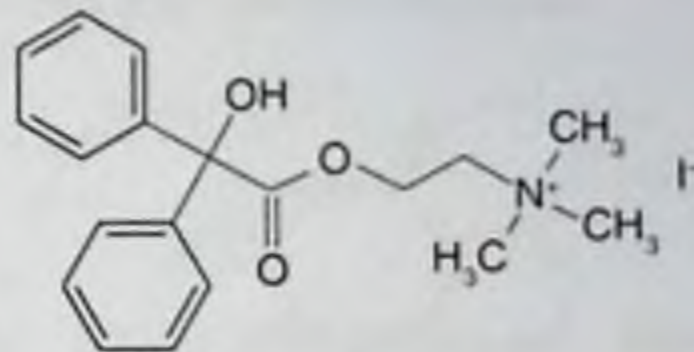


Fig. 2.32. (2-Hydroxyethyl) trimethylammonium iodide benzilate

Ipratropium bromide (Atrovent*)

- ▶ Quaternary ammonium compound (does not cross the BBB). Relatively selective: predominantly blocks bronchial M3 receptors. Hydrophilic substance, poorly absorbed through the mucous membranes, including the respiratory tract (10–30%), therefore has essentially no systemic side effects. Has a pronounced bronchodilating effect. The effect occurs in 15–30 minutes, reaches its maximum in 1–2 hours, and lasts 6–8 hours.

Dilates predominantly large and medium bronchi. Reduces secretions from the bronchial glands, does not reduce mucociliary clearance.

- ▶ The portion of the drug entering the systemic bloodstream undergoes biotransformation in the liver to form inactive metabolites. Elimination: as metabolites in the bile and urine. $T_{1/2}$: 2 hours. For administration by oral inhalation as an aerosol, solution for inhalation through a nebulizer 3–4 times daily.

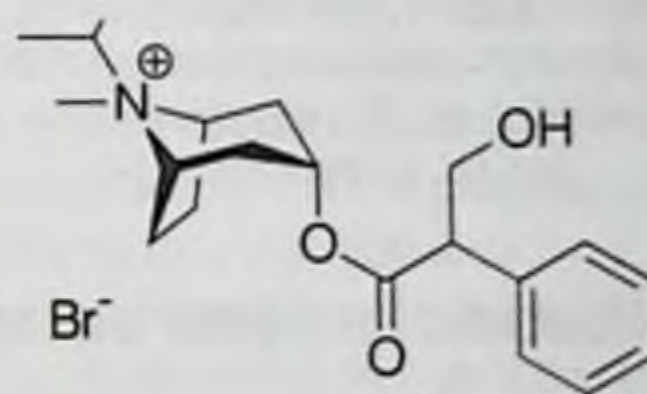


Fig. 2.33. (endo,syn)-(±)-3-(3-Hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane bromide

Tiotropium bromide (Spiriva*)

- ▶ Quaternary scopine derivative, polar hydrophilic compound, poorly penetrates cell membranes. Does not cross the BBB. Predominantly blocks bronchial M3 receptors. The effect lasts about 24 hours. Does not reduce mucociliary clearance. Reduces bronchial remodeling, including

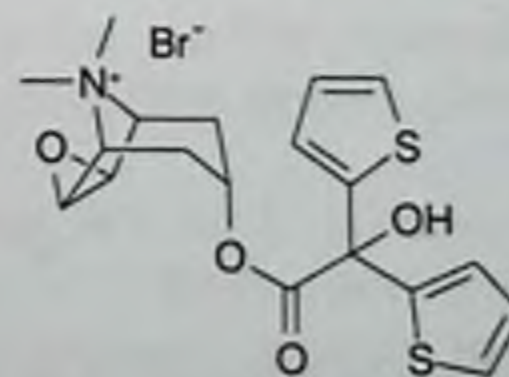


Fig. 2.34. (1 α ,2 β ,4 β ,7 β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}]nonane

bronchial wall thickening, mucous gland hypertrophy, and smooth muscle hyperreactivity (reduction of eosinophilic and neutrophilic inflammation).

- Metabolism occurs in the liver with involvement of the cytochrome P450 enzymes, $T_{1/2}$: 27–45 hours, the drug is excreted in the urine. For administration once daily as a solution and capsules for inhalation.

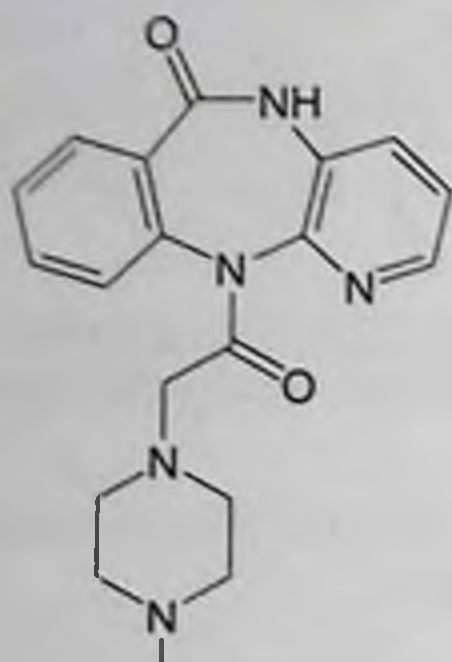


Fig. 2.35. 5,11-Dihydro-11-[(4-methyl-1-piperazinyl)acetyl]-6H-pyrido[2,3-b] [1,4]benzodiazepin-6-one (as a dihydrochloride)

Pirenzepine (Gastrozepin[®])

- Selectively blocks M_1 receptors of enterochromaffin-like cells in the gastric mucosa, inhibits the basal and stimulated secretion of HCl and pepsinogen by the gastric glands. Bioavailability: 20–30%, 10–20% when taken with food.
- $T_{1/2}$: 10–12 hours, excreted mainly in the bile and in small amounts in the urine as unchanged drug. For oral administration 2 times daily, for intramuscular, intravenous administration (every 8–12 hours).

Nicotinic receptor antagonists

Ganglionic blockers

Ganglionic blockers are drugs that block transmission at the sympathetic and parasympathetic ganglia.

Classification

- Bisquaternary
 - Azamethonium bromide (Pentamine[®]).
 - Trepirium iodide (Hygronium[®]).

Specifics of individual products

Azamethonium bromide (Pentamine[®])

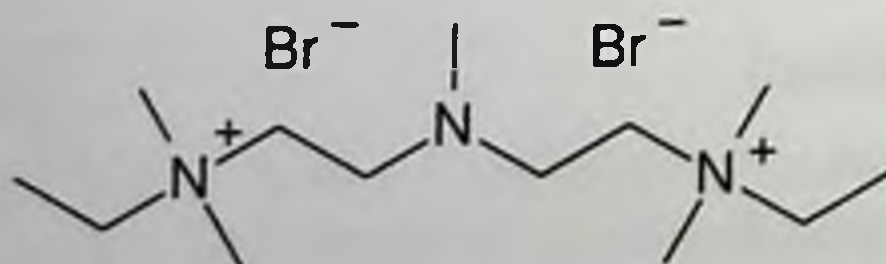


Fig. 2.36. 3-Methyl-1,5-bis-(N,N-dimethyl-N-ethylammonium)-3-azapentane dibromide

- Bisquaternary ammonium, hydrophilic, polar compound. Does not cross the BBB. Poorly absorbed in the GI tract. Exhibits high activity, but the duration

of action is short (2–4 hours following intravenous administration). Exerts antihypertensive action. For intramuscular, intravenous administration.

Trepirium iodide (Hygronium[®])

Bisquaternary ammonium compound, hydrophilic, polar. Does not cross the BBB. The antihypertensive effect occurs 2–3 min following intravenous administration and lasts 10–20 min. For intravenous administration.

Mechanism of action

These drugs block N_n receptors on neurons of sympathetic and parasympathetic ganglia:

- ▶ reduce the stimulatory effects of the sympathetic system on the vascular tone and heart: the arteries and veins dilate, preload and stroke volume are reduced, resulting in lower blood pressure in the arteries and veins.
- ▶ reduce the stimulatory effects of the parasympathetic system: paralysis of accommodation, tachycardia, decreased smooth muscle tone of the bronchi, GI tract and urinary bladder, inhibition of exocrine gland secretions.

Block N_n receptors on chromaffin cells in the adrenal gland. Reduce the release of adrenaline and noradrenaline, which also leads to a decrease in blood pressure.

Therapeutic indications: controlled hypotension during surgery on blood vessels and organs with a rich blood supply; management of hypertensive crisis; pulmonary edema; cerebral edema

Side effects: orthostatic hypotension (to prevent this effect, to the person must lie down for at least 1.5–2.0 hours after administration), tachycardia, atropine-like effects

Contraindications: acute phase of myocardial infarction, tachycardia, hypotension, prostate hyperplasia, renal and hepatic insufficiency, closed-angle glaucoma

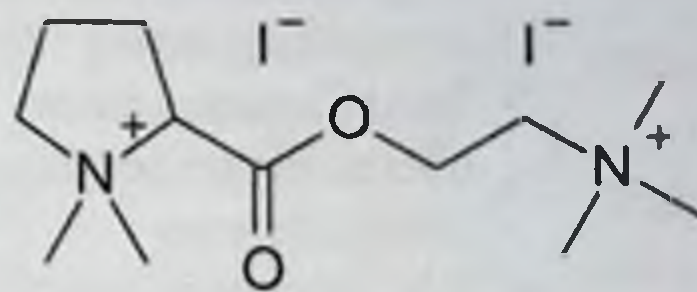


Fig. 2.37. Dimethylaminoethyl ester
N-methyl, -pyrrolidinecarboxylic acid
diiodomethylete

Muscle relaxants

These are drugs that decrease skeletal muscle tone.

In 1617, W. Raleigh, an English explorer and writer, discovered that indigenous people in South America used a substance called “curare” (“a liquid that quickly kills birds”) for hunting. Curare was first used in clinical practice by West in 1932, in patients with tetanus. In 1935, H. King isolated tubocurarine, the first curare alkaloid obtained from the plants of the *Strychnos* and *Chondrodendron* species growing in South America.

Muscle relaxation induced by curare-like drugs occurs in a particular order. Most of them first block neuromuscular junctions in the muscles of the face and neck, then the muscles of the limbs and torso. Respiratory muscles are more resistant to muscle relaxants. Finally, paralysis of the intercostal muscles and diaphragm occurs, which results in respiratory arrest.

Classification

1. Peripheral (quaternary, block N_m receptors)

A. Non-depolarizing

- Short-acting (10–20 min)
 - Benzylisoquinolines
 - ◊ Mivacurium chloride (Mivacron[®])
- Intermediate-acting (20–30 min)
 - Benzylisoquinolines
 - ◊ Atracurium besylate (Tracrium[®])
 - Aminosteroids
 - ◊ Vecuronium bromide (Norcuron[®])
 - ◊ Rocuronium bromide (Esmeron[®])
- Long-acting (> 30 min)
 - Aminosteroids
 - ◊ Pipecuronium bromide (Arduan[®]).
 - ◊ Pancuronium bromide (Pavulon[®]).

B. Depolarizing

- Short-acting (5–10 min)
 - Suxamethonium iodide (Dithylin-Darnitsa[®]).
2. Central (tertiary)
- Tolperisone (Mydocalm[®]).

Peripherally acting muscle relaxants**Non-depolarizing**

Mechanism of action: These drugs block Nm receptors at the skeletal muscle endplate, preventing their interaction with ACh; this prevents ACh from causing depolarization of the muscle fiber membrane: the muscles do not contract, and neuromuscular blockade occurs. These drugs are intended for intravenous administration.

Therapeutic indications: skeletal muscle relaxation during surgery and endoscopic procedures; facilitation of endotracheal intubation; spasms in tetanus and strychnine poisoning.

Side effects: muscle weakness, shallow breathing; benzylisoquinolines release histamine, which results in hypotension, bronchospasm, skin redness and other anaphylactic reactions; aminosteroids have moderate muscarinic receptor blocking activity and therefore cause tachycardia

Contraindications: myasthenia gravis, myopathy, myotonia, hereditary paroxysmal myoplegia

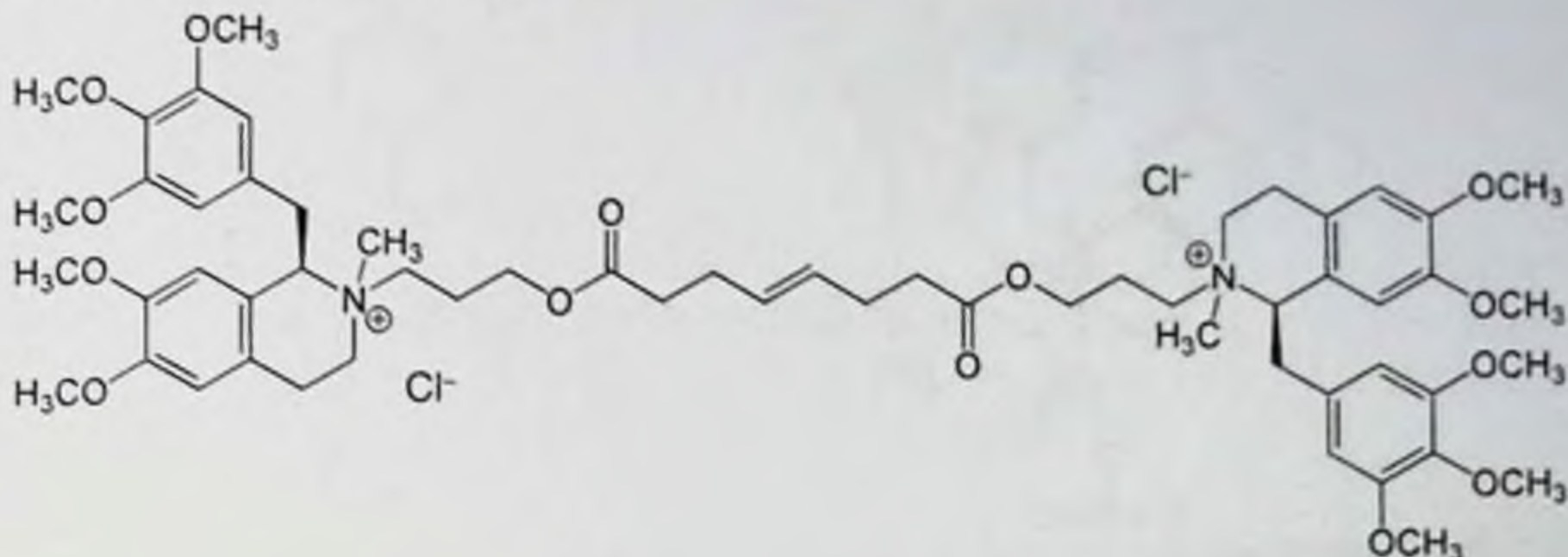
Mivacurium chloride (Mivacron®)

Fig. 2.38. 2,2' -[(1,8-Dioxo-4-octene-1,8-diyl)bis(oxy-3,1-propanediyl)] bis[(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-[(3,4,5-trimethoxyphenyl)methyl])isoquinolinium dichloride

- ▶ Bisquaternary benzyloisoquinoline derivative, short-acting. Causes release of histamine from tissues. The effect occurs within 2.0–2.5 min following intravenous administration of 0.15–0.25 mg/kg. The duration of action is 16 min for the 0.15 mg/kg dose, 20–23 min for the 0.20–0.25 mg/kg dose in adults. Neuromuscular conduction recovery is two-times faster than that of any intermediate-acting muscle relaxant, independent of the dose or duration of infusion.
- ▶ It undergoes enzymatic hydrolysis in the plasma, with involvement of pseudocholinesterase, to form quaternary alcohol and quaternary monoester; the role of true cholinesterase in the metabolism of mivacurium is insignificant. Biotransformation may be substantially delayed in patients with abnormal or reduced cholinesterase activity, especially in homozygotes for the atypical cholinesterase gene. $T_{1/2}$ is 2.3, 2.1, and 55 min for trans-trans-, cis-trans-, and cis-cis stereoisomers, respectively. However, cis-cis isomers have only 1/10th the activity of the two other isomers in the development of neuromuscular blockade and, despite the long $T_{1/2}$, does not affect the properties of the mixture. Excreted in the urine and bile as inactive metabolites.

Atracurium besylate (Tracrium®)

- ▶ Benzyloisoquinoline derivative. Synthetic bisquaternary ammonium compound, poorly penetrates the BBB, placental barrier. Produces a rapid and easily reversible muscle relaxing effect. The onset of action is 1–2 min, the duration of action is 15–35 min. 25% recovery of neuromuscular transmission occurs in 35–45 min and 95% recovery occurs in 60–70 min with balanced anesthesia, or 40 min after the start of recovery with inhalation anesthesia.
- ▶ Undergoes biotransformation by ester hydrolysis with involvement of non-specific plasma esterases and spontaneously by non-enzymatic passive conversion to the inactive form. Laudanosine, its major metabolite, has no muscle relaxing activity but causes hypotension. Excreted within 20 min in the urine (with about 90% excreted as metabolites) and bile (with less than 10% excreted as unchanged drug).

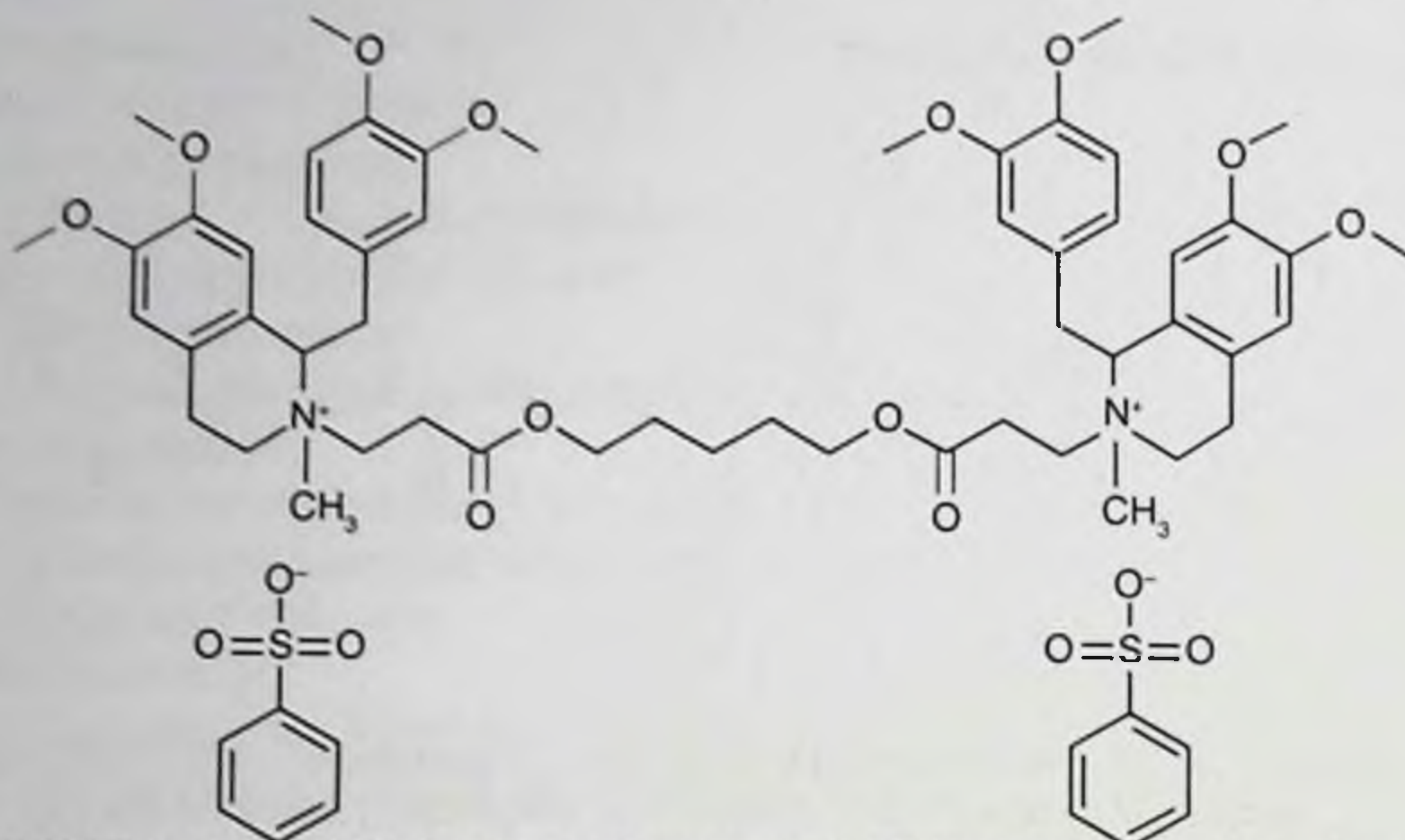


Fig. 2.39. 2,2'-[1,5-Pentanediy-bis-[oxy(3-oxo-3,1-propanediyl)]]-bis-[1-[(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl]isoquinolinium dibenzenesulfonate

Vecuronium bromide (Norcuron[®])

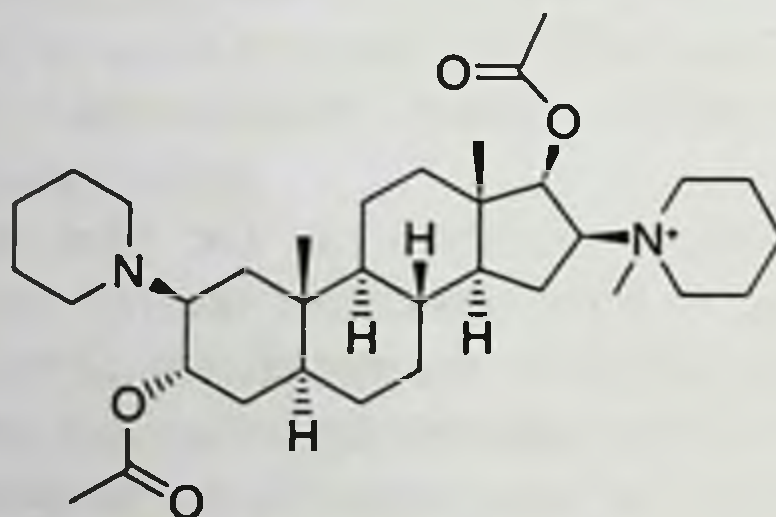


Fig. 2.40. 1-[(2β,3α,5α,16β,17β)-3,17-bis-(Acetyloxy)-2-(1-piperidinyl)androst-16-en-16-yl]-1-methylpiperidinium bromide

- ▶ **Aminosteroid.** Its structure is close to that of pipecuronium bromide, but it is a monoquaternary aminosteroid compound. The onset of action is 1.5–2.0 min following intravenous administration, the duration of action is 20–30 min. 25% recovery of neuromuscular transmission occurs in 25–40 min and 95% recovery occurs in 45–65 min with balanced anesthesia.
- ▶ Metabolized in the liver to form 5-hydroxyvecuronium. $T_{1/2}$: 4 min. 65% is excreted in the bile as inactive metabolites, 35% is excreted in the urine as unchanged drug.

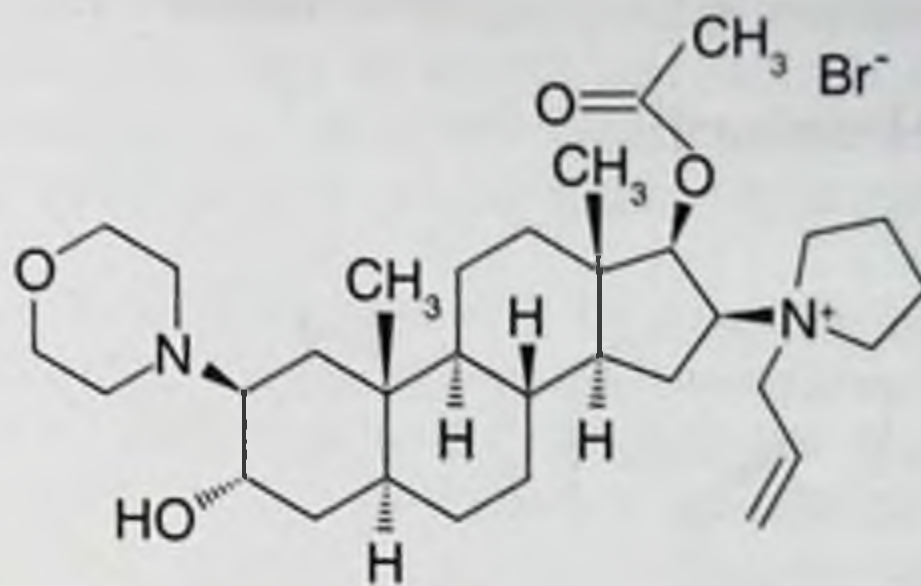
Rocuronium bromide (Esmeron®)

Fig. 2.41 1-[(2 β ,3 α ,5 α ,16 β ,17 β)-17-(Acetyloxy)-3-hydroxy-2-(4-morpholinyl)androstane-16-yl]-1-(2-propenyl)pyrrolidinium bromide

- ▶ Synthetic monoquaternary aminosteroid analog of vecuronium. Essentially does not affect histamine release. Crosses the placental barrier. The onset of action is 2 min, the duration of effect is 20 min in adults. 25% recovery of neuromuscular transmission occurs in 30–40 min and 95% recovery occurs in 50 min following administration with balanced anesthesia.
- ▶ Metabolized in the liver to form 17-deacetyl-rocuronium, which exhibits mild muscle relaxing activity. Eliminated with the bile (70%), urine (30%).

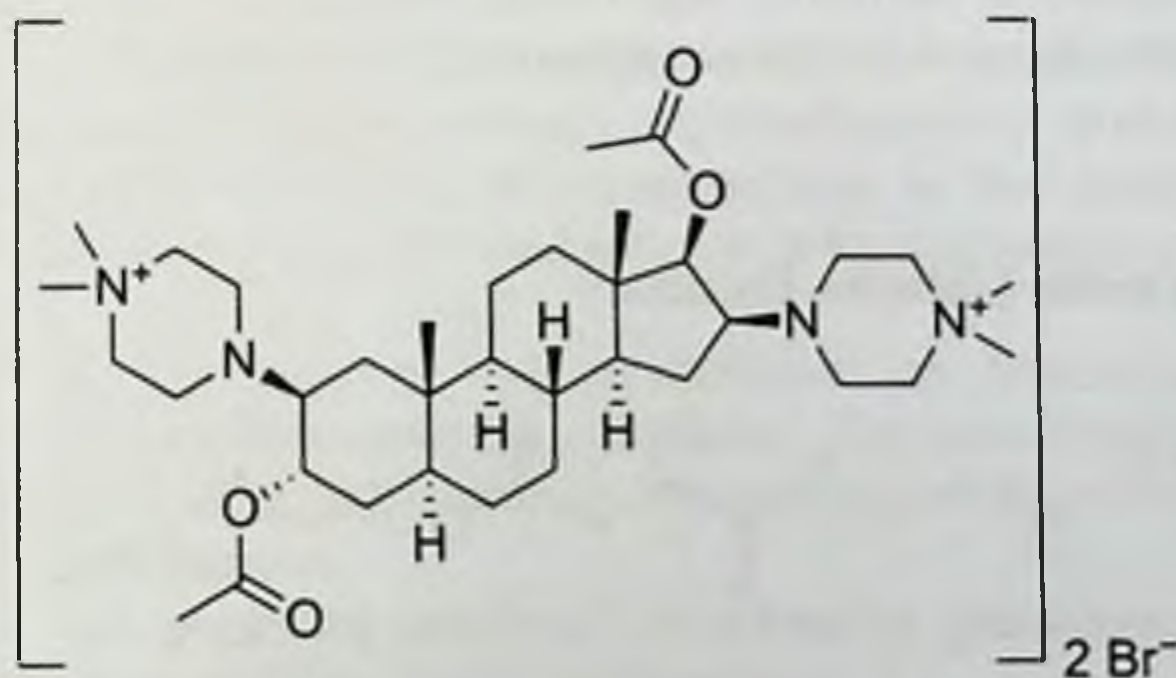
Pipecuronium bromide (Arduan®)

Fig. 2.42 2 β ,16 β -bis(4-Dimethyl-1-piperazino)-3 α ,17 β -diacetoxy-5 α -androstane dibromide

- ▶ Synthetic bisquaternary aminosteroid compound. Does not cause tachycardia. Crosses the placental barrier. Muscle relaxation occurs in 1 min, the peak effect occurs in 3.0–4.5 min and lasts 35–45 min. The therapeutic window for prolonged muscle paralysis is small.

- ▶ Insignificant amounts are metabolized in the liver. $T_{1/2}$: 1.5–2.0 hours, predominantly excreted in the urine (80%), the rest is excreted in the bile.

Pancuronium bromide (Pavulon®)

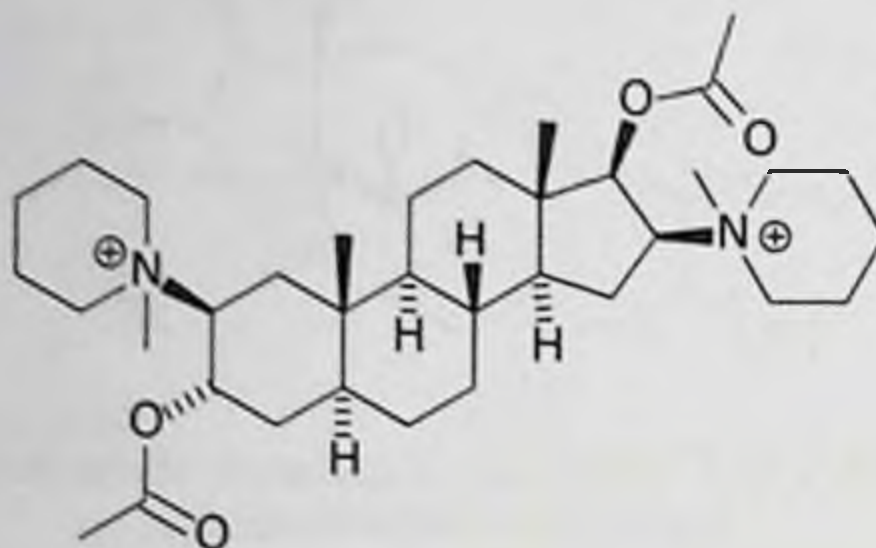


Fig. 2.43. 1,1'-(3 α ,17 β -Dioxy-5 α -androstane-2 β ,16 β -ylen)bis[1-methylpiperidinium] dibromidediacetate

- ▶ Bisquaternary ammonium compound of aminosteroid structure. Poorly penetrates the placenta. Blockade of neuromuscular conduction occurs in 2–3 min following intravenous administration, reaches its maximum in 3.5–4.0 min, and lasts 35–45 min. The therapeutic window for prolonged muscle paralysis is small. 25–50% recovery of spontaneous muscular activity occurs in 24 min, 75% recovery occurs in 33 min.
- ▶ A small portion undergoes biotransformation in the liver to form metabolites. Excreted mainly in the urine, with 11% excreted in the bile.
- ▶ This drug can be used during caesarean section procedures.

Depolarizing

Suxamethonium iodide (Dithylin-Darnitsa®)

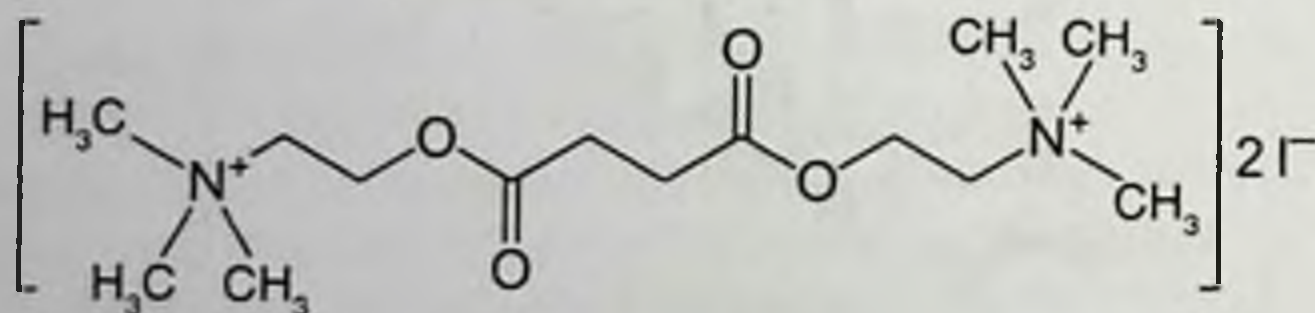


Fig. 2.44. 2,2'-[(1,4-Dioxo-1,4-butanediyl)bis(oxy)]bis[N,N,N-trimethylethanaminium iodide

- ▶ The chemical structure corresponds to a double ACh molecule (diacetylcholine). Crosses the placental barrier. The onset of action is 2–4 min following intramuscular administration and 54–60 seconds following intravenous administration; muscle relaxation reaches its maximum in 2–3 min, the duration of action is 5–10 min. The rapid onset of the effect and subsequent rapid muscle tone recovery creates controlled and manageable muscle relaxation. In case of genetic butyrylcholinesterase deficiency, the action can go on for 2–6 hours.

- ▶ Following administration, it undergoes biotransformation in the blood: rapid hydrolysis of pseudocholinesterase plasma to succinylmonocholine (mild muscle relaxing action), then to choline and succinic acid. $T_{1/2}$: 90 seconds (in individuals with normal pseudocholinesterase activity). Excreted in the urine (with 10% excreted as unchanged drug). For intramuscular, intravenous administration.

Mechanism of action: By interacting with N_m receptors, suxamethonium causes depolarization of the endplate. The process spreads to the adjacent membranes, causing generalized disorganized contraction of the myofibrils (i.e. blockade is preceded by muscle twitching, due to short-term facilitation of neuromuscular transmission). The membranes, still depolarized, do not respond to additional impulses, since repeated impulses related to repolarization of the endplate are required to maintain muscle tone.

As a result of depolarization, K^+ ions leave myocytes and their concentration in the extracellular fluid and plasma increases, which could induce cardiac arrest [particularly in patients with chronic heart failure (CHF) receiving cardiac glycosides and diuretics, as well as in patients with burns, injuries, rhabdomyolysis, spinal cord injury].

Therapeutic indications: short-duration surgeries (reduction of dislocations, repositioning of bone fragments, tracheal intubation, endoscopic procedures)

Side effects: postoperative muscle pain due to microtrauma from muscle twitches, respiratory depression, hyperkalemia, hypertension, bradycardia, hyperthermia, increased intracranial and intraocular pressure

Contraindications: hyperkalemia, glaucoma, plasma cholinesterase deficiency, bronchial asthma, pregnancy, myasthenia gravis, myotonia, acute liver failure

Supportive measures in case of overdose

If overdose with non-polarizing muscle relaxants occurs, the antidote is anticholinesterase drugs. While inhibiting acetylcholinesterase activity, these drugs prevent ACh hydrolysis, increasing the concentration in the synaptic cleft. ACh displaces the muscle relaxant from the bond with nAChRs, thus restoring neuromuscular transmission.

Sugammadex (Bridion*) can be used to eliminate the neuromuscular blockade caused by aminosteroids (vecuronium, rocuronium). The drug forms a complex with aminosteroids, encapsulating them within its structure, preventing interaction with the nAChRs of the skeletal muscles.

Overdose with non-polarizing muscle relaxants requires intravenous administration of fresh citrated blood containing butyrylcholinesterase.

Centrally acting muscle relaxants

Tolperisone (Mydocalm*)

- ▶ Exerts central antispasmodic action. Inhibits impulse conduction in primary afferent fibers and motor neurons, which results in blockade of spinal monosynaptic and polysynaptic reflexes, isolation of mediators by inhibition of Ca^{2+} ion flow into synapses. Reduces excitation conduction in the brainstem via the reticulospinal tract.

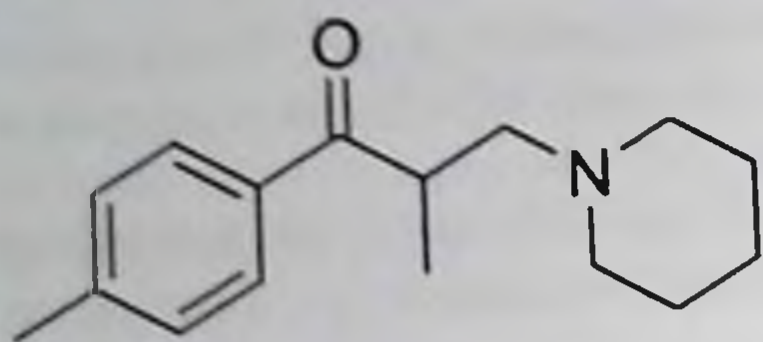


Fig. 2.45. 2-Methyl-1-(4-methylphenyl)-3-(1-piperidinyl)-1-propanone (as a hydrochloride)

► Metabolized in the liver. $T_{1/2}$: 1.5–2.5 hours. Excreted in the urine. For oral administration 2–3 times daily.

Therapeutic indications: diseases accompanied by increased skeletal muscle tone due to organic CNS disorders, musculoskeletal system disorders

Side effects: myasthenia gravis, headache, hypotension, nausea, vomiting

Contraindications: myasthenia gravis, pregnancy, breastfeeding

Anticholinergics

Trihexyphenidyl (Cyclodol*), biperiden (Akineton*), triperiden (Norakin®).

3. DRUGS AFFECTING ADRENERGIC SYNAPSES

At the beginning of the 20th century, J. Langley, a British physiologist who theorized that there are chemical receptors participating in the effects of adrenaline, nicotine, and curare, described a series of autonomic nerve pathways extending from the CNS, their anatomical and functional features, and divided autonomic nerves into sympathetic and parasympathetic. In 1905, T. Elliott (Langley's student at Cambridge) found that the adrenal hormone adrenaline produces effects similar to those caused by irritation of the sympathetic nerves, suggested that an adrenaline-like substance acts as a mediator of the sympathetic system. In 1910, H. Dale, an English physiologist, established a link between the chemical structure and the pharmacological action of adrenergic agonists. In 1946, U. Euler, a Swedish physiologist and pharmacologist, discovered the neuromodulatory role of noradrenaline.

Basic anatomy and physiology of the sympathetic nervous system

Adrenergic neurons are located in the CNS (locus coeruleus, pons, medulla oblongata) and in the sympathetic ganglia (Fig. 3.1).

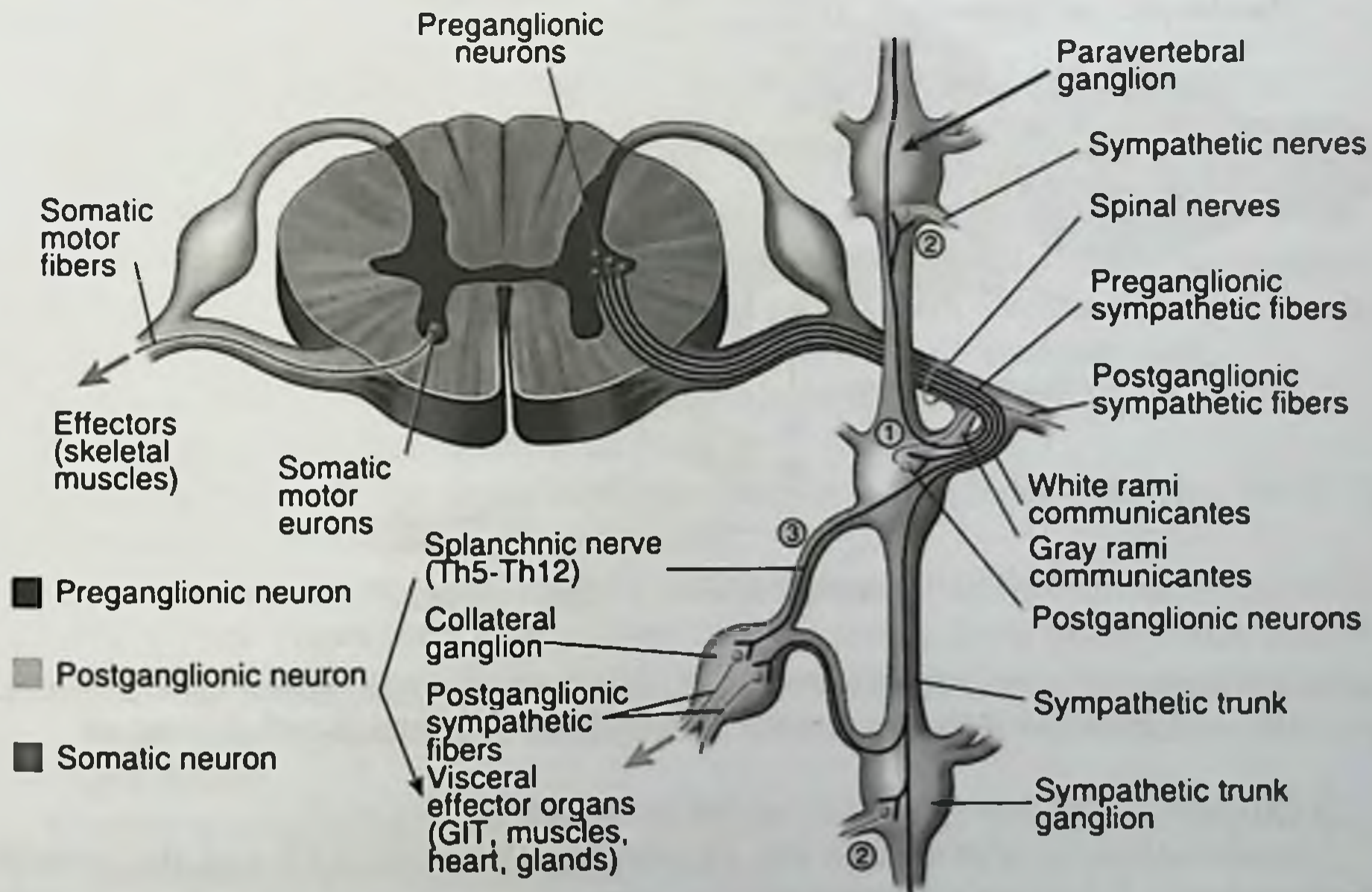


Fig. 3.1. Sympathetic autonomic nervous system (Kenneth S.S., 2021)

Peripheral adrenergic synapses are formed by varicosities in the branches of postganglionic sympathetic fibers. Noradrenaline is the main mediator of peripheral adrenergic synapses (Fig. 3.2).

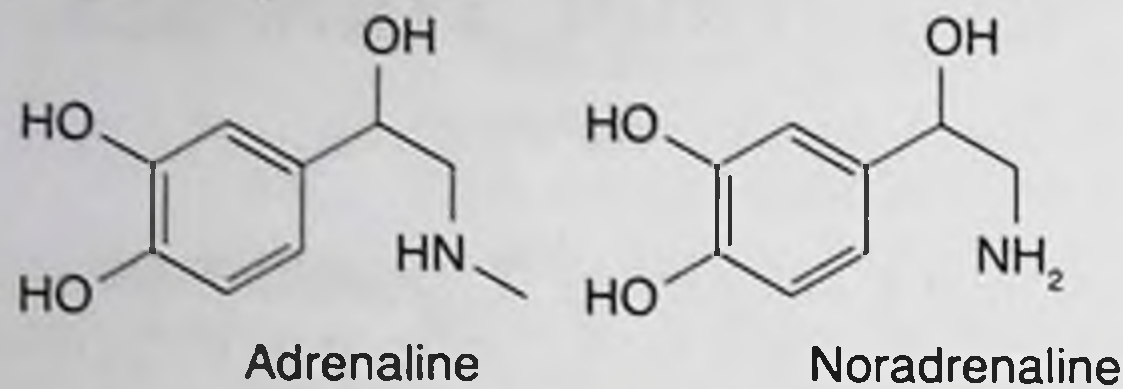


Fig. 3.2. Chemical structure of adrenaline and noradrenaline

Adrenergic synapse functions

1. Biosynthesis of noradrenaline:

Noradrenaline is synthesized from tyrosine. The conversion of phenylalanine to tyrosine is a non-specific process that occurs in the liver. Tyrosine enters adrenergic terminals by active transport. Tyrosine is converted to dihydroxyphenylalanine in the cytoplasm; this reaction is catalyzed by tyrosine hydroxylase. Dihydroxyphenylalanine is then converted to dopamine, transported to vesicles by active transport and converted to noradrenaline inside the synaptic vesicles (Fig. 3.3, 3.4).

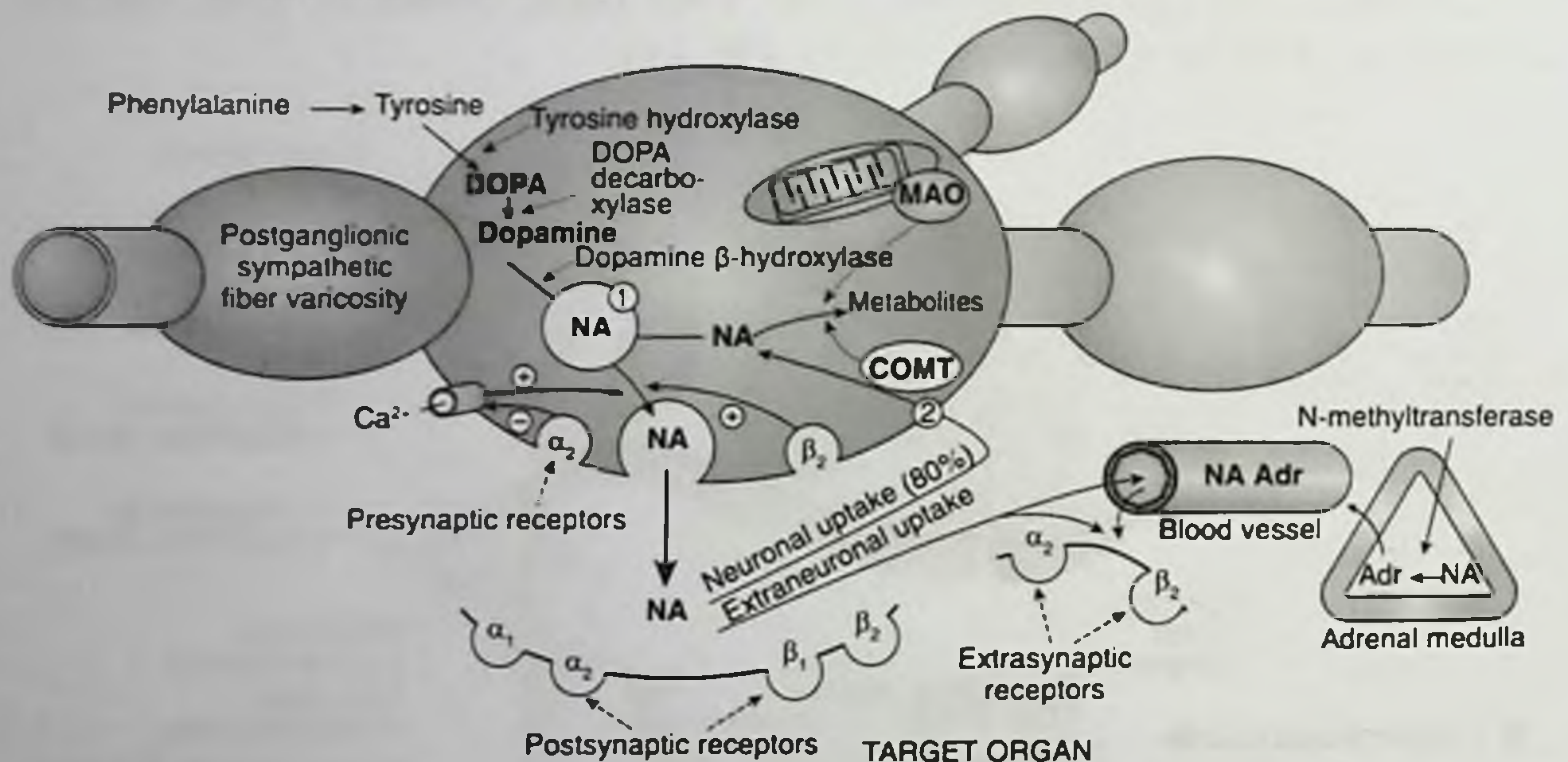


Fig 3.3. Adrenergic synapse (Alyautdin R.N. et al., 2020) DOPA — dihydroxyphenylalanine; Adr — adrenaline; NA — noradrenaline; MAO — monoamine oxidase; COMT — catechol-O-methyltransferase

2. Noradrenaline deposition in vesicles (granules):

Noradrenaline is deposited in the vesicles together with ATP and the protein chromogranin. Enzymes and modulating neuropeptides (enkephalins, neuropeptide Y) were also discovered in the granules.

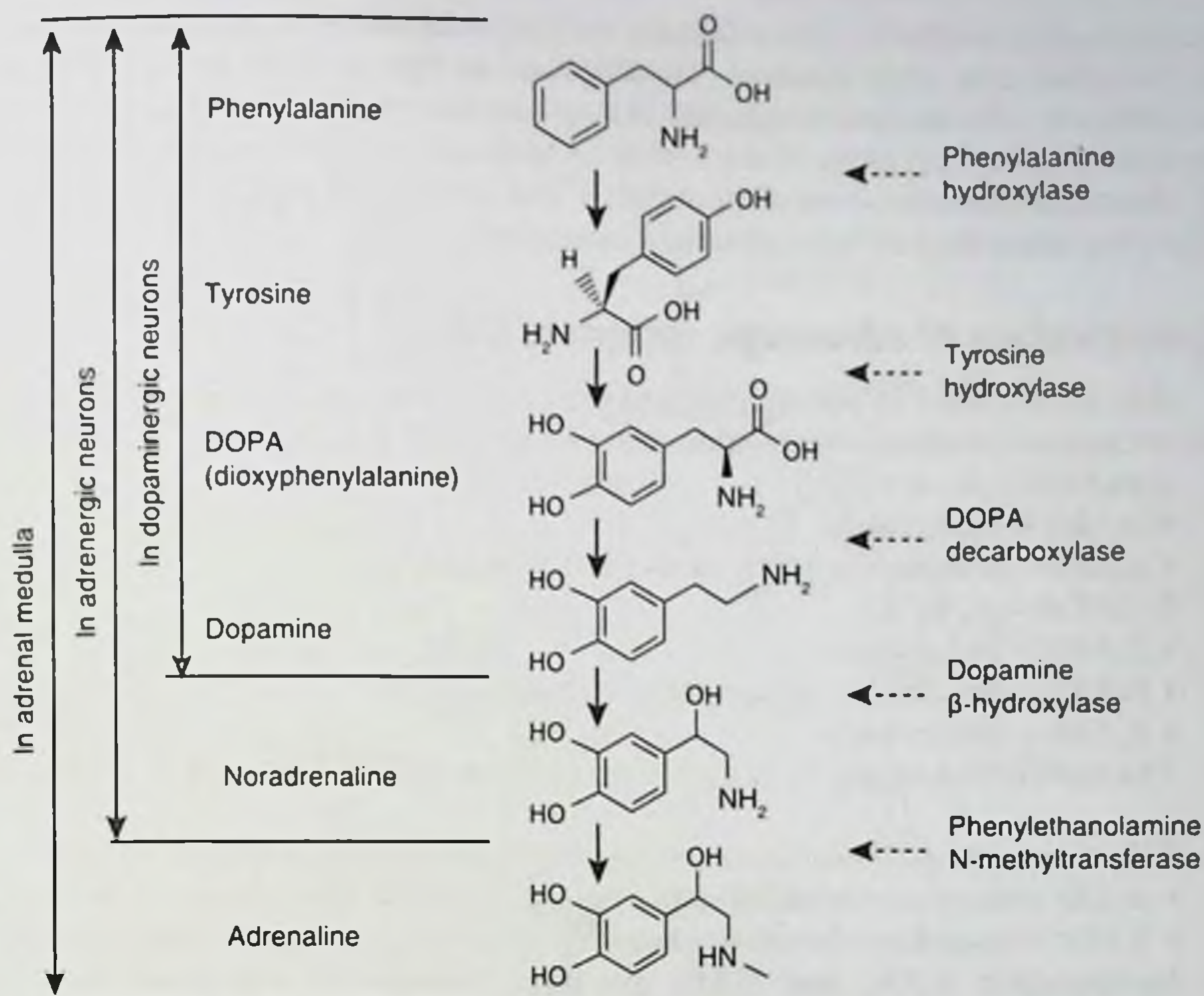


Fig. 3.4. Biosynthesis of dopamine, noradrenaline, and adrenaline (Kharkevich D.A., 2021)

3. Release of mediator into synaptic cleft:

The presynaptic membrane is depolarized by a nerve impulse, causing voltage-gated calcium channels to open and Ca^{2+} ions enter through them into varicosities: the concentration of Ca^{2+} ions in the varicosity cytoplasm increases, which results in vesicle exocytosis and release of noradrenaline into the synaptic cleft.

4. Interaction between noradrenaline and adrenergic receptors

5. Enzymatic mediator inactivation

After dissociation of noradrenaline–receptor complexes, the mediator is inactivated through a number of mechanisms:

- ▶ neuronal uptake (uptake-1) — 80%, active transport first through the presynaptic membrane (associated with release of Na^+ ions), then through the granule membrane under the influence of ATP-dependent proton translocase (when one molecule of noradrenaline enters the granules, two protons are released into the cytoplasm)
- ▶ extraneuronal uptake (uptake-2) — 10%, by neuroglia, fibroblasts, myocardium, endothelium, and vascular smooth muscle
- ▶ enzymatic inactivation — 10% noradrenaline.

Catecholamine inactivation enzymes are monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). MAO, localized in the outer mitochondrial membrane and granules, catalyzes the oxidative deamination of catecholamines to

form biogenic aldehydes. The aldehydes are then oxidized by nicotinamide adenine dinucleotide-dependent aldehyde dehydrogenase to form acids or they are reduced by aldehyde reductase to form glycols. The cytoplasmic enzyme COMT catalyzes the transfer of the methyl group to the 3-position hydroxyl (only if 4-position is present). S-adenosylmethionine serves as the methyl donor. Methylated products are 200–2000 times less active than noradrenaline and adrenaline.

Classification of adrenergic receptors (ARs)

ARs are localized in postsynaptic and presynaptic membranes and in organs that do not receive adrenergic innervation (extrasynaptically) (Fig. 3.5).

α (α ARs) — α_1 , α_2 :

- ▶ α_1 ARs — postsynaptic
- ▶ α_2 ARs — presynaptic, postsynaptic, and extrasynaptic

β (β ARs) — β_1 , β_2 , β_3 :

- ▶ β_1 ARs — postsynaptic
- ▶ β_2 ARs — presynaptic, postsynaptic, and extrasynaptic
- ▶ β_3 ARs — postsynaptic

The main effects caused by stimulation of various ARs are presented in Table 3.1.

Effects caused by stimulation of presynaptic α_2 ARs and β_2 ARs (Fig. 3.5):

- ▶ α_2 ARs: reduced noradrenaline release from varicosities (negative feedback principle)
- ▶ β_2 ARs: increased noradrenaline release from varicosities (positive feedback principle)

Extrasynaptic α_2 ARs and β_2 ARs are more sensitive to adrenaline than to noradrenaline, i.e. more sensitive to humoral factors of regulation than to neuronal ones; since they are located in vascular smooth muscle cells, their excitation results in vasoconstriction.

Mechanisms of adrenergic receptor stimulation

When evaluating the interaction of substances with membrane receptors transmitting the signal from the outer membrane surface to the inner one, the intermediate links that connect the receptor with the effector must also be considered. The most important components of this system are G proteins, a group of enzymes (adenylate cyclase, guanylate cyclase, phospholipase C), and secondary transporters (cAMP, cGMP, inositol triphosphate, diacylglycerol, Ca^{2+}).

Increased production of secondary mediators results in activation of protein kinases that cause intracellular phosphorylation of important regulatory proteins and various other effects (Fig. 3.6).

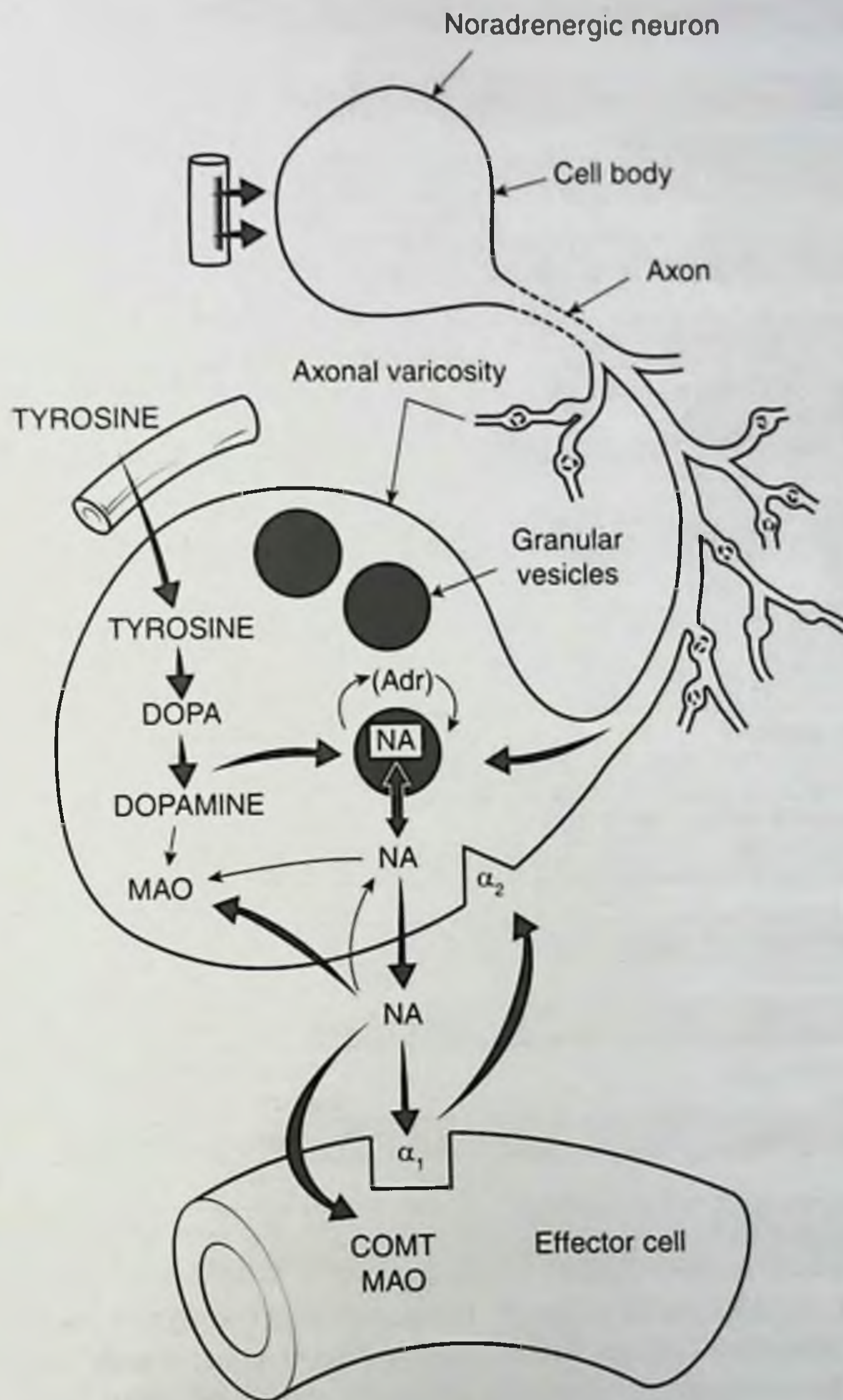


Fig. 3.5. Adrenergic synapse (vascular smooth muscle cell used as an example) (Tetzlaff J.E., 2010). Stimulation of presynaptic α_2 receptors by previously released noradrenaline results in inhibition of additional noradrenaline release from the sympathetic neuron. Stimulation of postsynaptic α_1 receptors results in smooth muscle contraction. DOPA — dihydroxyphenylalanine; Adr — adrenaline; NA — noradrenaline; MAO — monoamine oxidase; COMT — catechol-O-methyltransferase

Table 3.1. Preferential localization of adrenergic receptors (AR) and effects caused by their stimulation

Preferential localization	Effects caused by stimulation
α_1 AR	
Blood vessels (skin, mucous membranes, intestines, kidneys)	Constriction
Radial muscle of iris (pupillary dilator)	Contraction (mydriasis)
GI and bladder sphincters	Contraction
Myometrium	Contraction
Splenic trabeculae	Contraction
Prostate	Smooth muscle contraction
α_2 AR	
CNS (vasomotor center, solitary nuclei, vagal nucleus)	Depression (sedation, analgesia, hypotension, bradycardia)
Platelets	Stimulation of aggregation
Smooth muscles of the GI tract	Relaxation
Pancreas	Reduced insulin secretion
β_1 AR	
Cardiomyocytes	Increased cardiac contractile force, heart rate, stroke volume and cardiac output, oxygen consumption
Juxtaglomerular apparatus	Increased renin release
β_2 AR	
Blood vessels (skeletal muscles, chest organs)	Dilation
Bronchi	Decreased tone
Myometrium	Decreased tone
Smooth muscles of the GI tract, urinary tract	Decreased tone
Liver	Increased glycogenolysis, gluconeogenesis
Skeletal muscles	Increased contractile activity
Thyroid	Increased secretion of iodine-containing hormones
Juxtaglomerular apparatus	Increased renin release
β_3 AR	
Adipose tissue	Increased lipolysis and thermogenesis of adipose tissue

- ▶ α_2 , β_1 , β_2 , β_3 ARs are functionally interconnected through G proteins with the enzyme adenylate cyclase, which is located in the effector cells' membrane and triggers the synthesis of 3',5'-cyclic adenosine monophosphate.

- ▶ α_1 ARs are functionally interconnected through G proteins with phospholipase C.

Modes of pharmacological action on excitation transmission in adrenergic synapses: noradrenaline synthesis, deposition, enzymatic noradrenaline inactivation, noradrenaline release from terminals, reuptake of noradrenaline, direct action on ARs.

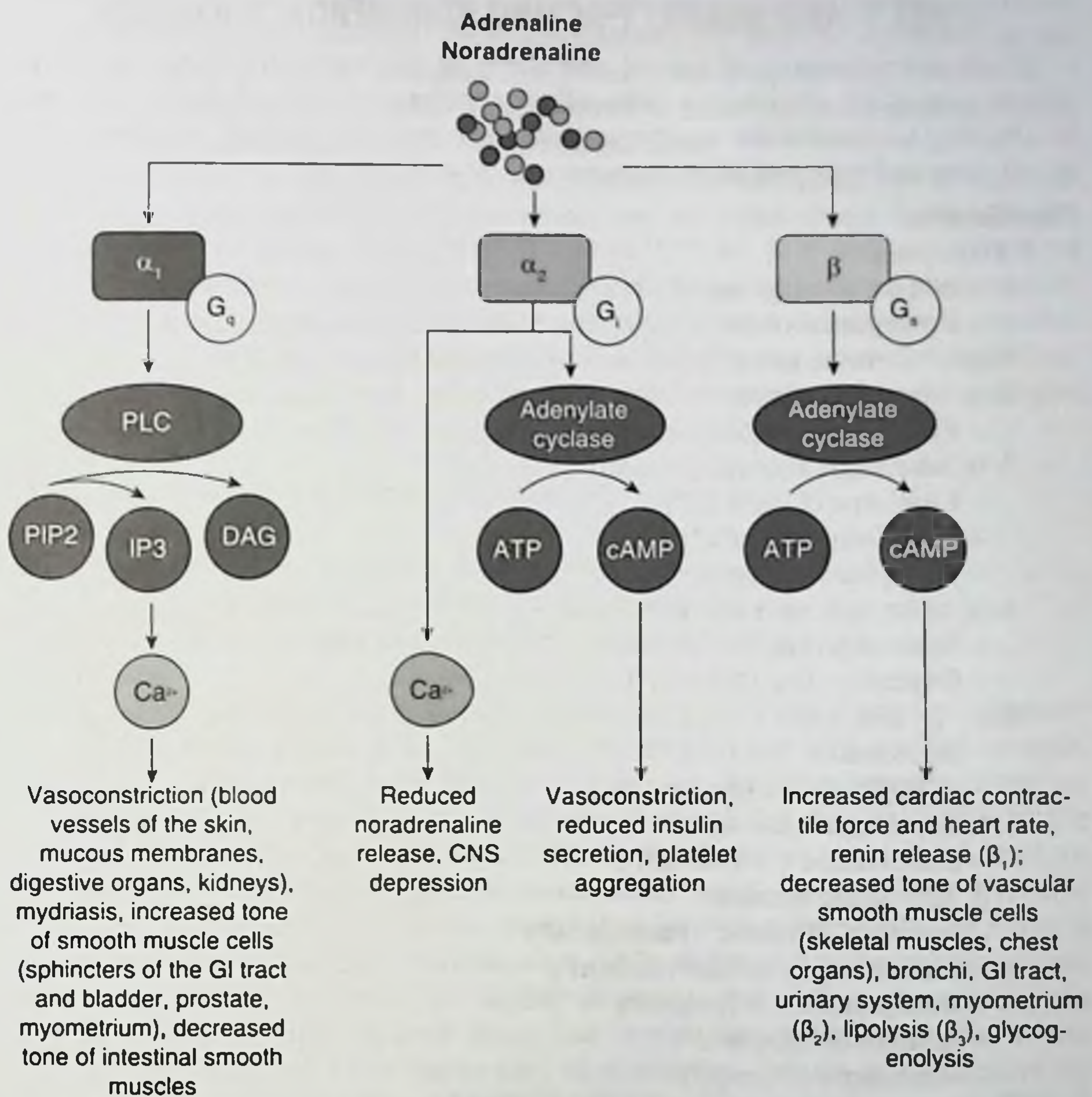


Fig. 3.6. Receptor mechanism of action of catecholamines (original image taken from https://en.wikipedia.org/wiki/Adrenergic_receptor)

Grouping of drugs affecting adrenergic synapses

1. Acting directly on ARs (direct-acting)
 - Adrenergic agonists (AAs)
 - Adrenergic blockers (ABs)
2. Presynaptic (indirect-acting)
 - Sympathomimetics
 - Sympatholytics

DIRECT- AND INDIRECT-ACTING ADRENERGIC AGONISTS

These are substances of natural and synthetic origin that reproduce the effects of endogenous catecholamines (adrenaline, noradrenaline) in animals and humans by affecting adrenoactive structures (ARs, structural cell elements involved in the metabolism and transport of endogenous catecholamines, etc.).

Classification

I. Direct-acting

1. α and β adrenergic agonists

– Epinephrine (Adrenaline hydrochloride-Vial[®]) (α_1 , α_2 and β_1 , β_2)

Norepinephrine (noradrenaline hydrotartrate[®]) (α_1 , α_2 and β_1)

2. α_1 adrenergic agonists

– Phenylephrine (Mesaton[®])

3. α_2 adrenergic agonists (central)

– Clonidine (Clonidine[®])

– Guanfacine (Estulic[®])

– Methyldopa (Dopegyt[®])

4. α_2 adrenergic agonists (peripheral)

– Xylometazoline (Galazolin[®])

– Oxymetazoline (Nasivin[®]).

5. β_1 , β_2 adrenergic agonists

– Isoprenaline (Isadrine[®])

– Orciprenaline (Asthmopent[®])

6. β_1 adrenergic agonists

– Dobutamine (Dobutrex[®])

7. β_2 adrenergic agonists

– Fenoterol (Berotec[®], Partusisten[®])

– Salbutamol (Ventolin[®], Salgim[®])

– Hexoprenaline (Gynipral[®])

– Salmeterol (Serevent[®])

– Formoterol (Foradil[®])

II. Indirect-acting (sympathomimetics)

– Ephedrine (Ephedrine hydrochloride[®])

Specifics of individual products

Direct-acting AAs

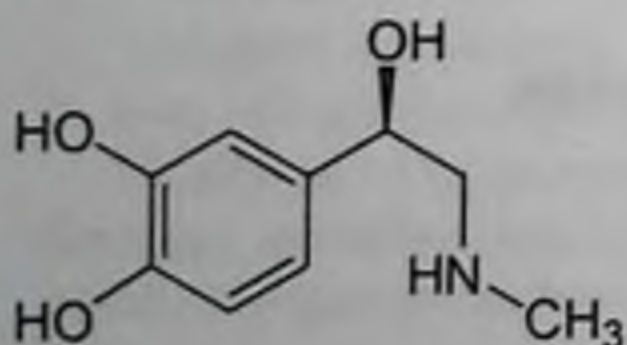


Fig. 3.7. (R)-4-[1-Hydroxy-2-(methylamino)ethyl]-1,2-benzenediol (as a hydrochloride or tartrate)

Epinephrine (Adrenaline hydrochloride-Vial[®])

► Has a direct stimulatory effect on α_1 , α_2 , β_1 , β_2 ARs. Synthesized or extracted from the adrenal glands of slaughtered cattle. Phenylalkylamine derivative. Its chemical structure is close to that of biogenic catecholamine. Predominantly excites β ARs at low doses and concentrations (at rate $< 0.01 \mu\text{g/kg}$ per minute, lowers BP due to dilation of skeletal muscle blood vessels; at $0.04\text{--}0.10 \mu\text{g/kg}$ per minute, increases heart

rate and cardiac contractile force, stroke volume and cardiac output, decreases total peripheral resistance [TPR]), acts on α ARs and β ARs at high doses (at rate $> 0.2 \mu\text{g/kg}$ per minute, narrows blood vessels, increases BP and TPR; at rate $> 0.3 \mu\text{g/kg}$ per minute, reduces renal blood flow, blood supply to internal organs, GI tone and motility). Poorly penetrates the BBB.

- ▶ Short-acting (about 5 min for intravenous administration, < 30 min for subcutaneous administration) due to its rapid neuronal uptake and enzymatic cleavage with involvement of COMT and partly MAO ($T_{1/2}$: 1–2 min). Excreted in the urine mainly as metabolites: vanillylmandelic acid, sulfates, glucuronides, and as unchanged drug in small amounts. For intravenous, intramuscular, subcutaneous, topical administration. Epifrin eye drops (abroad). Dipivefrine eye drops (prodrug: easily penetrates the anterior chamber where it undergoes enzymatic hydrolysis to form adrenaline).

Main clinically significant pharmacological effects

Local

- ▶ Vasospasm of the skin and mucous membranes
- ▶ Pupil dilation (contraction of the iris dilator muscle)
- ▶ IOP reduction (decreased production of intraocular fluid)

Systemic

- ▶ Cardiostimulatory: tachycardia, increased AP conduction, increased contractions, resulting in increased stroke volume and cardiac output. The systole becomes more intense and shorter. Reduces energy conversion efficiency by increasing cardiac oxygen demand. Intense oxidation in the myocardium of free fatty acids entering the heart as a result of lipolysis results in increased oxygen demand. Fatty acids, as well as adrenaline itself, decouple oxidation and phosphorylation in mitochondria. Energy is released as heat, without concomitant ATP synthesis. The heart's functional and metabolic reserves are rapidly depleted. Adrenaline, increasing the automatism of the Purkinje fibers and ventricular myocardium, facilitates the formation of heterotopic foci of excitation, which is manifested by ventricular extrasystoles and even fibrillation. The arrhythmogenic effect is especially prominent in myocardial ischemia, hypertension, thyrotoxicosis, cardiac glycoside poisoning, phthorothane anesthesia. Adrenaline, by causing arterial and venous constriction, increases preload (volume that fills the heart from venous return) and afterload (pressure that the heart must work against peripheral vascular resistance).
- ▶ Increases mean arterial pressure (MAP). When given as rapid intravenous bolus injection, it changes BP in four phases:
 - phase 1: BP increases due to increased cardiac output
 - phase 2: BP increases more slowly, along with short-term reflex bradycardia
 - phase 3: BP reaches peak due to increased vasospasm and stimulation of renin secretion
 - phase 4: BP decreases due to skeletal muscle vasodilation.
- ▶ Dilates coronary vessels of the heart muscle. The improved coronary blood flow is also caused by an increase in blood pressure in the aorta and a response to

increased myocardial oxygen demand. By contracting precapillary sphincters, it reduces blood supply to internal organs, switches bioenergetics to anaerobic oxidation, causes hypoxia and metabolic acidosis.

- Dilates the bronchi (in bronchial obstructive syndrome, in addition to dilation of the bronchi, eliminates mucosal edema), relaxes the urinary bladder; decreases GI tone and peristalsis, causes spasm of the sphincters of the GI tract and urinary bladder, ureters, contraction of the splenic trabeculae.
- Induces hyperglycemia due to the stimulation of glycogenolysis and gluconeogenesis in the liver, glycogenolysis in the skeletal muscles, inhibits insulin secretion. Increases lipolysis with resulting increase in circulating free fatty acid levels.

Therapeutic indications: cardiac arrest, AV block, relief of bronchospasm, anaphylactic shock, hypoglycemic coma, hypotension, glaucoma (open-angle type), in combination with local anesthetics (bupivacaine, lidocaine, articaine, etc.), rhinitis (in drops and ointments), to stop local bleeding

Side effects: tachyarrhythmias (ventricular extrasystoles, fibrillation), myocardial ischemia; pulmonary edema (at high doses), restlessness, tremor, headache; dyspepsia; topical administration: eye burning and redness, lacrimation, periorbital hyperpigmentation

Contraindications: hypertension, CHF, myocardial infarction, aneurysm; thyrotoxicosis, diabetes mellitus, closed-angle glaucoma, phthorothane anesthesia, pregnancy

Norepinephrine (noradrenaline hydrotartrate^o)

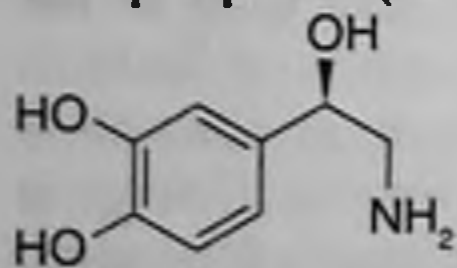


Fig. 3.8. (R)-4-(2-Amino-1-hydroxyethyl)-1,2-benzenediol (as a hydrochloride or tartrate)

- α_1 , α_2 , β_1 AA; phenylalkylamine derivative, catecholamine. In contrast to adrenaline, it predominantly affects vascular α_1 ARs and produces a more potent but short-lived (a few minutes, $T_{1/2}$: 1–2 min) pressor effect (5–10 times stronger), which results in increased systolic and diastolic BP, TPR. There is no final hypotensive phase when it is administered as IV infusion. The action on β_1 ARs results in increased stroke volume, without changing the cardiac output, decreased HR due to reflex effects from vascular mechanoreceptors in response to rapid onset hypertension.

- Metabolized in the liver, kidneys, and plasma, with MAO and COMT involvement, to form inactive metabolites. Excreted in the urine. Administered as IV drip.

Therapeutic indications: acute hypotonia

Side effects: subcutaneous and intramuscular administration cause severe vasospasm that could result in ischemia and tissue necrosis, bradycardia, tremor, headache, dizziness

Contraindications: phthorothane anesthesia, heart failure, bradycardia, AV block, severely marked atherosclerosis, pregnancy

Phenylephrine (Mesaton^o)

- ▶ α_1 AA. Synthetic drug, phenylalkylamine derivative. It is not a catecholamine because it contains only one hydroxyl group in the aromatic nucleus. Its effects on the vascular system are similar to those of noradrenaline but weaker and longer. Induces reflex bradycardia. The onset of action following intravenous administration is immediate, the duration of action is up to 20 min. The onset of action following intramuscular administration is 10–15 min, the duration of action is 1–2 hours.

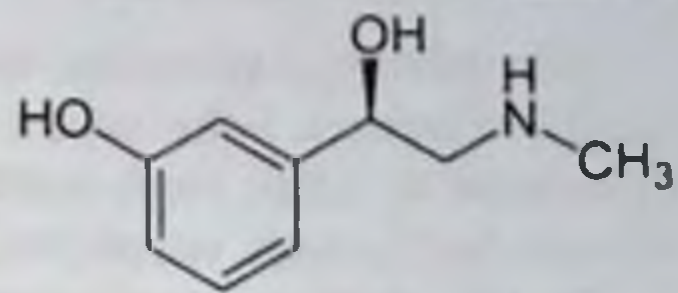


Fig. 3.9. (R)-3-Hydroxy- α -[(methylamino)methyl] benzenemethanol (as a hydrochloride)

- ▶ Metabolized in the liver (without COMT involvement). $T_{1/2}$: about 3 hours. Excreted as metabolites in the urine. For intravenous, intramuscular, subcutaneous, topical [nasal drops (in Vibrocil combination drug), Iridrin eye drops] administration.

Pharmacological effects: Vasoconstrictor effect: increases BP (mostly systolic BP), mydriasis (4–6 hours), reduces IOP; decongestant (when used topically)

Therapeutic indications: acute hypotonia (drug of choice), vasomotor rhinitis, conjunctivitis, iritis, iridocyclitis, open-angle glaucoma, pupil dilation (for diagnostic and therapeutic purposes); combination with local anesthetics (adrenaline alternative)

Side effects: bradycardia, headache, fear, restlessness, insomnia, tremor, paresthesia

Contraindications: bradycardia, hypertension, decompensated heart failure, coronary heart disease, marked atherosclerosis, thyrotoxicosis, closed-angle glaucoma

Clonidine (Clonidine*)

- ▶ Central α_2 AA, imidazoline derivative. Also stimulates I₁ (imidazoline) receptors. Crosses the BBB, placental barrier, excreted into breast milk.
- ▶ Metabolized in the liver. $T_{1/2}$: 12–16 hours. 40–60% is excreted in the urine (50% as unchanged drug), the remaining portion is excreted in the bile. For subcutaneous, intramuscular, intravenous, sublingual, topical (as eye drops, in Proxofeline combination drug; Isoglacon abroad) administration.

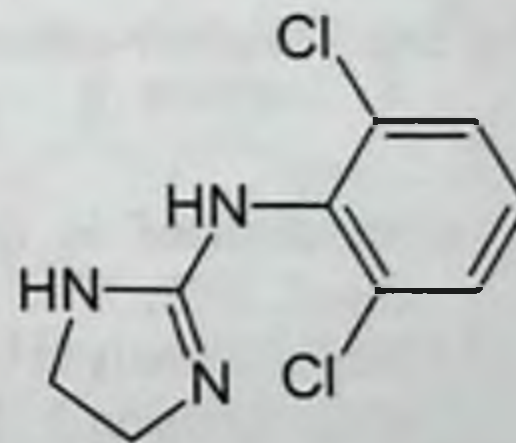


Fig. 3.10. 2,6-Dichloro-N-2-imidazolidinylidenbenzamine (as a hydrochloride)

Pharmacological effects: Primary effect: antihypertensive (the onset of action following oral administration is 30–60 min, the maximum effect occurs in 2–4 hours, the duration of action is 6–12 hours). Secondary effects: sedative, anxiolytic, analgesic, potentiating, alleviation of withdrawal, IOP reduction.

Mechanism of antihypertensive action: Excitation of postsynaptic α_2 ARs (neurons of the solitary tract nuclei in the medulla oblongata) and stimulation of I₁ receptors decrease the activity of the vasomotor center, decrease the sympathetic tone, resulting in decreased TPR, BP, HR.

Therapeutic indications: management of hypertensive crisis (sublingual, slow intravenous, intramuscular, subcutaneous administration), open-angle glaucoma, alcohol and opiate withdrawal

Side effects: hypotonia, orthostatic hypotension (parenteral administration), rapid intravenous bolus causes an initially short increase in BP (due to stimulation of vascular α_1 ARs); bradycardia, somnolence, dry mouth (xerostomia), obstipation, erectile dysfunction, edema, withdrawal syndrome

Contraindications: cardiogenic shock, hypotension, 2nd-3rd degree AV block, sick sinus syndrome, pregnancy, breastfeeding, age below 18 years. Restrictions related to the patient's occupation

Guanfacine (Estulic⁺)

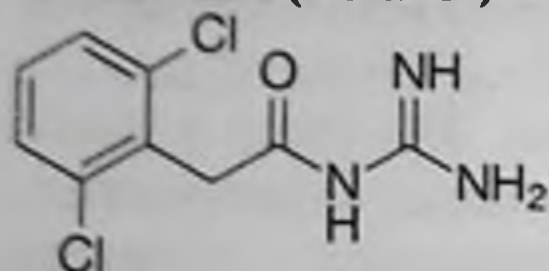


Fig. 3.11.

N-(Aminoiminomethyl)-2,6-dichlorobenzeneacetamide (as a monohydrochloride)

- ▶ α_2 AA, phenylacetyl-guanidine derivative. Selectively stimulates α_2 ARs of the CNS. The undesirable effects of sedation and xerostomia are less prominent. Long-acting.
- ▶ Bioavailability: about 80%. $T_{1/2}$: 14 hours. Metabolized in the liver. Excreted in the urine, with about 40% excreted as unchanged drug. For oral administration once daily.

Therapeutic indications: Hypertension

Other side effects and contraindications: see "Clonidine"

Methyldopa (Dopegyt⁺)

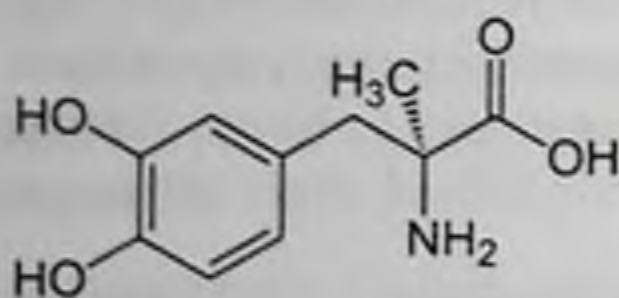


Fig. 3.12. 33-Hydroxy- α -methyl-L-tyrosine

- ▶ Stimulates α_2 ARs of the CNS, phenylalkylamine derivative. Prodrug whose biotransformation starts in the GI mucosa (to form orthosulfonated derivatives). Penetrates the CNS, where about 10% of the dose is decarboxylated to α -methyldopamine and then to α -methylnoradrenaline (active metabolite). Maximum BP reduction occurs in 4–6 hours and lasts 1–2 days.

- ▶ Metabolized in the liver to form conjugates with sulfates. Bioavailability: about 50%, $T_{1/2}$: 2–8 hours, excreted in the urine (approximately 70%), predominantly as unchanged drug and as mono-O-sulfate conjugates. For oral administration 2–3 times daily.

Therapeutic indications: Hypertension (including during pregnancy)

Side effects: headache, generalized weakness, dizziness, hepatotoxicity

Contraindications: acute hepatitis, liver cirrhosis, depression, acute myocardial infarction, pheochromocytoma

Tizanidine (Sirdalud⁺)

- ▶ Imidazoline derivative. Has the properties of a central muscle relaxant, also producing a central, moderately pronounced analgesic effect. Antihypertensive activity is 10–50 times inferior to clonidine.
- ▶ Bioavailability: about 34%. Metabolized in the liver (about 95%) to form inactive metabolites. $T_{1/2}$: 2–4 hours. Excreted in the urine as metabolites, with about 4.5% excreted as unchanged substance. For oral administration 3 times daily.

Mechanism of action: Stimulates presynaptic α_2 ARs in the spinal cord, reducing the release of excitatory amino acids, which stimulate N-methyl-D-aspartate receptors,

from nerve endings. Polysynaptic transmission of excitation is suppressed at interneurons, muscle tone decreases.

Therapeutic indications: painful muscle spasms associated with static and functional disorders of the spine, following surgery (for herniated intervertebral disc or hip osteoarthritis); skeletal muscle spasticity in neurological conditions (multiple sclerosis, chronic myelopathy, degenerative spinal cord disease, sequelae of cerebrovascular accidents and cerebral palsy)

Side effects: bradycardia, hypotonia, dizziness, somnolence, dyspepsia, elevated liver transaminases, dry mouth, muscle weakness

Contraindications: marked hepatic dysfunction, history of allergic reactions

Kylometazoline (Galazolin*)

- ▶ Peripheral α_2 AA, decongestant, imidazoline derivative. Has a local vasoconstrictor effect, essentially not absorbed. Longer duration of action than Mesaton (up to 8–10 hours).

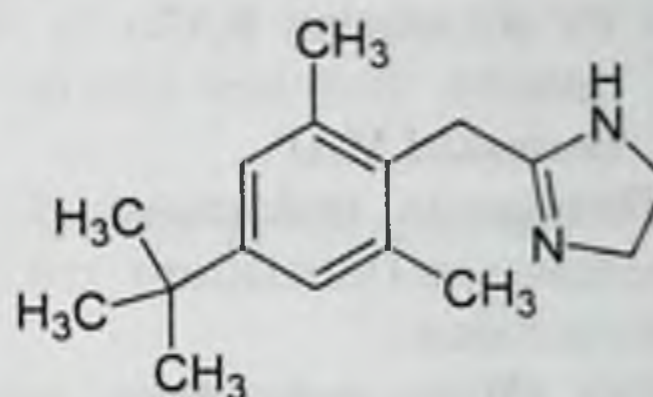


Fig. 3.14. 2-[[4-(1,1-Dimethylethyl)-2,6-dimethylphenyl]methyl]-4,5-dihydro-1H-imidazole (as a hydrochloride)

Oxymetazoline (Nasivin*)

- ▶ Peripheral α_2 AA, decongestant, imidazoline derivative. Duration of action: up to 12 hours.

For topical administration.

Therapeutic indications: acute rhinitis, laryngitis, sinusitis, maxillary sinusitis, otitis media (combination therapy), eustachitis, hay fever, allergic conjunctivitis (for oxymetazoline)

Side effects: dryness and burning sensation in the nasal mucosa, dry mouth or throat, sneezing, rebound swelling of the nasal mucosa (increased nasal discharge or nasal congestion). Long-term topical administration can cause atrophy of the nasal mucosa; should not be used for more than 5 days (to prevent tolerance).

Contraindications: hypertension, tachycardia, marked atherosclerosis, glaucoma, atrophic rhinitis, hyperthyroidism, pregnancy

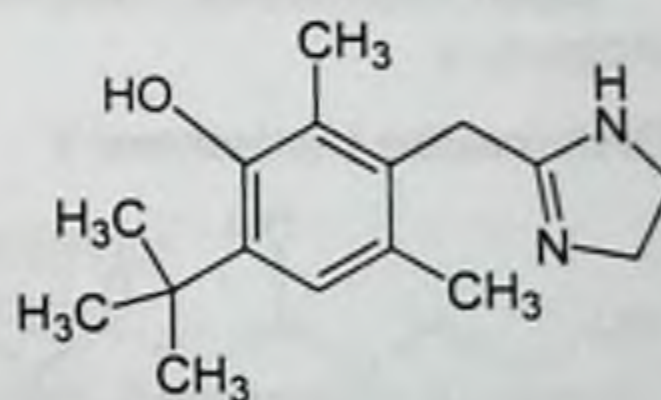


Fig. 3.15. 3-[(4,5-Dihydro-1H-imidazol-2-yl)methyl]-6-(1,1-dimethylethyl)-2,4-dimethylphenol (as a hydrochloride)

Isoprenaline (Isadrine®)

- ▶ First β_1 , β_2 AA. Synthetic drug, phenylalkylamine derivative. Its structure is different from that of adrenaline since an isopropyl radical is present in the amino group instead of a methyl radical.
- ▶ Metabolized with COMT and phenol sulfotransferase involvement. Considerable first-pass metabolism significantly reduces oral bioavailability. $T_{1/2}$: 2 hours. For sublingual, inhalation, intravenous administration.

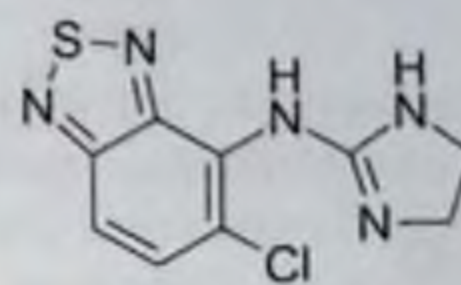


Fig. 3.13. 5-Chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-benzo[c][1,2,5]thiadiazol-4-amine (as a hydrochloride)

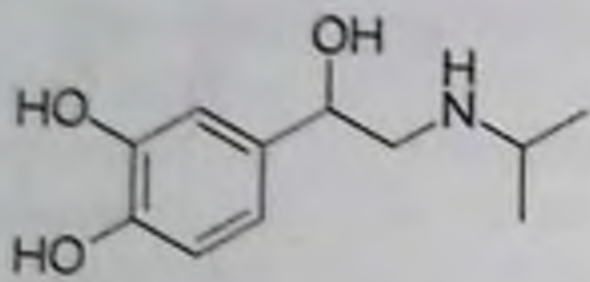


Fig. 3.16. 44-[1-Hydroxy-2-[(1-methylethyl)amino]ethyl]-1,2-benzenediol (as a hydrochloride, sulfate, or tartrate)

Pharmacological effects and their mechanisms

- ▶ Excitation of β_2 ARs in the bronchi is the primary effect, which is superior to the other effects when administered by inhalation. It stimulates secretion of Na^+ ions and water into their lumen, increases the drainage function of the ciliated epithelium, increases the production of alveolar surfactant. Exerts bronchodilator action within 1–2 min following inhalation, duration of action is 1–2 hours.
- ▶ By stimulating β_1 ARs, it increases heart rate and cardiac contractile force, facilitates AV conduction, increases automaticity, increases cardiac output and myocardial oxygen consumption.
- ▶ By stimulating β_2 ARs, it dilates blood vessels of the heart, lungs, skeletal muscles. Increases systolic BP and decreases diastolic BP, which results in decreased MAP.

Therapeutic indications: AV block (sublingual administration), relief of bronchospasm (inhalation), management of Stokes-Adams syndrome (intravenous administration)

Side effects: tachycardia; increased myocardial oxygen demand — ineffective contractions, disruption in myocardial metabolism, resulting in ischemia and arrhythmia; tremor, headache

Contraindications: myocardial infarction, angina pectoris, thyrotoxicosis, pregnancy

Orciprenaline (Asthmopent*)

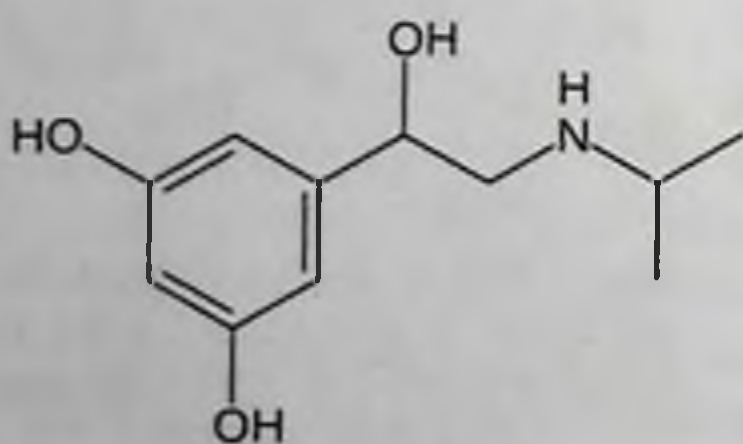


Fig. 3.17. 5-[1-Hydroxy-2-[(1-methylethyl)amino]ethyl]-1,3-benzenediol (as a sulfate or resinate); racemic mixture of two optically active isomers

- ▶ Synthetic β_1 , β_2 AA. Its structure is similar to that of Isadrine, thus it has similar pharmacological effects but has more selective β_2 adrenergic agonist effects and dilates the bronchi 10–40 times less than Isadrine within 10–15 min following inhalation; the duration of action is 4–5 hours.
- ▶ Gastrointestinal absorption: 40%. Metabolized in the liver. $T_{1/2}$: 4–6 hours. Excreted in the urine as glucuronide. For inhalation, subcutaneous, intramuscular, intravenous, oral administration.

Therapeutic indications: prevention and relief of bronchospasm, marked bradycardia, AV block, prophylaxis of Stokes-Adams syndrome

Side effects and contraindications: see “Isoprenaline”

Long-term administration of β AAs may cause tolerance, destruction of the ciliated epithelium, deterioration of bronchial drainage function, mucosal edema, bronchial hyperresponsiveness to allergens and non-specific stimuli. The mechanism of tolerance development is associated with a decrease in the number of β_2 ARs in the bronchi, along with their homologous and heterologous desensitization.

Dobutamine (Dobutrex®)

- ▶ β_1 AA, dopamine derivative, different from dopamine due to the presence of a paraoxyphenylmethylpropyl radical in the amino group, catecholamine. Cardiotonic (causes positive inotropic and mild chronotropic action). Increases cardiac contractile force and improves AV conduction, moderately increases myocardial oxygen demand.
- ▶ Metabolized in the liver to form inactive metabolites, with 3-O-methyldobutamine being the major one. $T_{1/2}$: 2–3 min due to rapid inactivation under the influence of MAO, the effect is achieved in 10 min with continuous infusion. Excreted predominantly in the urine. For intravenous administration.

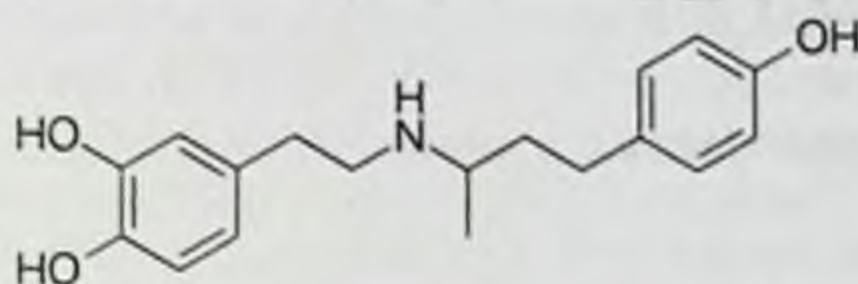


Fig. 3.18. ($\pm$)-4-[2-[[3-(4-Hydroxyphenyl)-1-methylpropyl]amino]ethyl]-1,2-benzenediol (as a hydrochloride)

Therapeutic indications: heart failure (acute or chronic decompensated), septic, cardiogenic shock

Side effects: tachyarrhythmias, increased BP, chest pain, headache, dyspepsia

Contraindications: aortic stenosis, pheochromocytoma, ventricular arrhythmias

 β_2 adrenergic agonists

Pharmacological effects:

- ▶ relaxation of bronchial smooth muscles (bronchodilating)
- ▶ decreased myometrial tone and contractility (tocolytic)

Fenoterol (Berotec®, Partusisten®), Salbutamol (Ventolin®, Salgim®), Hexoprenaline (Gynipral®).

These are short-acting, hydrophilic compounds that rapidly interact with the active site of β_2 ARs, with bronchodilation occurring within 2–3 min following inhalation and lasting 4–6 hours. About 10–30% of the substance released following inhalation reaches the lower respiratory tract. The rest is swallowed and undergoes biotransformation due to first-pass metabolism in the liver. They also exhibit tocolytic action.

- ▶ Salbutamol undergoes active metabolism during its first pass through the liver, transforming into a phenolic sulfate. Unchanged salbutamol and its conjugate are excreted in the urine. For inhalation, oral, subcutaneous, intramuscular, intravenous administration.
- ▶ Fenoterol undergoes biotransformation by conjugation with sulfates predominantly in the intestinal wall. Excreted in the urine and bile as inactive sulfate conjugates. For inhalation, oral, intravenous administration.

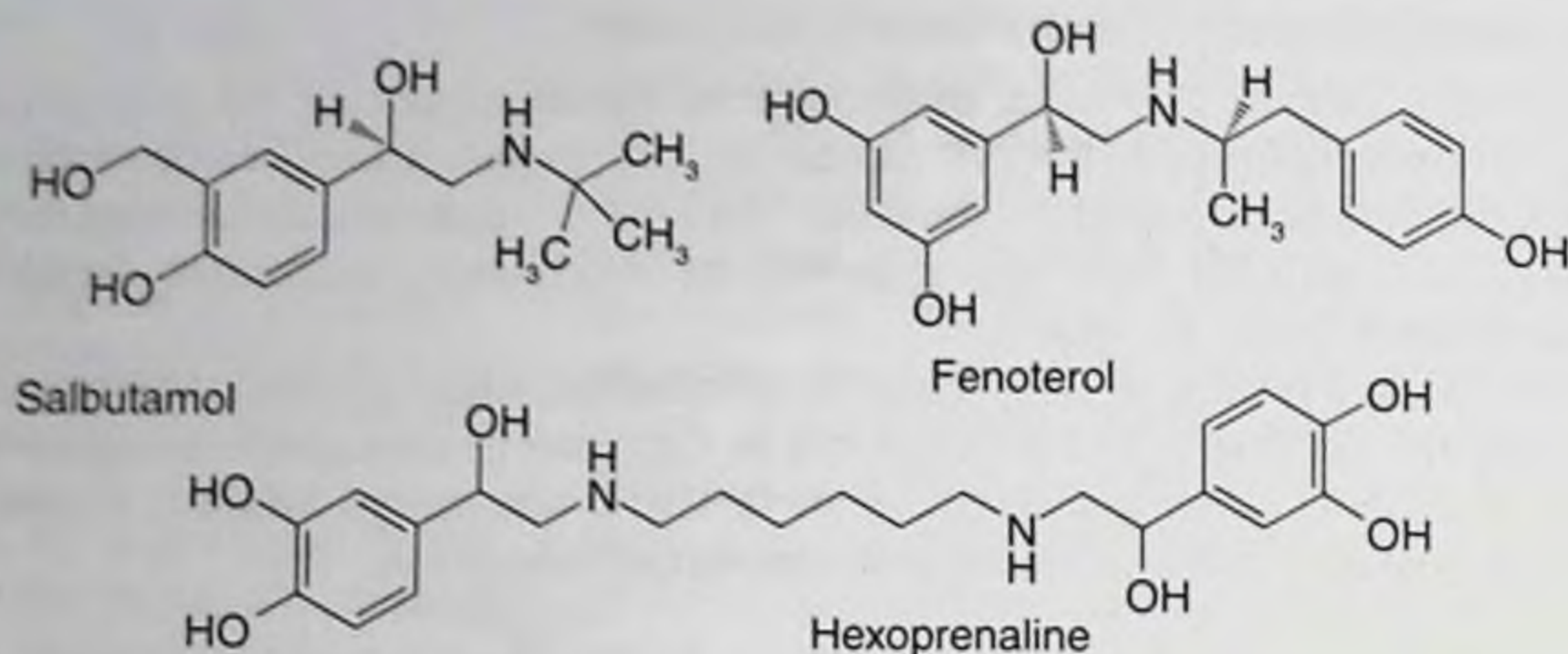


Fig. 3.19. Structural formulae of short-acting β_2 AAs: Salbutamol: (RS)-2-tert-butylamino-1-(4-oxy-3-oxymethyl-phenyl)-ethanol. Fenoterol: (RR,SS)-5-(1-hydroxy-2-[(2-(4-hydroxyphenyl)-1-methylethyl)amino]ethyl)benzene-1,3-diol. Hexoprenaline: 4,4'-[1,6-hexane diylbis(imino(1-hydroxy-2,1-ethandiyl))] bis[1,2-benzenediol] (as a dihydrochloride or sulfate)

- ▶ A hexoprenaline molecule consists of two catecholamine groups that undergo methylation by COMT. Excreted mainly in the urine as unchanged drug and as metabolites (monomethyl metabolite, dimethyl metabolite) and related compounds (glucuronide and sulfate). For intravenous, oral administration.

Therapeutic indications: relief of bronchospasm and prevention of exercise-induced asthma attacks, COPD; threat of miscarriage, preterm birth, and placental insufficiency

Salmeterol (Serevent*), Formoterol (Foradil*)

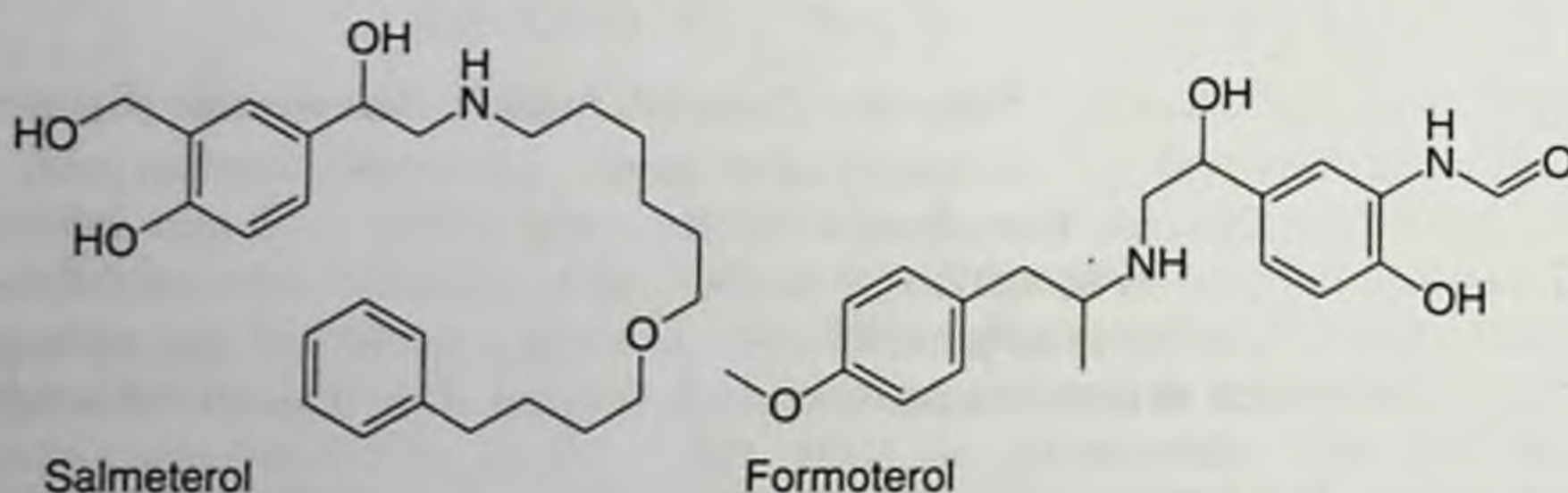


Fig. 3.20. Structural formulae of long-acting β_2 AAs: Salmeterol: (RS)-2-(hydroxymethyl)-4-[1-hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl]phenol. Formoterol: rac-(R,R)-N-[2-hydroxy-5-[1-hydroxy-2-[1-(4-methoxyphenyl)propan-2-ylamino]ethyl]phenyl]formamide

Lipophilic compounds (accumulate between the layers of cell membranes, forming a depot), long-acting (up to 10–12 hours). For administration by inhalation 2 times daily: the bronchodilating effect of salmeterol occurs in 30 min, the bronchodilating effect of formoterol occurs in 3–5 min.

- ▶ Salmeterol is metabolized in the liver, excreted in the bile, predominantly as hydroxylated metabolite.

- ▶ Formoterol undergoes O-demethylation followed by glucuronidation; 2/3 is excreted in the urine, 1/3 is excreted in the bile.

Therapeutic indications: treatment of bronchial asthma, COPD

Side effects (do not occur when administered by inhalation): tachycardia, decreased diastolic BP, tremor, dizziness, restlessness, anxiety, tachyphylaxis (fenoterol, formoterol)

Contraindications: thyrotoxicosis, CAD, tachyarrhythmias, heart failure, diabetes mellitus

Combination drugs

Berodual[®] (ipratropium bromide [MRA], fenoterol [β_2 AA])

Therapeutic indications: treatment, prophylaxis and relief of bronchial asthma attacks, COPD. Higher efficacy compared with monotherapy and fewer undesirable effects.

Ditec[®] (Cromoglicic acid [mast cell stabilizer], fenoterol [β_2 AA])

Therapeutic indications: prophylaxis and treatment of bronchial asthma (more effective in atopic asthma and exercise-induced asthma), COPD, respiratory failure in chronic respiratory diseases

Seretide[®] (Salmeterol [β_2 AA], fluticasone [inhaled glucocorticoid])

Symbicort[®] (budesonide [inhaled glucocorticoid], formoterol [β_2 AA])

Therapeutic indications: treatment of bronchial asthma, COPD

Indirect-acting adrenergic agonists (sympathomimetics)

Ephedrine (Ephedrine hydrochloride[®])

- ▶ In the Russian Federation, the possession, use, or sale of ephedrine preparations with a concentration greater than 10% is restricted; ephedrine and pseudoephedrine are included on the list of drug precursors for narcotics. It is a performance-enhancing drug, and its use in athletes is banned.
- ▶ Alkaloid found in the plants of the Ephedra genus. It has two asymmetric carbon atoms, so there are four optically active isomers and two racemates. Of all the isomers, ephedrine (cis-isomer) and pseudoephedrine (trans-isomer), which are spatial isomers, are used. The cis-isomer is a left-rotating alkaloid, the trans-isomer is a right-rotating alkaloid.
- ▶ Its activity is inferior to that of adrenaline, it has low polarity, high lipophilicity and a longer duration of action. Less potent than catecholamines, acts on the cardiovascular system and smooth muscles. The onset of the therapeutic effect is 15–60 min following oral administration, the duration of action is 3–5 hours; the onset and duration of action following intramuscular administration are 10–20 min and 0.5–1.0 hours, respectively. Repeated dosing with 10–30 min

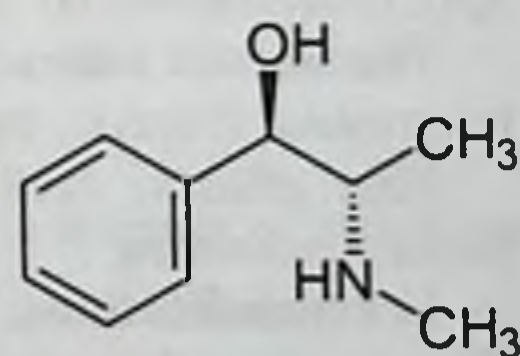


Fig. 3.21. [R-(R*), S*)]- α -[1-(Methylamino)ethyl] benzenemethanol (and as a hydrochloride)

intervals results in a rapidly decreasing pressor effect (tachyphylaxis associated with progressive depletion of norepinephrine in varicosities).

- ▶ Metabolized in the liver. $T_{1/2}$: 3–6 hours. Excreted predominantly as unchanged drug in the urine. For subcutaneous, intramuscular, intravenous, nasal, oral, topical administration.

Pharmacological effects

Local: Dilates the pupil, without affecting accommodation and IOP, induces vasospasm of the skin and mucous membranes.

Systemic:

- ▶ Psychostimulatory effect: increases physical and mental performance, increases vigor, temporarily reduces the need for sleep, improves mood, increases the activity of the respiratory and vasomotor centers of the medulla oblongata. Stimulation of psychomotor functions is caused by indirect adreno- and dopaminomimetic action of ephedrine on the synapses of the reticular formation, thalamus, hypothalamus, limbic system.
- ▶ Cardiotonic and hypertensive effects: increases cardiac activity and BP, less potent than adrenaline but lasts 7–10 times longer. Administration of ephedrine may not change heart rate since the excitation of cardiac β_1 ARs is counterbalanced by reflex activation of the vagus nerve. Ephedrine increases BP, toning the vasomotor center.
- ▶ Improves blood flow in the heart and skeletal muscles but narrows the blood vessels of the skin, mucous membranes and abdominal organs. Moderately dilates the bronchi, relaxes the intestines, myometrium, induces hyperglycemia.

Mechanism of action: Competitively displaces noradrenaline from the granules of adrenergic terminals (no exocytosis of the other granule components), inhibits MAO and COMT, inhibits neuronal uptake of noradrenaline, directly stimulates ARs (predominantly β ARs).

Therapeutic indications (limited): bronchial asthma and other allergic diseases, hypotonia, rhinitis, mydriasis for diagnostic purposes, narcolepsy, enuresis

Side effects: tachyphylaxis, increased BP, agitation, insomnia, tremor, nausea, vomiting

Contraindications: insomnia, hypertension, atherosclerosis, organic heart disease, pheochromocytoma, hyperthyroidism

Combination drugs with ephedrine:

- ▶ Broncholytin* (glaucine, ephedrine, [ocimum basilicum oil])
- ▶ Theophedrin-N* (ephedrine, theophylline)
- ▶ Clarinase-12* (d-ephedrine [pseudoephedrine], loratadine)
- ▶ Grippex* (d-ephedrine [pseudoephedrine], paracetamol, dextromethorphan)

DIRECT- AND INDIRECT-ACTING ADRENERGIC BLOCKERS

Substances of natural and synthetic origin that block the effects of catecholamines by affecting adrenoactive structures (ARs, structural cell

elements involved in the metabolism and transport of catecholamines, etc.). Adrenergic blockers (ABs) do not inhibit noradrenaline synthesis.

The first β AB (dichloroisoproterenol) was isolated by C. F. Powell. The first use of β ABs in clinical practice was in 1962 when propranolol was synthesized. In 1964, B. Prichard and P. Gillam discovered its antihypertensive and antiarrhythmic effects. In 1988, J. W. Black and colleagues discovered its antianginal effects and shared the Nobel Prize for the development of β ABs and their implementation in clinical practice. Lands divided β ABs into β_1 and β_2 AR blockers.

Classification

I. Direct-acting

1. α_1, α_2 adrenergic blockers
 - Phentolamine (Regitine[®])
 - Dihydroergotoxine (Redergin[®])
2. α_1 adrenergic blockers
 - Prazosin (Minipress[®])
 - Doxazosin (Cardura[®])
 - Tamsulosin (Omnice[®])
3. β_1, β_2 adrenergic blockers
 - Propranolol (Anaprilin[®])
 - Timolol (Timolol[®], Arutimol[®])
4. β_1 adrenergic blockers
 - Metoprolol (Betalo[®], Egilok[®])
 - Atenolol (Betacard[®])
 - Bisoprolol (Concor[®])
 - Betaxolol (Lokren[®], Betoptic[®])
 - Nebivolol (Nebilet[®])
5. $\alpha_1, \beta_1, \beta_2$ adrenergic blockers
 - Carvedilol (Dilatrend[®])
 - Labetalol (Trandate[®]) (excluded from Russian State Register of Medicinal Products)

II. Indirect-acting (sympatholytics)

- Reserpine

Combination drugs:

- ▶ Adelphane-Esidrex[®] (hydrochlorothiazide, dihydralazine, reserpine)
- ▶ Normatens[®] (dihydroergocristine, clopamide, reserpine)

Direct-acting adrenergic blockers

Adrenergic blocking agents prevent the action of catecholamines on the effector cells by directly binding to its ARs.

Specific drug properties by group

α_1 , α_2 adrenergic blockers (alpha-blockers)

Pharmacological effects

- ▶ Vasodilating effect: dilation of arteries (predominantly arterioles), precapillary sphincters and veins results in decreased TPR and BP. Dilation of pulmonary arterioles leads to decreased pressure in the pulmonary circulation circuit and reduced myocardial load. Dilation of veins results in blood deposition and reduced venous return, orthostatic (postural) hypotension, and tachycardia (also resulting from blockade of presynaptic α_2 ARs).
- ▶ Decreased tone of smooth muscle structures of the bladder neck and prostate leads to decreased obstruction and improved urination.

Phentolamine (Regitine®)

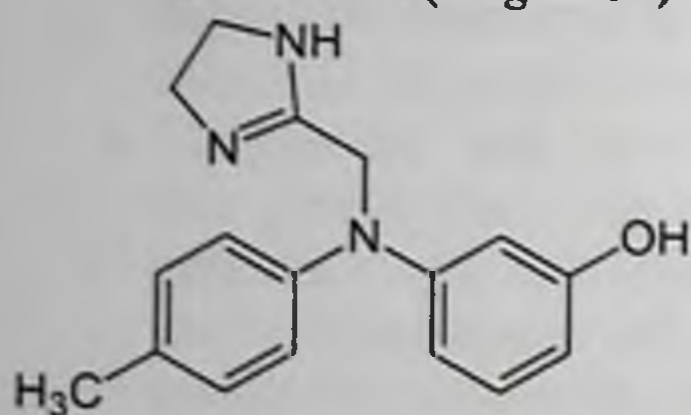


Fig. 3.22. 3-[[[4,5-Dihydro-1H-imidazol-2-yl)methyl](4-methylphenyl)amino]phenol (and as a hydrochloride or mesylate)

- ▶ Synthetic α_1 , α_2 AB, imidazoline derivative
- ▶ Bioavailability: 20%. 70% of the drug and its metabolites are excreted in the urine within first 24 hours, the remaining 30% is excreted in the bile. For oral, intravenous (methanesulfonate) administration 3–4 times daily.

Mechanism of action: Blocks postsynaptic and presynaptic α ARs, dilates peripheral blood vessels, especially arterioles and precapillaries, improves blood supply of muscles, skin, mucous membranes; decreases BP, inducing tachycardia (reflex tachycardia due to decreased BP and blockade of presynaptic α_2 ARs).

Therapeutic indications: diagnosis of pheochromocytoma; hypertensive crisis accompanied by hypercatecholaminemia (pheochromocytoma, Clophelin withdrawal, “cheese syndrome” during treatment with antidepressants which are MAO inhibitors); peripheral circulation disorders (Raynaud syndrome, endarteritis, acrocyanosis, etc.); treatment of trophic ulcers of the extremities, chronic non-healing wounds, bedsores, and frostbite.

Side effects: tachycardia, hypotension; dizziness; skin redness and pruritus; swelling of the nasal mucosa; nausea, vomiting, diarrhea

Contraindications: hypotension, CAD, cerebral atherosclerosis, renal insufficiency

Dihydroergotoxine (Redergin®)

- ▶ α_1 , α_2 AB. Contains a mixture of dihydrogenated forms of ergocryptine, ergocristine, and ergocornine (ergot alkaloids), semi-synthetic drug, available as methanesulfonate (mesylate).
- ▶ Dihydrogenation of the ring (partial reduction with addition of two hydrogen atoms to the lysergic acid nucleus) of D-lysergic acid makes ergot alkaloids potent α ABs, with less vasoconstrictive effects and no stimulatory effects on the myometrium.
- ▶ Passes through the BBB, placental barrier. For oral, subcutaneous, intramuscular, intravenous, intraarterial (for endarteritis) administration.

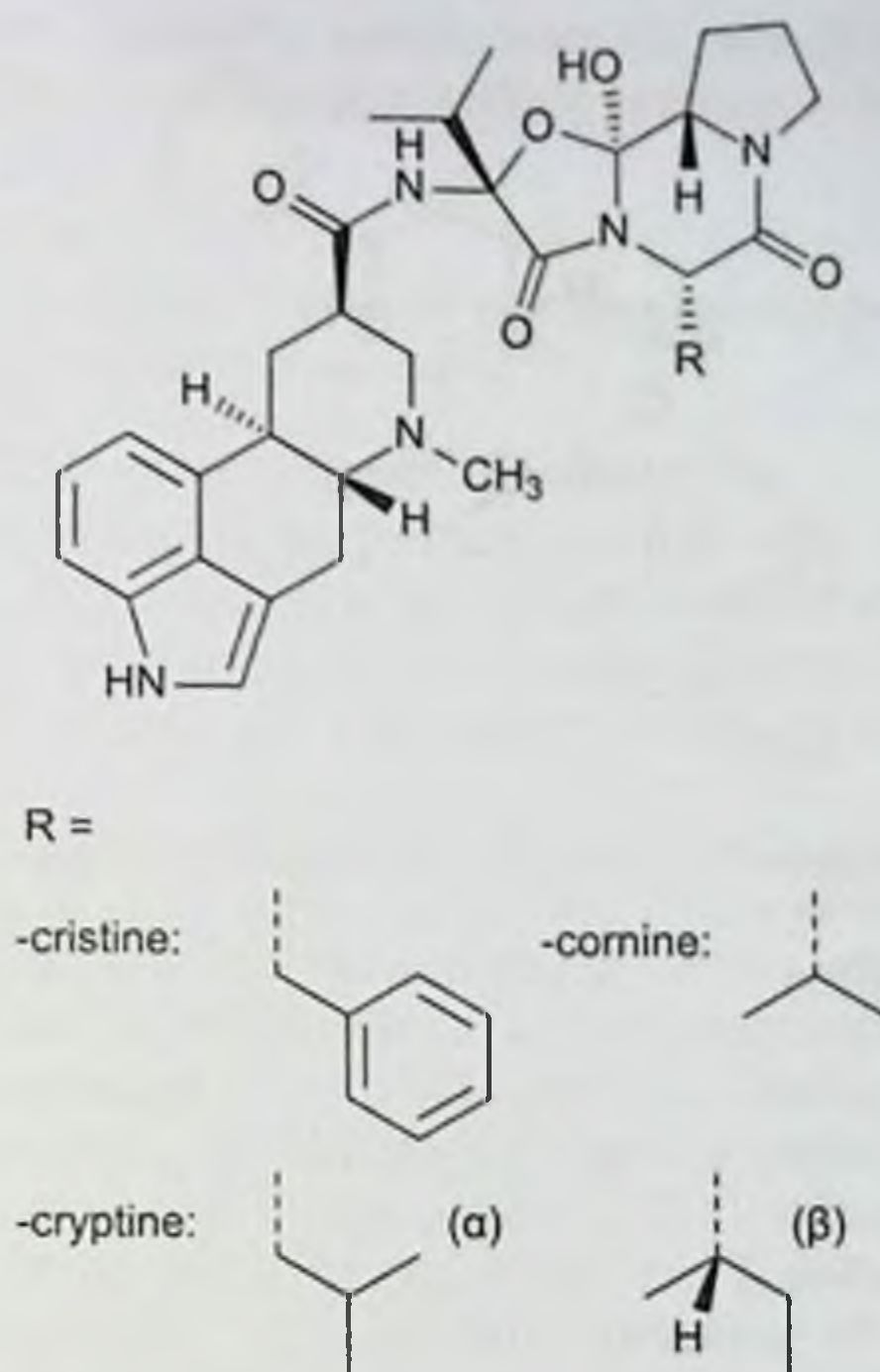


Fig. 3.23. Dihydrogenated forms of ergocryptine, ergocristine and ergocornine

Mechanism of action: Blocks presynaptic and postsynaptic α ARs and dopamine receptors, suppresses the pressor action of catecholamines, causes dilatation of peripheral blood vessels. Increases norepinephrine release, increases myocardial contractility.

Therapeutic indications: cerebral and peripheral circulation disorders (Buerger's disease, diabetic angiopathy, thrombophlebitis, Raynaud's disease, endarteritis), hypertension, migraine, Ménière's disease, retinal circulation disorders, cochleovestibular syndrome of vascular origin.

Side effects: orthostatic hypotension, dyspepsia, anorexia, visual impairment, allergic skin reactions

Contraindications: decompensated CAD, renal impairment

Nicergoline (Sermion[®])

- ▶ α_1 , α_2 , AB
- ▶ Synthetic analog of ergot alkaloids with an ergoline nucleus and bromine-substituted nicotinic acid residue in its structure
- ▶ Exerts vasodilating action (including cerebral arteries). The nicotinic acid residue exerts direct myotropic spasmolytic action on the medial layer of arterioles. Increases cerebral, pulmonary, and renal blood flow. Improves blood flow in the extremities, particularly in circulatory insufficiency due to functional arteriopathies.

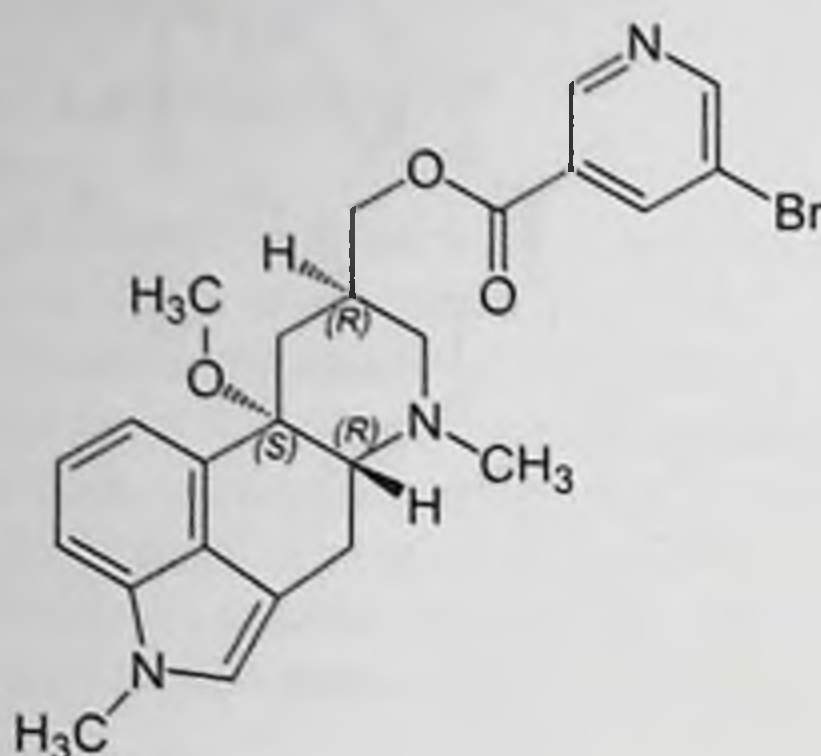


Fig. 3.24. 1,6-Dimethyl-8β-(5-bromo-nicotinoyl-oxymethyl)-10α-methoxyergoline

- ▶ **Bioavailability:** about 60%. Approximately 90% is metabolized in the liver by hydrolysis, demethylation, and glucuronidation to 1,6-dimethyl-8-β-oxymethyl-10-α-methoxyergoline (1-MMDL), 1-hydroxymethyl-6-methyl-8-β-oxymethyl-10-α-methoxyergoline (1-OHMMDL), and 6-methyl-β-oxymethyl-10-α-methoxyergoline (MDL — main active metabolite). About 70–80% of the drug and metabolites is excreted in the urine within 70–100 hours following administration. 20% is excreted in the bile. $T_{1/2}$: 2.5 hours, MDL: 12–17 hours, 1-MMDL: 2–4 hours. For long-term oral administration (sometimes for several months), intramuscular, intravenous, intraarterial administration.

Therapeutic indications: stroke, migraine, dementia; vascular disorders of the peripheral circulation system (arteriopathy of the extremities, Raynaud's disease, obliterating endarteritis, diabetic retinopathy and angiopathy); corneal dystrophies, retinal and choroidal vascular diseases, ischemic optic neuropathy; vestibular and labyrinth disorders of vascular genesis

Side effects: hypotension; dizziness, headache; nausea, vomiting, dyspepsia; redness of the face and upper half of the body, pruritus

Contraindications: hypotension, organic cardiovascular disease, exertional angina pectoris, pregnancy, breastfeeding

Combination drugs with dihydrogenated ergot alkaloids

Vasobral* (dihydroergocryptine, caffeine).

- ▶ Contains dihydroergocryptine mesylate and caffeine
- ▶ Dihydroergocryptine is a dihydrogenated ergot alkaloid (its pharmacological properties are close to those of dihydroergotoxine) that exhibits α_1 , α_2 blocking and partial central serotonergic and dopaminergic activity, exerts vasodilating action. The combination of dihydroergocryptine and caffeine is designed to increase their effects on cerebral blood vessels, reduce platelet aggregation, and improve metabolic processes in the brain. Dihydroergocryptine absorption is accelerated in the presence of caffeine. $T_{1/2}$: about 2 hours. For oral administration.

Therapeutic indications: cerebrovascular insufficiency, sequelae of strokes, peripheral circulation disorders, migraine prophylaxis

Side effects: dizziness, headache, nausea, vomiting, allergic skin reactions

Contraindications: history of allergic reactions, pregnancy, breastfeeding

α_1 adrenergic blockers

The α_1 adrenergic blockers are divided into two subgroups based their effect on vascular tone: vasoactive and non-vasoactive.

Vasoactive α_1 adrenergic blockers (prazosin, doxazosin)

Block both vascular (α_1 BARs) and prostate (α_1 AARs) ARs:

- ▶ exhibit pronounced vasodilating properties, decrease BP and myocardial preload
- ▶ dilate the urethral lumen, without reducing the function of the detrusor muscle (muscle layer of the bladder), which improves urinary outflow (elimination of dynamic obstruction).

Other effects: has beneficial effects on lipid metabolism (decreased triglycerides, total cholesterol and increased plasma high-density lipoproteins)

Prazosin (Minipress®)

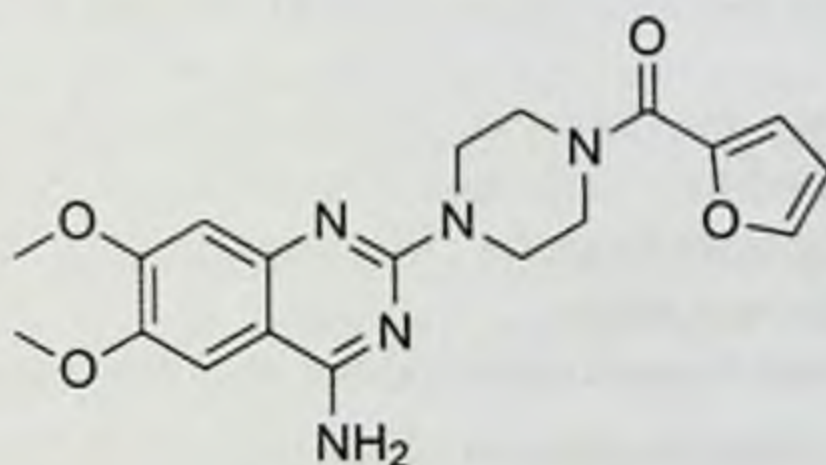


Fig. 3.25. 1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl) piperazine (as a hydrochloride)

- ▶ Blocks postsynaptic α_1 ABs 10 times more effectively than phentolamine. Decreases regional vascular resistance, peripheral vascular tone, induces severe orthostatic hypotension, particularly after the first dose (first-dose phenomenon). The first dose should be minimal and be administered at bedtime. The antihypertensive effect occurs 1–4 hours after oral administration and lasts 6–8 hours. When prazosin is administered as a treatment course, stable BP reduction occurs in 2–3 days and lasts for several days following discontinuation.
- ▶ Bioavailability: 50–85%. Metabolized in the liver by detachment of the methyl group and conjugation to form four active metabolites, which account for 25% of the pharmacological activity. $T_{1/2}$: 2–4 hours, excreted predominantly in the bile. For oral administration.

Therapeutic indications: hypertension, benign prostatic hyperplasia

Side effects: first-dose phenomenon, dizziness, headache, nasal congestion, nausea

Contraindications: hypotension, history of allergic reactions, pregnancy, breastfeeding

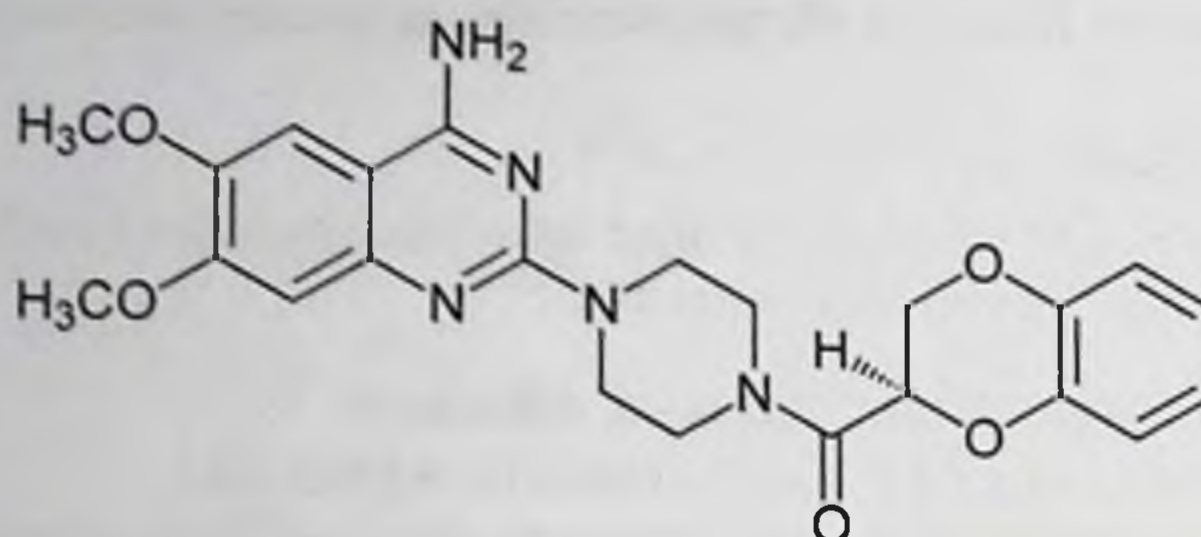
Doxazosin (Cardura®)

Fig. 3.26. 1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-[(1,4-benzodioxan-2-yl)-carbonyl] piperazine [as a monomethanesulfonate (mesylate)]

- ▶ Structural analog of prazosin, contains a benzodioxane radical. Has prolonged action compared to prazosin. Following a single dose, the antihypertensive effect is achieved in 2–6 hours and lasts 24 hours. Patients who are being treated for hypertension do not have differences in BP values in upright versus supine positions.
- ▶ Bioavailability: 60–70% (first-pass metabolism). Metabolized in the liver by O-demethylation and hydroxylation. $T_{1/2}$: 19–22 hours. Excreted mainly in the bile, predominantly as metabolites, 5% as unchanged drug, 9% in the urine. For oral administration once daily.

Therapeutic indications: hypertension (alone or in combination), benign prostatic hyperplasia

Non-vasoactive α_1 adrenergic blockers (tamsulosin)

- ▶ Block α_1 AARs in the prostatic urethra and bladder neck, dilate the urethral lumen, without reducing the function of the detrusor muscle, which improves urinary flow (elimination of dynamic obstruction)
- ▶ Used only for the treatment of benign prostatic hyperplasia

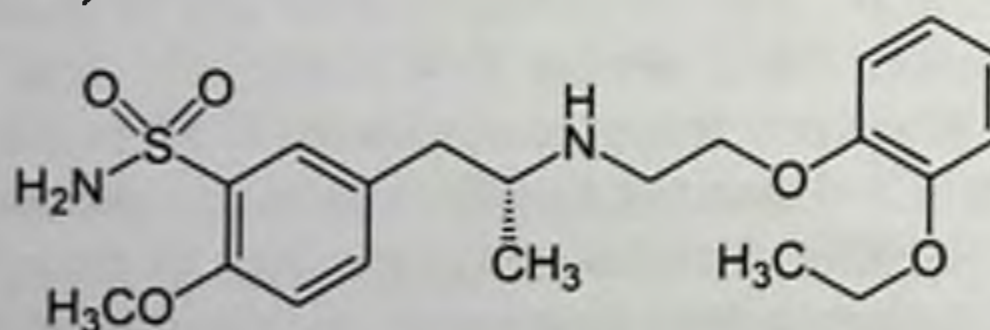
Tamsulosin (Omnice®)

Fig. 3.27. (-)-(-)-(R)-5-[2-[[2-(O-Ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide (as a hydrochloride)

- ▶ Its structure is different from that of prazosin and its analogs due to the absence of quinazolinyl and furan fragments. $T_{1/2}$: 10 hours
- ▶ Has absolute bioavailability. Slowly metabolized in the liver to form less-active metabolites. Most of the tamsulosin is present in plasma in unchanged form. The drug and its metabolites are excreted in the urine, about 9% is excreted as unchanged substance. For oral administration once daily.

Side effects: dizziness, abnormal ejaculation, dyspepsia, skin rash, pruritus

Contraindications: severe hepatic insufficiency, less than 18 years of age

β_1 , β_2 adrenergic blockers (beta-blockers)

Main pharmacological effects and their mechanisms

1. Antianginal

Blockade of β_1 ARs reduces myocardial oxygen demand and results in:

- ▶ reduced HR, longer diastole
- ▶ reduced cardiac output due to decreased myocardial contractility
- ▶ limited oxidation of free fatty acids (oxidation of fatty acids requires more oxygen).

β_1 , β_2 blockers restore the balance between myocardial oxygen demand and oxygen delivery. However, they can decrease total coronary blood flow, causing coronary vasospasm (narrowing of coronary arteries occurs due to β_2 AR blockade). Despite narrowing of the coronary vessels, they can improve blood flow in ischemic regions, since arteries in the myocardial regions affected by hypoxia are in a state of paralytic dilatation due to increased concentrations of carbon dioxide, hydrogen ions, and other acid products; narrowing of arteries in the unaffected myocardial regions promotes blood redistribution through dilated vessels to the ischemic region under the influence of β ABs.

2. Antiarrhythmic: β_1 AR blockade results in decreased automaticity and excitability of the sinoatrial node, AV node, ectopic foci, inhibition of AV conduction.

3. Antihypertensive:

- ▶ blockade of postsynaptic β_1 ARs results in reduced cardiac output
- ▶ blockade of postsynaptic β_1 , β_2 ARs results in inhibition of renin secretion
- ▶ blockade of presynaptic β_2 ARs results in reduced noradrenaline release in the synaptic cleft.

Diastolic BP can increase in the first days of treatment due to elimination of the vasodilating effect of β_2 ARs, as well as arterial spasm in response to insufficient irritation of aortic and carotid sinus baroreceptors by reduced cardiac output. It decreases after 1–2 weeks of treatment.

4. IOP reduction:

- ▶ Blockade of β_1 , β_2 ARs of the ciliary body results in reduced secretion of intraocular fluid and contraction of ciliary arterioles, which leads to reduced ciliary perfusion and filtration [propranolol (Anaprilin*), timolol, betaxolol].
- ▶ Blockade of β_2 ARs in the trabecular meshwork slightly increases the outflow of fluid from the eye due to dilatation of intertrabecular clefts.

5. Psychotropic: relief of fear, anxiety, panic states, and pathological aggression, attenuation of central links activating the cardiovascular system during exertion and emotional stress [propranolol (Anaprilin*), metoprolol]

Therapeutic indications: CAD; hypertension; supraventricular tachyarrhythmias, extrasystoles (supraventricular and ventricular); CHF (metoprolol, bisoprolol, nebivolol), open-angle glaucoma [propranolol (Anaprilin*), timolol, betaxolol]

Side effects: marked bradycardia, AV block; hypotension; aggravation of heart failure; increase in triglycerides, very-low-density lipoproteins and decrease in

high-density lipoproteins; hypoglycemia; bronchospasm; increased peripheral vascular tone; fatigue, weakness, decreased performance, depression (for lipophilic drugs); increased peristalsis; erectile dysfunction, low sex drive; topical administration: decreased tear secretion, blepharitis, conjunctivitis, keratitis, blepharoptosis, diplopia, allergic reactions; withdrawal syndrome.

Administration of β ABs for 3 months is sufficient to cause withdrawal syndrome after abrupt treatment discontinuation (disturbances are most pronounced in the first 7 days: restlessness, shivers, elevated blood pressure, increased heart rate). Treatment is accompanied by formation of β ARs, inhibition of conversion of thyroxine to triiodothyronine, inhibition of renin secretion, decreased platelet aggregation. Following discontinuation, noradrenaline and adrenaline excite a new generation of β ARs, triiodothyronine, renin, thromboxane A₂ (TXA₂) concentrations increase. The dose of β -blockers is gradually reduced over 2 weeks to prevent withdrawal. They are discontinued 48 hours before elective surgery and resumed thereafter.

Contraindications: sinoatrial block, 2nd–3rd degree AV block, marked sinus bradycardia (< 50 beats per minute); sick sinus syndrome; hypotension; acute or chronic decompensated heart failure; cardiogenic shock; peripheral vascular spasm; metabolic acidosis (including diabetic acidosis); bronchial asthma, COPD; pregnancy, breastfeeding; for topical administration: corneal dystrophy, keratoconjunctivitis sicca

Propranolol (Anaprilin[®])

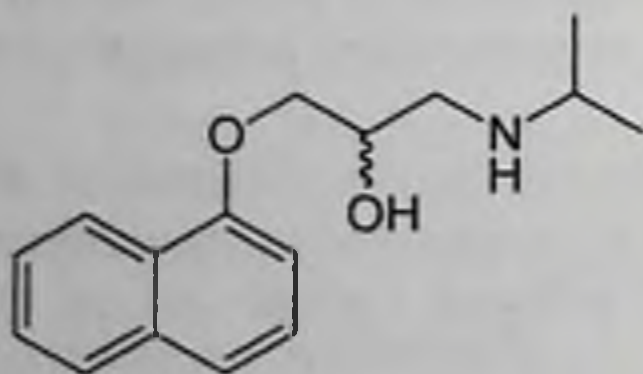


Fig. 3.28. 1-[(1-Methylethyl)amino]-3-(1-naphthalenyloxy)-2-propanol (as a hydrochloride)

- ▶ Lipophilic β_1 , β_2 AB with membrane-stabilizing effects. Crosses the BBB and placental barrier, excreted into breast milk. Duration of action: 4–6 hours.
- ▶ Bioavailability is 30–40% (first-pass metabolism in the liver, microsomal oxidation) and increases with long-term administration (forms 4-hydroxypropranolol, a metabolite that inhibits liver enzymes), $T_{1/2}$: 2–5 hours. Excreted in the urine as metabolites, with less than 1% excreted as unchanged drug. For oral, intravenous, intravenous, topical (eye drops) administration 3–4 times daily.

Additional therapeutic indications: essential tremor, migraine (prophylaxis of migraine attacks), hyperthyroidism; in obstetrics and gynecology: for the induction and enhancement of labor in the event of initial weak uterine contractions and for the prophylaxis of postpartum complications associated with poor uterine contractility.

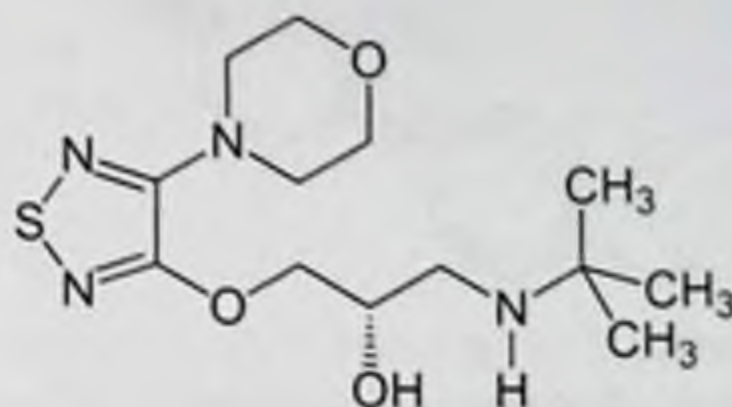
Timolol (Timolol*, Arutimol*)

Fig. 3.29. (S)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol (hemihydrate or maleate)

- ▶ Long-acting lipophilic β_1 , β_2 AB (administered once daily). Excreted into breast milk, crosses the BBB and placental barrier. Readily absorbed through the retina. 90% is absorbed in the GI tract, the bioavailability does not exceed 50% due to the first-pass effect. $T_{1/2}$ following topical application: 30 min, $T_{1/2}$ following oral administration: 4 hours.
- ▶ Metabolized in the liver, excreted in the urine (20%) and in the bile as unchanged substance and metabolites. For oral, topical administration (Arutimol eye drops). Instillation in the conjunctival sac results in IOP reduction with both baseline normal and increased ophthalmic tone. The effect usually occurs in 20 min following instillation, reaches its maximum in 1–2 hours, and lasts 24 hours.

Combination drugs with timolol:

- ▶ Xalacom* (latanoprost, timolol)
- ▶ Cosopt* (dorzolamide, timolol)

Cardioselective β adrenergic blockers (antagonists)

Predominantly block β_1 ARs, acting to a much lesser extent on β_2 ARs. To characterize β_1 ABs, a cardioselectivity ratio is used to reflect the relative β_1 , β_2 AR blockade:

- ▶ metoprolol — 25/1
- ▶ betaxolol — 25/1
- ▶ atenolol — 35/1
- ▶ bisoprolol — 75/1
- ▶ nebivolol — 290/1

Therapeutic indications: see “Non-selective β_1 , β_2 ABs”

Although β_1 ABs have less prominent extracardiac side effects than non-selective beta-blockers, selective β_1 ABs are relatively contraindicated in all cases where non-selective β ABs are contraindicated. This is due to the non-homogeneous distribution of β ARs in organs and tissues, where both receptor types are present but one of them is predominant. The cardioselectivity of ABs is significantly reduced when these drugs are used at high doses.

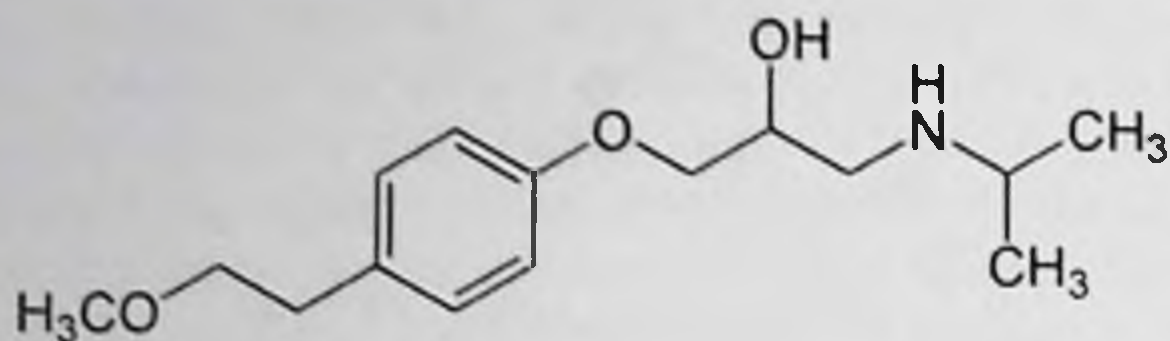
Metoprolol (Betaloc[®], Egilok[®])

Fig. 3.30. (±)-1-[4-(2-Methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]-2-propanol (as a tartrate or succinate)

- ▶ Lipophilic β_1 AB. Crosses the BBB, placental barrier, excreted into breast milk.
- ▶ Undergoes extensive first-pass metabolism, with about 50% of the dose reaching systemic blood circulation following oral administration. Repeated dosing results in an increase in systemic bioavailability up to 70%. Simultaneous intake of food increases the bioavailability by 20–40%. $T_{1/2}$: 3–7 hours, excreted predominantly in the urine (about 95%). Approximately 5% of the administered dose is excreted as unchanged drug. For oral, intravenous administration 2–4 times daily.
- ▶ Can be administered during the acute phase of myocardial infarction (combination therapy).

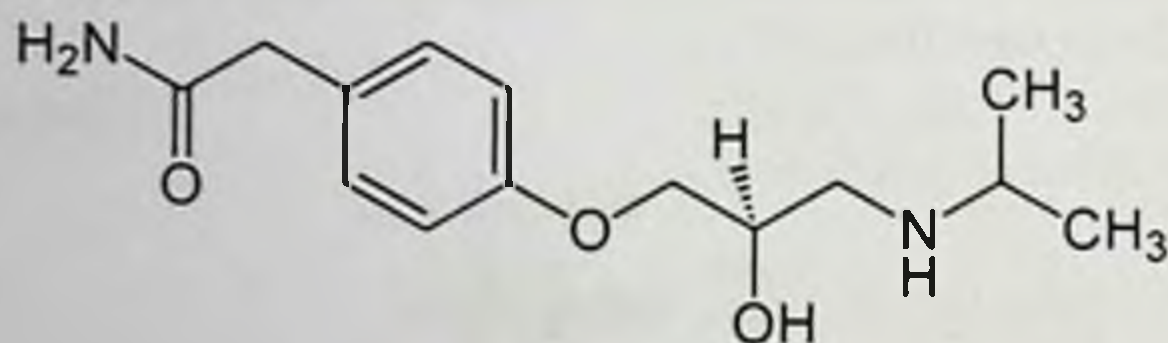
Atenolol (Betacard[®])

Fig. 3.31. 4-[2-Hydroxy-3-[(1-methylethyl)amino]propoxy]benzeneacetamide (as a monohydrochloride)

- ▶ Long-acting hydrophilic β_1 AB. Poorly penetrates the BBB and placental barrier, excreted into breast milk.
- ▶ Essentially not metabolized in the liver. Bioavailability: 40–50%. $T_{1/2}$: 6–9 hours. Excreted in the urine (85–100% excreted as unchanged drug). For oral administration 1–2 times daily.

Betaxolol (Lokren[®], Betoptic[®])

- ▶ Long-acting lipophilic β_1 AB. Administered orally once daily, the maximum antihypertensive effect is achieved in 1–2 weeks. When used topically (eye drops), the onset of action is 30 min, the maximum decrease in ophthalmic tone occurs in 2 hours. The effect lasts 12 hours following a single instillation.
- ▶ Rapidly and completely absorbed in the GI tract. Bioavailability: 85%. Metabolized in the liver to form inactive metabolites. The systemic absorption is low for topical administration. $T_{1/2}$: 15–20 hours. Excreted predominantly in the urine.

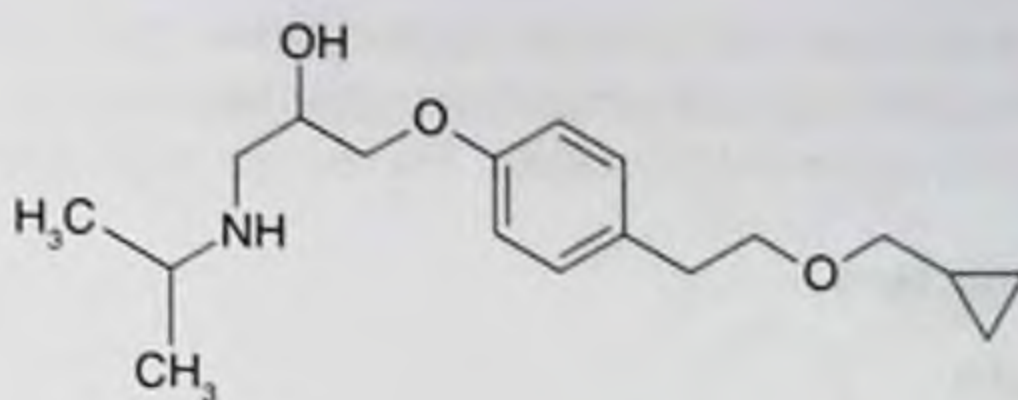


Fig. 3.32. 1-[4-[2-(Cyclopropylmethoxy)ethyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol (as a hydrochloride)

Bisoprolol (Concor[®])

- ▶ Long-acting, highly cardioselective lipophilic AB. The antihypertensive effect occurs in 3–4 hours following administration and lasts more than 24 hours; $T_{1/2}$: 10–12 hours.
- ▶ Bioavailability: 90%. Metabolized by oxidation without subsequent conjugation. About 50% of the dose is metabolized in the liver to form inactive metabolites. The major metabolites found in the plasma and urine do not exhibit any pharmacological action. About 98% is excreted in the urine, with 50% excreted as unchanged drug; less than 2% is excreted in the bile. For oral administration once daily.

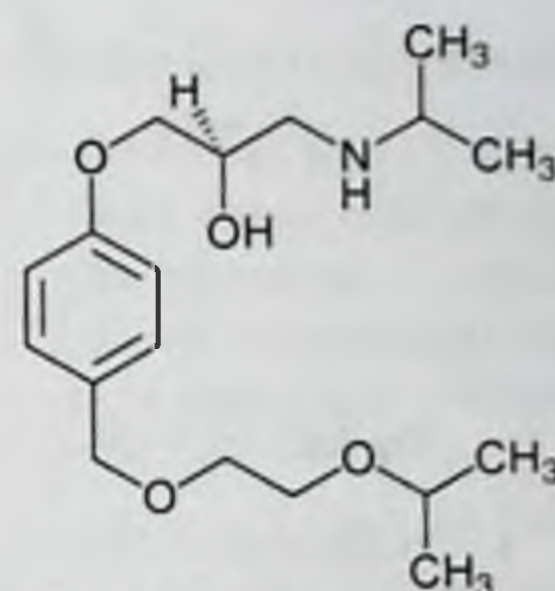


Fig. 3.33.
1-[4-[[2-(1-Methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol (as a fumarate)

Nebivolol (Nebilet[®])

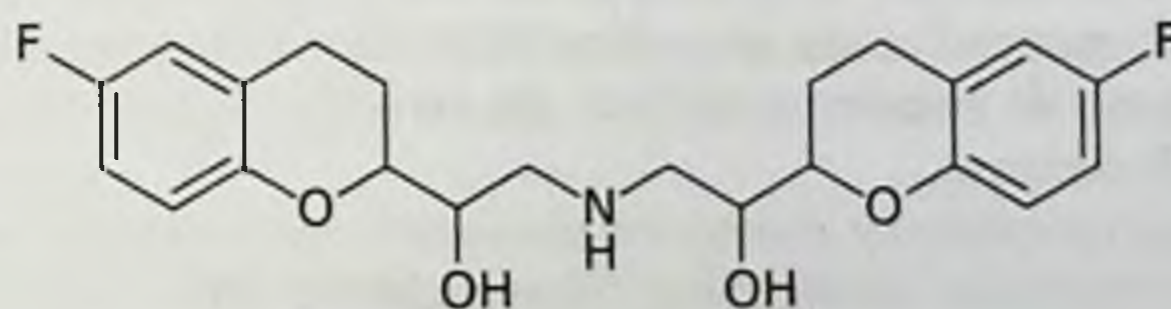


Fig. 3.34. α,α' -[iminobis(methylene)bis[6-fluoro-3,4-dihydro]-2H-1-benzopyran-2-methanol; racemic combination of two enantiomers, D- and L-nebivolol

- ▶ Long-acting, highly cardioselective lipophilic AB. Racemic combination of L- and D-isomers, of which D-isomer exerts β adrenergic blocking activity, L-isomer causes NO release (which additionally increases the vasodilating effect). In addition, it exerts antioxidant, antithrombotic action (reduces platelet adhesion and aggregation), decreases triglyceride levels and increases high-density lipoprotein levels, increases tissue glucose utilization and decreases insulin resistance in type 2 diabetes mellitus. The antihypertensive effect usually occurs in 1–2 weeks and stabilizes in 4 weeks. Crosses the BBB, excreted into breast milk.

- ▶ Metabolized by alicyclic and aromatic hydroxylation, partial N-dealkylation and glucuronidation, forming hydroxymetabolite glucuronides. $T_{1/2}$: 10 hours. Excreted in the urine (40%) and in the bile (60%). For oral administration once daily.

α_1 , β_1 , β_2 adrenergic blockers

Carvedilol (Dilatrend*)

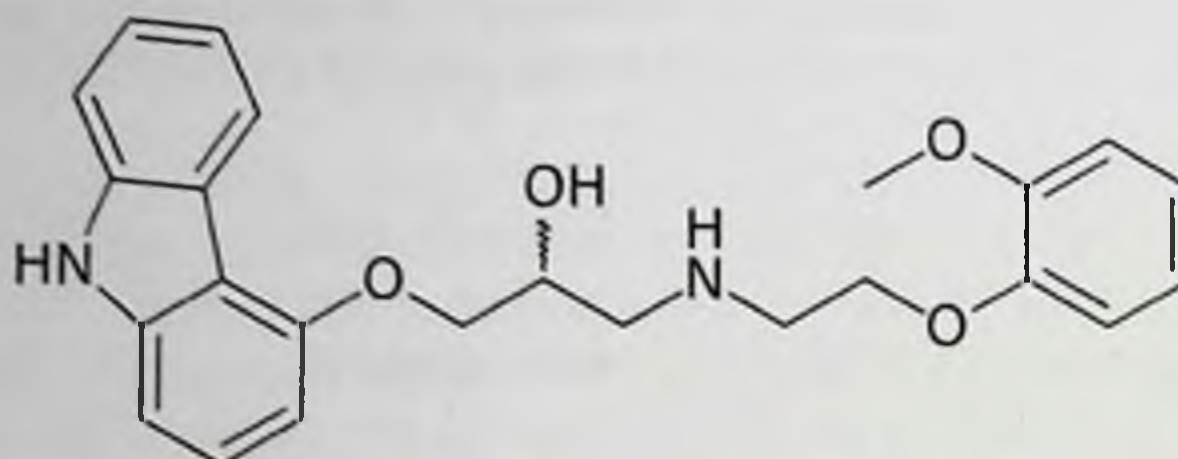


Fig. 3.35. ($\pm$)-1-(9H-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]propanol

- ▶ Combination of two enantiomers: S-enantiomer blocks β_1 , β_2 ARs and α_1 ARs, R-enantiomer blocks only α_1 ARs. Blocks β ARs 10–100 times more than α_1 ARs. Its action on β_1 ARs is 12 times more potent than metoprolol. Its antianginal and antihypertensive effects are significantly superior to propranolol (Anaprilin*). Exhibits antioxidant, cardioprotective, and antiatherosclerotic effects. Reduces apoptosis of cardiomyocytes, prevents connective tissue proliferation in the myocardium and myocardial remodeling, inhibits development of smooth muscle hypertrophy and endothelial dysfunction.

Mechanism of action: Blockade of α_1 ARs results in dilated peripheral blood vessels and decreased TPR; blockade of cardiac β_1 ARs results in decreased HR and cardiac contractile force, reduced renin secretion; blockade of presynaptic β_2 ARs results in decreased release of noradrenaline into the synaptic cleft. Cardiac preload and afterload, and BP decrease.

- ▶ Exhibits high lipophilicity, crosses the placental barrier, excreted into breast milk.
- ▶ Subject to first-pass elimination, bioavailability: 25%. Demethylation and hydroxylation at phenol ring results in formation of metabolites with β adrenergic blocking activity: 4'-hydroxyphenol metabolite is 13 times more active compared with carvedilol; hydroxycarbazole metabolites are potent antioxidants (30–80 times higher than in carvedilol). Food slows absorption but does not affect bioavailability. $T_{1/2}$: 6–10 hours. Excreted in the bile. For oral administration 1–2 times daily.

Therapeutic indications: hypertension, CAD, CHF

Side effects: orthostatic hypotension, bradycardia, 2nd–3rd degree AV block, bronchospasm, dizziness, headache, weakness, fatigue, sleep disturbances, nausea, diarrhea, abdominal pain

Contraindications: same as other β ABs

Labetalol (Trandate®)

Excluded from the Russian State Register of Medicinal Products.

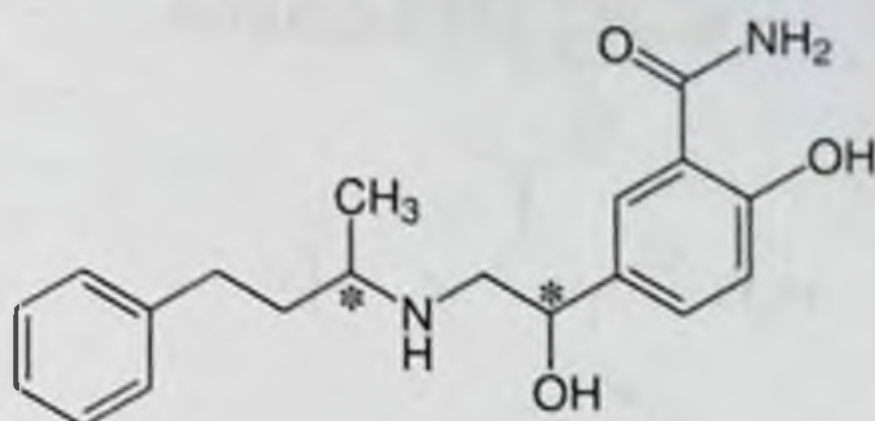


Fig. 3.36. 2-Hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]benzamide (as a hydrochloride)

- ▶ Selectively blocks α 1ARs and non-selectively blocks β ARs. It is 2–7 times less effective than phentolamine as an α 1AB and 3–16 times less potent than propranolol (Anaprilin®) as a β AB. The ratio of α adrenergic blocking activity to β adrenergic blocking activity is 1:3 (for oral administration) and 1:7 (for intravenous administration). Induces orthostatic hypotension without concomitant tachycardia.
- ▶ Exhibits moderate lipophilicity. Crosses the placental barrier. Subject to first-pass metabolism, bioavailability: 25%. The maximum blood concentration is reached in 2–4 hours following a single oral dose. $T_{1/2}$: 6–8 hours. Metabolized in the liver and excreted in the bile and urine. For oral, intravenous administration 2–3 times daily.

Therapeutic indications: Hypertension (including in hypertensive crisis), CAD

Side effects: see “Carvedilol”

Contraindications: same as other β ABs

Indirect-acting adrenergic blockers (sympatholytics)

Adrenergic antagonists that reduce the amount of the mediator released in sympathetic nerve terminals and inhibit the transmission of adrenergic excitation.

Reserpine

- ▶ Indole alkaloid isolated in 1952 from the plant Indian snakeroot (*Rauvolfia serpentina*) which is native to India, Sri Lanka, Java, and the Malay Peninsula. The root of *Rauvolfia serpentina* historically had been used to treat snakebites, insomnia, hypertension. It was named to honor L. Rauwolf, a German botanist and physician from Augsburg, who described the plant. The use of *Rauvolfia* root for the treatment of mental disorders and hypertension was first reported in an Indian medical journal in 1931.
- ▶ The antihypertensive effect occurs over several days and reaches its maximum in 3–6 weeks. The duration of action is 1–6 weeks. Long-term shutdown of sympathetic innervation results in predominant parasympathetic influences in the body.
- ▶ Absorption: 40%, bioavailability: 50–60%, crosses the placental barrier, BBB, excreted into breast milk. The drug and its metabolites are excreted in two stages (α phase and β phase): $T_{1/2}$ for α phase: 4.5 hours, $T_{1/2}$ for β phase: 271 hours. 8% of the dose is excreted in the urine within 96 hours (predominantly as inactive

metabolites), and 62% is excreted in the bile (predominantly as unchanged drug). For oral administration 2–3 times daily.

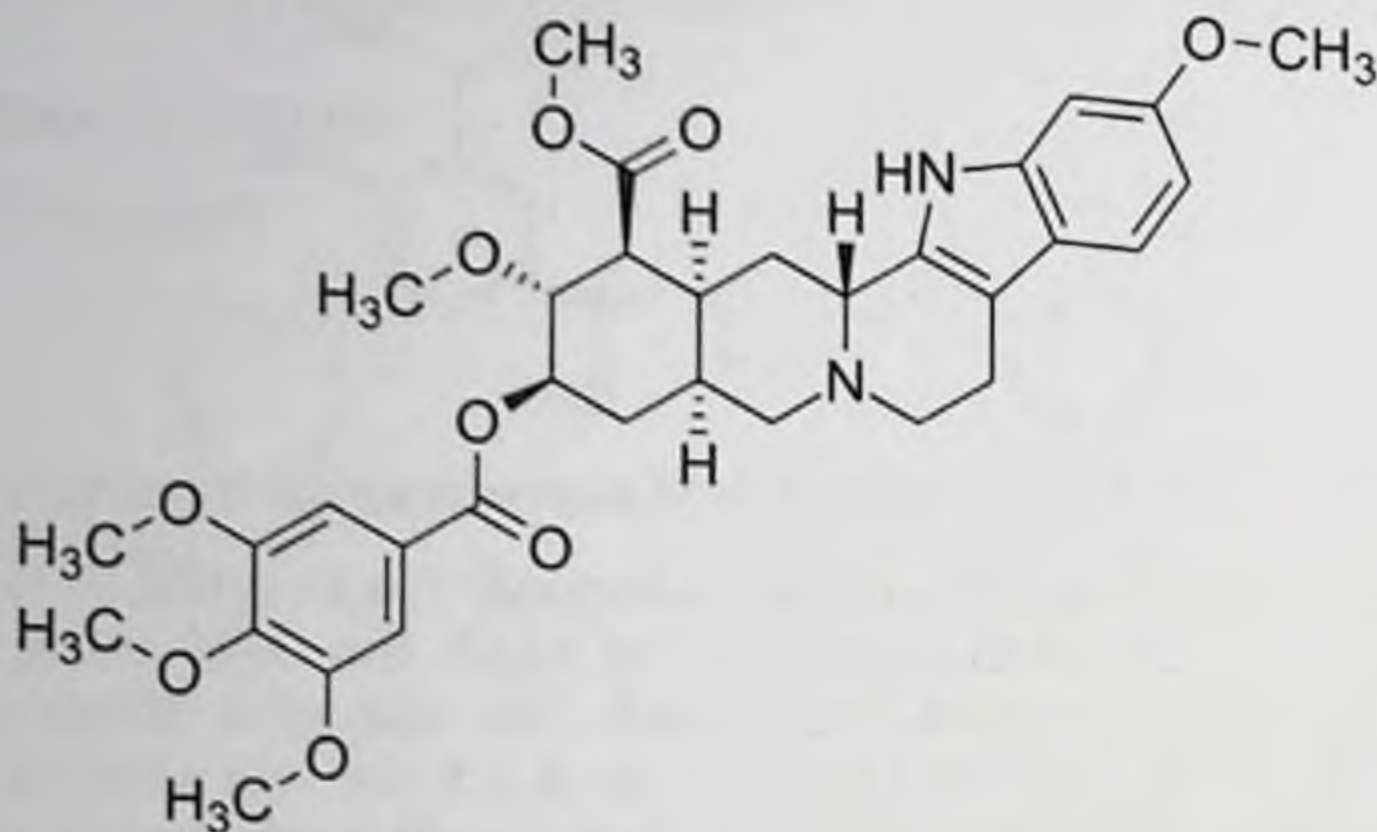


Fig. 3.37. Methyl ester (3 β ,16 β ,17 α ,18 β ,20 α)-11,17-dimethoxy-18-[(3,4,5-trimethoxybenzoyl)oxy]yohimban-16-carboxylic acid

Pharmacological effects

- ▶ Antihypertensive: BP reduction is gradual (several days). Hypotension is associated with decreased cardiac output, decreased TPR, and suppression of pressor reflexes. Does not induce orthostatic hypotension.
- ▶ Antipsychotic: depletes catecholamines and serotonin in the CNS
- ▶ Sedative
- ▶ Potentiating with respect to hypnotic drugs with narcotic action, general anesthetics

This drug is not currently used as an antipsychotic.

Mechanism of action: Enters the nerve endings by simple diffusion, disrupts the deposition of noradrenaline and dopamine in the vesicles, depleting mediator reserves in the granules. Noradrenaline accumulated in the axoplasm is inactivated by MAO through deamination (does not affect MAO activity or neuronal reuptake in the synapse).

Therapeutic indications: Hypertension

The drug substance is not used as monotherapy but is included in combination drugs:

- ▶ Adelphane-Esidrex[®] (hydrochlorothiazide, dihydralazine, reserpine)
- ▶ Normatens[®] (dihydroergocristine, clopamide, reserpine)

Side effects: bradycardia; bronchospasm; diarrhea, intestinal spasms; gastric hypersecretion; difficulty with nasal breathing; increased uterine tone; somnolence, generalized weakness, depression, Parkinsonism; gynecomastia, abnormal ovarian cycle; erectile dysfunction, low sex drive

Contraindications: bradycardia, AV blocks; decompensated heart failure; severe renal failure; epilepsy, Parkinson's disease, depression; bronchial asthma, respiratory failure; stomach and duodenal ulcers; pregnancy and breastfeeding

4. GENERAL AND LOCAL ANESTHETICS

GENERAL ANESTHETICS

General anesthetics (or narcosis-inducing drugs, from the Greek *narkōsis*, meaning “numbing”) are drugs that induce a state characterized by reversible CNS depression, manifested as a loss of consciousness, sensitivity (including sensitivity to pain), reflexes, and decreased skeletal muscle tone.

In 1846, W. Morton used ether to anesthetize a patient for the first time. In 1847, F. I. Inozemtsev, a Professor at Moscow University, was the first in Russia to use ether anesthesia. That same year, the surgeon N. I. Pirogov operated twice using ether anesthesia in Saint Petersburg. In 1902, N. P. Kravkov was the first to use hedonal for intravenous anesthesia. In 1956, halothane was introduced in the clinical practice of anesthesia. Enflurane was developed by R. Terrell, an American chemist, in 1963 and first used in clinical practice in 1966.

Stages of general anesthesia using ether as an example: I — analgesia or induction, II — excitement, III — surgical anesthesia, IV — overdose/medullary depression.

Classification

I. Inhalational anesthetics

- Volatile anesthetics
 - Halothane (Phthorothane[•])
 - Enflurane (Ethrane[•])
 - Isoflurane (Forane[•])
 - Sevoflurane (Sevorane[•])
- Gases
 - Dinitrogen oxide (nitrous oxide[•])
 - Xenon (Medxenon[•])

II. Non-inhalational anesthetics

- Short-acting (< 15 min)
 - Propanidid (Sombrevin[•])
 - Propofol (Diprivan[•])
 - Ketamine (Calypsol[•], Ketalar[•])
- Intermediate-acting (20–30 min)
 - Sodium thiopental (Thiopental[•])
 - Hexobarbital (Hexenal[•])
- Long-acting (60 min and more)
 - Sodium oxybutyrate (Sodium oxybate[•])

Combined use of anesthetics

- ▶ Maintenance anesthesia is anesthesia during which a surgical intervention is performed.
- ▶ Induction anesthesia is short-term, fast-onset anesthesia. It reduces how much of the main narcotic substance is being used.
- ▶ Combined anesthesia consists of using different general anesthetics during surgery (e.g. combination of propofol and sevoflurane).
- ▶ Potentiated anesthesia is anesthesia where its action is enhanced by preliminary (premedication) and/or concomitant administration of other drugs that do not induce general anesthesia (narcotic analgesics, neuroleptics, benzodiazepine anxiolytics, sedating antihistamines).

Mechanisms of action: Inhibition of excitatory neurotransmission in the CNS: disruption of afferent impulse transmission, alteration of cortico-subcortical connections, functions of the interbrain, midbrain, spinal cord, etc. The resulting widespread neurodepression triggers the development of anesthesia.

Theories of narcosis

- ▶ Coagulation theory (1864): coagulation of intracellular protein results in disruption of nerve cell functions.
- ▶ Lipoid theory (1899, 1901): the solubility of anesthetics in the lipid membranes of neurons disrupts their functions.
- ▶ Adsorption theory (surface tension theory, 1904–1913): a decrease in the surface tension of the neuronal membrane disrupts their functions.
- ▶ Theory of disrupted oxidation processes (1912): the functions of enzymes regulating metabolism in nerve cells are inhibited.
- ▶ Pauling's microcrystal theory (1961): general anesthetics in aqueous solutions form crystals that disrupt the ion permeability of the neuronal membrane and block the process of depolarization.
- ▶ Membrane theory (1963): disruption of lipid connection with fast-acting neurotransmitter channels; sodium and potassium channels in the cell membrane close, inhibiting nerve impulse transmission.

One of the modern theories suggests a receptor-mediated mechanism of action.

- ▶ The action of hexobarbital, sodium thiopental, and sodium oxybutyrate is associated with the GABAA-benzodiazepine-barbiturate receptor complex. At therapeutic concentrations, they activate GABAA receptors, resulting in the opening of Cl^- channels in neurons, increased flow of ions inside the neuron and then membrane hyperpolarization, which enhances the inhibitory effects (Fig. 4.1).
- ▶ Ketamine, xenon and nitrous oxide act by blocking the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors, preventing glutamate from interacting with these receptors. Ion channels are closed, reducing the neuronal cell's permeability for cations, especially Ca^{2+} , which causes CNS inhibition (Fig. 4.2).

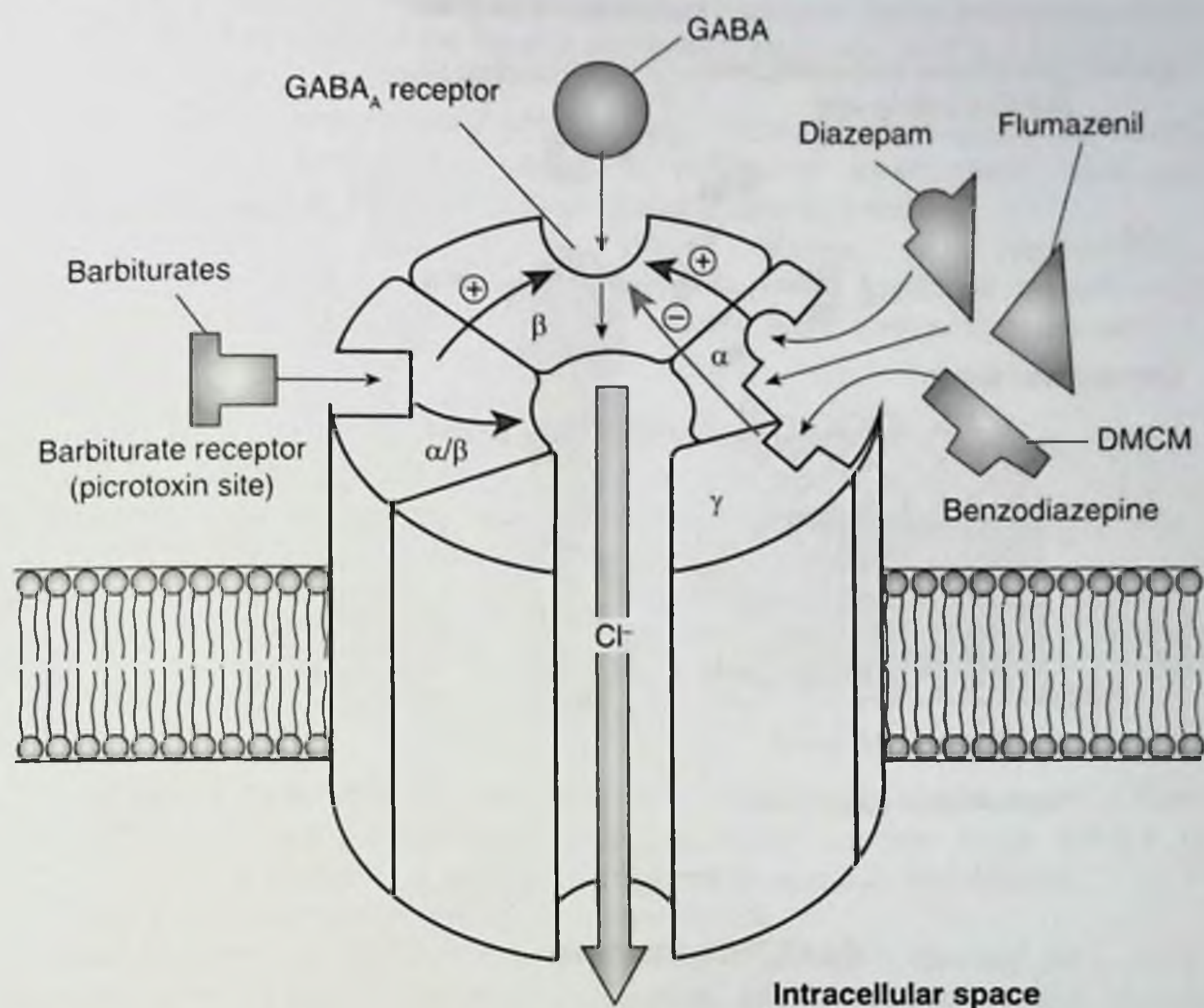


Fig. 4.1. GABA_A receptor (original image taken from <http://www.pharmacy180.com/article/barbiturates-1142/>). GABA — γ -aminobutyric acid; DMCM — methyl-6,7-dimethoxy-4-ethyl- β -carboline-3-carboxylate (β -carboline, GABA_A receptor negative allosteric modulator)

Inhalation anesthesia

Advantages: wide range of narcotic action, significant muscle relaxation and sufficient depth of anesthesia, painless induction, convenient to manage, rapid emergence

Disadvantages: presence of excitement stage, irritation of mucous membranes of respiratory tract; the anesthetic gas mixture can enter into the operating room air, special equipment is required, high costs. Certain drugs are combustible or explosive

Therapeutic indications: induction and/or maintenance anesthesia in surgical interventions

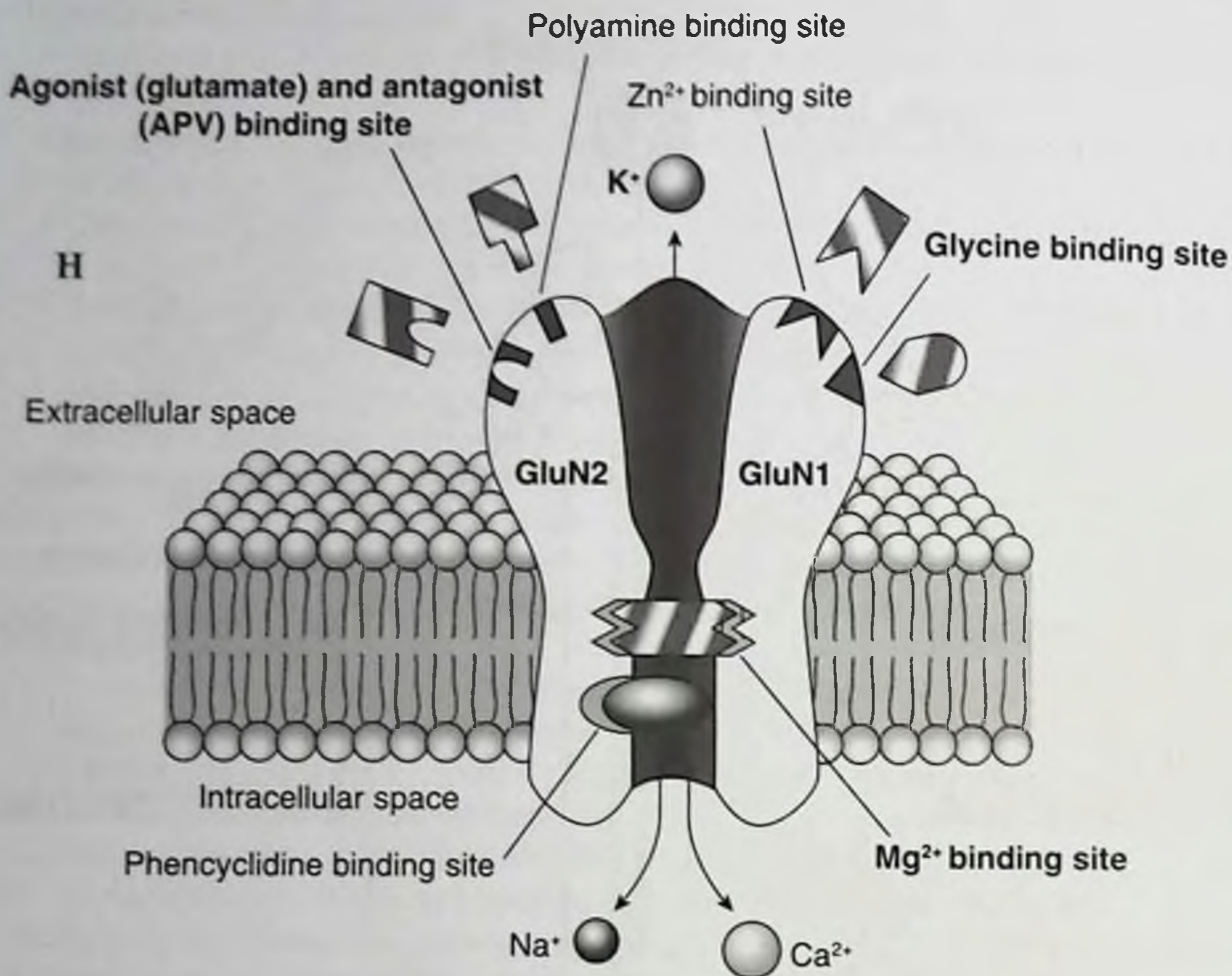


Fig. 4.2. NMDA receptor (Mor A. et al., 2007)

Specifics of individual products

Halothane (Phthorothane*)

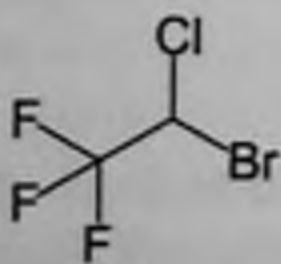


Fig. 4.3. 2-bromo-1,1,1-trifluoro-2-chloroethane

► Fluorine-containing aliphatic compound, high narcotic activity (50 times higher than nitrous oxide). The excitement stage is minimal, the onset of general anesthesia is 3–5 min, the emergence period is 5–10 min. Non-flammable and non-explosive. Does not irritate mucous membrane of the respiratory tract, rapidly enters highly vascularized organs (brain, heart, liver), muscles and adipose tissue, crosses the BBB and placental barrier. Muscle relaxing effect is not sufficient (used in combination with non-depolarizing muscle relaxants). Depresses the vasomotor center, blocks the ganglia of the sympathetic nervous system, directly stimulates smooth muscle activity in the blood vessels: reduces cerebral vascular resistance (increases cerebral blood flow and ICP), decreases BP. Sensitizes cardiomyocytes to catecholamines (possibility of arrhythmias). Increases vagal tone, causing bradycardia.

- ▶ Metabolized in the liver to form chlorides, bromides, and trifluoroacetic acid. 60–80% is excreted by the lungs as unchanged substance, 20% is excreted in the urine as inactive metabolites.

Side effects: arrhythmias, hypotension, increased intracranial pressure; hepatotoxicity; nephrotoxicity; respiratory depression; eosinophilia; malignant hyperthermia; after awakening: headache, tremor, nausea, vomiting

Contraindications: liver and/or kidney disease, pheochromocytoma, hypercatecholaminemia, hypotension, myasthenia gravis, malignant hyperthermia (history thereof), pregnancy (first trimester), childbirth and early postpartum period

Enflurane (Ethrane*)

- ▶ Fluorine-containing aliphatic compound, structural isomer of isoflurane. Non-flammable and non-explosive. No excitation stage. Decreases myocardial contractility but increases HR, induces peripheral vasodilation. Sensitizes the myocardium to catecholamines to less than halothane. Mild muscle relaxing action. Increases cerebral blood flow, ICP, decreases brain tissue oxygen consumption. Relaxes the myometrium.

- ▶ A negligible amount (2.4%) undergoes metabolism in the liver to form difluoromethoxydifluoroacetic acid; excreted by the lungs (80%) as unchanged substance, partially excreted in the urine as metabolites.

Additional therapeutic indication: caesarean section

Side effects: labile BP, arrhythmias, hepatic impairment, elevated AST, ALT, respiratory depression, malignant hyperthermia, after awakening: chills, nausea, vomiting

Contraindications: malignant hyperthermia (history thereof), pregnancy (except during childbirth), breastfeeding

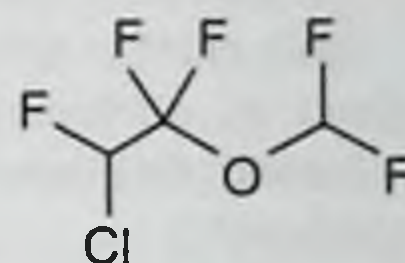


Fig. 4.4. 2-Chloro-1-(difluoromethoxy)-1,1,2-trifluoroethane

Isoflurane (Forane*)

- ▶ Enflurane isomer. Depresses respiration less than enflurane but more than halothane. Sensitizes the myocardium to catecholamines less than enflurane. Dilates blood vessels, induces profound muscle relaxation, does not affect cerebral blood flow.

- ▶ A negligible amount (0.2%) undergoes metabolism in the liver to form trifluoroacetic acid; excreted by the lungs (95%) as unchanged substance, partially excreted in the urine as metabolites.

Additional therapeutic indication: caesarean section

Side effects: respiratory depression, arrhythmias, hypotension, irritation of the mucous membrane of the respiratory tract; during awakening: tremor, nausea, vomiting

Contraindications: malignant hyperthermia (history thereof), pregnancy (except during childbirth), breastfeeding

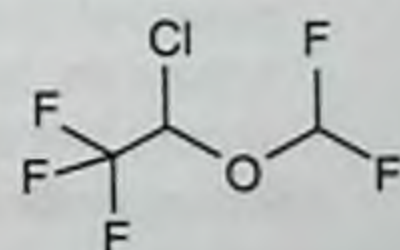


Fig. 4.5. 2-Chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane

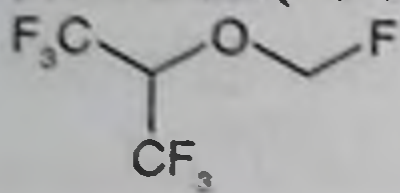
Sevoflurane (Sevorane[®])

Fig. 4.6. 1,1,1,3,3,3-Hexafluoro-2-(fluoromethoxy)-propane

- ▶ Fluorine-containing aliphatic compound, non-flammable and non-explosive. It is the only fluorinated inhalational anesthetic that is not metabolized to trifluoroacetic acid (toxic metabolite). Does not affect myocardial sensitivity to catecholamines. The effect on cerebral circulation is comparable for sevoflurane and isoflurane.

- ▶ A negligible amount (5%) undergoes metabolism in the liver (defluorination to form hexafluoroisopropanol that binds to glucuronic acid); excreted by the lungs (95%) as unchanged drug, partially excreted in the urine as a non-toxic metabolite.

Side effects: arrhythmias, hypotension, respiratory depression, mental disorders (agitation), somnolence, dizziness, headache, laryngospasm

Contraindications: malignant hyperthermia (history thereof), pregnancy, breastfeeding

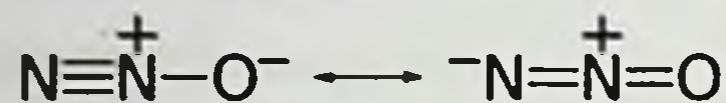
Dinitrogen oxide (nitrous oxide⁺, N₂O, laughing gas)

Fig. 4.7. Dinitrogen oxide

- ▶ Exhibits low narcotic activity and is used in combination with other inhalational anesthetics. Typically a mixture of 80% nitrous oxide and 20% oxygen is used to prevent hypoxia. It induces pronounced analgesia, but depth of narcosis is not sufficient; does not induce muscle relaxation. The analgesia stage occurs in 2–3 min. After 6–8 minutes, plane I of surgical anesthesia occurs. Emergence occurs in 3–5 minutes following drug discontinuation. Crosses the BBB and placental barrier. Non-flammable, non-explosive, but combustible. Does not irritate the mucous membrane of the respiratory tract. Exerts cardiodepressive action. Not metabolized. T_{1/2}: 5–6 min, excreted by the lungs in 10–15 min.

Additional therapeutic indications: severe pain (myocardial infarction, acute pancreatitis, etc.)

Side effects: bradycardia, circulatory failure, megaloblastic anemia, leukopenia and thrombocytopenia (inactivates the vitamin B12-dependent enzyme, methionine synthase); postoperative delirium (anxiety, confusion, agitation, hallucinations, nervousness); nausea, vomiting, somnolence, postoperative shivering

Contraindications: severe mental illness (schizophrenia, etc.)

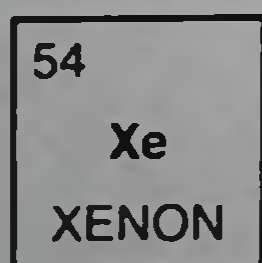


Fig. 4.8. Xenon

Xenon (Medxenon[®])

- ▶ Noble gas, non-flammable and non-combustible. High narcotic activity (2 times higher than nitrous oxide). Used in a 60:40, 70:30, 80:20 mixture with oxygen for anesthesia. Surgical anesthesia occurs in 4–5 min. Short-term euphoria

and psychomotor agitation possible at the start of inhalation. Produces anesthetic, analgesic, and muscle relaxing effects. Has cardioprotective and neuroprotective effects. Does not irritate the bronchial mucosa or affect the peripheral vascular tone; does not increase ICP. Not metabolized, excreted by the lungs in 4–5 min.

Therapeutic indications: see “Dinitrogen oxide (nitrous oxide♦)”

Side effects: nausea, vomiting, hoarseness, metallic taste in mouth

Contraindications: surgery on the lungs, trachea, and bronchi related to pneumothorax when hyperoxic gas mixtures are needed; procedures and manipulations performed in non-invasive ventilation conditions (reconstructive surgery of the trachea and bronchi); pregnancy, breastfeeding

Non-inhalation anesthesia

Advantages: convenient and easy to use; rapid onset of anesthesia; no excitement stage; used for induction and maintenance anesthesia

Disadvantages: difficult to manage, insufficient depth of anesthesia; risk of phlebitis, thrombophlebitis; mostly short-term anesthesia; narrow range of narcotic action

Therapeutic indications:

- ▶ Induction and maintenance anesthesia for surgical interventions in outpatient and inpatient settings
- ▶ Painful diagnostic and treatment procedures (endoscopy, cardiac catheterization, treatment of burn injuries, etc.)

Propanidid (Sombrevin®)

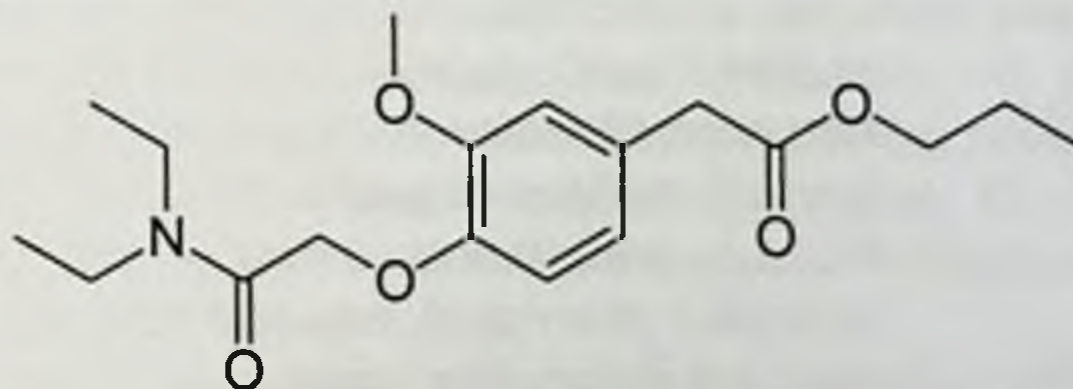


Fig. 4.9. 4-[2-(Diethylamino)-2-oxoethoxy]-3-methoxybenzoic acid propyl ester

- ▶ Ultra short-acting (3 min), rapidly hydrolyzed by plasma cholinesterase. The analgesic effect is mild, occurring in 20–40 seconds following intravenous administration; the stage of surgical anesthesia lasts 3–5 min. Consciousness restored in 2–3 min following drug discontinuation. No post-anesthesia CNS depression. Decreases cardiac output, TPR, dilates coronary vessels, decreases BP, induces tachycardia. Decreases skeletal muscle tone, cerebral blood flow, brain oxygen consumption, ICP, and cerebral perfusion pressure. Facilitates histamine release from mast cells.
- ▶ Metabolized in the liver, excreted in the urine. For intravenous administration.

Side effects: hyperventilation with short-term apnea, bronchospasm, tachycardia, hypotension, nausea, vomiting, muscle twitching, thrombophlebitis, hemolysis (at high doses)

Contraindications: hemolytic jaundice, liver and kidney failure, CHF, hypotension, epilepsy, bronchial asthma

Propofol (Diprivan*)

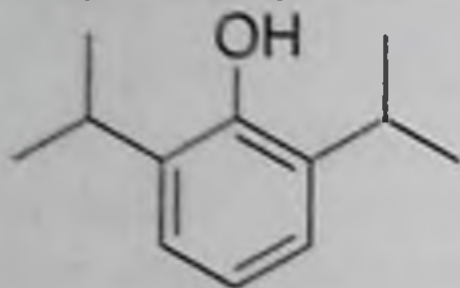


Fig. 4.10. 2,6-bis-(1-Methylethyl)phenol

► Phenol derivative. Lipid-soluble, crosses the BBB and placental barrier. Onset of action: 30–60 seconds, duration of action: 3–10 min. Rapid recovery. Exerts neuroprotective action. Induces sufficient muscle relaxation. Decreases ICP and cerebral perfusion pressure. The mechanism of action is associated with potentiation and modulation of the GABA_A receptor activity, which slows down ion channel closure.

Propofol at high doses is a GABA_A receptor agonist.

- Metabolized in the liver by conjugation to form water-soluble inactive metabolites (glucuronides and sulfates), excreted in the urine. For intravenous administration.

Side effects: short-term respiratory arrest, hypotension, bradycardia, decreased cerebral circulation, fever, phlebitis and venous thrombosis

Contraindications: history of allergic reactions to chicken egg yolk and propofol, hyperlipidemia, cerebrovascular disease, pregnancy

Ketamine (Calypsol*)

- Lipophilic compound, crosses the BBB and placental barrier. Non-competitive NMDA receptor antagonist (binds to phencyclidine sites on the inner surface of NMDA receptor channels) in the CNS. Induces dissociative anesthesia due to

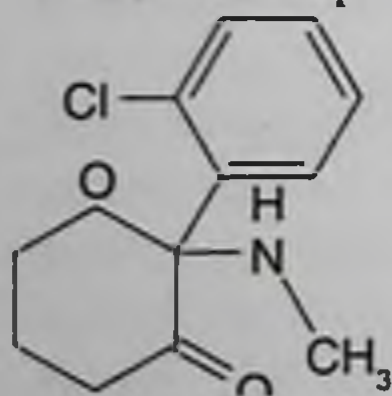


Fig. 4.11. (±)-2-(Methylamino)-2-(2-chlorophenyl)cyclohexanone (as a hydrochloride)

impaired conduction of associative pathways of the brain (interrupts thalamocortical connections), resulting in sensory blockade and loss of general sensitivity: the patient does not feel pain, partially loses consciousness, but their reflexes are preserved (pharyngeal, laryngeal, cough). Surgical anesthesia does not occur. The effect occurs in 30–60 seconds and lasts 5–10 min following intravenous administration; when administered intramuscularly, the effect occurs in 2–6 min and lasts 15–30 min. No muscle relaxation. Increases BP, myocardial contractility, cardiac output, myocardial oxygen demand, cerebral blood flow, brain oxygen consumption,

ICP; does not depress respiratory center at therapeutic doses.

- Metabolized in the liver by demethylation; T_{1/2}: 2–3 hours, excreted in the urine. For intravenous, intramuscular administration.

Side effects: increased BP, tachycardia; hypersalivation, bronchorrhea, nausea; diplopia, nystagmus, increased IOP; involuntary muscle activity, hypertonicity, psychomotor agitation, hallucinations, disorientation; with rapid intravenous administration: respiratory depression; tenderness and hyperemia along the vein at the injection site

Contraindications: hypertension, angina pectoris, myocardial infarction, decompensated heart failure; chronic kidney failure; cerebrovascular disease; pre-eclampsia, eclampsia; epilepsy and other disorders accompanied by seizure susceptibility; alcoholism; pregnancy and breastfeeding

Sodium thiopental (Thiopental[®])

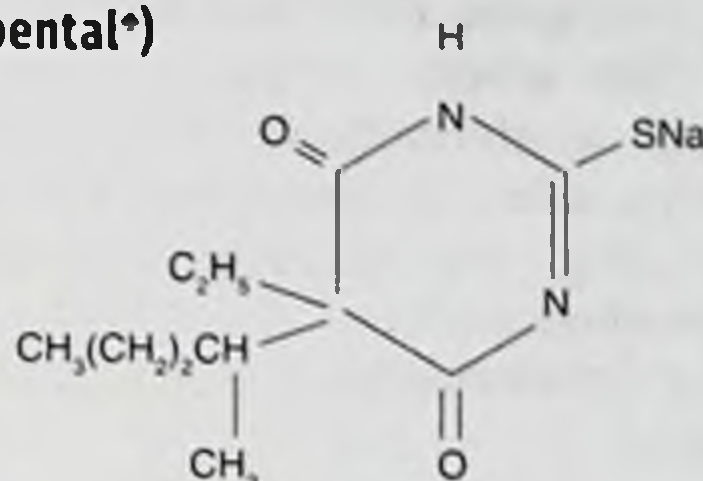


Fig. 4.12. 5-Ethylidihydro-5-(1-methylbutyl)-2-thioxo-4,6-(1H,5H)-pyrimidinedione monosodium salt

- ▶ Thiobarbituric acid derivative. Its pharmacological properties are similar to those of Hexenal. Exerts sedative, hypnotic, anticonvulsant action (inhibits midbrain reticular formation and attenuates its activating effect on the cerebral cortex). The onset of general anesthesia is 30–40 seconds; the effect lasts 10–30 min. The duration of action is associated with the drug accumulating in large quantities in adipose tissues (drug concentration in adipose tissue depots is 6–12 times higher than in plasma). Has cardiodepressive action, decreases hepatic blood flow and glomerular filtration rate, excites vagus nerve. Decreases the brain's metabolic processes, thus the use of glucose and oxygen by the brain.
- ▶ Metabolized in the liver to form inactive metabolites; 3–5% of the dose is desulfated to pentobarbital, a negligible amount is inactivated in the kidneys and brain; $T_{1/2}$ at the distribution phase: 5–9 min, $T_{1/2}$ at the elimination phase: 3–8 hours; excreted in the urine. Repeated dosing results in accumulation. Prescribed for very slow intravenous administration since it depresses the respiratory and vasomotor centers when blood concentrations increase rapidly (causes apnea and collapse).

Additional therapeutic indications: status epilepticus, prophylaxis of cerebral hypoxia (artificial circulation, neurosurgical procedures)

Side effects: respiratory depression, laryngospasm, bronchospasm, bradycardia, hypotension, anterograde amnesia, phlebitis and vein thrombosis

Contraindications: liver disease, kidney disease, heart failure, porphyria, collapse, diabetes mellitus, bronchial asthma, fever, sepsis

Hexobarbital (Hexenal[®])

- ▶ Barbituric acid derivative. Exerts hypnotic, narcotic action. Depresses the respiratory and vasomotor centers, blocks sympathetic ganglia. Exerts cardiodepressive action, dilates peripheral blood vessels and increases vagal tone to a lesser extent than sodium thiopental. Anesthesia occurs in 1.0–1.5 min and lasts 20–30 min. In plasma, the water-soluble form is quickly converted to the non-ionized lipophilic form, which crosses the BBB and placental barrier.

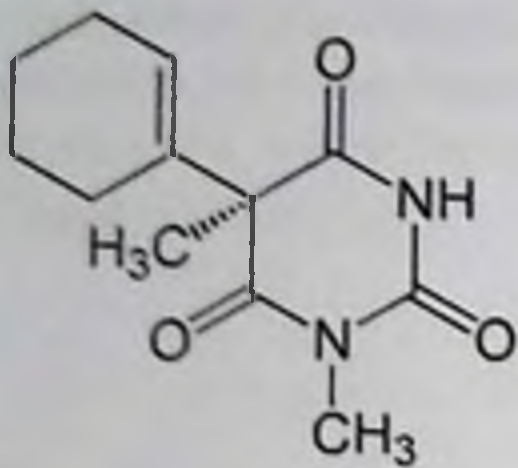


Fig. 4.13. 5-(1-Cyclohexen-1-yl)-1,5-dimethyl-2,4,6-trimethylpyrimidinetrione (as a sodium salt)

► Metabolized in the liver by oxidation to form oxy-, keto- and carboxybarbituric compounds, dealkylation or destruction of the barbituric ring to substituted urea derivatives. Excreted in the urine as free substance and conjugates. For intravenous administration.

Side effects: respiratory depression (particularly with rapid administration), bradycardia, hypotension (reflex tachycardia); at awakening: tremor, convulsions, nausea, vomiting; hypersalivation, laryngospasm, bronchospasm, thrombophlebitis

Contraindications: renal and hepatic impairment, heart failure, hypotension

Sodium oxybutyrate (Sodium oxybate[®])

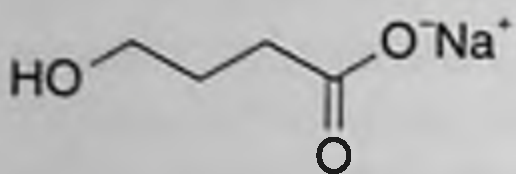


Fig. 4.14. Sodium salt of γ -hydroxybutyric acid

► Crosses the BBB. Surgical anesthesia occurs in 30–40 min and lasts 1.5–3.0 hours. Exerts sedative, hypnotic, anesthetic, and antihypoxic action. Has a tranquilizing effect at low doses but induces narcosis and muscle relaxation at high doses. Increases myocardial contractility and glomerular filtration, exhibits anticonvulsant activity. Slows down breathing rate and increases breathing depth.

► Metabolized in the liver to form carbon dioxide and water. $T_{1/2}$: 40–50 min. Excreted in the urine. For intravenous, intramuscular administration.

Additional therapeutic indication: hypoxic cerebral edema (combination therapy)

Side effects: nausea, vomiting; following rapid intravenous administration: agitation, muscle hyperactivity, respiratory impairment including respiratory arrest; recovery from anesthesia: motor and speech excitation

Contraindications: myasthenia gravis, pregnancy

LOCAL ANESTHETICS

Local anesthetics (from the Greek *an-*, meaning “without”, and *aísthēsis*, meaning “sensation”) are a group of drugs that reduce the excitability of sensory nerve endings or nerve trunks and block the conduction of afferent impulses.

In 1860, A. Niemann, a German scientist, isolated cocaine from the leaves of the shrub *Erythroxylum coca* which is native to South America and has local anesthetic effects. In 1905, Procaine (Novocaine[®]) was synthesized and used by A. Einhorn, a German chemist. N. Löfgren and B. Lundqvist, Swedish chemists, discovered lidocaine in 1943 (first used in 1948) and trimecaine in 1946. A. F. Ekenstam synthesized mepivacaine and bupivacaine in the USA in 1957–1958, while P. Rusching and M. Lipp synthesized articaine in Germany in 1969.

Cocaine, a benzoic acid derivative, was the first local anesthetic. By the beginning of the 20th century, it had been completely eliminated from medical practice due to its high toxicity. Its systemic action mainly stimulates the CNS: euphoria and psychomotor agitation are typical, convulsions are possible. Repeated dosing results

in addition. In 1963, cocaine was included in the "Bulletin on Narcotics I" of the Single Convention on Narcotic Drugs by the United Nations.

Classification

1. Drugs for topical (terminal) anesthesia
 - Esters
 - Benzocaine (Anesthesin[®])
 - Tetracaine (Dicaine[®])
 - Substituted amides
 - Bupivacaine (Bupivacaine[®]).
2. Drugs used for infiltration, conduction, epidural, spinal anesthesia
 - Esters
 - Procaine (Novocaine[®]).
 - Substituted amides
 - Bupivacaine (Bupivacaine[®]).
 - Articaine (Ultracaine[®], Septonest[®]).
 - Mepivacaine (Scandonest[®], Mepivastesin[®]).
 - Ropivacaine (Naropin[®]).
3. Drugs used for all types of anesthesia
 - Substituted amides
 - Lidocaine (Xylocaine[®], Xycaine[®])
 - Trimecaine (Mesocain[®])

Local anesthetics have the following chemical structure: "aromatic part — intermediary link — amine part" (Fig. 4.15).

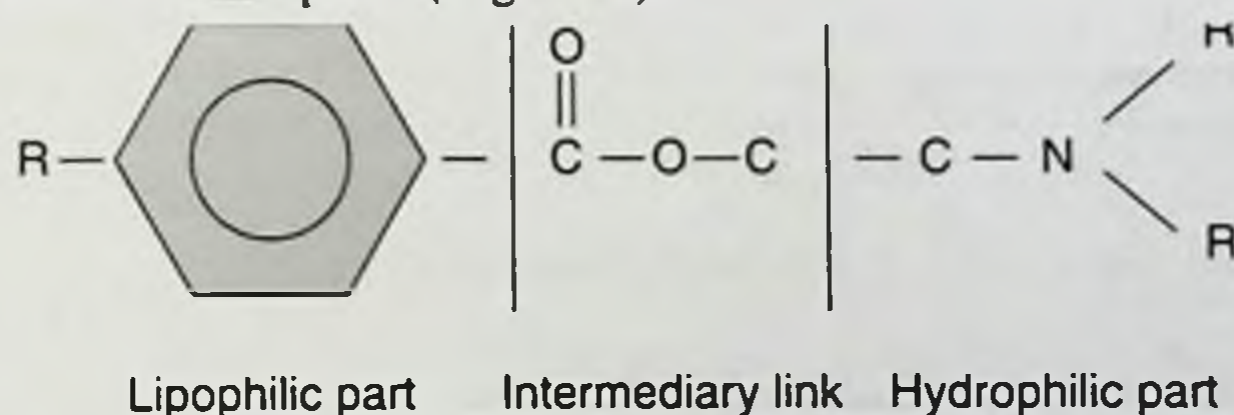


Fig. 4.15. Chemical structure of local anesthetics

The aromatic part determines the drug's lipophilicity, while the amine part determines its hydrophilicity. The intermediary link is an ester or amide group. Attaching additional groups to the aromatic ring or to the amine group enhances the anesthetic's effect.

Local anesthetics are divided into ester and amide anesthetics.

- ▶ Esters (amino esters) with an ester bond located between the aromatic end and the intermediary link; PABA derivatives; undergo rapid hydrolysis by plasma and tissue pseudocholinesterase, often cause allergic reactions; excreted in the urine as water-soluble metabolites.
- ▶ Amides (amino amides) with an amine bond between the aromatic ring and the intermediary link; lipophilic, superior to esters with regard to the onset and duration of anesthesia. Less likely to cause allergic reactions, metabolized in the liver; metabolism is significantly slower than hydrolysis of ester local anesthetics.

Mechanism of action: Block voltage-gated sodium channels of plasma membranes in nerve fibers, therefore increasing their excitation threshold and decreasing AP. This prevents membrane depolarization and disrupts impulse transmission via nerve fibers. Hydrophobic (non-ionized) compounds pass through the axonal membrane and block the sodium channels on the inside of the cell. Hydrophilic (ionized) compounds produce a blocking effect by penetrating open sodium channels (Fig. 4.16).

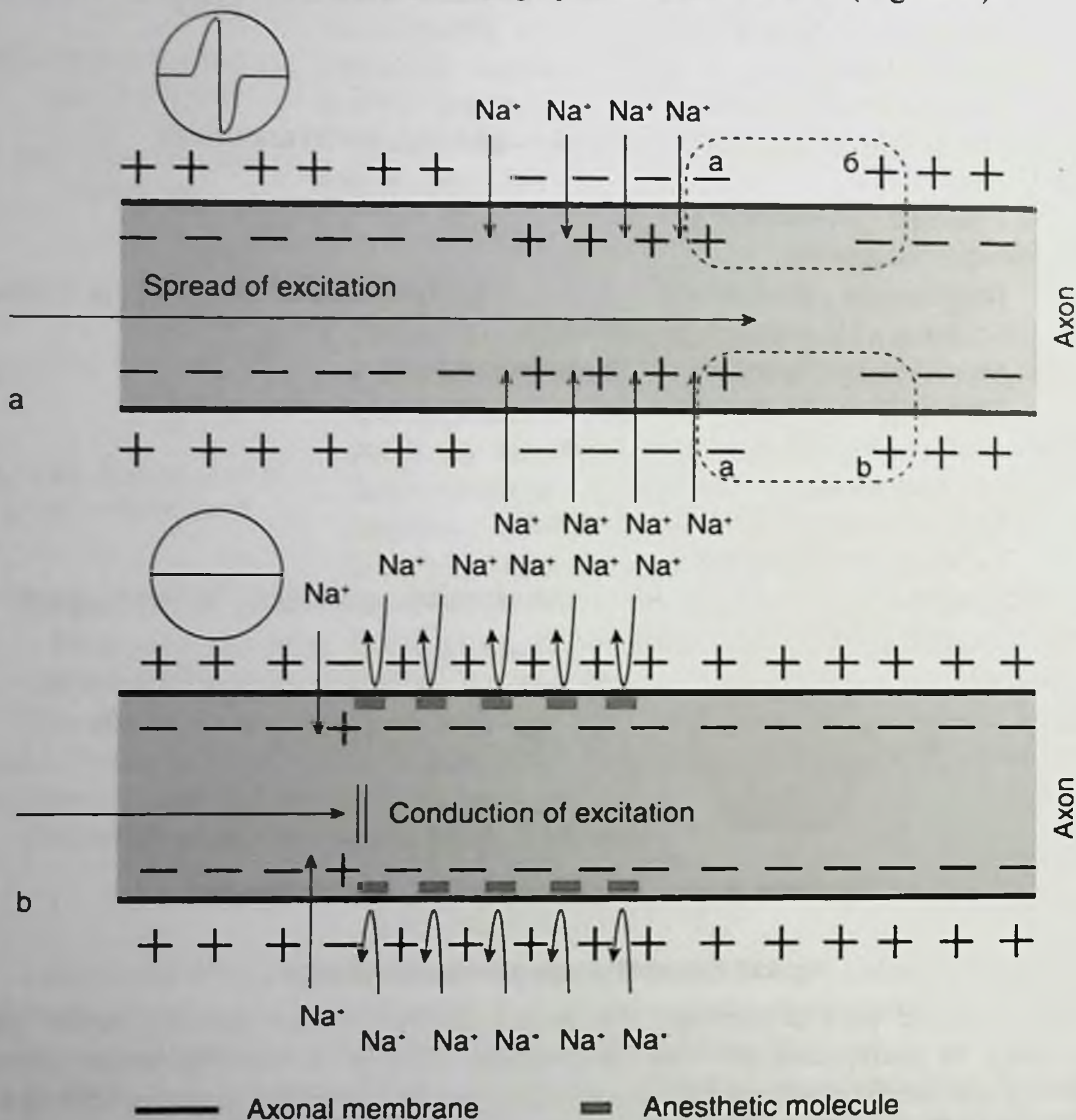


Fig. 4.16. Action of anesthetics on excitation conduction via nerve fibers (Kharkevich D.A., 2021): a — before administration of an anesthetic. Excitation spreads along the nerve. The local current between points "a" and "b" causes mild depolarization in the "b" area, increasing the membrane's permeability for sodium ions. Their influx inside the axon increases the degree of depolarization. At a certain level of depolarization, the action potential appears (the screen of an oscilloscope with the action potential is marked with a circle above) and the excitation wave continues to spread; b — after administration of an anesthetic. By binding to the membrane, the anesthetic prevents sodium ions from crossing into it and causing depolarization, thereby preventing the action potential and blocking excitation.

Specifics of individual products

Benzocaine (Anesthesin⁺)

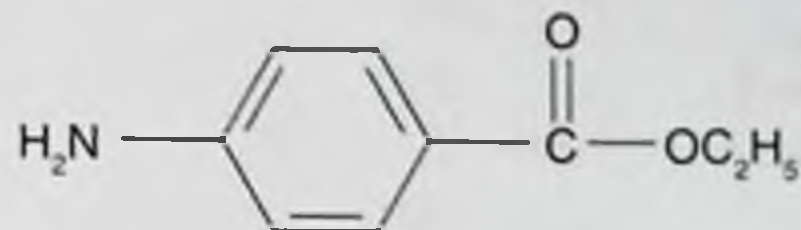


Fig. 4.17. Para-aminobenzoic acid ethyl ester

- ▶ Para-aminobenzoic acid derivative. Poorly water-soluble. The absorption is minimal with topical and oral administration; when applied to mucous membranes, the onset of action is 1 min, and the duration of action is 15–20 min.
- ▶ Metabolized by plasma pseudocholinesterase to form para-aminobenzoic acid and ethanol. Excreted in the urine as metabolites. For topical, oral, rectal administration.

Therapeutic indications: topical anesthesia; diagnostic procedures involving mucous membranes (gastroscopy, rectoscopy, otoscopy, ureteroscopy, gynecological procedures); gastralgia, esophagitis, stomach and duodenal ulcers; rectal disorders (perianal fissures, hemorrhoids); otitis, skin conditions

Side effects: allergic reactions

Contraindications: history of allergic reactions, breastfeeding

Combination drugs with benzocaine:

- ▶ Bellasthesin⁺ (belladonna extract, benzocaine)
- ▶ Anesthesol⁺ (benzocaine, bismuth subgallate, zinc oxide, levomenthol)
- ▶ Nigepan⁺ (sodium heparin, benzocaine)
- ▶ Almagel A⁺ (algedrate, benzocaine, magnesium hydroxide)

Tetracaine (Dicaine⁺)

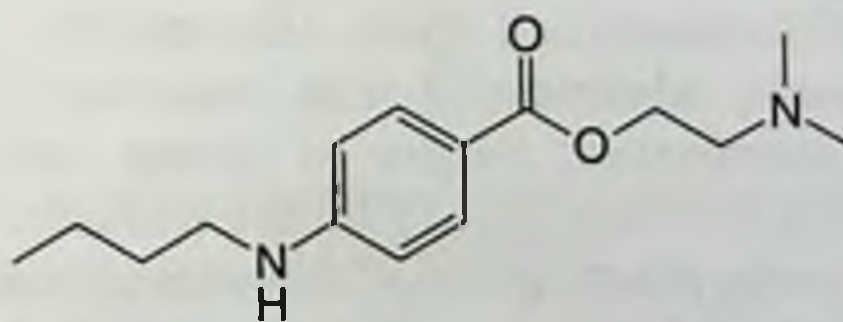


Fig. 4.18. 2-(Dimethylamino)ethyl-4-(butylamino)benzoate

- ▶ It is included in the product “Anti-Angin” in combination with chlorhexidine for the prophylaxis and treatment of infectious and inflammatory diseases of the mouth and throat. For topical administration.
- ▶ When applied to the mucous membrane of the eye, does not affect IOP and accommodation, does not dilate the pupils. Anesthesia occurs in 2–5 min and lasts 15–20 min. Limited use due to high toxicity (10 times more toxic than Procaine).

Therapeutic indications: topical anesthesia

Side effects: irritation of mucous membranes, allergic contact dermatitis, burning sensation, swelling at application site; with long-term administration: keratitis, persistent corneal opacity, delayed re-epithelialization

Contraindications: injury or inflammation of the conjunctiva

Bumecaine (Pyromecaine®)

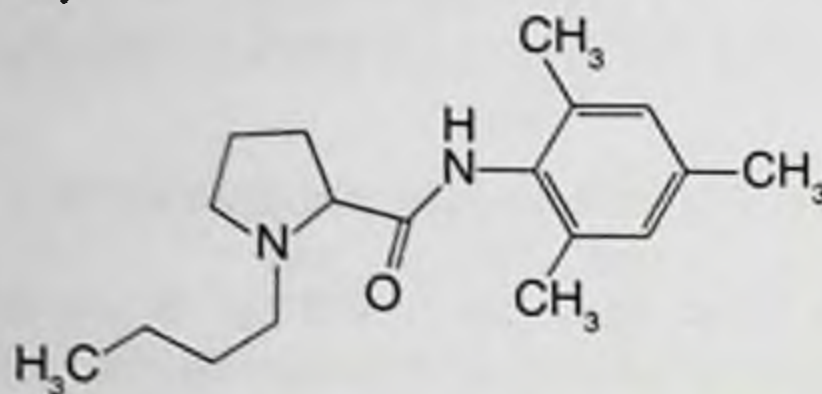


Fig. 4.19. 1-Butyl-2',4',6'-trimethyl-2-pyrrolidinecarboxanilide

- ▶ Its chemical structure is similar to that of trimecaine. Non-inferior to lidocaine with regard to duration of action; less toxic. The onset of anesthesia is 1–2 min, the duration of anesthesia is 30–40 min.

Therapeutic indications: topical anesthesia

Side effects: allergic reactions

Contraindications: allergic reactions

Procaine (Novocaine®)

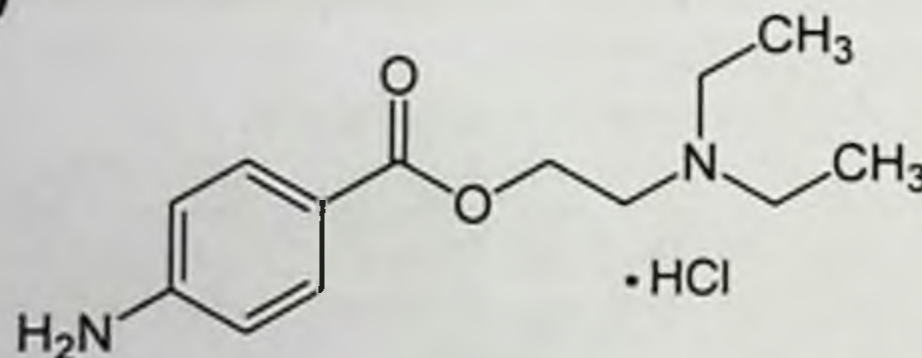


Fig. 4.20. 2-(Diethylamino)ethyl-4-aminobenzoate (as a hydrochloride)

- ▶ Ester of diethylaminoethanol and PABA. Low toxicity, wide therapeutic range. Dilates blood vessels, administered with vasoconstrictors. Poorly absorbed through mucous membranes, inferior to amides with regard to anesthetic activity, short-acting (the duration of infiltration anesthesia is 0.5–1.0 hours).
- ▶ Undergoes hydrolysis by plasma pseudocholinesterase to form active metabolites, diethylaminoethanol, and para-aminobenzoic acid. Excreted predominantly as metabolites in the urine, $T_{1/2}$: 30–50 s.

Therapeutic indications: infiltration, conduction, epidural, spinal anesthesia, hemorrhoids, anal fissures

Side effects: dizziness, weakness, hypotension, collapse, nausea, vomiting, allergic reactions

Contraindications: allergic reactions

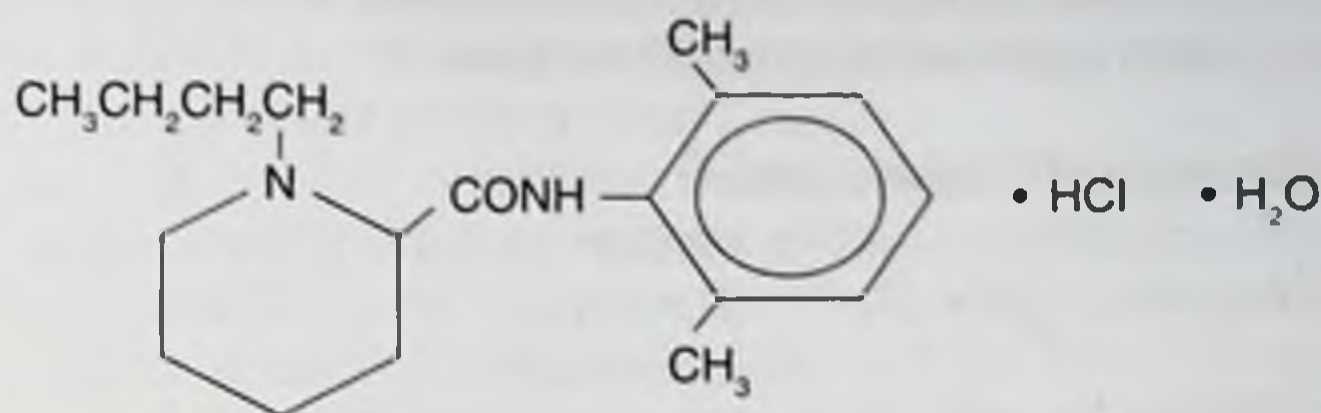
Bupivacaine (Marcaine®)

Fig. 4.21. 1-Butyl-N-(2,6-dimethylphenyl)-piperidine-2-carboxamide (and as a hydrochloride)

- ▶ Its chemical structure is close to that of lidocaine. Superior to lidocaine in its activity (4 times more effective); long-acting local anesthetic. Exhibits relatively high toxicity. Anesthesia occurs in 5–10 min, the duration of action is 3–4 hours following epidural administration and 7 hours following conduction anesthesia. Exerts vasodilating action, used in combination with vasoconstrictors.
- ▶ Metabolized in the liver by conjugation with glucuronic acid, $T_{1/2}$: 2.7 hours, excreted in the urine (6% is excreted as unchanged substance).

Therapeutic indications: infiltration, conduction, epidural, spinal anesthesia

Side effects: ventricular arrhythmias, decompensated heart failure, cardiac arrest, hypotension; tremor, convulsions, visual and hearing impairment

Contraindications: hypovolemia, hypotension, CHF, pregnancy, breastfeeding

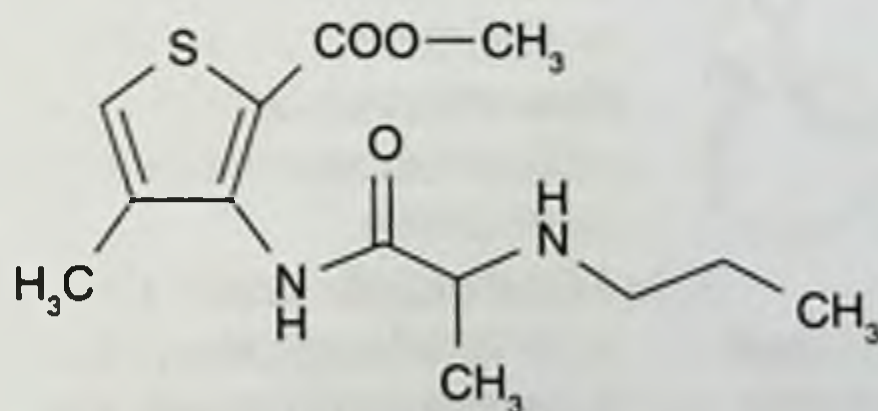
Articaine (Ultracaine®)

Fig. 4.22. Methyl-3-[[1-oxo-2-(propylamino)propyl]amino]-2-thiophenecarboxylic acid methyl ester (as a hydrochloride)

- ▶ Thiophenecarboxylic acid amide that is 4–5 times more active than Procaine and 1.5 times more active than lidocaine. Dilates blood vessels, thus administered with vasoconstrictors. The onset of infiltration, conduction anesthesia is 1–5 min. The duration of action is 60 min without vasoconstrictors and 2.5–3.0 hours with vasoconstrictors. Poorly crosses the placental barrier, making it the drug of choice in pregnant and breastfeeding women.
- ▶ Metabolized in the liver to form an inactive metabolite (articainic acid), $T_{1/2}$: 60–80 min. Excreted in the urine and bile. For topical administration.

Therapeutic indications: infiltration, conduction, spinal, epidural anesthesia

Side effects: headache, diplopia, blurred vision; muscle twitching, allergic reactions

Contraindications: hypotension, allergic reactions

Mepivacaine (Scandonest⁺, Mepivastesin⁺)

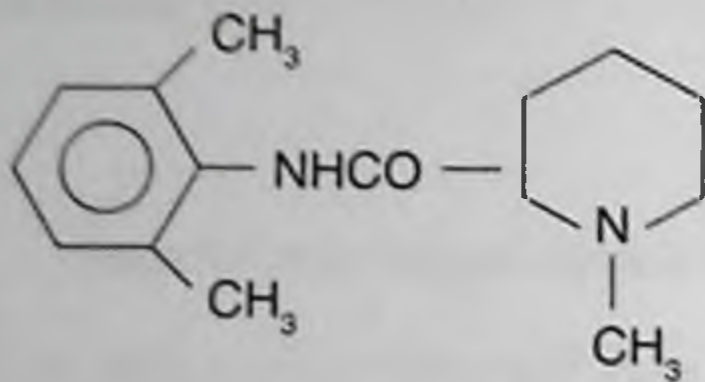


Fig. 4.23. N-(2,6-Dimethylphenyl)-1-methyl-2-piperidinecarboxamide

► Methyl analog of bupivacaine. Does not dilate blood vessels and can be used without a vasoconstrictor. Onset of action is 3–20 min, duration of action is up to 3 hours.

► Metabolized in the liver by hydroxylation and dealkylation to t-hydroxymepivacaine, p-hydroxymepivacaine, pipecolylxylidine; undergoes enterohepatic recirculation. $T_{1/2}$: 2–3 hours. Metabolites are excreted in the bile, 5–10% is excreted in the urine as unchanged drug.

Therapeutic indications: infiltration, conduction, epidural anesthesia

Side effects: headache, tinnitus, weakness; slurred speech, difficulty swallowing, visual impairment; convulsions, tremor; bradycardia, ventricular arrhythmia, nausea, vomiting; allergic reactions

Contraindications: severe liver disease, myasthenia gravis, acute heart failure, hypotension, allergic reactions

Ropivacaine (Naropin⁺)

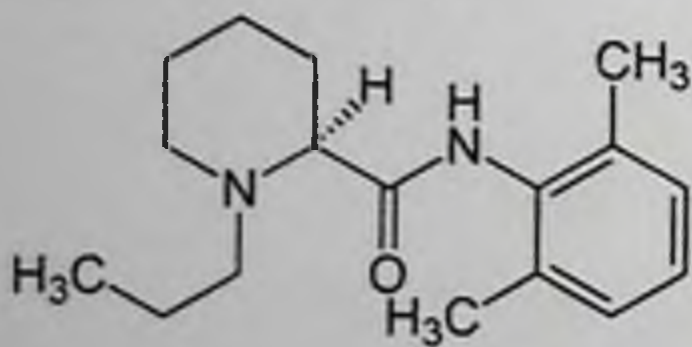


Fig. 4.24. (S)-N-(2,6-Dimethylphenyl)-1-propyl-2-piperidinecarboxamide

► The onset of action for epidural anesthesia is 10–20 min, the duration of action is 3–6 hours; the onset and duration of action for conduction and infiltration anesthesia is 1–15 min and 2–6 hours, respectively.

► Metabolized in the liver by aromatic hydroxylation to 3-hydroxy-ropivacaine and 4-hydroxyropivacaine, excreted in the urine.

Therapeutic indications: infiltration, conduction, epidural anesthesia

Side effects: labile BP, arrhythmias, neuropathies, nausea, vomiting, allergic reactions

Contraindication: allergic reactions

Lidocaine (Xycaine⁺, Xylocaine⁺)

► Acetanilide derivative. Crosses the BBB, placental barrier, excreted into breast milk. Its anesthetic activity is 2.5–4.0 times higher than that of Procaine and lasts 2 times longer. Dilates blood vessels, combined with vasoconstrictors. Does not cause local irritation. The anesthetic effect occurs in 2–4 min, the duration of action is 30–75 min without vasoconstrictors and 2–4 hours with vasoconstrictors. Exerts marked antiarrhythmic action (blocks the flow of Na^+ ions in myocardial cells, inhibits the automatism of ectopic foci, does not affect

conductivity and contractility). The effect occurs in 1 min following intravenous administration and 15 min following intramuscular administration. The duration of action is 10–20 min following intravenous administration and about 60–90 min following intramuscular administration.

- ▶ Metabolized in the liver by oxidative deethylation of the amino group, breakage of the amide bond to form active metabolites (monoethylglycinexylidine and glycinexylidine), $T_{1/2}$: 2 and 10 hours, respectively. Metabolites are excreted in the urine, with the content of unchanged lidocaine in the urine not exceeding 10%.

Therapeutic indications: all types of local anesthesia, ventricular tachycardia, extrasystole, fibrillation (including the acute phase of myocardial infarction, intravenous, intramuscular administration)

Side effects: headache, dizziness, somnolence, tinnitus, diplopia, eye floaters, twitching, tremor, allergic reactions, decreased BP, bradycardia

Contraindications: sick sinus syndrome, marked bradycardia, AV block, decompensated heart failure, cardiogenic shock, hypotension, hepatic insufficiency, myasthenia gravis, history of epileptiform convulsions to lidocaine

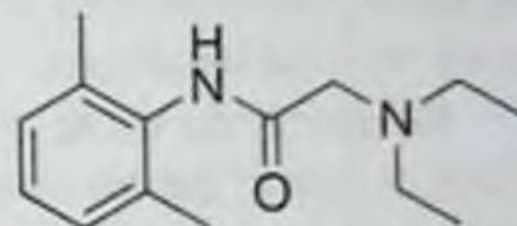


Fig. 4.25. (2-Diethylamino)-N-(2,6-dimethylphenyl)acetamide (and as a hydrochloride)

Trimecaine (Mesocain[®])

- ▶ Its chemical structure is similar to that of lidocaine, 2–3 times more effective than Procaine, duration of action: 2–4 hours. Dilates blood vessels, administered with vasoconstrictors.

- ▶ Metabolized in the liver, excreted in the urine.

Therapeutic indications: infiltration, conduction, epidural anesthesia

Side effects: burning sensation at administration site

Contraindication: allergic reactions

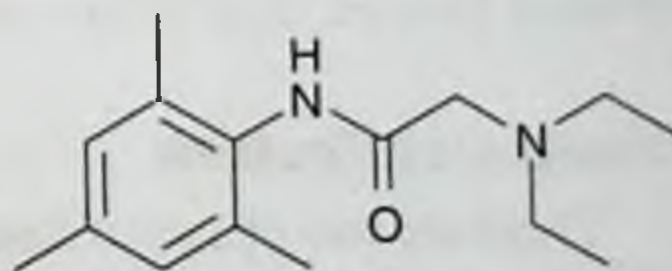


Fig. 4.26. 2-(Diethylamino)-N-(2,4,6-trimethylphenyl)acetamide (as a hydrochloride)

5. HYPNOTICS

Hypnotics (hypnotic agents, from the Lat. *hypnotica*) are a group of psychoactive DP's used to promote sleep onset and ensure its continuity. They promote the onset of sleep, normalize its depth, staging and duration, prevent night awakenings and are used to treat insomnia.

Research on using drugs to treat insomnia evolved throughout the last half of the 20th century. Barbiturates emerged as the first class of drugs in the early 1900s, after which chemical substitution led to the synthesis of derivative compounds. During the 1970s, quinazolinones and benzodiazepines were introduced as safer alternatives to barbiturates; by the late 1970s, benzodiazepines emerged as the safest group of drugs. Nonbenzodiazepines are the most recent development (1990s—present).

Sleep is an active process in which the activity of hypnogenic (synchronizing) brain structures is increased and that of the ascending reticular activating system is reduced. Hypnogenic regions have been identified in the thalamus, hypothalamus and caudal portions of the reticular formation. Hypnotic agents affect how these two systems interact, tipping the balance in favor of the sleep-inducing one.

Sleep architecture

There are two phases of sleep: slow-wave (orthodox) and fast-wave (paradoxical). The slow-wave phase accounts for 75–80% of total sleep time and the fast-wave phase accounts for 20–25%. Slow-wave sleep (non-rapid eye movement [NREM] sleep) is supported by the synchronizing system of the thalamus, anterior hypothalamus, and serotonergic neurons of the raphe nuclei. The orthodox sleep phase involves a decrease in skeletal muscle tone, body temperature, blood pressure, respiratory rate and heart rate within the physiological range, and an increase in anabolic processes such as the synthesis of ATP, ribonucleic acid (RNA), proteins, and the secretion of growth hormone, prolactin, melatonin. Parasympathetic tone predominates. Fast-wave sleep (rapid eye movement [REM] sleep) is regulated by the hindbrain's reticular formation. Complete skeletal muscle relaxation, rapid eye movements, respiratory and cardiac acceleration, slightly elevated blood pressure are typical of this phase. Dreams occur during REM sleep. Adrenaline and glucocorticoids are secreted and the sympathetic nervous system tone increase. Slow-wave sleep deprivation is accompanied by fatigue, anxiety, irritability, mental impairment, and motor imbalance. Insufficient duration of REM sleep leads to difficulties in solving interpersonal and professional problems, excitation, and neuroses.

Causes of sleep disorders: physiological (abnormal biorhythm), psychological (emotions), pathological (depression, delusions, hallucinations, fear), pharmacological (psychostimulants, antidepressants, steroids, etc.), idiopathic (for no apparent cause).

Types of sleep disorders: presomniac (impaired sleep onset), intrasomniac (superficial sleep, frequent awakenings), postsomniac (early awakening), sleep architecture disturbances, sleep desynchronization during air travel or forced extended wakefulness.

Classification of hypnotics

I. Benzodiazepine receptor agonists

A. Benzodiazepine derivatives

1. Intermediate-acting

- $T_{1/2}$: 12–18 hours
 - ◊ Lorazepam (Lorafen[®], Ativan[®])
 - ◊ Oxazepam (Nozepam[®], Tazepam[®])
 - ◊ Temazepam (Restoril[®])
- $T_{1/2}$: 24 hours
 - ◊ Nitrazepam (Radedorm 5[®], Eunoctin[®])
 - ◊ Flunitrazepam (Rohypnol[®])

2. Long-acting ($T_{1/2}$: 30–40 hours or longer)

- Bromdihydrochlorphenylbenzodiazepine (Phenazepam[®], Elzepam[®])
- Diazepam (Sibazon[®], Seduxen[®], Relanium[®])

B. Nonbenzodiazepine compounds (Z-drugs)

- Nonbenzodiazepine compounds (Z-drugs)
 - Zopiclone (Imovane[®])
- Imidazopyridine derivative
 - Zolpidem (Ivadal[®])
- Pyrazolopyrimidine derivative
 - Zaleplon (Andante[®])

II. Melatonin receptor agonists

- Melatonin (Melaxen[®])
- Ramelteon (Rozerem[®])

III. H_1 -receptor antagonists — ethanolamine derivatives

- Doxylamine (Donormyl[®])

IV. Orexin receptor antagonists

- Suvorexant (Belsomra[®])

V. Other hypnotics

1. Heterocyclic compounds with narcotic action — barbiturates

- Phenobarbital (Luminal[®])

2. Aliphatic compounds

- Bromisoval (Bromural[®])

3. Amino acids

- Glycine (Glycine[®])

Specifics of products by groups

Benzodiazepine receptor agonists

Mechanism of action: Benzodiazepines interact non-selectively with various benzodiazepine receptor subtypes (referred to as BZ_1 , BZ_2 , BZ_3 or ω_1 , ω_2 , ω_3).

respectively), which are part of a macromolecular complex. This complex includes GABA_A receptors sensitive to γ -aminobutyric acid (GABA), benzodiazepine and barbituric receptors, as well as Cl⁻ ionophores (Fig. 1.5). GABA decreases neuronal excitability by binding to GABA_A receptors. The GABA_A receptor is a heteromeric protein complex consisting of five subunits located in the neuronal synapses. GABA_A receptors, which form various combinations of subunit subtypes, have different properties, brain distribution, pharmacological and clinical effects. In addition, GABA_A receptor subtypes are distributed differently in distinct brain regions. The activation of different GABA_A receptor subtypes by benzodiazepines can lead to different pharmacological effects. GABA_A receptors contain ion channels that allow the passage of Cl⁻ ions into neurons through cell membranes.

Benzodiazepines bind at the α and γ subunit interface of GABA_A receptors. Once bound, the benzodiazepine ligand locks the GABA_A receptor into a conformation where it has higher affinity for the GABA neurotransmitter. In this case, the frequency of ion channel openings increases, which allows Cl⁻ ions to enter neurons through cell membranes. This causes hyperpolarization of the postsynaptic membrane and makes neurons more resistant to excitation. The inhibitory effect of GABA is potentiated leading to hypnotic and anxiolytic effects. In addition, different benzodiazepines may have different affinities for benzodiazepine receptors with different subunit combinations.

The hypnotic effect is associated with the effect of DPs on benzodiazepine receptors of the limbic system and its interaction with other brain regions that produce the cyclic changes between wakefulness and sleep, and to a lesser extent, the reticular formation. Numerous benzodiazepine receptors are located in the limbic system (anxiolytic effect), brain stem and cortex (anticonvulsant effect), spinal cord (muscle relaxant effect), cerebellum (ataxic effect).

Pharmacological effects

- ▶ Hypnotic, antianxiety (anxiolytic), sedative, anticonvulsant, central muscle relaxant, potentiating.

Reduces neuronal excitability in the subcortical brain regions, cerebellum, cortex and other parts of the central nervous system. Inhibits conditioned and polysynaptic spinal reflexes, reduces the number of awakenings during sleep, increases the depth and duration of sleep. Potentiates and prolongs the action of anesthetics, neuroleptics, tranquilizers.

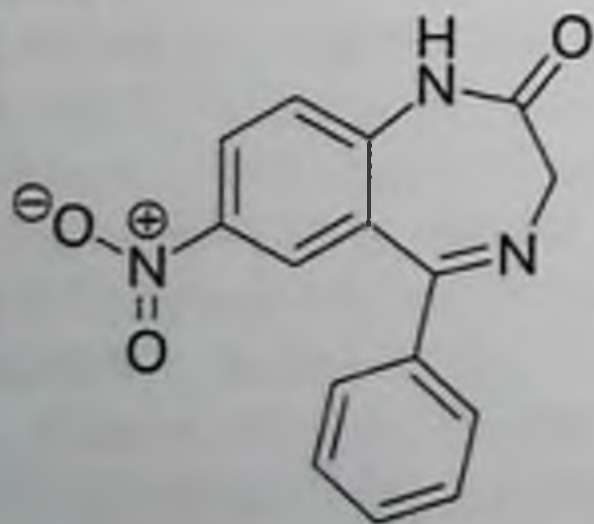


Fig. 5.1. 3-Dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one

Nitrazepam (Radedorm[®], Eunocin[®])

Intermediate-acting benzodiazepine derivative.

- ▶ Bioavailability: 80%. Maximum blood concentration: within 2–3 hours. The hypnotic effect occurs in 30–45 minutes and lasts 6–8 hours. It crosses the BBB, placental barrier, and is excreted into breast milk.
- ▶ It undergoes biotransformation in the liver by reducing the nitro group with subsequent acetylation to form inactive acetyl derivatives. Excreted mainly as

metabolites by the kidneys with about 5% excreted unchanged. $T_{1/2}$: 16–48 hours. For oral administration 30 minutes before bedtime.

Flunitrazepam (Rohypnol[®])

- ▶ Intermediate-acting benzodiazepine, similar to nitrazepam in structure and action (it also contains a fluorine atom and a methyl group). The hypnotic effect lasts 6–8 hours. Bioavailability: 70–90%. Maximum blood concentration: within 0.75–2 hours. It crosses the BBB, placental barrier, and is excreted into breast milk.
- ▶ Metabolized in the liver (10–15% on the first pass). Excreted mainly by the kidneys and with bile. $T_{1/2}$: 16–35 hours. For oral (30 minutes before bedtime), intramuscular or intravenous administration.

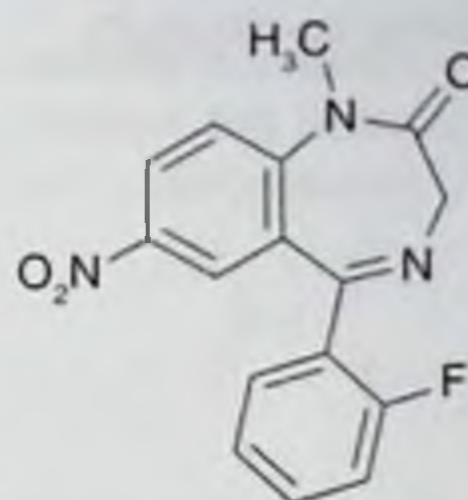


Fig. 5.2.5-(2-Fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-2H-1,4-benzodiazepin-2-one

Nonbenzodiazepine compounds (Z-drugs)

Mechanism of action: The distribution and function of the main subtypes of benzodiazepine receptors (ω_1 , ω_2 and ω_3) have been determined. The ω_1 subtype is found mainly in the cortical and subcortical regions and is responsible for the hypnotic effect; the ω_2 and ω_3 subtypes are located mainly in the spinal cord and peripheral tissues and are associated with the other effects (muscle relaxant, anticonvulsant, etc.). Z-drugs are characterized by the highest selectivity for the ω benzodiazepine receptor: the biological substrate of action is the ω_1 subtype of the benzodiazepine receptor, which is associated with the hypnotic effect. Compared to benzodiazepine hypnotics, Z-drugs have a significantly better safety profile with lower likelihood of addiction, dependence, cognitive and behavioral toxicity. They have almost no anticonvulsant, muscle relaxant, or anxiolytic effects.

Pharmacological effects

They promote sleep onset, reduce the number of night awakenings, extend sleep duration, and improve sleep quality.

Zopiclone (Imovane[®])

- ▶ Cyclopyrrolone derivative. Maximum blood concentration: within 1–3 hours. It crosses the BBB, placental barrier, and is excreted into breast milk. Sleep occurs within 20–30 minutes after ingestion and lasts 6–8 hours.
- ▶ Biotransformation in the liver with N-oxide and N-dimethyl zopiclone formation. Excreted mainly as metabolites by the kidneys (80%), with bile (16%). $T_{1/2}$ of these kidney metabolites is 4.5 and 7.4

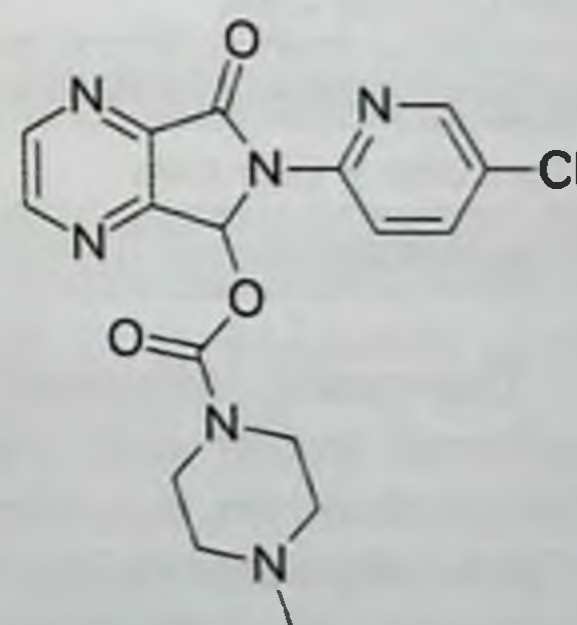


Fig. 5.3. 4-Methyl-1-piperazine-carboxylic acid 6-(5-Chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4- β]pyrazin-5-yl ester

hours, respectively; 5 hours for unchanged zopiclone. For oral administration 30 minutes before bedtime.

Zolpidem (Ivadal®)

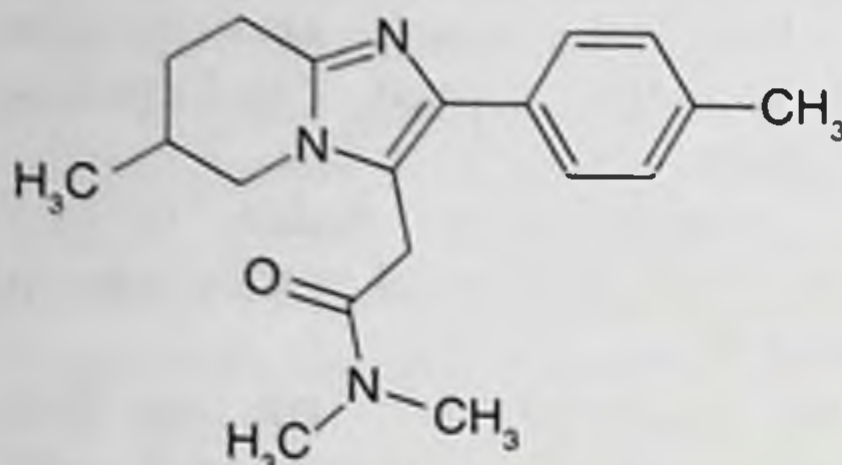


Fig. 5.4. N,N,6-Trimethyl-2-(4-methylphenyl)imidazo[1,2- α]pyridine-3-acetamide (and as tartrate)

- ▶ Imidazopyridine derivative. Bioavailability: 70%, maximum blood concentration: within 0.5–3.0 hours. It crosses the BBB, placental barrier, and is excreted into breast milk. The characteristics of zolpidem and nitrazepam are compared in Table 5.1.
- ▶ Metabolized in the liver. Excreted mainly as inactive metabolites by the kidneys (56%) and with bile (37%). $T_{1/2}$: 1.4–4.5 hours. For oral administration 20–30 minutes before bedtime.

Table 5.1. Comparison of benzodiazepine derivatives and nonbenzodiazepine benzodiazepine receptor agonists

Parameter	Nitrazepam	Zolpidem
Mechanism of action	++	++
Sleep architecture disturbances	++	+/-
Anxiolytic action	++	+/-
Muscle relaxing action	++	+/-
Anticonvulsant action	++	+/-
Abuse and dependence potential	+	+
Aggravation of sleep apnea	+ / ++	+
Elimination half-life	16–48 h	Up to 3 h

Therapeutic indications: sleep disturbances (difficulty falling asleep, frequent nocturnal and/or early morning awakenings), including adjustment, short-term, chronic insomnia; secondary sleep disturbances in mental disorders

Side effects: somnolence, ataxia, dizziness, headache, gastrointestinal symptoms, bitter or metallic taste in the mouth (zopiclone), dyspepsia, anterograde amnesia. For additional side effects of benzodiazepine derivatives, see Tranquilizers

Contraindications: severe respiratory failure, sleep apnea, pregnancy, breastfeeding, children (under 18 years of age). For additional contraindications of benzodiazepine derivatives, see Tranquilizers.

Flumazenil is an antidote for acute intoxication with benzodiazepine receptor agonists.

Flumazenil (Anexate®)

Mechanism of action: It competitively blocks benzodiazepine receptors and removes the central psychomotor effects of the DS; it neutralizes the hypnotic-sedative effect and restores independent breathing and consciousness. It has weak internal agonistic activity related to benzodiazepine receptors and has an anticonvulsant effect. At a dose of 1.5 mg, Flumazenil occupies 50% of benzodiazepine receptors and at a dose of 15 mg, it completely blocks the benzodiazepine allosteric site in the receptor complex.

- ▶ Imidazobenzodiazepine derivative. Intensively distributed in the extravascular space.
- ▶ Subject to intensive metabolism in the liver. The main inactive metabolite is carboxylic acid. Excreted by the kidneys (90–95%) and with bile (5–10%). $T_{1/2}$: 40–80 minutes. For intravenous administration (bolus or infusion).

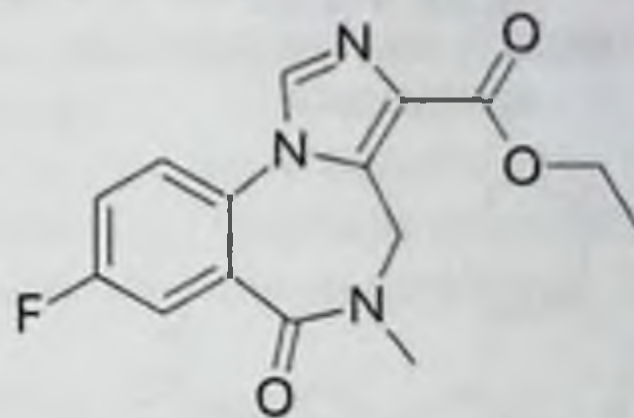


Fig. 5.5. Ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5- α][1,4]benzodiazepine-3-carboxylate

Melatonin receptor agonists

Mechanism of action: The pineal hormone melatonin (N-acetyl-5-methoxytryptamine) is synthesized in pineal cells (pinealocytes) from serotonin. It is a derivative of the amino acid tryptophan. The maximum amount of melatonin is produced at night; its synthesis increases when the retina receives less intense light stimulation. Its regulating effect on circadian rhythms (especially on sleep) is pronounced during rapid time zone changes (for example, when flying over long distances). This effect of melatonin is manifested when it interacts with specific type 1 and type 2 melatonin receptors located in the CNS. Activation of melatonin receptors is associated with adenylate cyclase inhibition and decreased intracellular levels of cAMP. They increase the midbrain and hypothalamus concentration of GABA and serotonin by changing the activity of a pyridoxal kinase, which is involved in the synthesis of GABA, dopamine and serotonin.

Pharmacological effects

- ▶ Resets circadian rhythms
- ▶ Regulates the sleep-wake cycle. The effect is related to adaptation of the hormonal activity of the pineal gland to rapid time zone changes.

Melatonin (Melaxen®)

- ▶ The chemical structure is similar to that of serotonin (5-hydroxytryptamine) and 5-methoxytryptamine hydrochloride (it is an O-methylated and N-acetylated serotonin derivative). Bioavailability is 15% (first-pass metabolism is 85%).
- ▶ Metabolized in the liver. Excreted by the kidneys: 90% — as sulfate and glucuronic conjugates of 6-hydroxymelatonin; 2–10% — unchanged. $T_{1/2}$ is 45 min. For oral administration.

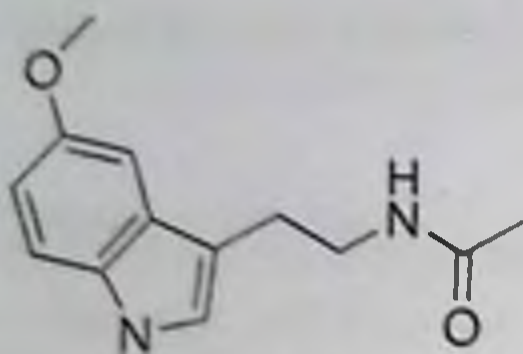


Fig. 5.6. N-[2-(5-Methoxy-1H-indol-3-yl)ethyl]acetamide

- Use of this product alone to treat insomnia is limited due to its low efficacy.

Therapeutic indications: sleep disorders, including those caused by circadian rhythm disorders, such as desynchronosis (a rapid change in time zones).

Side effects: somnolence, dizziness

Contraindications: autoimmune diseases, hepatic and/or renal impairment, pregnancy, breastfeeding, children (under 18 years of age).

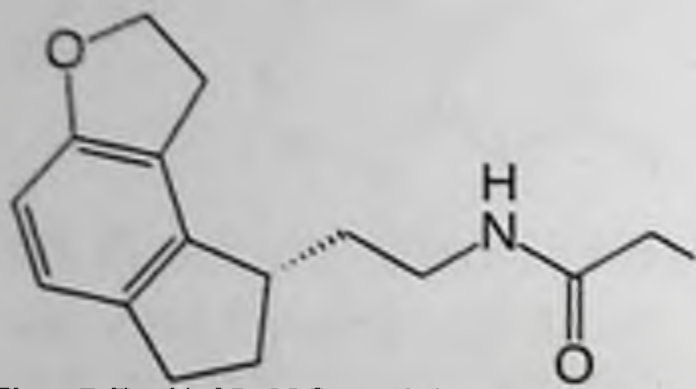


Fig. 5.7. N-[2-(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethylpropanamide

Ramelteon (Rozerem®)

- A synthetic analogue of melatonin.
- Metabolized in the liver. One of the metabolites is a melatonin receptor agonist, but it is less effective than the parent compound. $T_{1/2}$: 1–3 hours, for an active metabolite: 5 hours. For oral administration.

H₁ receptor antagonists

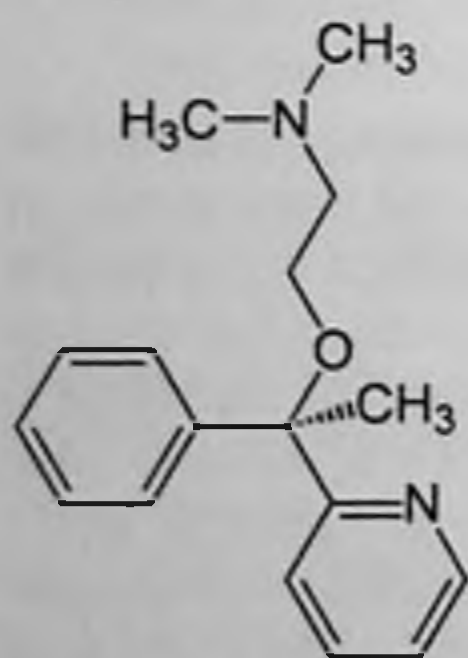


Fig. 5.8. N,N-Dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]ethamine

Doxylamine (Donormyl®)

- **Mechanism of action:** It blocks H₁ receptors and M-cholinoceptors in the reticular formation. It promotes sleep onset, reduces the total duration of nocturnal awakenings, does not change sleep phases, and suppresses recurrent insomnia that occurs after discontinuation of other hypnotic agents.
- Ethanolamine derivative. Maximum blood concentration: within 2 hours. It crosses blood-tissue barriers (including the BBB). Duration of action: 6–8 hours.
- It undergoes biotransformation in the liver. Excreted by the kidneys (60% — unchanged) and partially with bile. $T_{1/2}$: 10 hours. For oral administration.

Therapeutic indications: insomnia

Side effects: dry skin and mucous membranes, increased IOP, constipation, urinary retention, tachycardia

Contraindications: angle-closure glaucoma, intestinal atony, bladder atony, prostate adenoma, breastfeeding

Orexin receptor antagonists

This group of hypnotics appeared after the discovery of a system of endogenous neuropeptides—orexins (orexin A and orexin B) and their receptors (OX₁R and OX₂R). Orexin-producing neurons are concentrated in the hypothalamus. Both orexins are synthesized from a common precursor (prepro-orexin). Orexin A is

33 amino acids long and has two disulfide bonds (Cys6–Cys12, Cys7–Cys14) necessary for its function. Orexin B is a linear 28-amino-acid peptide. Orexin A has approximately the same affinity for both receptors while Orexin B reacts mainly with OX2 and is 5 times weaker than Orexin A. Orexins play a critical role in maintaining wakefulness. Their deficiency causes a state of narcolepsy (hypersomnia and other symptoms). Suppression of the activating action of orexins by blocking their receptors promotes the hypnotic effect.

Mechanism of action: The orexin neuropeptide signaling system is the main mechanism that maintains the state of wakefulness.

Suvorexant triggers the physiological brain transition from wakefulness to sleep by reversibly blocking the binding of wakefulness neuropeptides (orexins A and B) to OX1R and OX2R receptors, thereby suppressing the maintenance of wakefulness (Fig. 5.9).

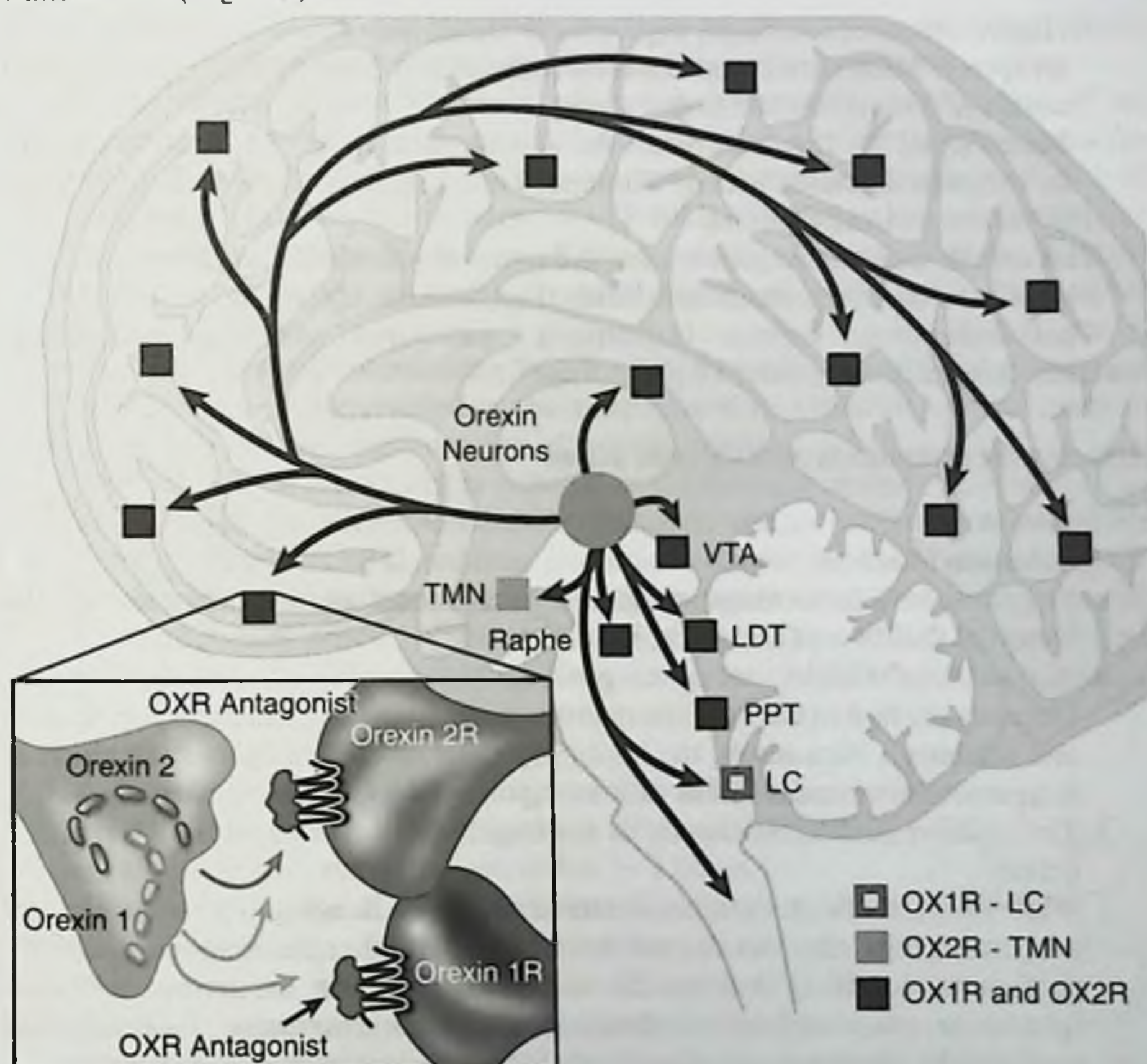


Fig. 5.9. Mechanism of action of orexin receptor antagonists (Bigal M.E. et al., 2013): LC, locus coeruleus (norepinephrine); LDT, laterodorsal tegmental nucleus (cholinergic); PPT, pedunculopontine tegmental nucleus (cholinergic); Raphe, raphe nuclei (serotonergic); TMN, tuberomammillary nucleus (histaminergic); VTA, ventral tegmental area (dopaminergic)

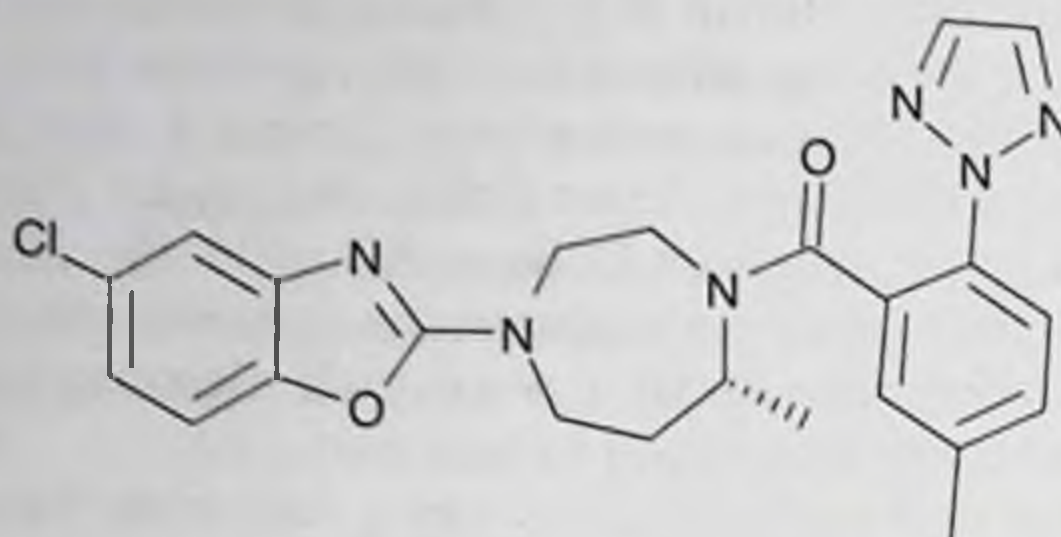
Suvorexant (Belsomra®)

Fig. 5.10. [5-Methyl-2-(2H-1,2,3-triazol-2-yl)phenyl][(7R)-4-(7-methyl-5-chloro-1,3-benzoxazol-2-yl)-1,4-diazepan-1-yl]methanone

- ▶ Highly selective, reversible, high-affinity antagonist of orexin OX1R and OX2R receptors. Maximum blood concentration: within 2 hours. The hypnotic effect occurs in 30 minutes and lasts 7 hours.
- ▶ Metabolized in the liver with the involvement of CYP3A and CYP2C19 isoenzymes. Excreted mainly with bile. $T_{1/2}$ is 12 hours. For oral administration 30 minutes before bedtime.

Therapeutic indications: presomniac and intrasomniac sleep disorders

Side effects: diurnal somnolence, headache, dizziness, dyspepsia

Contraindications: hepatic impairment, narcolepsy, cataplexy, pregnancy, breastfeeding, children (under 18 years of age)

Heterocyclic compounds with narcotic action

Barbiturates

Mechanism of action:

- ▶ They are barbituric receptor ligands. Small doses allosterically enhance the action of GABA on GABA_A receptors.
- ▶ Activation of GABA_A receptors prolongs the opening of chloride channels, increases the flow of Cl⁻ ions into neurons, and causes neuronal hyperpolarization and inhibition. As a result, the inhibitory effect of GABA and the inhibition of interneuronal transmission in various regions of the CNS are enhanced.
- ▶ The sedative and hypnotic effects are largely related to their GABA-mimetic action.
- ▶ While interacting with the neuronal membrane and changing its physicochemical properties, they can also disrupt the function of other ion channels (sodium, potassium, calcium) and exhibit antagonism against excitatory mediators (glutamate, etc.): they inhibit glutamatergic neurotransmission, especially that mediated by glutamate α -amino-5-methylisoxazole-4-propionate receptors.
- ▶ They suppress the midbrain reticular formation, which promotes sleep onset. They also inhibit the hindbrain hypnogenic system, which is responsible for REM sleep. This results in the dominating synchronizing effect of slow-wave sleep on the cerebral cortex — thalamus, anterior hypothalamus, and raphe nuclei.

Pharmacological effects (using phenobarbital as an example)

The product has a non-selective inhibitory effect on the CNS: it depresses the sensory cortex, decreases motor activity and produces drowsiness, sedation and sleep.

- ▶ The sedative-hypnotic effect is mainly related to inhibition of the cells in the ascending activating reticular formation of the brain stem, thalamic nuclei, and inhibition of the interaction of these structures with the cerebral cortex. Barbiturate-induced sleep differs structurally from physiological sleep as the REM (paradoxical) phase of sleep is shortened. The hypnotic effect occurs within 0.5–1.0 hour, lasts 6–8 hours and decreases after 2 weeks of administration. Various processes are involved in the termination of the product's hypnotic effect. One of them is enzymatic inactivation by hepatic microsomal enzymes.
- ▶ Small doses have a sedative effect and the combination with other agents (antispasmodics, vasodilators) is effective in neurovegetative disorders.
- ▶ Phenobarbital is an inducer of microsomal enzymes, so the rate of its metabolism increases with repeated administration: when administered for more than 3–5 days, it stimulates its own biotransformation (the rate of enzymatic reactions can increase 10–12-fold). The latter is one of the major contributors to the development of tolerance. The induction of microsomal enzymes affects the rate of biotransformation of compounds from other chemical groups.
- ▶ The anti-hyperbilirubinemia effect is related to induction of the glucuronyl transferase enzyme regulating the conjugation of bilirubin, which leads to decreased plasma concentration of free bilirubin.
- ▶ The anticonvulsant effect is related to GABAergic system activation, the effect on voltage-dependent sodium channels, and the inhibition of glutamate activity. Phenobarbital reduces neuronal excitability in the epileptogenic focus and prevents the initiation and propagation of impulses. It blocks high-frequency repetitive discharges of neurons (due to the effect of Na⁺ ions on the current). Barbiturates also increase the threshold for electrical stimulation of the motor cortex.

Phenobarbital (Luminal[®])

- ▶ Barbituric acid derivative. It crosses the BBB, placental barrier, and is excreted into breast milk. Bioavailability: 80%; maximum blood concentration: within 1–2 hours.
- ▶ Metabolized in the liver by microsomal enzymes to form pharmacologically inactive metabolites. Excreted by the kidneys as glucuronides and unchanged (25–50%). T_{1/2}: 53–118 hours (average 79 hours). For oral administration.

Therapeutic indications: epilepsy, chorea, spastic paralysis, hemolytic disease, neurosis-like conditions (as part of combined agents)

Side effects: addiction, drug dependence (psychological and physical), withdrawal syndrome, cumulation; somnolence, nightmares (sleep architecture disturbance), ataxia, hyperkinesia (in children),

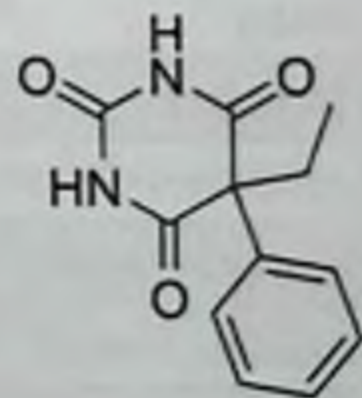


Fig. 5.11. 5-Ethyl-5-phenyl-2,4,6(1H,3H,5H)-pyrimidinetrione

thought disorder, paradoxical reaction (insomnia) — especially in children, elderly, aftereffect (asthenia, feeling of weakness, fatigue, decreased psychomotor abilities and alertness); agranulocytosis, thrombocytopenia and megaloblastic anemia (with prolonged use), bradycardia, hypotension, vascular collapse; nausea, vomiting, constipation; allergic reactions, including exfoliative dermatitis (Stevens-Johnson syndrome, toxic epidermal necrolysis); teratogenic effect; with prolonged use: liver damage (scleral or dermal icterus), folate deficiency, hypocalcemia, osteomalacia, impaired libido, impotence.

Contraindications: a history of acute or latent porphyria (aggravation of symptoms due to the induction of enzymes responsible for porphyrin synthesis); severe anemia; respiratory diseases accompanied by shortness of breath or airway obstruction; hepatic and/or renal impairment; myasthenia gravis; alcoholism; pregnancy (especially the first trimester), breastfeeding; a history of allergic reactions.

Barbiturates differ from benzodiazepine derivatives in that they alter sleep architecture to a greater extent, have a narrow therapeutic index, thus a higher risk of intoxication, induce hepatic microsomal enzymes more strongly, and have higher risk of drug dependence (Table 5.2).

Barbiturate intoxication

Causes: in 85% of cases, a person is driven to take hypnotics because they want to die painlessly.

Such desires arise due to serious emotional and psychological trauma, incurable disease, exacerbation of diseases, difficult life situations, unrequited love. Suicide attempts end in the most severe intoxication since the volume of drug taken is many times higher than the therapeutic dose. The wrong dose is usually the result of irrational self-medication. To enhance and force the action, a person takes 2-3 times the number of tablets than the maximum allowable dose. Iatrogenic overdoses are extremely rare. Renal or hepatic impairment leads to delayed metabolism and product elimination. With daily intake, the product accumulates.

A single dose of 1 g in adults causes intoxication. The lethal dose is more than 2 g.

Table 5.2. Comparison of barbiturates and benzodiazepines

Parameter	Benzodiazepines	Barbiturates
Effect on sleep architecture (decreased REM phase)	Moderate	Significant
Therapeutic index	High	Narrow
Addiction	Develops slowly	Develops fast
Drug dependence	+	++
Induction of hepatic microsomal enzymes	+	++
Specific antagonist	Flumazenil	None

Symptoms of acute intoxication

First stage: fatigue, lethargy, somnolence, preserved reactions to strong stimuli and tendon reflexes; breathing is deep, slow, rhythmic, normal pulse and blood pressure.

Second stage: comatose state, no response to pain and sound stimuli, hyporeflexia, muscle hypotension, dilated pupils, preserved light reflex, shallow breathing, muffled heart sounds, weak and rapid pulse, tachyarrhythmia, decreased blood pressure, oliguria.

Third stage: deep coma, anergy, areflexia, skin pallor and cyanosis, Cheyne-Stokes respiration, muffled heart sounds, thready pulse, circulatory collapse, prerenal anuria, hypothermia. Death occurs due to respiratory paralysis.

Treatment consists in accelerating the drug's elimination and maintaining vital functions. If the administered barbiturate is not completely absorbed from the GI tract, gastric lavage is performed, sorbents (activated charcoal) and saline laxatives are given. To accelerate the elimination of an already absorbed substance, hemodialysis (elimination increases 40–50-fold), hemoadsorption, peritoneal dialysis are used; in case of preserved renal function, forced diuresis is performed (water load and intravenous administration of osmotic diuretics or furosemide). To correct the electrolyte composition and pH of the blood, potassium chloride and sodium bicarbonate are administered intravenously, which resolve acidosis and accelerate the removal of barbiturates from the blood. Sodium bicarbonate creates an alkaline medium in the primary urine while phenobarbital, as a weak acid, dissociates into ions, loses lipid solubility and the ability to reabsorb. Its elimination is accelerated 8–10-fold. In cases of mild intoxication, the analeptic bemegride is used as an antidote: 5–10 mL of a 0.5% solution is injected intravenously; in case of insufficient or no effect, injections are repeated every 2–3 minutes until reflexes are restored, breathing is deeper or completely normalized, pulse and blood pressure are back to normal. In cases of severe intoxication, the use of bemegride is contraindicated since convulsions and increased brain oxygen consumption are possible. In this case, mechanical ventilation is performed. Symptomatic therapy aimed at eliminating severe cardiac, renal or pulmonary disorders is carried out.

Aliphatic compounds

Bromisoval (Bromural*)

- ▶ It depresses the central nervous system, enhances the inhibition processes and promotes their concentration.
- ▶ For oral administration 30 minutes before bedtime.

Therapeutic indications: insomnia, neurosis, neurosis-like states, chorea

Side effects: bromism (dysarthria, conjunctivitis, rhinitis, skin rash, cough, tachycardia)

Contraindications: acute porphyria, renal, hepatic, respiratory failure, pregnancy, breastfeeding

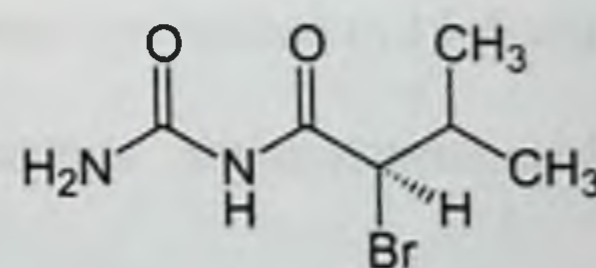


Fig. 5.12. N-(Aminocarbonyl)-2-bromo-3-methylbutanamide

Amino acids

Glycine

- ▶ A metabolic regulator, it normalizes and activates protective inhibition in the CNS, reduces psycho-emotional stress, improves mental performance, promotes

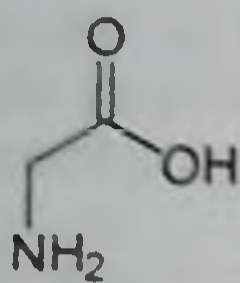


Fig. 5.13.
Aminoacetic acid
(aminoethanoic
acid)

sleep onset, and normalizes sleep. It has GABAergic, $\alpha 1$ -blocking, antioxidant, antitoxic actions; regulates the activity of N-methyl-D-aspartate receptors.

► It penetrates into most body fluids and tissues, including the brain. It is metabolized to water and carbon dioxide and does not accumulate in tissues. For sublingual, buccal administration 30 minutes before bedtime.

Therapeutic indications: sleep disturbances; psycho-emotional stress in stressful situations; functional disorders and organic diseases of the nervous system accompanied by hyperexcitability, mood swing; neuroses, neurosis-like states; vegetative-vascular dystonia.

Side effects: allergic reactions

Contraindications: allergic reactions

6. NARCOTIC ANALGESICS

Narcotic (opioid) analgesics (from the Greek *algos* "pain" and *an* "without") are drug products (DP) that have an analgesic effect due to the stimulation of opioid receptors. The natural source of narcotic analgesics is opium (from the Greek *opos* "juice"), the dried milky juice of the opium poppy (*Papaver somniferum*). The term "narcotic" is derived from the Greek word *narkotikos*, meaning "numbness" or "stupor".

Narcotic analgesics, unlike non-narcotic ones, are characterized by:

- ▶ pronounced analgesic activity
- ▶ euphoria, physical and psychological dependence
- ▶ respiratory depression
- ▶ addiction
- ▶ withdrawal syndrome.

The first reference to opium is found in the writings of the ancient Greek philosopher Theophrastus in the 3rd century BC. Arab traders brought opium to the East where it was used mainly to combat dysentery. In 1806, F. Serturmer, a Hanoverian pharmacist, was the first to isolate morphine by crystallization. The alkaloid was named after Morpheus, the ancient Greek winged god of dreams, the son of Hypnos (from the Greek *morphe* "form", since the god appeared in dreams in the form of humans, animals and natural elements). In 1832, P. Robiquet, a French chemist, discovered codeine (from the Greek *kodeia* "poppy head"). In 1948, I.N. Nazarov, a Soviet chemist, invented trimeperidine (Promedol*). In 1959, P. Janssen, a German chemist, synthesized fentanyl (which has been used since 1960). In 1961, based on the theoretical work of H. Blumberg, M. Lewenstein and J. Fishman synthesized naloxone at the Sloan Kettering Cancer Center in New York, which was approved for clinical use in the USA in 1971. Sufentanil was synthesized in 1974 and approved for intravenous use in 1984.

The chemical structure of opium alkaloids represents phenanthrene and isoquinoline derivatives (Fig. 6.1):

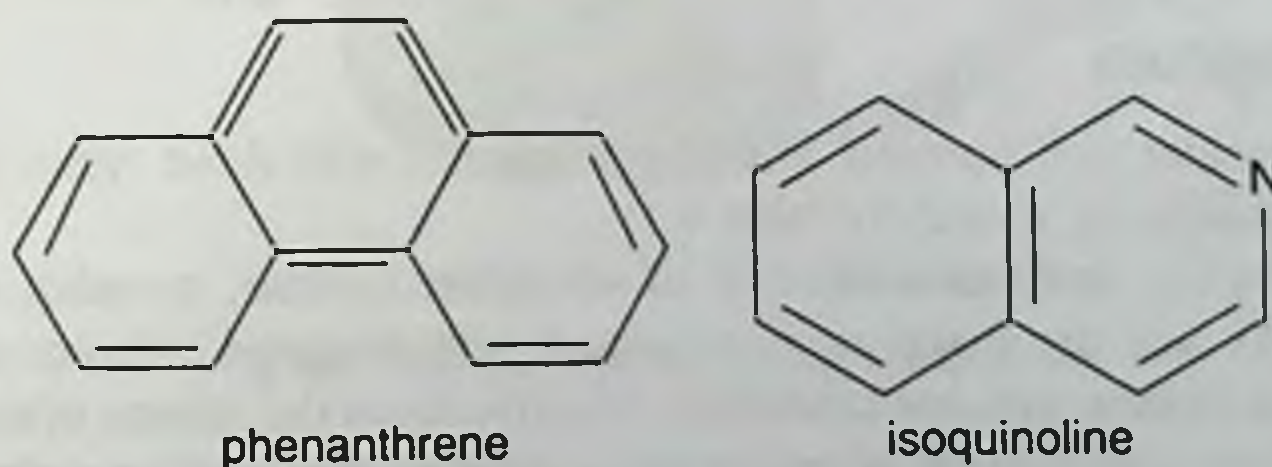


Fig. 6.1. Structural formulas of phenanthrene and isoquinoline

- ▶ phenanthrene derivatives: morphine, codeine, thebaine (have analgesic activity)

- ▶ isoquinoline derivatives: papaverine, narcotine (Noscapine[†]) (act as antispasmodics; they are not narcotic analgesics).

Pain pathways

- ▶ Pain is perceived by special receptors (nociceptors) located in the skin, muscles, capsules of joints and internal organs, periosteum and that can be stimulated by mechanical, thermal and chemical stimuli (Fig. 6.2).
- ▶ Nociceptive impulses propagate along the afferent nerve C and A δ fibers and enter the CNS into the dorsal horn neurons.
- ▶ Excitation then spreads in three ways through the system of interneurons:
 1. Into the ventral horns to the motor neurons. Their excitation produces a rapid protective motor reflex from the skeletal muscles.
 2. Into the lateral horns to the autonomic neurons of the sympathetic nervous system, the stimulation of which leads to functional adaptation of the internal organs.
 3. Into the dorsal horns along the ascending afferent pathways to the higher structures of pain perception and assessment—the brain stem, reticular formation, thalamus, limbic system, cerebral cortex.
- ▶
- ▶ The dorsal horn neurons are key in the perception and assessment of pain information. Their activity is controlled by ascending antinociceptive pathways.
- ▶ The subcortical structures (such as the periaqueductal gray matter, nucleus raphe magnus, locus coeruleus) contain neurons with axons that form the descending inhibitory pathways that end at the dorsal horn neurons.
- ▶ Activation of the descending inhibitory pathways reduces the release of nociceptive mediators (substance P, glutamate, etc.) and reduces the activation of interneurons that transmit pain information. Therefore, activation of ascending antinociceptive pathways inhibits the conduction of pain impulses along primary afferent fibers, which increases the pain threshold.

The neurons of the periaqueductal gray matter, nucleus raphe magnus, and dorsal horns contain opioid receptors, which are specific binding sites interacting with endogenous analgesic peptides: enkephalins, dynorphins, and endorphins.

Opioid receptors

Opioid peptides and narcotic analgesics interact with three types of G-protein coupled receptors — μ , κ , and δ (Table 6.1).

Their activation leads to inhibition of adenylate cyclase, opening of potassium channels (μ , δ), and decreased current through voltage-gated calcium channels (κ). This causes membrane hyperpolarization, which reduces the release of mediators and thereby blocks the conduction of excitation in different nociceptive pathways.

SOMATOSENSORY CORTEX

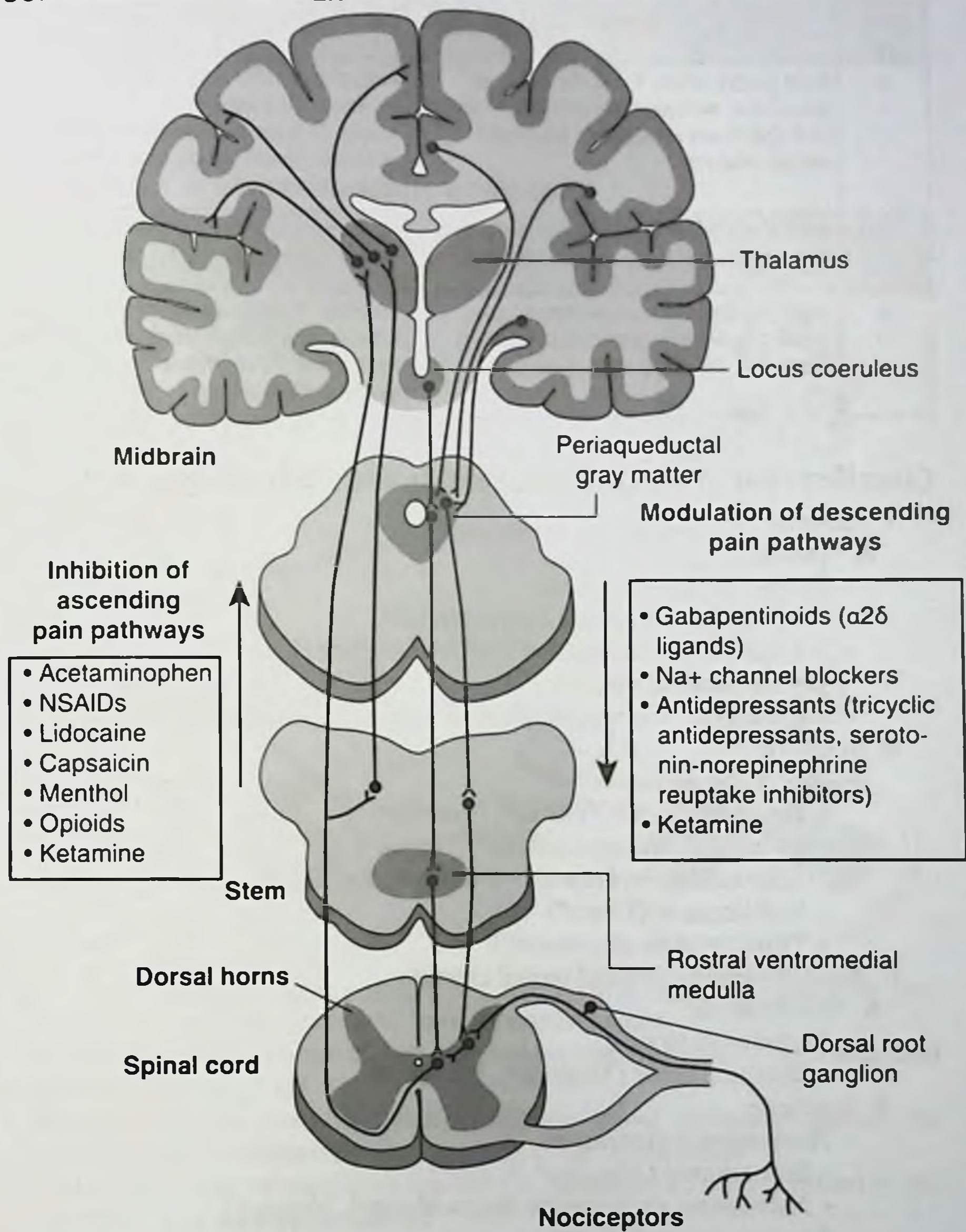


Fig. 6.2. Nociceptive and antinociceptive systems

Table 6.1. Opioid receptors and the effects of their stimulation

Sub-type	Location	Effects caused by stimulation
μ	Brain [cortex (layers III and IV), thalamus, striosomes, periaqueductal gray matter, spinal cord (gelatinous substance)], peripheral sensory neurons	Analgesia, sedation, respiratory depression, euphoria, drug dependence, bradycardia, miosis, decreased gastrointestinal motility, increased smooth muscle tone in internal organs, hypothermia
δ	Brain (pontine nucleus, amygdala, thalamus, deep cortex), peripheral sensory neurons	Analgesia, respiratory depression, decreased gastrointestinal motility, hypotension
κ	Brain (hypothalamus, periaqueductal gray matter, claustrum), spinal cord (gelatinous substance), peripheral sensory neurons	Inhibition of the conduction of pain impulses at the spinal cord (spinal analgesia), sedation, miosis, physical dependence, decreased gastrointestinal motility

Classification of narcotic analgesics and their antagonists

I. Agonists

A. Natural

- Phenanthrene derivatives
 - Morphine (morphine hydrochloride^{*})
 - Codeine hydrochloride^o (methymorphine^o)
- Opium alkaloid mixture
 - Omnopon^{*} (codeine, morphine, noscapine, papaverine hydrochloride, thebaine)

B. Synthetic

- Piperidine derivatives
 - Fentanyl (fentanyl citrate^{*}, Fendivia^{*})
 - Sufentanil citrate^o (Sufenta^o, Dsuvia^o)
 - Alfentanil hydrochloride^o (Alfenta^o, Rapifen^o)
 - Remifentanil (Ultiva^{*})
 - Trimeperidine (Promedol^{*})

II. Agonists-antagonists and partial agonists

A. Semisynthetic

- Thebaine derivative
 - Buprenorphine (Torgesic^o, Transtec^{*})

B. Synthetic

- Phenanthrene derivatives
 - Butorphanol (Moradol^{*}, Stadol^{*})
 - Nalbuphine (nalbuphine hydrochloride^{*}, Nubain^o)
- Benzomorphan derivative
 - Pentazocine (Lexir^o, Fortral^{*})

III. Antagonists

- Phenanthrene derivatives
 - Naloxone (naloxone hydrochloride^{*}, Narcan^o)
 - Naltrexone (Vivitrol^{*})

- Nalmefene (Revex[®], Selincro[®])
- IV. Multimodal analgesics (opioid and non-opioid)
- Cyclohexanol derivative
 - Tramadol (Tramadol[®], Tramal[®])

Mechanism of action of narcotic analgesics

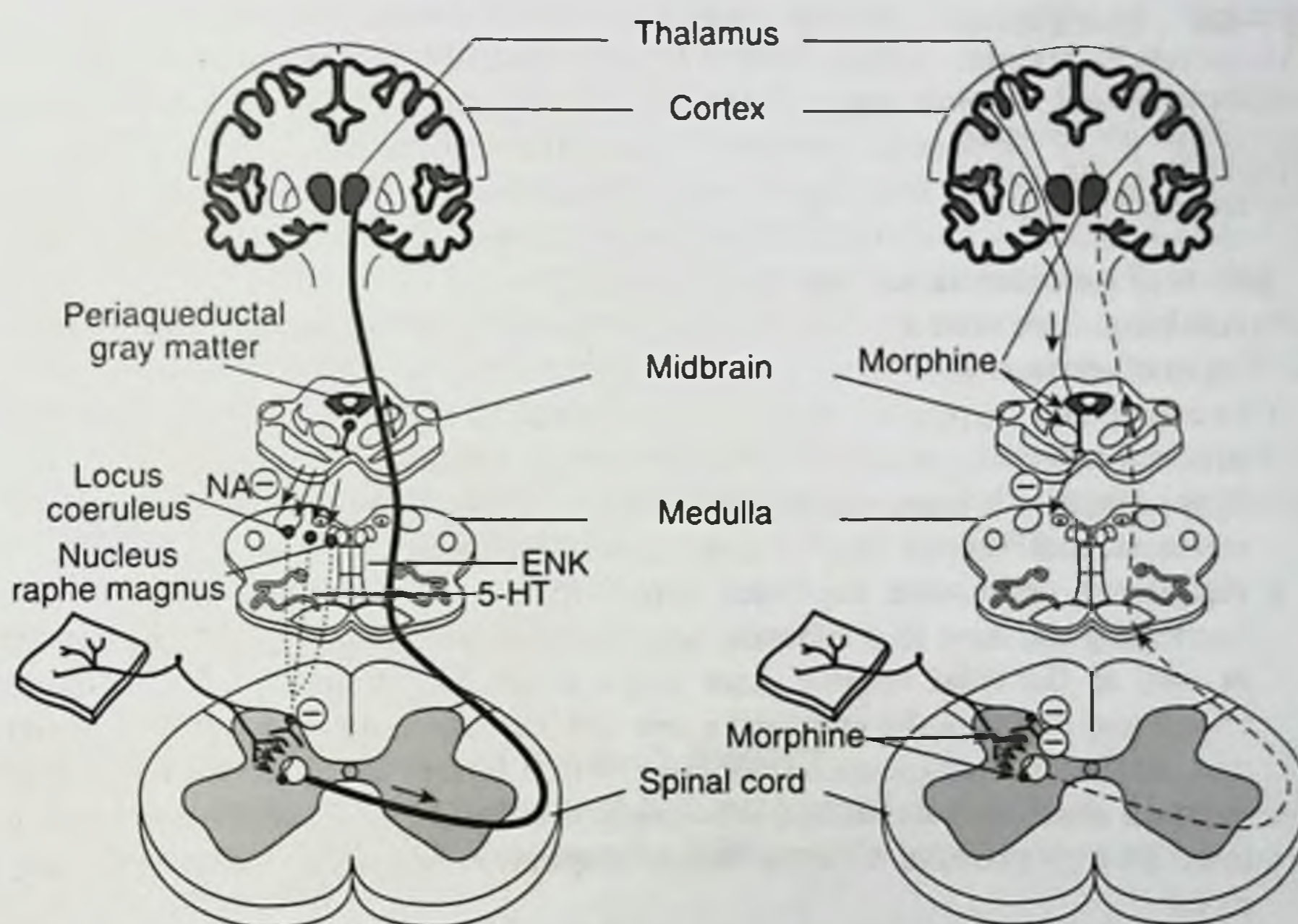


Fig. 6.3. Mechanism of action of opioid analgesics (R.N. Alyautdin et al., 2020). NA, noradrenalin; ENK, enkephalin; 5-HT, serotonin; •, opioid receptor

They inhibit the transmission of pain impulses between neurons in the central part of the afferent pathway (Fig. 6.3):

- ▶ stimulate opioid receptors, directly inhibit spinal neurons, disrupt the transmission of excitation between neurons at the dorsal horns
- ▶ reduce the release of mediators (glutamate, substance P, etc.) involved in the transmission of nociceptive stimuli
- ▶ affect the subjective emotional perception of pain and the body's response to it: inhibit cortex activation and the response of the limbic system, thalamus and hypothalamus to afferent impulses, induce a state of euphoria.

Specifics of individual products

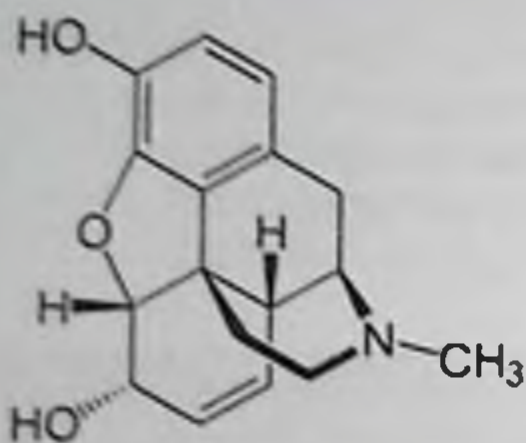


Fig. 6.4. 7,8-didehydro-4,5 α -epoxy-17-methyl-morphinan-3,6 α -diol (as hydrochloride [for parenteral administration] and sulfate [for oral administration])

Morphine (morphine hydrochloride*)

- ▶ Opioid receptor agonist ($\mu > \kappa = \delta$). Phenanthrene derivative. Bioavailability: 25–30% due to first-pass elimination. It is involved in enterohepatic circulation, crosses the BBB, placental barrier, and is excreted into breast milk. The analgesic effect occurs 5–15 minutes after subcutaneous or intramuscular administration and 20–30 minutes after oral ingestion and lasts 4–6 hours.
- ▶ Metabolized in the liver to form an inactive metabolite, morphine-3-glucuronide (65–75%), and an active metabolite, morphine-6-glucuronide (0.3–33.0%). $T_{1/2}$: 2–3 hours. Excreted mainly by the kidneys. For oral, intravenous, intramuscular, subcutaneous administration.

Effects of morphine on the central nervous system

- ▶ Analgesic: not accompanied by loss of consciousness or disturbance of other types of sensitivity.
- ▶ Sedative and hypnotic: effect on the cortical neurons, on the ascending reticular activating system of the brainstem, as well as on the limbic system and hypothalamus. It manifests as somnolence, decreased motor activity, decreased alertness, indifference. Higher doses induce deep sleep.
- ▶ Respiratory depression: decreased respiratory rate offset by increased amplitude. Increasing the dose to a subtoxic one decreases the respiratory rate and depth as well as the tidal volume. Low single doses for parenteral administration (5–10 mg) decrease the respiratory rate and increase respiratory depth; medium and maximum therapeutic doses (10–20 mg) further decrease the respiratory rate and depth with decreased pulmonary ventilation. Toxic single doses (more than 20 mg) provoke Cheyne-Stokes respiration and subsequent respiratory arrest.
- ▶ Antitussive and antiemetic: inhibition of the coughing and vomiting centers. It can stimulate chemoreceptor trigger zones of the vomiting center and induce nausea and vomiting.
- ▶ Hypothermic (at a toxic dose): inhibition of hypothalamic thermoregulatory center and decreased heat production.
- ▶ Hypothalamic-pituitary-adrenal axis: reduces the release of releasing hormones (gonadotropins and adrenocorticotrophic hormone); secondarily inhibits the secretion of gonadotropins, glucocorticoids and testosterone.
- ▶ Euphoria (from the Greek eu “well”, phero “to bear”) is characterized by a feeling of emotional satisfaction, the elimination of fear, anxiety. Dysphoria is possible (from the Greek dys “difficult”, phero “to bear”) in the form of fear, excitation, discomfort.
- ▶ Miosis: excitation of the oculomotor nucleus

- ▶ Bradycardia: stimulation of the vagus nerve
- ▶ Increased secretion of antidiuretic hormone and prolactin, which is associated with hypothalamus stimulation.

Peripheral effects of morphine

Inhibits gastrointestinal motility

Increases the smooth muscle tone of internal organs:

- ▶ GI tract, biliary, ureteral and urinary sphincters (spasmodic effect)
- ▶ bronchi.

Inhibits secretions from gastric, intestinal and pancreatic glands

Decreases blood pressure (at high doses, vasomotor center inhibition, histamine release — peripheral vasodilation, excitation of vagus nerve— bradycardia).

Therapeutic indications: severe acute and chronic pain (trauma, burn, myocardial infarction, pre- and postoperative periods, malignant neoplasms, etc.); pulmonary edema (reduces venous return to the right atrium and its afterload, depresses the respiratory center and has a sedative effect; colic (only in combination with antispasmodics); life-threatening cough (e.g. in open pneumothorax).

Side effects: drug dependence, addiction; respiratory depression, bradycardia, bronchospasm; obstipation, decreased diuresis, impaired urinary elimination; confusion, pruritus, rash.

Contraindications: respiratory depression; paralytic intestinal obstruction (ileus); abdominal pain of unclear etiology, wheezing; cachexia, hepatic and renal impairment; pregnancy, breastfeeding.

Long-acting morphine dosage forms

Morphine sulfate (MST Continus⁺, M-Eslon⁺, Skenan⁺)

- ▶ The analgesic effect occurs within 2–4 hours and lasts 12 hours. The first-pass effect is more than 50%. It crosses the BBB and placental barrier and is excreted into breast milk.
- ▶ Metabolized in the liver to form glucuronides and sulfates. Excreted mainly by the kidneys. For oral administration.

Therapeutic indications: severe pain that is predominantly chronic in nature (e.g., in oncologic conditions).

For side effects, contraindications, see Morphine.

Morphine solution (Morphilongum⁺)

0.5% morphine (morphine hydrochloride⁺) solution in 30% aqueous polyvinylpyrrolidone solution. The analgesic effect occurs within 30–40 minutes and lasts 22–24 hours. For intramuscular administration.

Therapeutic indications: severe pain that is predominantly chronic in nature (e.g., in oncologic conditions).

For side effects, contraindications, see Morphine.

Omnopon[®] (codeine, morphine, noscapine, papaverine hydrochloride, thebaine)

A mixture of hydrochlorides of the phenanthrene (morphine, codeine, thebaine) and isoquinoline (papaverine, narcotine) opium alkaloids. Its analgesic activity is 2-fold inferior to morphine. It increases smooth muscle tone to a lesser extent than morphine. For subcutaneous administration.

Therapeutic indications: pain syndrome of various etiologies, including intestinal, biliary, renal colic.

For side effects, contraindications, see Morphine.

Codeine hydrochloride[®] (methymorphine[®])

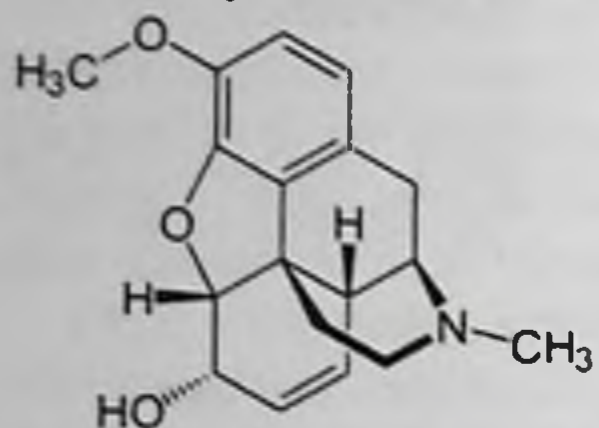


Fig. 6.5. (5 α ,6 α)-7,8-Didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol (as hydrochloride or phosphate)

- ▶ Opioid receptor agonist ($\mu > \kappa = \delta$). Alkaloid, phenanthrene derivative, morphine monomethyl ester. Bioavailability: 50%. Analgesia occurs within 30–60 minutes and lasts 4 hours. The cough reflex is blocked for 4–6 hours. The analgesic effect is 6–10 times weaker than that of morphine, and the antitussive effect is 2 times weaker (codeine depresses the cough center at doses that do not affect the respiratory center).
- ▶ Metabolized in the liver; 10% is metabolized into morphine by demethylation. $T_{1/2}$: 2.5–4.0 hours. Excreted by the kidneys: 5–15% as codeine and 10% as morphine and its metabolites. For oral administration.

Therapeutic indications: symptomatic treatment of nonproductive (dry) cough

Fixed combinations of codeine with other drugs and their formulations:

- ▶ Codterpin[®] (codeine, sodium bicarbonate, terpin hydrate)
- ▶ Pentalgin-N[®] (codeine, caffeine, metamizole sodium, naproxen, phenobarbital)
- ▶ Sedalgin-Neo[®] (codeine, caffeine, metamizole sodium, acetaminophen, phenobarbital)
- ▶ Terpincod[®] (codeine, sodium bicarbonate, terpin hydrate)
- ▶ Codelmicst[®] (codeine, acetaminophen)
- ▶ Solpadeine Fast[®] (caffeine, acetaminophen)

Trimeperidine (Promedol[®])

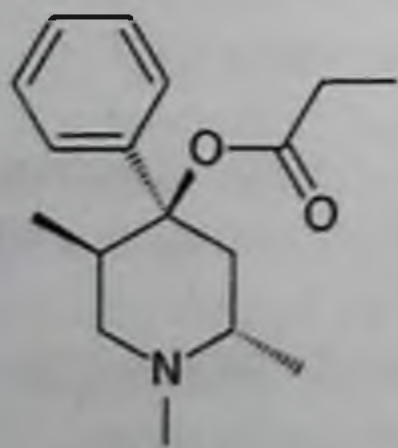


Fig. 6.6. 1,2,5-Trimethyl-4-propionyloxy-4-phenylpiperidine hydrochloride

- ▶ Opioid receptor agonist ($\mu > \kappa = \delta$), piperidine derivative. When administered parenterally, the analgesic effect occurs within 10–20 minutes with peak concentration at 40 minutes and lasts 2–4 hours. Its analgesic activity is 2–4 times weaker than that of morphine. It has a moderate antispasmodic effect on the bronchial and ureteral smooth muscles and, to a lesser extent than morphine, it increases the intestinal and biliary tone. It depresses the respiratory and vomiting centers to a lesser extent than morphine. It increases myometrial contractility and relaxes the cervix. It is used for pain relief and is the drug of choice to induce labor.

- ▶ Metabolized in the liver by hydrolysis with the formation of meperidinic and normeperidinic acids followed by conjugation. $T_{1/2}$: 2–4 hours. Excreted with bile and in small amounts by the kidneys. For oral, subcutaneous, intramuscular, intravenous administration.

Additional side effects: tremor, muscle twitching, hyperreflexia, convulsions

Fentanyl (fentanyl citrate⁺, Fendivia⁺)

- ▶ Piperidine derivative. It is rapidly redistributed from the blood and brain to muscles and adipose tissue, has good CNS penetration and very high lipophilicity. Its analgesic activity is 100–400-fold superior to morphine. When administered intravenously, the analgesic effect occurs within 1–3 minutes with peak concentration at 5–7 minutes and lasts 20–60 minutes. When administered intramuscularly, the analgesic effect occurs within 7–15 minutes. It causes severe (up to respiratory arrest) but short-lived respiratory depression.

- ▶ Metabolized in the liver (N-dealkylation and hydroxylation), kidneys, intestines and adrenal glands. $T_{1/2}$: 10–30 min. Excreted by the kidneys (75% as metabolites and 10% unchanged) and with bile. For oral, intramuscular administration.

Additional therapeutic indication: neuroleptanalgesia (in combination with droperidol)

For side effects, contraindications, see Morphine.

Fentanyl (Durogesic⁺)

- ▶ TTS (prolonged dosage form). Diffusion of fentanyl from the patch occurs over 72 hours; the serum concentration gradually increases within the first 12–24 hours. $T_{1/2}$: 17 hours.

Therapeutic indications: chronic cancer pain, non-cancer pain (diabetic polyneuropathy, syringomyelia, etc.)

Sufentanil citrate⁺ (Sufenta⁺, Dsuvia⁺)

- ▶ Synthetic fentanyl analogue. It is structurally different from fentanyl in that a methoxymethyl group was added to the piperidine ring, making it 5–10 times more potent. The total duration of action does not exceed 3 hours. A dose of 12.9 $\mu\text{g/kg}$ induces deep analgesia; the person loses consciousness in 3 minutes after a dose of 18.9 $\mu\text{g/kg}$. When administered epidurally, the analgesic effect occurs within 5–10 minutes and lasts 4–6 hours. For intravenous, intramuscular, subcutaneous, intrathecal, epidural administration.

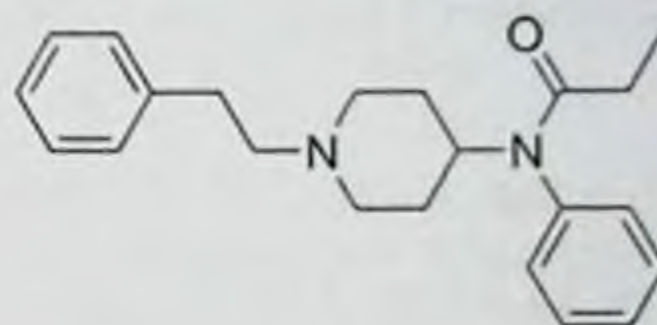


Fig. 6.7. N-(1-Phenylethylpiperidin-4-yl)-N-phenylpropanamide

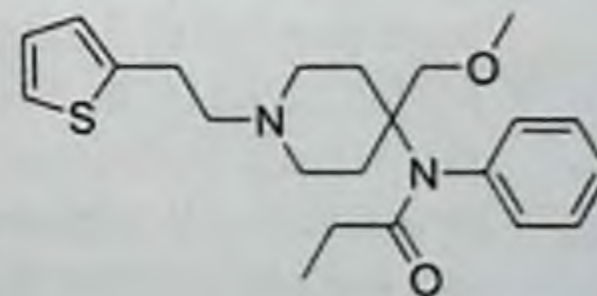


Fig. 6.8. N-[4-(Methoxymethyl)-1-(2-thiofuran-2-ylethyl)-4-piperidyl]-N-phenylpropanamide

- ▶ Metabolized in the liver to inactive metabolites.

Therapeutic indications: during surgery in combination with other products, induction and maintenance of anesthesia during major surgery, during or after caesarean section.

Alfentanil hydrochloride[®] (Alfenta[®], Rapifen[®])

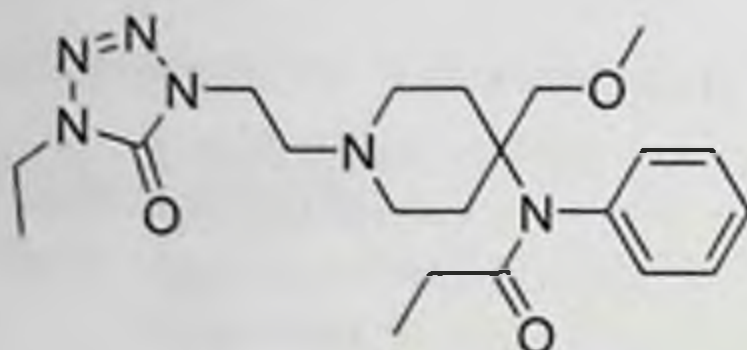


Fig. 6.9. N-[1-[2-(4-ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-4-(methoxymethyl)-4-piperidiny]propionanilide

- ▶ Synthetic fentanyl analogue. Its action is 4–10 times weaker than that of fentanyl. The maximum analgesic effect occurs within 1–2 minutes after intravenous administration, the duration of action is 3 times less than that of fentanyl and depends on the dose.
- ▶ Metabolized in the liver by demethylation to noralfentanil, which is then conjugated and excreted in the urine. $T_{1/2}$: 8–32 min. For intravenous administration.

Remifentanyl (Ultiva[®])

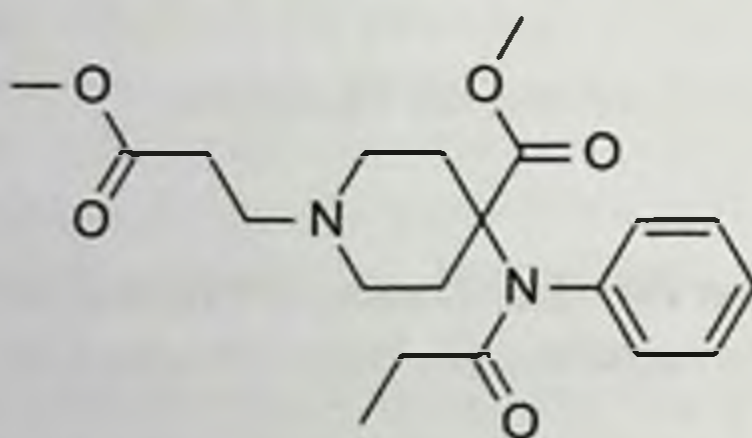


Fig. 6.10. 4-(Methoxycarbonyl)-4-[(1-oxopropyl)phenylamino]-1-piperidinepropanoic acid methyl ester

- ▶ Short-acting synthetic analgesic, μ receptor agonist. It is 100–200 times more potent than morphine. The analgesic effect occurs within 1 minute, the maximum after 2 minutes and it lasts 5–10 minutes.
- ▶ Metabolized in the liver to an inactive form (carboxylic metabolite — remifentanyl acid) due to hydrolysis by nonspecific tissue and plasma esterases. $T_{1/2}$ of the drug product: 3–10 minutes. $T_{1/2}$ of the metabolite: 2 hours. Excreted by the kidneys as a metabolite. For intravenous administration.

Therapeutic indications: induction of anesthesia, anesthesia in the early postoperative period

Contraindications: epidural and spinal blockade, pregnancy, breastfeeding

For side effects, see Morphine.

Pentazocine (Lexir[®], Fortral[®])

- ▶ κ and δ agonist, μ receptor antagonist, benzomorphan derivative. It is well absorbed when administered orally, intramuscularly and subcutaneously. Its analgesic activity, which is observed 15–60 minutes after intramuscular administration and 1–3 hours after oral administration, is inferior to that of morphine. The onset of action and its maximum occur 2–3 and 15–30 minutes after intravenous administration, respectively; 15–30 and 30–60 minutes after intramuscular and enteral administration. The duration of action is up to 3 hours. The risk of abuse is lower than with morphine. It increases cardiac work, pulmonary artery pressure, central venous pressure, which leads to an increase in cardiac preload. It provokes withdrawal syndrome in patients with opioid dependence.
- ▶ Metabolized in the liver to form inactive metabolites. $T_{1/2}$: 2–3 hours. Excreted by the kidneys. For oral, subcutaneous, intravenous, intramuscular administration.

Therapeutic indications: moderate and severe pain of various origins

Side effects: dysphoria, hallucinations, tachycardia, increased blood pressure

Contraindications: myocardial infarction, bronchial asthma, traumatic brain injury, epilepsy, cholelithiasis and urolithiasis, hepatic and renal impairment, pregnancy, breastfeeding.

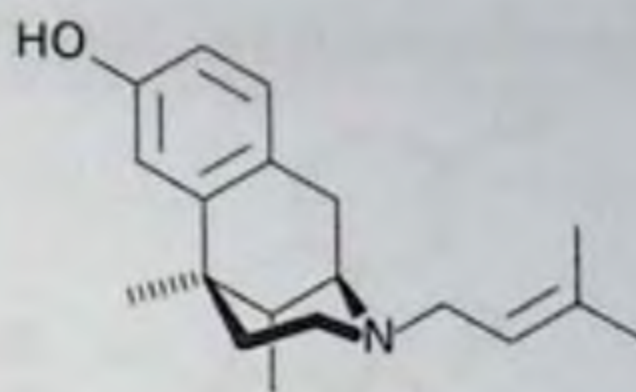


Fig. 6.11. (2 α ,6 α ,11R^{*})-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol

Butorphanol (Moradol[®], Stadol[®])

- ▶ Phenanthrene derivative. κ agonist and weak μ receptor antagonist. It is similar to pentazocine in its pharmacological properties. It also increases pulmonary artery pressure and cardiac work. It crosses the placental barrier and is excreted into breast milk. When administered intravenously, the analgesic effect occurs within 2–3 minutes, within 10–30 minutes when administered intramuscularly, within 15 minutes from the nasal mucosa. The duration of action is 3–4 hours when administered intramuscularly, 2–4 hours when administered intravenously. It increases systemic blood pressure. It depresses respiration to a lesser extent than morphine, and has a lower risk of drug dependence.
- ▶ Metabolized in the liver. $T_{1/2}$: 2.5–4.0 hours. Excreted by the kidneys, mainly as metabolites — 70–80% (5% — unchanged), in the feces — 15%. For intramuscular, intravenous, intranasal administration.

For therapeutic indications, side effects and contraindications, see Pentazocine.

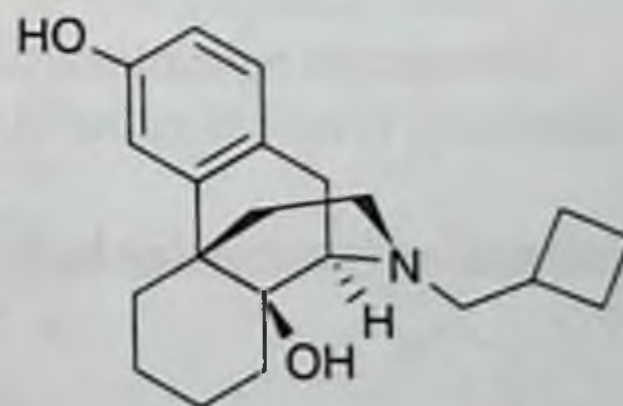


Fig. 6.12. 17-(Cyclobutylmethyl)morphinan-3,14-diol

Buprenorphine hydrochloride (Torgesic[®], Transtec[®])

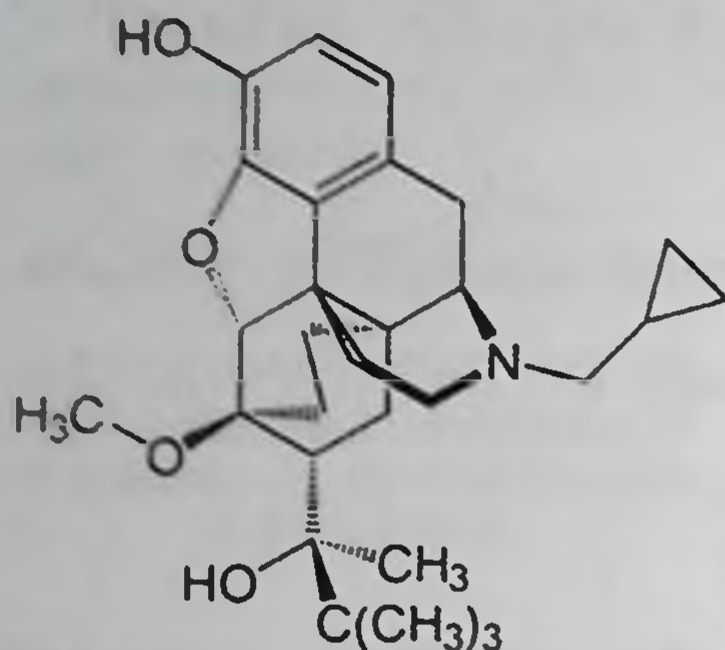


Fig. 6.13. 17-(Cyclopropylmethyl)-7,8-dihydro-7-[(1S)-2-hydroxy-3,3-dimethylbutyl-2]-6-methoxy-0-methyl-6,14-ethano-17-normorphine hydrochloride

- ▶ Partial μ receptor agonist, phenanthrene derivative, low abuse potential. It depresses respiration to a lesser extent than morphine and has a lower risk of drug dependence. Its analgesic activity is 20–60-fold superior to morphine. When administered intravenously, the analgesic effect occurs within 15 minutes, after intramuscular or sublingual administration it occurs within 30 minutes, and lasts 8–12 hours.
- ▶ Metabolized in the liver by N-dealkylation to form norbuprenorphine, a pharmacologically active metabolite.
- ▶ $T_{1/2}$: 3–6 hours. Excreted with bile and by the kidneys. For intravenous, intramuscular, sublingual administration.

Therapeutic indications: emergency care for major trauma, severe pain (burns, preoperative, intraoperative and postoperative periods, myocardial infarction, severe angina attacks, pain due to malignant tumors and other conditions causing severe pain).

Buprenorphine (Transtec[®])

- ▶ TTS (contains 20, 30, 40 mg of buprenorphine)
- ▶ After applying the patch, buprenorphine is absorbed through the skin; an adhesive polymer matrix continuously releases the DS.
- ▶ The plasma concentration of the product gradually increases and the minimum effective dose is reached within 12–59 hours (depending on the selected product concentration). $T_{1/2}$: 30 hours.

Therapeutic indications: severe pain (after surgery, in cancer patients, in myocardial infarction, renal colic, burns)

Nalbuphine (nalbuphine hydrochloride[®], Nubain[®])

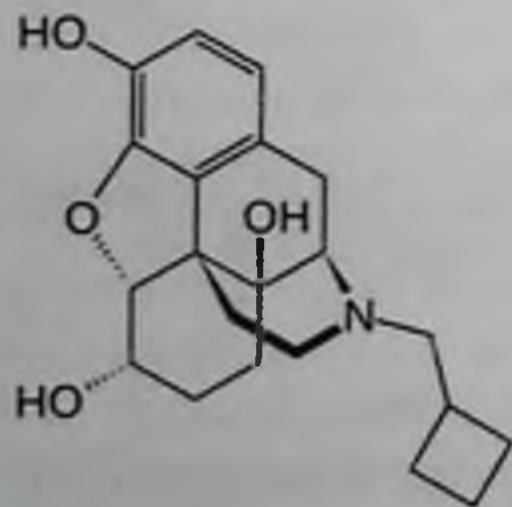


Fig. 6.14. (5 α ,6 α)-17-(Cyclobutylmethyl)-4,5-epoxymorphinan-3,6,14-triol

- ▶ Phenanthrene derivative. μ receptor agonist and κ receptor antagonist. It crosses the placental barrier and is excreted into breast milk (less than 1% of the administered dose). The analgesic effect occurs within 2–3 minutes after intravenous administration and 15 minutes after subcutaneous or intramuscular injection. Duration of action: 3–6 hours.
- ▶ Metabolized in the liver. $T_{1/2}$: 2.5–3.0 hours. Excreted as metabolites mainly in the bile and in small amounts by the kidneys. For intravenous, intramuscular, subcutaneous administration.

Therapeutic indications: for short-term treatment of moderate or severe pain (including in the pre- and postoperative period), as an additional agent during general anesthesia.

Naloxone (naloxone hydrochloride⁺, Narcan[®])

- ▶ Competitive antagonist at α , δ , μ opioid receptors, phenanthrene derivative. It prevents or stops the effects of opioids. The effect occurs within 1–2 minutes after intravenous administration, 2–5 minutes after intramuscular injection, reaching a maximum in 5–15 minutes. The effect after intravenous administration lasts 45 minutes; after intramuscular administration it lasts up to 4 hours. It crosses the placenta.
- ▶ Metabolized in the liver by conjugation with glucuronic acid. The main metabolite is naloxone-3-glucuronide. $T_{1/2}$: 1.0–1.5 hours. About 25–40% of the product is excreted as metabolites by the kidneys within 6 hours, and 60–70% of the product within 72 hours. For intravenous, intramuscular, subcutaneous administration.

Therapeutic indications: opiate overdose (first intravenously, then intramuscularly), to restore breathing in newborns after opioid analgesics are given to a woman in labor.

Side effects: dizziness, headache; tachycardia, blood pressure lability; nausea, vomiting

Contraindications: pregnancy, breastfeeding

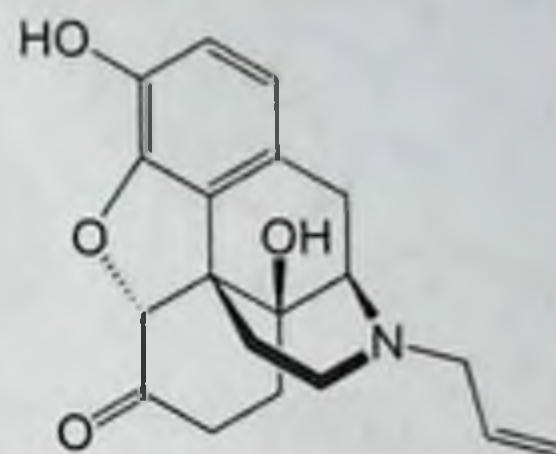


Fig. 6.15. (5 α)-4,5-Epoxy-3,14-dihydroxy-17-(2-propenyl)morphinan-6-OH

Naltrexone (Vivitrol⁺)

- ▶ Phenanthrene derivative, competitive antagonist at α , δ , μ opioid receptors. It causes acute withdrawal symptoms in patients with opioid dependence. In alcoholism, it binds to opioid receptors and blocks the effects of endorphins. It is effective when taken orally, since 96% of the product is absorbed in the GI tract. The effect occurs within 1–2 hours.
- ▶ Metabolized in the liver to form 6- β -naltrexol (the main metabolite), 2-hydroxy-3-methoxy-6- β -naltrexol and 2-hydroxy-3-methoxy-naltrexone. $T_{1/2}$ of the product: 4 hours; 13 hours for 6- β -naltrexol. Excreted mainly by the kidneys and with bile. For intramuscular (once monthly), oral administration.

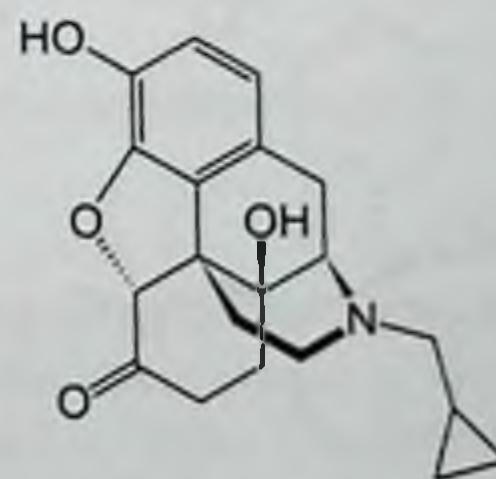


Fig. 6.16. (5 α)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one

Therapeutic indications: treatment of alcoholism and opioid dependence (in complex therapy)

Side effects: insomnia, depression, hallucinations, hepatotoxicity (elevated liver enzymes), nausea, joint pain

Contraindications: acute hepatitis, hepatic impairment, pregnancy, breastfeeding; less than 18 years of age

Nalmefene (Revex[®], Selincro[®])

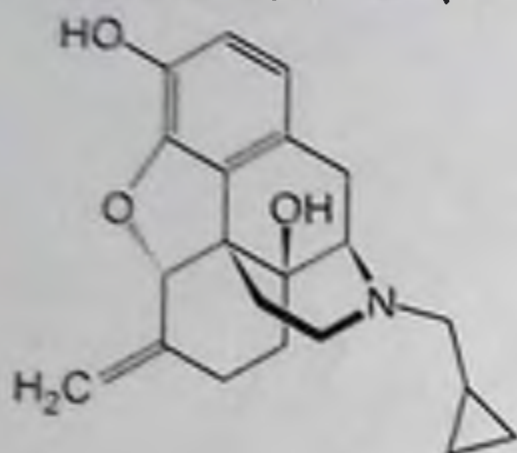


Fig. 6.17.
17--(Cyclopropylmethyl)-
4,5 α -epoxy-6-
methylenemorphinan-
3,14-diol

- ▶ Phenanthrene derivative. An opioid receptor antagonist with predominant affinity for the κ -opioid receptors and, to a lesser extent, for the μ -opioid receptors. Due to its long-term effect, the product is potentially preferred over naloxone. A dose of nalmefene 1 mg prevents respiratory depression for 4 hours, 2 mg — for 8 hours. It is 4 times more potent against κ receptors in acute overdose than naloxone.
- ▶ Metabolized in the liver to the main metabolites nalmefene-3-O-glucuronide, nornalmefene and nalmefene-3-O-sulfate.
- ▶ Nornalmefene, in turn, is converted to nornalmefene-3-O-glucuronide and nornalmefene-3-O-sulfate. Excreted by the kidneys. Nalmefene (Revex[®]) is for intravenous, intramuscular, subcutaneous administration; nalmefene (Selincro[®]) is for oral administration.

Therapeutic indications: opioid intoxication — nalmefene (Revex[®]), alcohol dependence — nalmefene (Selincro[®])

Side effects: dizziness, fatigue, lethargy, somnolence, agitation, irritability, muscle tension, myalgia, arthralgia, nausea, paresthesia, insomnia, headache, vomiting

Tramadol (Tramadol[®], Tramal[®])

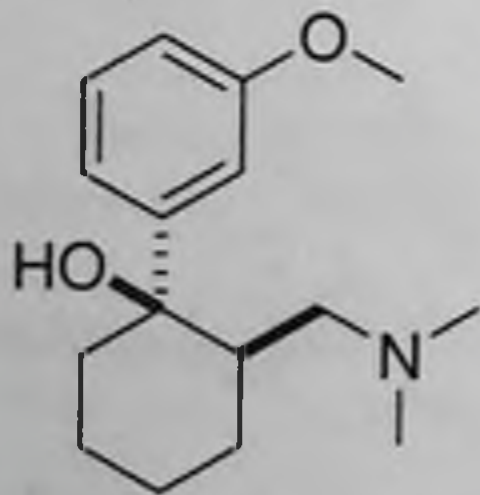


Fig. 6.18. Trans-(±)-
2-[(Dimethylamino)
methyl]-1-(3-methoxy-
phenyl)cyclohexanol
(as hydrochloride)

- ▶ Cyclohexanol derivative whose analgesic activity is 4–5-fold inferior to morphine. When administered intravenously, the effect occurs within 5–10 minutes, when administered orally it occurs within 30–40 minutes. The effect lasts 3–5 hours. Bioavailability when taken orally is 70%, rectally 80%. $T_{1/2}$: 6 hours. It crosses the placental barrier and is excreted into breast milk.
- ▶ Metabolized in the liver by demethylation and conjugation. Excreted from the body with urine (about 90%) mainly as metabolites. For oral, intravenous, intramuscular, subcutaneous, rectal administration.

Mechanism of action. Tramadol is a racemic mixture of stereoisomers. The D-isomer is a μ -opioid receptor agonist and disrupts neuronal serotonin uptake, the L-isomer inhibits neuronal norepinephrine (NA) uptake and is an α_2 -AR agonist. Both isomers stimulate the release of serotonin from presynaptic terminals. As a result, this potentiates the segmental and descending serotonergic inhibition of nociceptive impulses in the dorsal horns (Fig. 6.19).

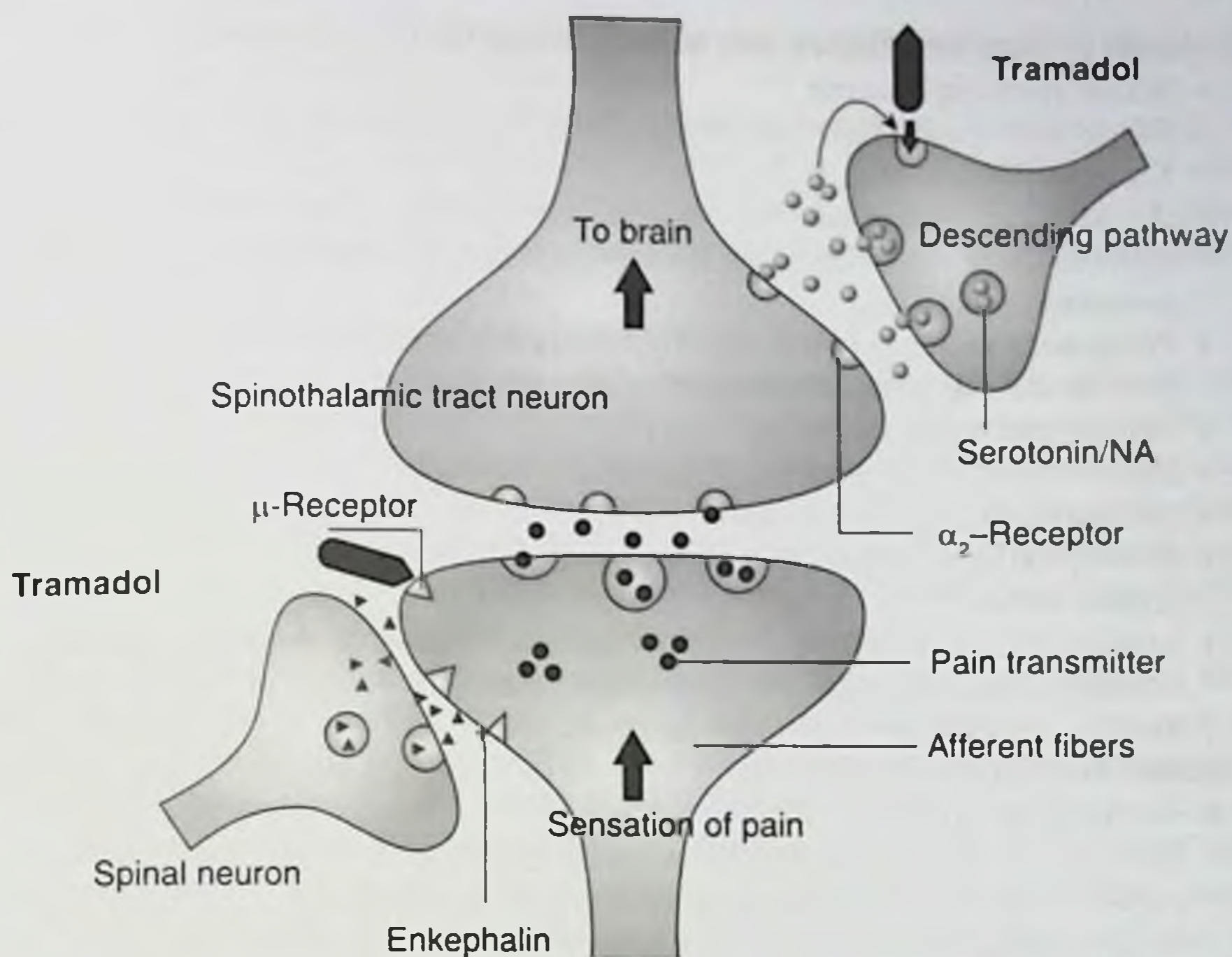


Fig. 6.19. Mechanism of action of tramadol

Therapeutic indications: postoperative pain, pain due to malignant tumors, injuries, etc.

Side effects: headache, dizziness, lethargy, hypotension, tachycardia, paresthesia, dry mouth, nausea, vomiting, constipation, drug dependence

Contraindications: acute alcohol intoxication, hepatic and renal impairment

Zaldiar® (acetaminophen, tramadol)

Fixed combination of 325 mg acetaminophen and 37.5 mg tramadol. It is rapidly and almost completely absorbed from the GI tract; the expected effect occurs in a few minutes. A single dose is 1–2 tablets, the maximum daily dose is 8 tablets. The interval between doses is at least 6 hours. For oral administration.

Therapeutic indications: acute or chronic moderate to severe pain

Side effects: headache, dizziness, lethargy, hypotension, tachycardia, paresthesia, dry mouth, nausea, vomiting, elevated AST and ALT levels, constipation, drug dependence

Contraindications: acute intoxication with alcohol, hypnotics, narcotic analgesics, opioids and psychotropic agents; severe hepatic and renal impairment.

Symptoms of acute intoxication with narcotic analgesics (e.g., morphine):

- ▶ Stupor resulting in coma
- ▶ Respiratory depression [bradypnea with apnea periods (Cheyne-Stokes or Kussmaul breathing)]
- ▶ Cerebral edema (hypoxia and acidosis, increased blood levels of carbon dioxide cause cerebral vasodilation, an increase in their permeability and in intracranial pressure)
- ▶ Pulmonary edema (in prolonged hypoxia, metabolic acidosis occurs in addition to respiratory acidosis, electrolyte balance is impaired)
- ▶ Urinary and bowel retention
- ▶ Hyperemia of the face, pruritus (histamine release)
- ▶ Bradyarrhythmia, hypotension
- ▶ Miosis, terminal mydriasis
- ▶ Hypothermia
- ▶ Inhibition of spinal tendon reflexes but preservation or even improvement of supraspinal monosynaptic (e.g., patellar) ones
- ▶ Death occurs due to respiratory paralysis.

Treatment of acute intoxication:

- ▶ Mechanical ventilation
- ▶ Intravenous administration of a competitive antagonist — naloxone [1–5 mL of a 0.04% solution (0.4–2.0 mg)], but only after airway patency has been restored since the increased brain activity with persistent hypoxia due to impaired airway patency leads to aggravation of toxic-hypoxic encephalopathy.
- ▶ If breathing is not restored, the same dose is administered again after 2–3 minutes. The maximum total dose is 10 mg (25 mL).
- ▶ For gastric lavage, a 0.05% solution of potassium permanganate is used repeatedly since morphine is involved in the enterohepatic circulation.
- ▶ Symptomatic treatment (bronchoalveolar lavage, introduction of intravenous sodium bicarbonate solutions to correct the acid-base balance, multicomponent saline solutions; mainly colloidal solutions are administered to prevent and treat cerebral and pulmonary edema. In cerebral edema, osmotic diuretics are administered).
- ▶ Forced diuresis, sorption detoxification, hemodialysis.

Chronic intoxication with narcotic analgesics

In drug addiction, psychological and physical dependence and addiction are formed.

At the stage of psychological dependence, drug withdrawal causes mental disorders — depression, irritability, aggression, insomnia, fear, prostration.

Psychological dependence. The euphoria induced by narcotic analgesics is the underlying cause of uncontrolled (compulsive) drug use. Drug dependence originates from the person's desire to experience euphoria once again.

Physical dependence is associated with withdrawal syndrome: rhinorrhea, lacrimation, oscitation, chills, piloerection, hyperventilation, hyperthermia, sharp

fluctuations in blood pressure, mydriasis, muscle and joint pain, vomiting, diarrhea, anxiety, hostility, insomnia and hallucinations.

In physical dependence, drug discontinuation or initiation of its antagonists is accompanied by an abstinence syndrome (derived from Latin *abstinentia* — “self-restraint”), a complex of psychopathological, neurological, somatic and autonomic disorders with potential rebound effects (functional disorders opposite to those caused by the drug).

Biochemical underpinnings of morphine withdrawal

- ▶ By activating opiate receptors, narcotic analgesics inhibit the release and synthesis of endogenous opioid peptides on a feedback loop, gradually replacing their activity. When the analgesic is withdrawn initially, the endogenous peptides are still suppressed. The above phenomena of deprivation (withdrawal) develop.
- ▶ The mechanism of opioid tolerance may be related to a decreased number of receptors; cellular changes in secondary messenger systems (intracellular Ca^{2+} , G proteins, etc.), synthesis of antibodies to drug products.

Treatment of an addicted person should be initiated in a hospital where the first stage (drug withdrawal and treatment of withdrawal symptoms) can be managed as painlessly and effectively as possible. This can be achieved through various methods:

1. Gradual reduction in the dose of narcotic analgesic over 10–14 days. This is done only when an immediate withdrawal of opioids could lead to death due to coexisting severe systemic diseases (e.g., coronary artery disease, post-infarction condition) or older age (above 70 years). In these cases, 1–2 mL of a 1% solution of morphine or promedol is administered 3 times on the first day of withdrawal symptoms. The daily dose is reduced up to complete withdrawal within 10–12 days.
2. Immediate discontinuation of opioids. Clonidine (Clophelin*), an α_2 -AA, is most often used to relieve withdrawal symptoms. It is administered intravenously (maximum daily dose is 0.8 mg), then orally (0.6 to 1.2 mg/day). It reverses both the signs and symptoms of opiate withdrawal but produces side effects including hypotension, dizziness, sedation, dry mouth, and orthostatic collapse.

7. NON-NARCOTIC ANALGESICS / NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Non-narcotic analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) are a broad class of drug products. Although their chemical structures differ, they have several effects in common (anti-inflammatory, analgesic, and antipyretic) with no tolerance or addiction potential.

The glycoside salicin was derived from willow bark in 1827 and salicylic acid was extracted in 1838. S.P. Botkin was one of the first worldwide to prescribe salicylic acid for acute rheumatic fever. In 1897 the German chemist Felix Hoffmann reported synthesizing acetylsalicylic acid. Butadion has been used for treatment of rheumatoid arthritis since 1949. Since 1963, indomethacin has been widely used for numerous indications in rheumatology. Metamizole sodium (Analgin[®]) was synthesized in 1920, and diclofenac in 1966. In 1971, John R. Vane showed that NSAIDs inhibit cyclooxygenase (COX) in different tissues, thus reducing the biosynthesis of prostaglandins (PG). He also discovered the antiplatelet properties of acetylsalicylic acid. Sune K. Bergström, Bengt I. Samuelsson and John R. Vane were jointly awarded the Nobel Prize in Physiology or Medicine in 1982 "for their discoveries concerning prostaglandins and related biologically active substances".

NON-NARCOTIC ANALGESICS

Classification.

1. Salicylic acid derivatives (salicylates)

- Acetylsalicylic acid (Aspirin[®])
- Methyl salicylate
- Choline salicylate (Otinum[®])
- Fixed combinations of acetylsalicylic acid with other drugs
 - Alka-Seltzer[®] (acetylsalicylic acid, citric acid, sodium bicarbonate)
 - Citrapak[®] (acetylsalicylic acid, caffeine, acetaminophen, ascorbic acid)
 - Aquacitramon[®] (acetylsalicylic acid, caffeine, acetaminophen)
 - Ascaff[®] (acetylsalicylic acid, caffeine)
 - Parcocet[®] (acetylsalicylic acid, codeine, caffeine, acetaminophen)

2. Pyrazolone derivatives

- Analgin[®] (metamizole sodium)

- Butadion* (phenylbutazone)
- Fixed combinations of metamizole sodium with other drugs
 - Spasgan* (metamizole sodium, pitofenone, fempiverinium bromide)
 - Tempalgin* (metamizole sodium, triacetanamine-4-toluensulfonate)
 - Tetralgin* (codeine, caffeine, metamizole sodium, phenobarbital)
- 3. Para-aminophenol derivatives
 - Acetaminophen* , Panadol* , Perfalgan* , Ifimol* (acetaminophen)
- Fixed combinations of acetaminophen with other drugs
 - Coldrex* (caffeine, acetaminophen, terpin hydrate, phenylephrine, ascorbic acid)
 - Solpadeine Fast* (caffeine, acetaminophen)
 - Citramon P* (acetylsalicylic acid, caffeine, acetaminophen)
 - Fervex* (acetaminophen, pheniramine, ascorbic acid)
 - Ibutlin* (ibuprofen, acetaminophen)

Pharmacological effects

- ▶ Analgesic
- ▶ Antipyretic
- ▶ Anti-inflammatory

Mechanisms of action

Three types of COX isoenzymes (Fig. 7.1) can be targeted:

- ▶ COX-1 is a structural (constitutive) enzyme that is always present in the endoplasmic reticulum. It is involved in the production of PGs that regulate physiological processes.
- ▶ COX-2 is involved in the development and progression of inflammation.
- ▶ COX-3 induces the synthesis of PGs in the CNS and plays a role in the development of pain and fever.

Analgesic effect

Peripheral: block COX-2 — inhibit the synthesis of PGs (PGE_2 , $\text{PGF}_{2\alpha}$) and prostacyclin (PGI_2) — factors that potentiate the action of interleukin-1, tumor necrosis factor- α , histamine, serotonin, bradykinin, neurokinins and prevent the development of hyperalgesia. By limiting exudation, they reduce pressure on pain receptors (Fig. 7.2).

Central: block COX-3, inhibit the synthesis of PGs in the CNS (acetaminophen).

Antipyretic effect

During hyperthermia, in the preoptic area of the hypothalamus, PGE_1 and PGE_2 contribute to cAMP accumulation, which disrupts the normal ratio of Na^+ and Ca^{2+} ions and allows the heat production functions to dominate over the heat dissipation functions. COX blockade reduces PG synthesis, thereby restoring the ion balance and eliminating the pyrogenic effect, which allows heat dissipation (skin vessels expand, sweating increases).

Anti-inflammatory effect

With COX-2 blockade, PG production decreases, which reduces the signs and symptoms of inflammation. In the alteration stage, lysosome membranes are stabilized.

hydrolytic enzymes (proteases, lipases, phosphatases, etc.) are not released, and lipid peroxidation is blocked. In the exudation stage, the release of inflammatory mediators decreases (histamine, serotonin, bradykinin, etc.) and hyaluronidase activity, vascular permeability and tissue edema are reduced. In the proliferation stage, fibroblast proliferation is limited, collagen synthesis and the formation of connective tissue are reduced, and ATP production, which is needed for proliferation, is disrupted.

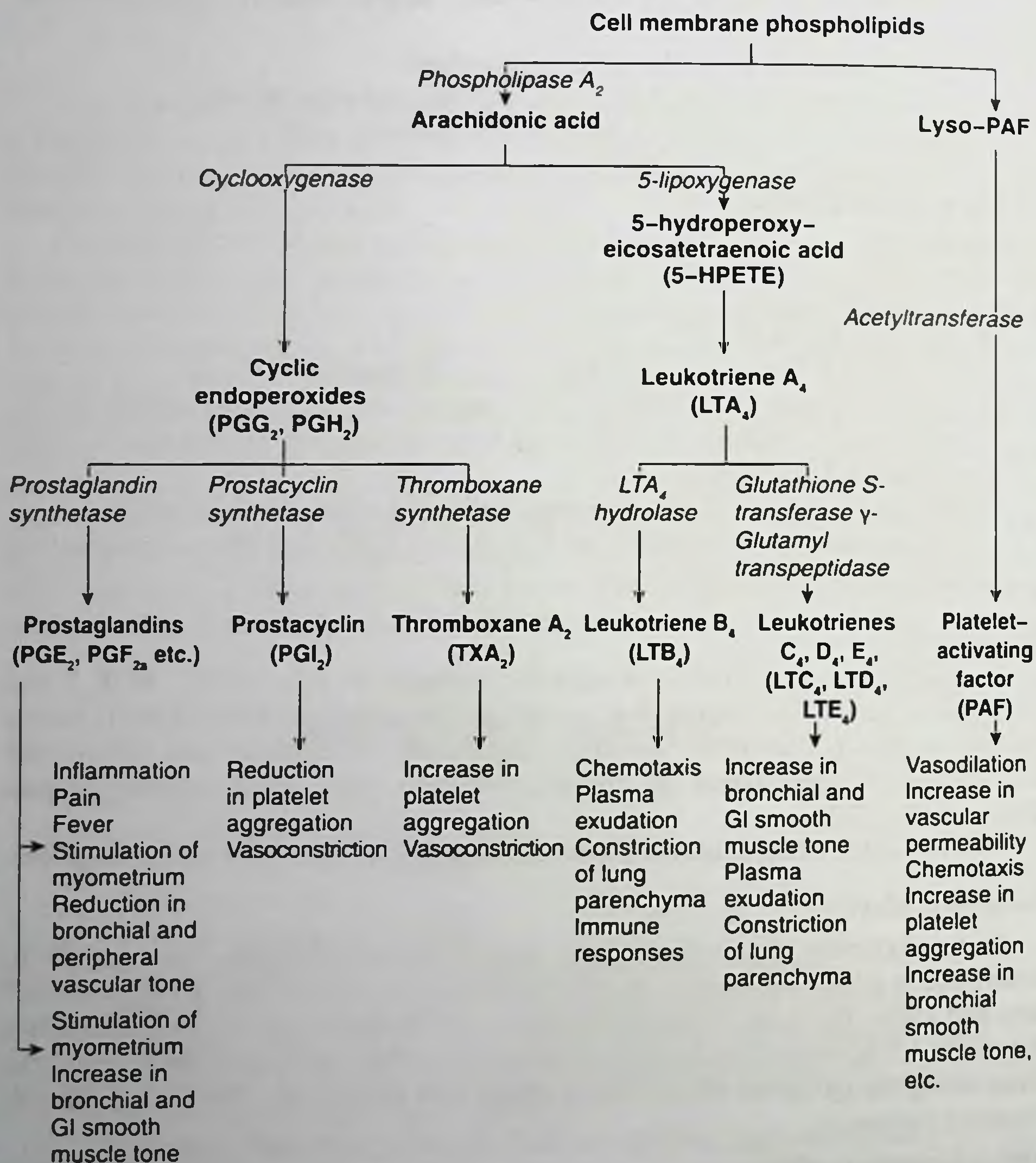
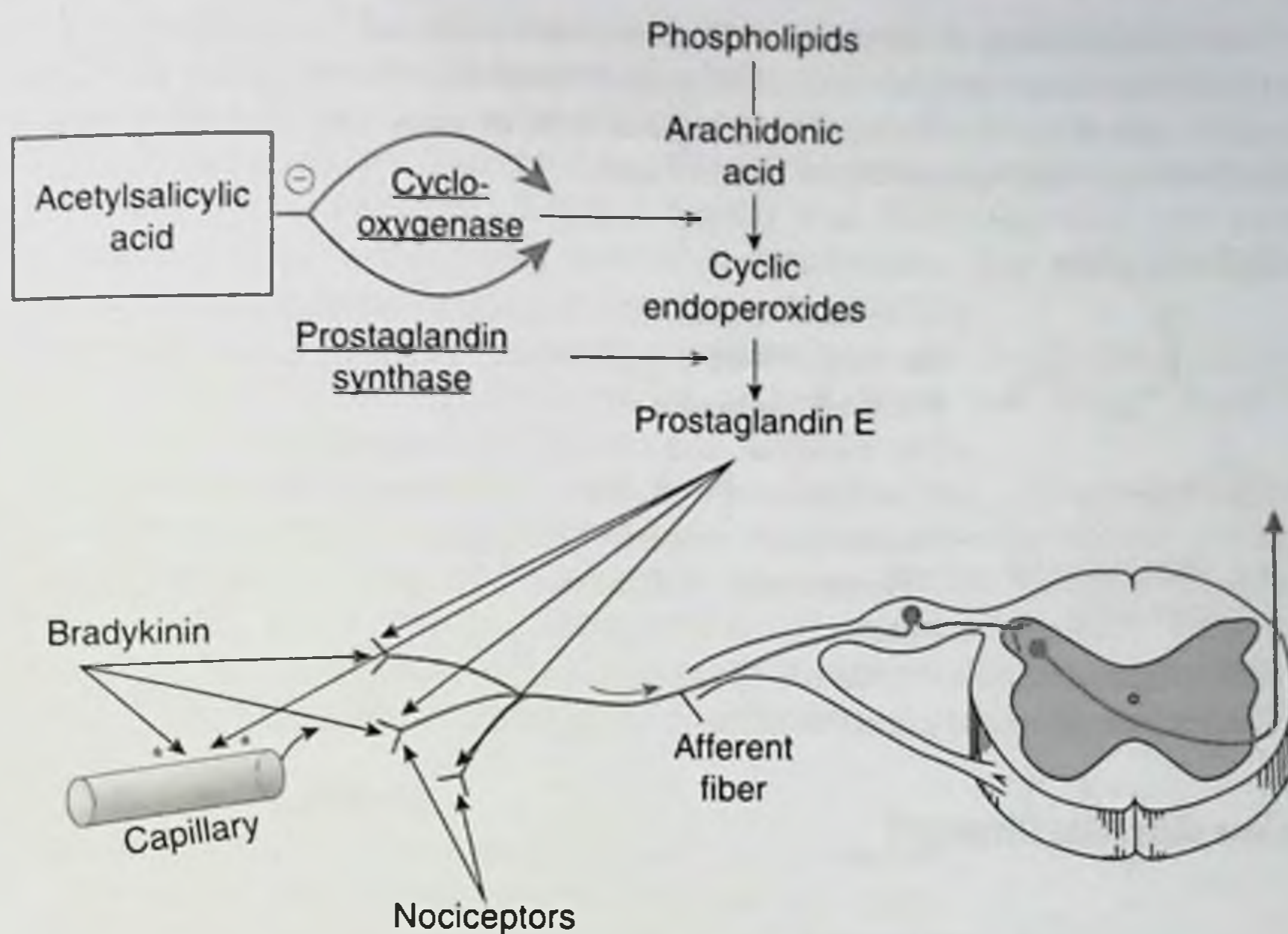


Fig. 7.1. Pattern of arachidonic acid metabolism



⊖ — inhibitory effect

* — effect on vascular wall microcirculation and permeability

Fig. 7.2. Mechanism of the analgesic action of non-narcotic analgesics (D.A. Kharkevich, 2021)

Specifics of individual products

Acetylsalicylic acid (Aspirin[®])

- ▶ The effects are dose-dependent: 75–300 mg — antiplatelet, 0.5–2.0 g — analgesic and antipyretic, 4–6 g — anti-inflammatory and uricosuric.
- ▶ Subject to first-pass elimination. Crosses the BBB and placental barrier. Metabolized in the liver by hydrolysis to form salicylic acid, followed by conjugation with glycine or glucuronide. $T_{1/2}$: 2–3 hours, elimination in urine as metabolites depends on urine pH (with urinary alkalization, the ionization of salicylates increases, reabsorption is reduced). For oral administration.

Therapeutic indications: pain (headache, toothache, myalgia, arthralgia, etc.); fever; prevention of thrombotic complications in patients with myocardial infarction, stroke and other cardiovascular diseases (as an antiplatelet agent).

Side effects: ulcerogenic effect, dyspepsia; bleeding at various locations, bone marrow suppression (anemia, thrombocytopenia, leukopenia); bronchospasm; Reye's syndrome in children under 15 years of age during the treatment of viral fever (encephalopathy and acute hepatic steatosis with the development of hepatic impairment); teratogenic effect.

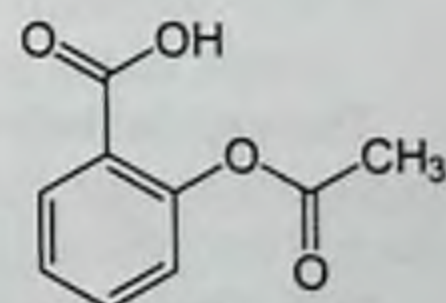


Fig. 7.3. 2-Acetyloxybenzoic acid

Contraindications: erosive and ulcerative gastrointestinal lesions; gastrointestinal or other bleeding; hemorrhagic diathesis, thrombocytopenia; bronchial asthma; decompensated heart failure; severe hepatic and/or renal impairment; pregnancy, breastfeeding; children (under 15 years of age).

Methyl salicylate

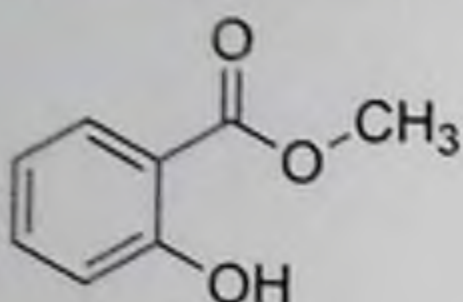


Fig. 7.4. Methyl ester of salicylic acid

- ▶ With local application, it quickly penetrates the deep layers of the skin, where it is absorbed, hydrolyzed and converted into a salicylic acid anion.
- ▶ Has analgesic and anti-inflammatory effect.
- ▶ A component of fixed combination products (Sanitas[®], Naphtalgin[®], Capsin[®]) for topical administration.

Therapeutic indications: arthritis, myalgia, orthopedic trauma, osteochondrosis

Side effects: irritation at the site of application, skin allergic reactions

Contraindications: allergic reactions to salicylic acid derivatives

Choline salicylate (Otinum[®])

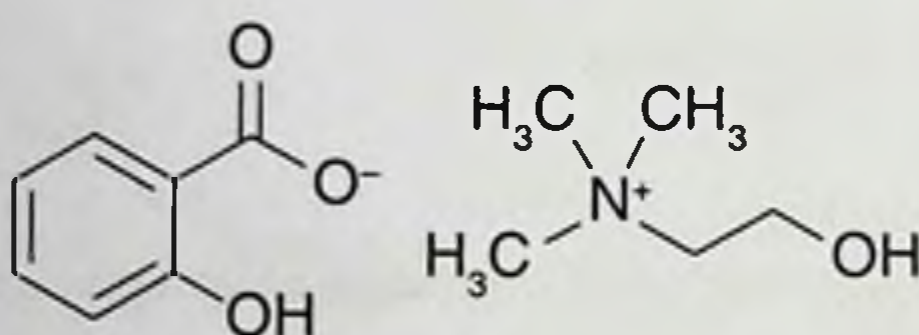


Fig. 7.5. (2-Hydroxyethyl)trimethylammonium salicylate

- ▶ Well absorbed from the mucous membranes. For topical administration (ear drops, dental gel).

Therapeutic indications: ear drops [choline salicylate (Otinum[®])]: otitis externa and otitis media; dental gel: infectious and inflammatory, ulcerative and necrotic, trophic oral mucosal lesions, aphthous stomatitis

Side effects: burning at the site of application, allergic reactions

Contraindications: perforated eardrum (for ear drops), allergic reactions

Metamizole sodium (Analgin[®])

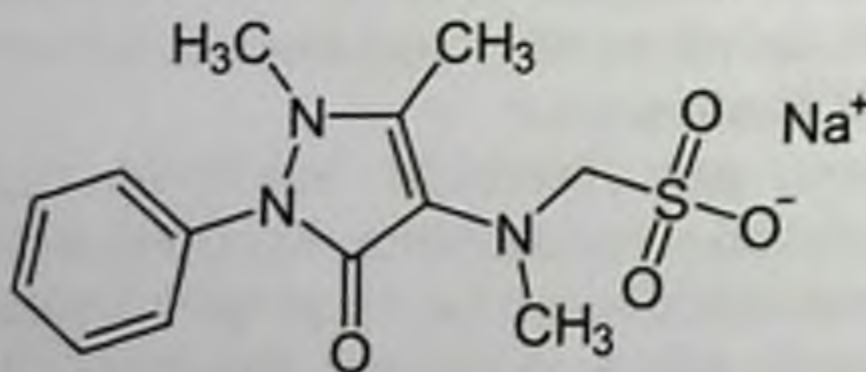


Fig. 7.6. [(2,3-Dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl)methylamino]methanesulfonic acid sodium salt (as monohydrate)

- ▶ When taken orally, the analgesic effect occurs within 20–40 minutes with a maximum after 2 hours and lasts up to 8 hours; when administered intravenously, the maximum effect occurs within 20–40 minutes.
- ▶ Metabolized in the liver to form 4N-methylaminoantipyrine and other metabolites, crosses the placental barrier and BBB, excreted into breast milk, excreted in the urine, mainly as metabolites. For oral, parenteral, rectal administration.

Therapeutic indications: pain of various origins (headache, toothache, neuralgia, myalgia, dysmenorrhea, postoperative pain, etc.), renal and biliary colic (in combination with antispasmodics), fever

Side effects: bone marrow suppression (leukopenia, thrombocytopenia, agranulocytosis), ulcerogenic effect, nephrotoxicity, hepatotoxicity, allergic reactions

Contraindications: bone marrow suppression (leukopenia, thrombocytopenia, agranulocytosis), severe hepatic and/or renal impairment, hereditary hemolytic anemia associated with deficiency of glucose-6-phosphate dehydrogenase (risk of hemolysis), bronchial asthma, pregnancy, breastfeeding

Phenylbutazone (Butadion⁺)

- ▶ Crosses the BBB, enters the joint cavity. Bioavailability: 90%; maximum blood concentration within 1–2 hours
- ▶ Metabolized in the liver, $T_{1/2}$: 19–24 hours, metabolite elimination in the urine and bile. For oral, topical administration.

Therapeutic indications: pain of various origins (headache, toothache, dysmenorrhea, postoperative pain, etc.), inflammatory musculoskeletal disorders, gout.

For side effects and contraindications, see Metamizole sodium.

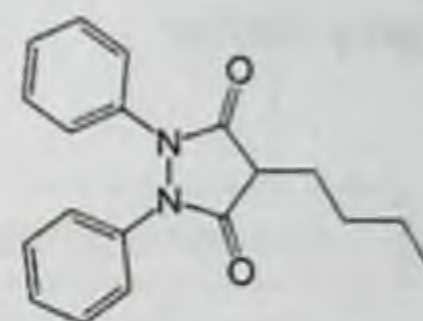


Fig. 7.7. 4-butyl-1,2-diphenyl-pyrazolidine-3,5-dione

Paracetamol (Acetaminophen⁺, Panadol⁺, Efferalgan⁺, Ifimol⁺)

- ▶ Para-aminophenol derivative, centrally acting analgesic. Low therapeutic index and very weak anti-inflammatory effect. When taken orally, the effect occurs within 30–60 minutes and lasts 4–6 hours; when administered intravenously, the effect occurs within 5–10 minutes with a maximum after 1 hour and lasts up to 6 hours. Crosses the BBB.
- ▶ The central analgesic action of acetaminophen has been attributed to its metabolism to N-arachidonoylaminophenol (AM404), a potent TRPV1 agonist and low-affinity ligand for CB1 in the brain and spinal cord (Fig. 7.9) and its ability to inhibit COX-3 in the CNS.

Metabolized in the liver to form glucuronides in adults and sulfates in children. $T_{1/2}$ in adults: 2.7 hours, in children: 1.5–2.0 hours, excreted in the urine as metabolites (Fig. 7.10).

For oral, intravenous (Ifimol, solution for injection), rectal administration.

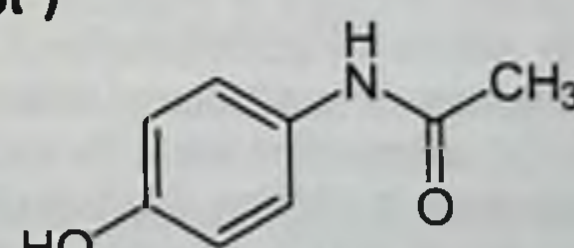


Fig. 7.8. N-(4-hydroxyphenyl)acetamide

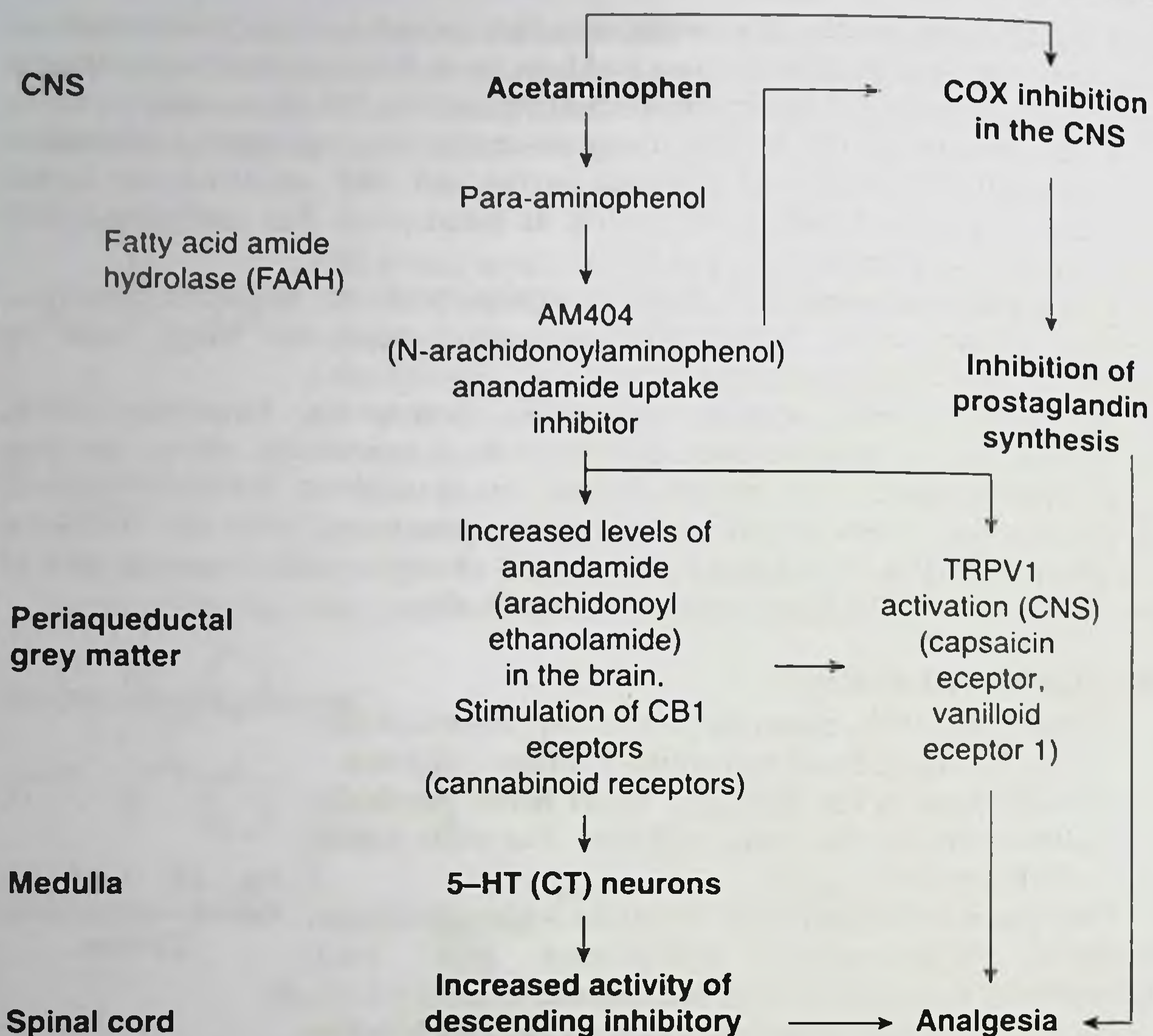


Fig 7.9. Mechanism of the central analgesic action of acetaminophen (Ohashi N. et al., 2020). Paracetamol (acetaminophen) is metabolized to para-aminophenol, which easily crosses the BBB and is converted to AM404 (N-arachidonoylaminophenol) by the action of fatty acid amide hydrolase. AM404 is an anandamide (arachidonoyl ethanolamide, CB1 receptor agonist, endocannabinoid) reuptake inhibitor that plays an important role in the mechanisms of pain, depression, appetite control, memory and reproductive function. In addition, COX3 blockade as well as TRPV1 (capsaicin receptor or vanilloid receptor 1) and serotonin (5HT3) activation involved in pain and thermoregulatory pathways play a role in the central analgesic effect of acetaminophen.

Therapeutic indications: pain (headache, toothache, myalgia, neuralgia, arthralgia, dysmenorrhea, postoperative pain, etc.), fever

Side effects: dyspepsia, allergic reactions

Contraindications: hepatic and/or renal impairment

Acetaminophen overdose

Administration of acetaminophen at doses exceeding therapeutic ones (the maximum single dose is 1 g; the maximum daily dose is 4 g) causes hepatotoxicity. Acetaminophen primarily forms conjugates with glucuronic acid (90%) with a certain amount (5–9%) oxidized by microsomal enzymes to form a toxic metabolite,

N-acetyl-p-benzoquinone imine, which binds to glutathione and is excreted in the urine (Fig. 7.10). In case of overdose, hepatic glutathione stores are depleted, the metabolite accumulates and the risk of oxidative damage to hepatocytes increases, leading to the formation of free radical compounds with nephrotoxicity.

Overdose symptoms:

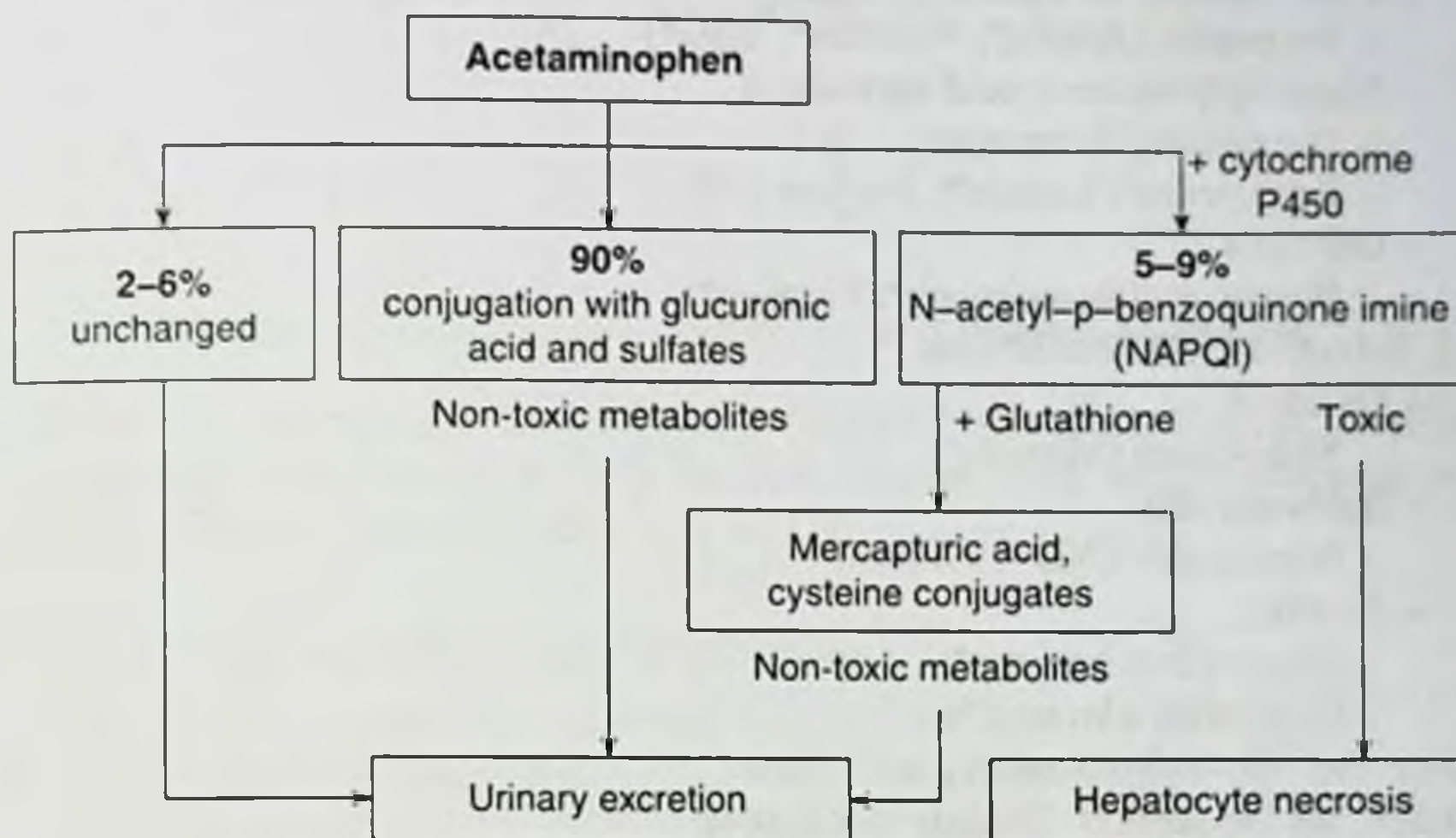


Fig. 7.10. Acetaminophen metabolism (Lancaster E.M. et al., 2015)

- ▶ Stage I (first 24 hours): anorexia, nausea and vomiting, pallor, excessive sweating, symptoms of pancreatic and cardiac distress
- ▶ Stage II (Day 1 to Day 3): right upper quadrant pain due to hepatomegaly, elevated levels of AST and ALT, bilirubin as well as prolonged prothrombin time.
- ▶ Stage III (Day 3 to Day 5): symptoms of hepatotoxicity, further elevation of AST, ALT, bilirubin; impaired consciousness (sopor), jaundice, impaired coagulation, hypoglycemia and encephalopathy; renal impairment and myocardiopathy
- ▶ Stage IV (after 5 days): death from hepatic impairment

Treatment (effective in the first 12 hours)

- ▶ Gastric emptying (emetics, lavage), administration of sorbents, saline laxatives
- ▶ Antidote
 - Acetylcysteine intravenously at a dose of 300 mg/kg for 20 hours, with half the dose in the first 15 minutes (contains a sulfhydryl group, promotes the formation of hepatic glutathione)
 - Methionine 2.5 g orally three times at 4-hour intervals (stimulates conjugation)
- ▶ Symptomatic treatment

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Classification

I. Non-selective COX-1, COX-2 inhibitors

- Indoleacetic acid derivatives
 - Indomethacin (Metindol*)

- Phenylacetic acid derivatives
 - Diclofenac (Diclofenac sodium[•], Voltaren[•], Ortophen[•])
 - Heteroaryl acetic acid derivatives
 - Ketorolac (Ketanov[•], Ketorol[•])
 - Phenylpropionic acid derivatives
 - Ibuprofen (Brufen[•], Nurofen[•], MIG[•])
 - Naphthylpropionic acid derivatives
 - Naproxen (Naprosyn[•])
 - Ketoprofen (Ketonal[•], Fastum gel[•])
 - Oxicams
 - Piroxicam (Remoxicam[•], Finalgel[•])
2. Selective COX-2 inhibitors
- Oxicams
 - Meloxicam (Movalis[•])
 - Sulfonamides
 - Nimesulide (Nise[•], Nimesil[•])
 - Coxibs
 - Celecoxib (Celebrex[•])
 - Etoricoxib (Arcoxia[•])

For the anti-inflammatory, antipyretic and analgesic mechanisms of action of NSAIDs, see the section "Non-narcotic analgesics".

Therapeutic indications: acute rheumatic fever; rheumatoid, gouty and psoriatic arthritis; radiculitis, sciatica, lumbago; spondyloarthropathy, osteoarthritis, myositis, peritendinitis, tendonitis, bursitis, tenosynovitis, trauma; postoperative pain, headache and toothache, dysmenorrhea, fever

Side effects: ulcerogenic effect (NSAID gastropathy), nausea, vomiting, epigastric pain, diarrhea; bleeding, bone marrow suppression (leukopenia, thrombocytopenia, aplastic anemia); bronchospasm; neurotoxicity (somnolence, depression, hallucinations, hearing impairment, diplopia), hepatotoxicity, nephrotoxicity, cardiotoxicity (tachyarrhythmias, aggravation of chronic heart failure), edema, increased blood pressure, allergic reactions

Contraindications: gastroduodenal ulcer, ulcerative colitis, Crohn's disease; bleeding at various locations, leukopenia, thrombocytopenia, aplastic anemia; bronchial asthma, renal and/or hepatic impairment; pregnancy, breastfeeding

Specifics of individual products

Indomethacin (Metindol[•])

- ▶ Pronounced anti-inflammatory effect but is the most toxic NSAID (side effects are observed in 30–50% of patients), limited use, bioavailability: 80–90%. It has a teratogenic effect, crosses the placental barrier and BBB, penetrates into the synovial cavity.
- ▶ Metabolized in the liver. $T_{1/2}$: 4–9 hours, 70% excreted in the urine, 30% excreted with bile and breast milk. For oral, intramuscular, topical, rectal, conjunctival administration 2 or 3 times daily.

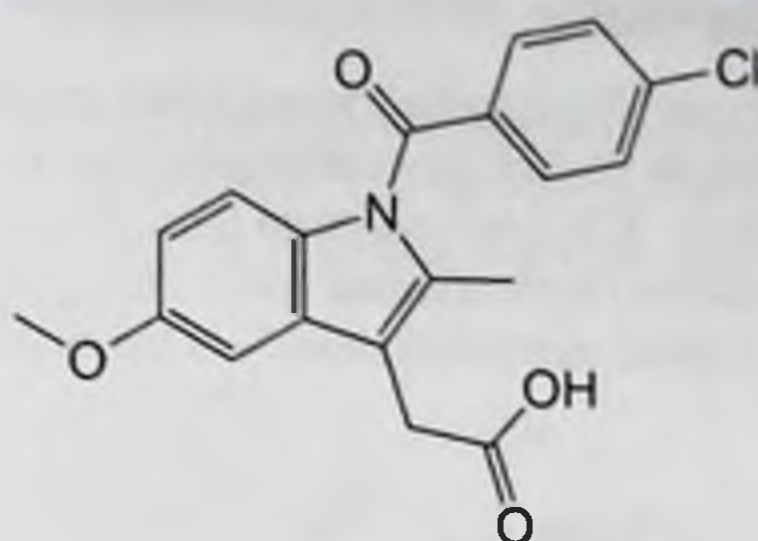


Fig. 7.11. 1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid

Additional therapeutic indications: treatment of patent ductus arteriosus in premature newborns (dose of 0.25–0.30 mg/kg body weight once or twice during the first 12 hours of life).

Diclofenac (Diclofenac sodium⁺, Voltaren⁺, Ortophen⁺)

- ▶ Its anti-inflammatory activity is similar to indomethacin and superior to ibuprofen, has a high therapeutic index, penetrates well into tissues and synovial fluid; bioavailability is 50%.
- ▶ Metabolized in the liver by glucuronidation and methoxylation. Plasma and synovial fluid $T_{1/2}$: 2 and 3–6 hours, respectively; excreted in the urine. For oral, intramuscular, intravenous, topical, rectal administration 2–3 times daily.

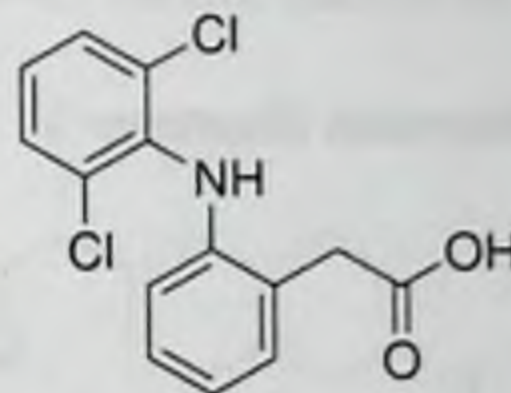


Fig. 7.12. 2-(2-(2,6-Dichlorophenylamino) phenyl)acetic acid (as sodium salt)

Ketorolac (Ketanov⁺, Ketorol⁺)

- ▶ Has the most potent analgesic effect (30 mg of ketorolac administered intramuscularly is equivalent to 12 mg of morphine). Bioavailability: more than 80%. When taken orally, the analgesic effect occurs within 1 hour with a maximum at 2–3 hours. When administered intramuscularly, the effect occurs within 30 minutes with a maximum at 1–2 hours.
- ▶ Metabolized in the liver by glucuronidation to form inactive metabolites. $T_{1/2}$: 4–6 hours. Excreted in the urine. For oral, intramuscular, topical administration thrice daily.

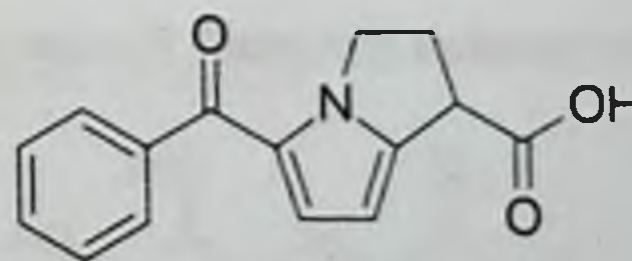


Fig. 7.13. (±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid (as compound with 2-amino-2-hydroxymethyl-1,3-propanediol)

Ibuprofen (Brufen⁺, Nurofen⁺, MIG⁺)

- ▶ Bioavailability: 80%, rapidly absorbed when taken orally, slowly penetrates into synovial fluid resulting in higher concentrations than in plasma.
- ▶ Metabolized in the liver. $T_{1/2}$: 2 hours, more than 90% of the product is excreted in the urine as metabolites (hydroxylated and carboxylated derivatives). For oral, intravenous, rectal, topical administration 3–4 times daily.

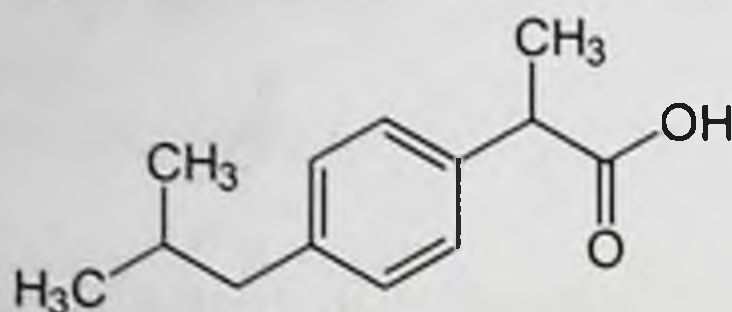
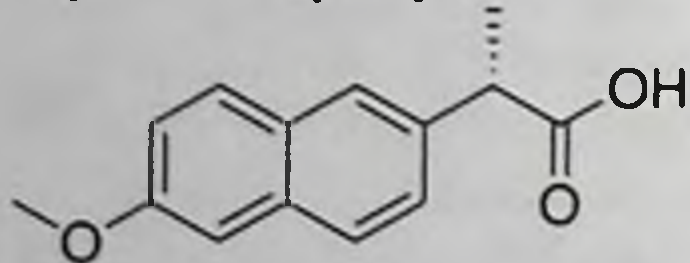


Fig. 7.14. (RS)-2-(4-isobutylphenyl)-propionic acid

Additional therapeutic indications: treatment of patent ductus arteriosus in premature newborns (intravenously once daily). When administered in the first 3–4 days of life, the efficacy reaches 75–80%.

Naproxen (Naprosyn⁺)Fig. 7.15. (S)-6-Methoxy- α -methyl-2-naphthaleneacetic acid (as sodium salt)

- ▶ Its anti-inflammatory activity is inferior to diclofenac but its analgesic effect is superior. Well absorbed when taken orally (bioavailability: 95%); food slows down but does not reduce the absorption, crosses placental barrier, excreted into breast milk.
- ▶ Metabolized in the liver to form dimethylnaproxen. $T_{1/2}$: 12–15 hours. Excreted in the urine as metabolites. For oral, rectal administration twice daily.

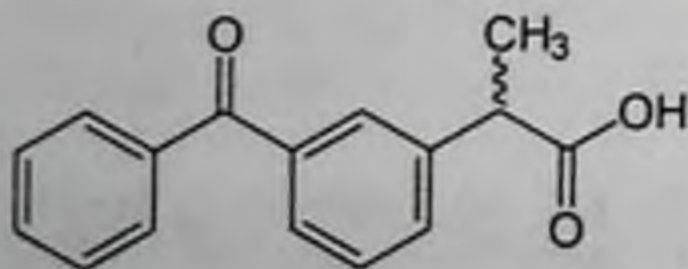
Ketoprofen (Ketonal⁺, Fastum gel⁺)

Fig. 7.16. 2-(3-benzoylphenyl)propanoic acid

- ▶ Similar to ibuprofen in structure and action. The anti-inflammatory effect occurs by the end of the first week of administration. Bioavailability: 90%; maximum plasma concentration within 1.5 hours.
- ▶ Metabolized in the liver with glucuronic acid by the action of hepatic microsomal enzymes to inactive metabolites. $T_{1/2}$: less than 2 hours. Excreted in the urine. For oral, intravenous, intramuscular, rectal, topical administration 2–3 times daily.

Piroxicam (Remoxicam⁺, Finalgel⁺)

- ▶ Well absorbed when taken orally, food slows down the absorption rate but does not affect the extent. Bioavailability is absolute. The analgesic effect occurs 30 minutes after oral administration, the anti-inflammatory effect occurs by the end of the 1st

week of treatment. Penetrates into synovial fluid (40–50%) and is excreted into breast milk.

- ▶ Metabolized in the liver by hydroxylation followed by conjugation with glucuronic acid to form inactive metabolites. $T_{1/2}$: 24–50 hours. Excreted as conjugates in the urine and, to a lesser extent, with bile. For oral, topical, intramuscular, rectal administration once daily.

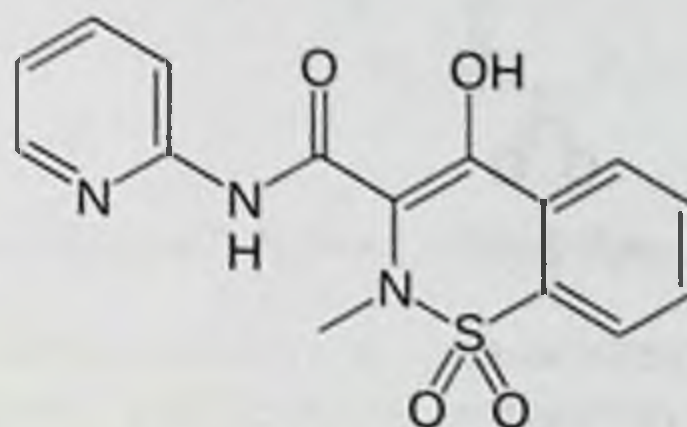


Fig. 7.17. 4-Hydroxy-2-methyl-N-2-pyridinyl-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide

Meloxicam (Movalis®)

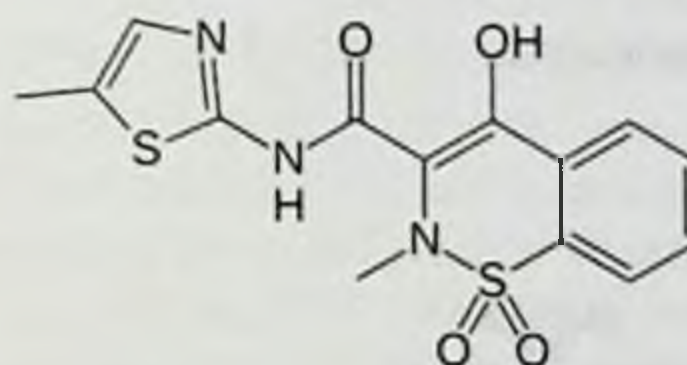


Fig. 7.18. 4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide

- ▶ Bioavailability when taken orally: 90%, regardless of the meal. It crosses blood–tissue barriers, the concentration in synovial fluid reaches 50% of the maximum plasma concentration.
- ▶ Metabolized in the liver to form inactive metabolites, excreted equally with bile and by the kidneys, mainly as metabolites. For oral, intramuscular, rectal administration once daily.

Additional therapeutic indications: prevention of colorectal cancer

Nimesulide (Nise®, Nimesil®)

- ▶ Rapidly and almost completely absorbed from the GI tract. The maximum plasma concentration is reached after 2–3 hours; crosses the synovial membrane and reaches a concentration in the periarticular fluid that exceeds that in plasma within 3 to 12 hours.
- ▶ Metabolized in the liver by tissue monooxygenases to the active metabolite (4-Hydroxy nimesulide). $T_{1/2}$: 2–5 hours, excreted in the urine as a free or conjugated metabolite and with bile. For oral, intravenous, intramuscular, rectal, topical administration twice daily.

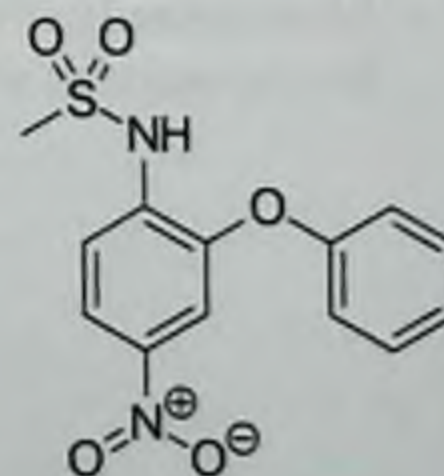


Fig. 7.19. N-(4-Nitro-2-phenoxyphenyl) methanesulfonanilide

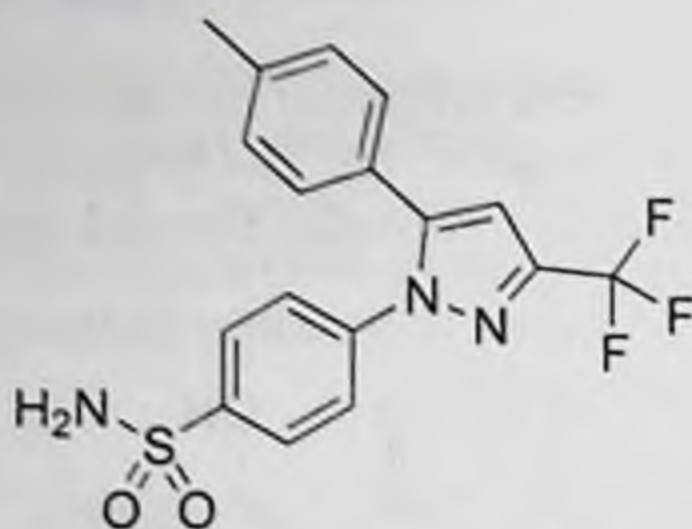
Celecoxib (Celebrex[®])

Fig. 7.20. 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

- ▶ When taken orally, serum concentration reaches a maximum after 2–4 hours. It is metabolized in the liver by hydroxylation, oxidation and partially glucuronidation to active metabolites. $T_{1/2}$: 11 hours, excreted in the urine and bile, mainly as a carboxyl metabolite and glucuronides, a small part is excreted unchanged. For oral administration once or twice daily.

Additional therapeutic indications: combination therapy for familial adenomatous polyposis of the colon

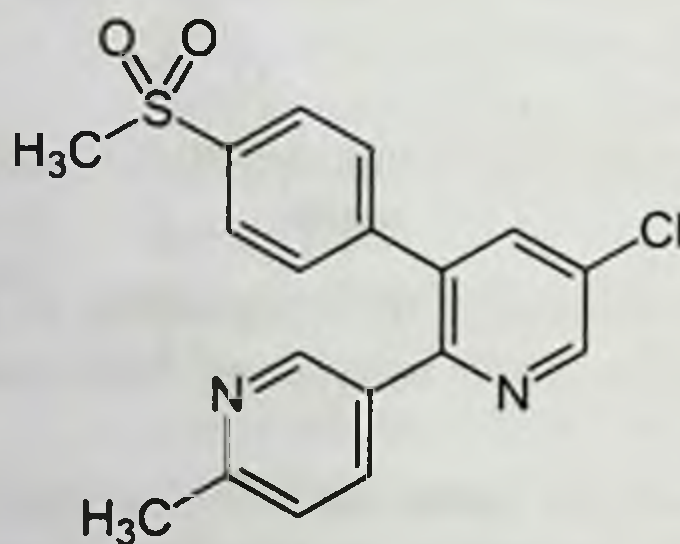
Etoricoxib (Arcoxia[®])

Fig. 7.21. 5-Chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine

- ▶ Bioavailability is absolute. Food intake does not affect absorption. It crosses the placental barrier and BBB. Time to reach maximum plasma concentration is 1 hour.
- ▶ Metabolized in the liver to form an inactive 6'-hydroxymethyl derivative. $T_{1/2}$: 22 hours, excreted with bile. For oral administration once daily.

8. PSYCHOTROPIC AGENTS WITH INHIBITORY ACTION: NEUROLEPTICS, TRANQUILIZERS, SEDATIVES

ANTIPSYCHOTIC DRUGS (NEUROLEPTICS)

The first antipsychotic agent, chlorpromazine, was synthesized in 1950 in France by the chemist P. Charpentier. In Russia, chlorpromazine was synthesized in 1955 at the All-Union Chemical-Pharmaceutical Institute and studied by M. D. Mashkovsky, Academician of the Russian Academy of Medical Sciences. In 1968, the atypical neuroleptic clozapine was derived. In 1980–1990, many modern antipsychotic agents were introduced into clinical practice, eliminating positive, negative and cognitive symptoms and improving cognitive functions in patients with schizophrenia without provocation of extrapyramidal disorders. The term “neuroleptics” was proposed in 1967 during the development of the first classification of psychotropic products.

These drug products have an antipsychotic effect and to some extent, a pronounced sedative effect. The antipsychotic effect is manifested by elimination of the positive psychosis symptoms (delusions, hallucinations), psychomotor agitation and by delaying disease development.

The psychosedative effect is characterized by general sedation with elimination of affective tension, decreased anxiety, psychic tension, and physical activity.

Classification

I. Typical neuroleptics

1. Phenothiazine derivatives

A. Aliphatic

- Chlorpromazine (Aminazin[♦])
- Levomepromazine (Tisercin[♦])

B. Piperazine

- Trifluoperazine (Triptazine[♦])
- Fluphenazine (Phthorphenazinum[®])
- Perphenazine (Etaperazin[♦])

C. Piperidine

- Thioridazine (Sonapax[♦])

- Periciazine (Neuleptil[®])
- 2. Butyrophenone derivatives
 - Haloperidol (Galofen[®])
 - Droperidol (Dridol[®], Droleptan[®])
 - Trifluoperidol (Trisedyl[®])
- 3. Thioxanthene derivatives
 - Chlorprothixene (Truxal[®])
- 4. Indole derivatives
 - Dicarbazine (Carbidinum[®])
- II. Atypical neuroleptics
 1. Benzodiazepine derivatives
 - clozapine (Azaleptin[®], Leponex[®])
 - olanzapine (Zyprexa[®])
 - quetiapine (Seroquel[®])
 2. Substituted benzamides
 - sulpiride (Eglonyl[®])
 3. Benzisoxazole derivatives
 - risperidone (Risipolept[®])

Mechanism of action: These drug products inhibit catecholamine-reactive (adrenergic and dopamine-reactive) systems of the hypothalamus and brain reticular formation and reduce their sensitivity to neurotransmitters. Decreased activity of the catecholaminergic systems in the brain is one of the mechanisms of action of neuroleptics: a number of psychopathological processes are associated with a change in the formation, accumulation and metabolism of norepinephrine and dopamine neurotransmitters (Fig. 8.1).

Antipsychotic action: These drug products competitively block dopamine receptors, predominantly postsynaptic dopamine-type 2 (D_2) receptors of the mesolimbic system. Approximately 70% of the receptors must be blocked for a clinical effect to occur. Blockade of dopamine receptors inhibits the increased activity of the limbic system and restores the striatum's ability to suppress information interference and regulate voluntary movements.

The main side effects—extrapyramidal symptoms—are also associated with inhibition of dopamine's mediator activity. In addition to blocking receptors sensitive to dopamine and norepinephrine, they disrupt the release of these biogenic amines and their neuronal uptake. The antipsychotic effect also results from neuroleptics interacting with serotonin receptors. Blockade of $5-HT_{2A}$ receptors in the cerebral cortex reduces the symptoms of psychosis, depression, and improves cognitive functions. Blockade of $5-HT_{2C}$ receptors has an anti-anxiety effect and stimulates appetite.

Sedative action: It is partially associated with an effect on the ascending reticular activating system. By blocking adrenergic receptors (α -AR) in the midbrain reticular formation, these drug inhibit the transmission of nerve impulses from the collaterals of specific afferent pathways to the reticular formation neurons. The effect on the limbic system and the hypothalamus also contributes to the sedative effect.

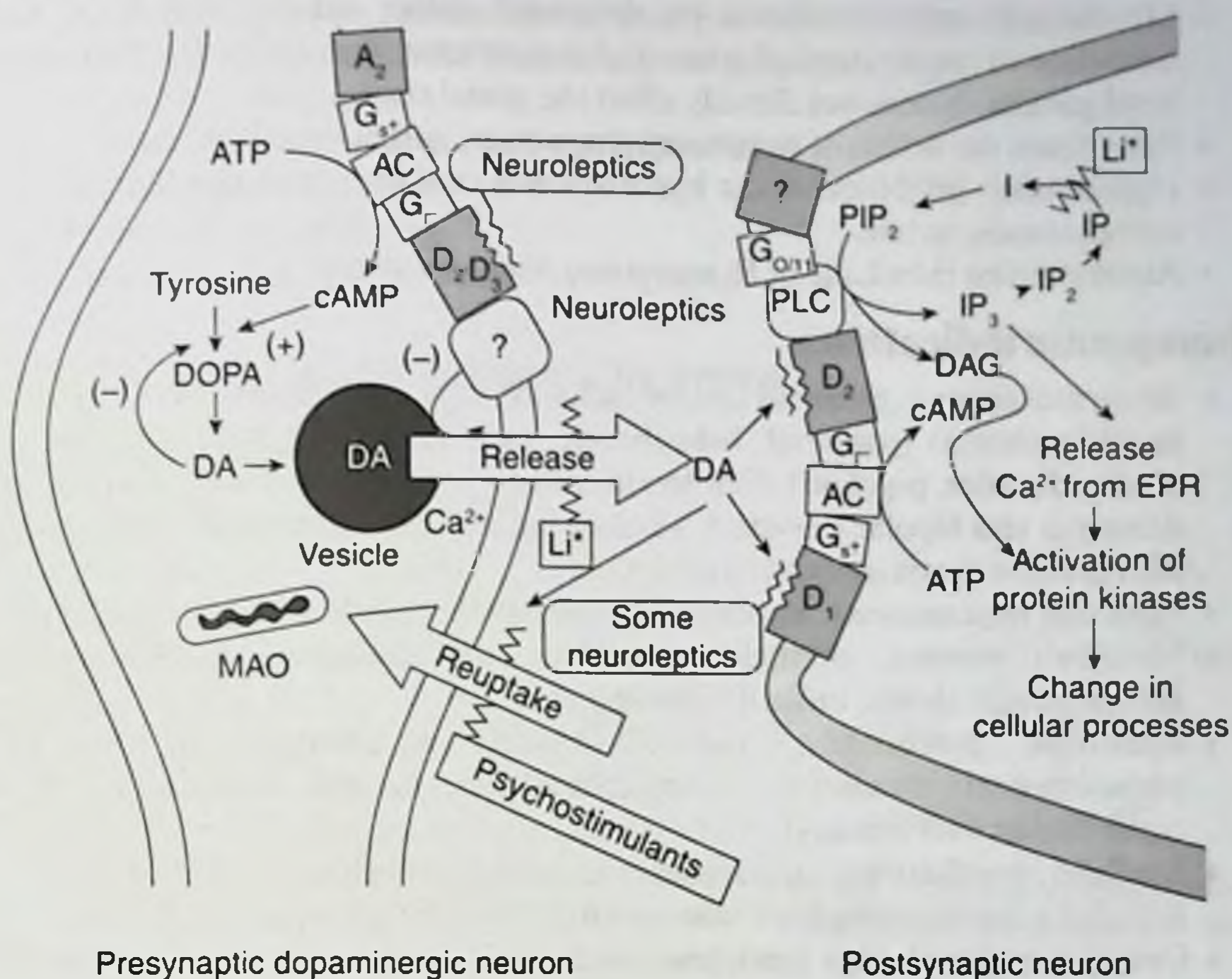


Fig. 8.1. Mechanism of action of neuroleptics (Gilman A.G. et al., 2006)

Pharmacological effects (using chlorpromazine as an example)

- ▶ Antipsychotic: suppresses the main manifestations of psychosis — hallucinations, delusions, aggression, and also reduces psychomotor agitation
- ▶ Neuroleptic: causes emotional indifference, i.e., suppresses negative and positive emotions while maintaining a clear mind
- ▶ Psychosedative: general depression, decreased motor activity, orienting responses; has a hypnotic effect at high doses: superficial sleep that is easily interrupted by external irritation
- ▶ Hypothermic: inhibition of the hypothalamus' heat production functions due to the blockade of its α -AR and serotonin receptors, skin vasodilation and increased heat dissipation
- ▶ Antiemetic: by blocking D_2 receptors in the chemoreceptor trigger zone and the solitary tract nucleus, it suppresses nausea and vomiting due to acute intoxication, peritonitis, radiation sickness, malignant tumors, radiation therapy and chemotherapy, and suppresses persistent pathological hiccups (e.g., in spinal cord tumors)

- ▶ Muscle relaxant: manifested by decreased motor activity associated with inhibition of the supraspinal control of muscle tone, mainly due to effect on the basal ganglia. It does not directly affect the spinal cord
- ▶ Potentiates the action of anesthetics, hypnotics, narcotic analgesics
- ▶ Hypotensive: inhibition of the hypothalamus centers; adrenergic blocking and antispasmodic action
- ▶ Antihistamine (blockade of H_1 receptors), local anesthetic

Therapeutic indications

- ▶ Acute and chronic paranoid and/or hallucinatory states, psychomotor agitation in schizophrenia (paranoid, hebephrenic, catatonic types), manic agitation in bipolar disorder, psychotic disorders in epilepsy, agitated depression (in presenile dementia and bipolar disorder), alcohol-induced psychosis, and other diseases with positive symptoms and agitation
- ▶ Muscular hypertonicity, status epilepticus (if other products are ineffective)
- ▶ Ménière's disease, pernicious vomiting of pregnancy, treatment with antineoplastic agents, radiation therapy
- ▶ Anesthetic potentiation, induced hypotension during surgeries with extracorporeal circulation, neuroleptanalgesia (specifically, droperidol in combination with fentanyl)
- ▶ Artificial hypothermia (cardiac, brain surgeries), malignant hyperthermia
- ▶ Relief of a hypertensive crisis when antihypertensive agents are ineffective
- ▶ Complex regional pain syndrome, including causalgia (in combination with analgesics); trigeminal neuralgia (levomepromazine)

Side effects

- ▶ Akathisia (impaired motor function with inner agitation, a need to be in constant motion), drug-induced parkinsonism, tardive dyskinesia (involuntary contractions of the muscles of the face, trunk, limbs), depression, catalepsy, neuroleptic malignant syndrome (progressive muscle rigidity, hyperthermia, autonomic disorders: tachycardia, fluctuations in blood pressure, profuse sweating, urinary incontinence, confusion, stupor, rhabdomyolysis)
- ▶ Arterial hypotension (especially when administered intravenously)
- ▶ Nausea, vomiting (when taken orally), cholestatic jaundice
- ▶ Leukopenia, agranulocytosis (clozapine)
- ▶ Menstrual disorders, galactorrhea, impotence, gynecomastia, weight gain
- ▶ Contact dermatitis, skin pigmentation, photosensitivity
- ▶ With prolonged use at high doses: product deposition in the cornea and lens, which can accelerate natural aging of the lens (chlorpromazine)
- ▶ Atropine-like effects: mydriasis, increased IOP, tachycardia, dry skin and mucous membranes, relaxation of GI and bladder smooth muscles
- ▶ Teratogenic effect

Contraindications

- ▶ Hepatic (cirrhosis, hepatitis, hemolytic jaundice, etc.) and renal (nephritis) disorders

- ▶ Progressive systemic diseases of the brain and spinal cord, parkinsonism
 - ▶ Severe depression of CNS function and coma (any etiology)
 - ▶ Traumatic brain injury
 - ▶ Cardiac decompensation, persistent hypotension
 - ▶ Hematopoietic disorders
 - ▶ Pregnancy, breastfeeding
- Restrictions related to the patient's occupation.

Specifics of individual products by group

Typical neuroleptics

Chlorpromazine (Aminazin*)

- ▶ Phenothiazine aliphatic derivative. When taken orally, the maximum blood concentration occurs after 2–4 hours; when administered intramuscularly, after 1–2 hours. Subject to first-pass effect, crosses the BBB.
- ▶ Hepatic metabolism includes hydroxylation, conjugation with glucuronic acid, N-oxidation, oxidation of sulfur atoms, dealkylation. $T_{1/2}$: about 30 hours. Excreted in the urine and bile as metabolites. For oral administration 3–4 times daily, for intramuscular, intravenous administration.

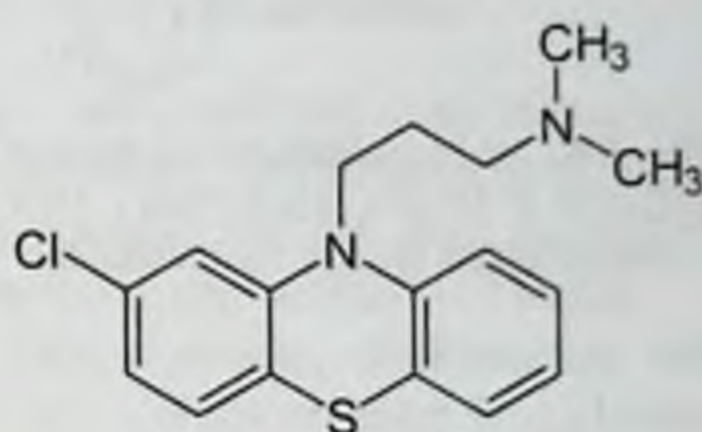


Fig. 8.2. 2-Chloro-N,N-dimethyl-10H-phenothiazine-10-propanamine (as hydrochloride)

Levomepromazine (Tisercin*)

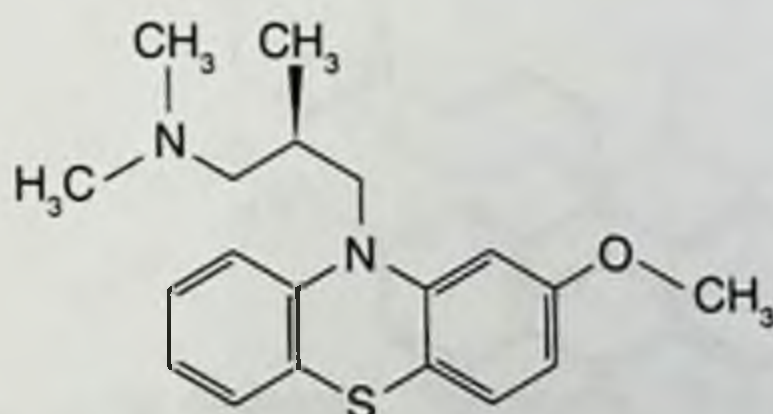


Fig. 8.3. (R)-2-Methoxy-N,N,β-trimethyl-10H-phenothiazine-10-propanamine [as maleate (1:1) or hydrochloride]

- ▶ Phenothiazine aliphatic derivative. Unlike chlorpromazine, it contains a methoxy group instead of a chlorine atom at position 2 of the phenothiazine nucleus and an additional methyl group in the alkylamine chain. Its pharmacological properties are similar to those of chlorpromazine. Has a potent analgesic effect and some antidepressant activity. The maximum blood concentration when taken orally and intramuscularly is 1–3 hours and 0.5–1.5 hours, respectively. Crosses the BBB.
- ▶ Metabolized in the liver by demethylation to form sulfate and glucuronide conjugates; N-desmethylmonomethotrimeprazine has pharmacological

activity, other metabolites are inactive. Excreted mainly as metabolites in the urine and bile. $T_{1/2}$: 15–30 hours. For oral administration 1–2 times daily, for intramuscular, intravenous administration.

Trifluoperazine (Triptazine[®])

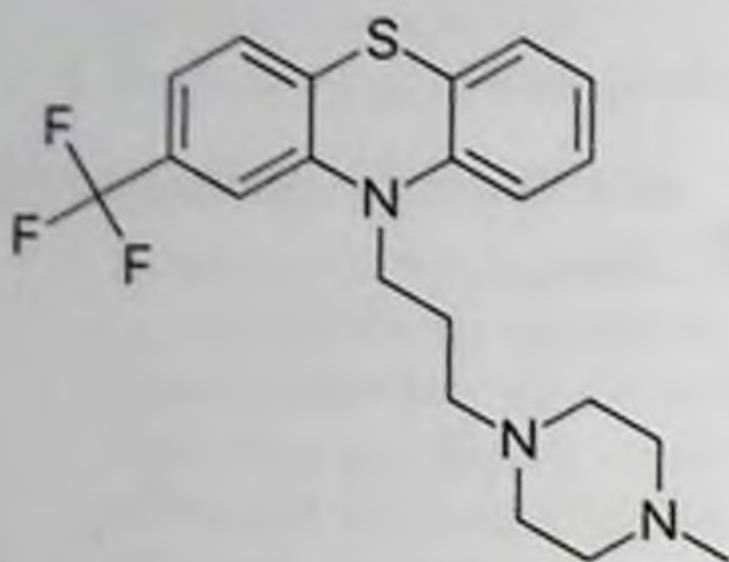


Fig. 8.4. 10-[3-(4-Methyl-1-piperazinyl)propyl]-2-(trifluoromethyl)-10H-phenothiazine (and as hydrochloride)

► Phenothiazine piperazine derivative. Unlike chlorpromazine, it contains a trifluoromethyl group instead of a chlorine atom at position 2 of the phenothiazine nucleus; in the side chain, it contains a piperazine nucleus substituted by a methyl group at the nitrogen atom at position 4. Antipsychotic action combined with a moderate stimulating effect. Compared with chlorpromazine, the adrenergic blocking action and potentiating effects are weak. Bioavailability: 35% (first-pass effect), the maximum blood concentration when taken orally occurs after 2–4 hours, when administered intramuscularly, after 1–2 hours. Crosses the BBB, excreted into breast milk.

► Metabolized in the liver to form pharmacologically inactive metabolites. Excreted in the urine and bile. $T_{1/2}$: 15–30 hours. For oral administration 2–3 times daily, for intramuscular administration.

Fluphenazine (Phthorphenazinum[®])

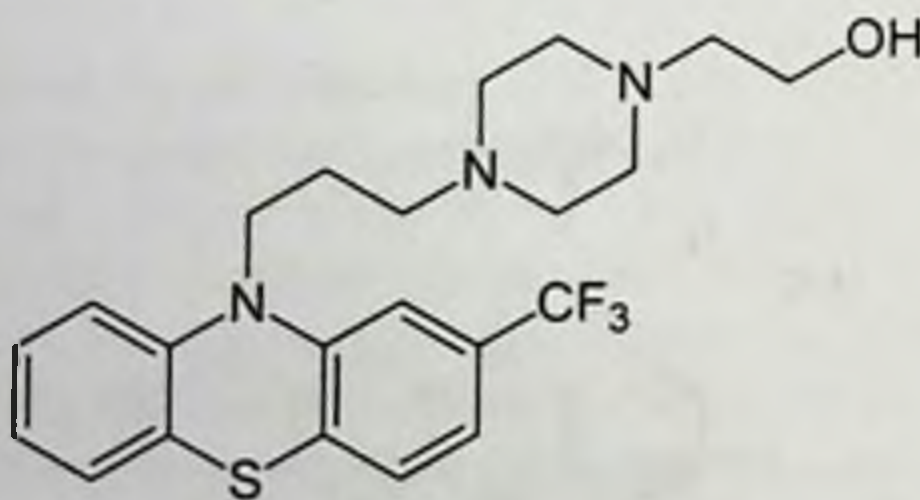


Fig. 8.5. 4-[3-[2-(Trifluoromethyl)-10H-phenothiazin-10-yl]propyl]-1-piperazineethanol

► Phenothiazine piperazine derivative. Like trifluoperazine, it contains a trifluoromethyl group at position 2 of the phenothiazine nucleus. Pronounced antipsychotic effect (25-fold superior to chlorpromazine) combined with slight activating effect. Sedative effect is observed with higher doses. It crosses the BBB and placental barrier.

► Metabolized in the liver with the involvement of cytochrome P450 enzymes (including the CYP2D6 isoenzyme). Excreted in the urine and bile. $T_{1/2}$: 15–20 hours. For oral administration 3–4 times daily, for intramuscular administration.

Fluphenazine (Moditen Depo[♦]) has a prolonged action.
Perphenazine (Etaperazin[♦])

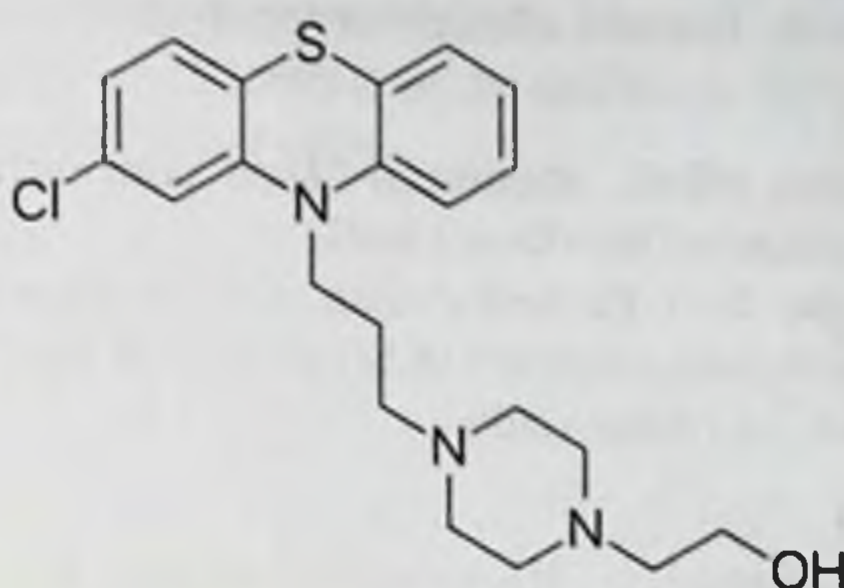


Fig. 8.6. 4-[3-(2-Chloro-10H-phenothiazin-10-yl)propyl]-1-piperazineethanol

- ▶ Phenothiazine piperazine derivative. Stronger antipsychotic and antiemetic action than chlorpromazine; also has an activating effect. The antipsychotic effect occurs within 4–7 days with a maximum after 1.5–6.0 months. Bioavailability: 40%; maximum plasma concentration when taken orally: within 1–3 hours.
- ▶ Metabolized in the liver by sulfoxidation, hydroxylation, dealkylation and glucuronidation. Excreted mainly by the kidneys. $T_{1/2}$ of the product: 9–12 hours, of metabolites: 10–19 hours. For oral administration 1–2 daily.

Thioridazine (Sonapax[♦]), Periciazine (Neuleptil[♦])

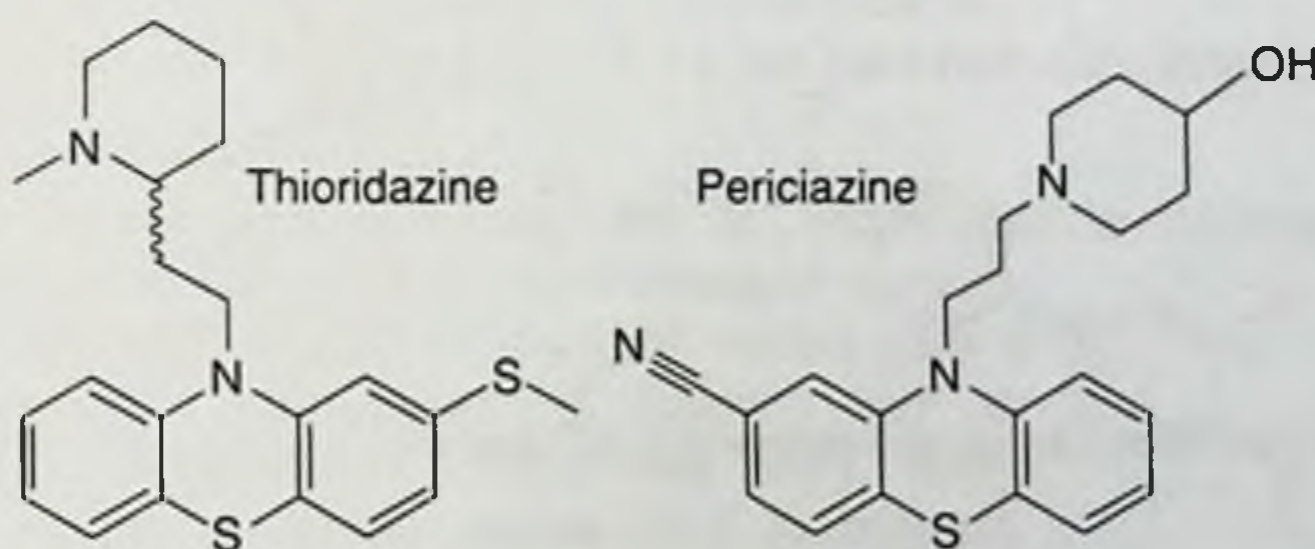


Fig. 8.7. Phenothiazine piperazine derivatives. Thioridazine: 10-[2-(1-Methyl-2-piperidinyl)ethyl]-2-(methylthio)-10H-phenothiazine. Periciazine: 10-[3-(4-Hydroxy-1-piperidinyl)propyl]-10H-phenothiazine-2-carbonitrile

Phenothiazine piperazine derivatives. They have a moderate antipsychotic and sedative effects and pronounced anti-anxiety effect. The anti-anxiety effect is manifested by resolution of fear, anxiety, aggression and is not accompanied by fatigue, lethargy, somnolence and emotional depression. Small and medium doses produce an antidepressant effect, have a mild sedative effect, reduce susceptibility of conflict, anger, aggression, and normalize behavioral reactions ("behavior correctors").

Thioridazine (Sonapax[♦])

- ▶ Bioavailability: 60%, maximum blood concentration within 1–4 hours. It crosses the BBB, placental barrier, and is excreted into breast milk.

- ▶ Metabolized in the liver with the involvement of the CYP2D6 isoenzyme to active metabolites (mesoridazine and sulforidazine), excreted in the urine and bile. $T_{1/2}$: 6–40 hours. For oral administration 2–3 times daily.

Periciazine (Neuleptil[®])

- ▶ Subject to first-pass effect, maximum blood concentration within 2 hours, crosses the BBB, excreted into breast milk.
- ▶ Metabolized in the liver (hydroxylation and conjugation), included in the enterohepatic circulation, excreted in the urine and bile. $T_{1/2}$: 12–30 hours. For oral administration 2–3 times daily.

Haloperidol (Galofen[®])

- ▶ Butyrophenone derivative. High antipsychotic activity combined with moderate sedative effect; has an activating effect. Its antiemetic effect is 50-fold superior to chlorpromazine. Bioavailability: 60–70%. Maximum plasma concentration when taken orally achieved after 2–6 hours, crosses the BBB and placental barrier.
- ▶ Undergoes hepatic biotransformation, excreted in the urine and bile as inactive metabolites. $T_{1/2}$: 12–37 hours. For oral administration 3 times daily, for intramuscular, intravenous administration.

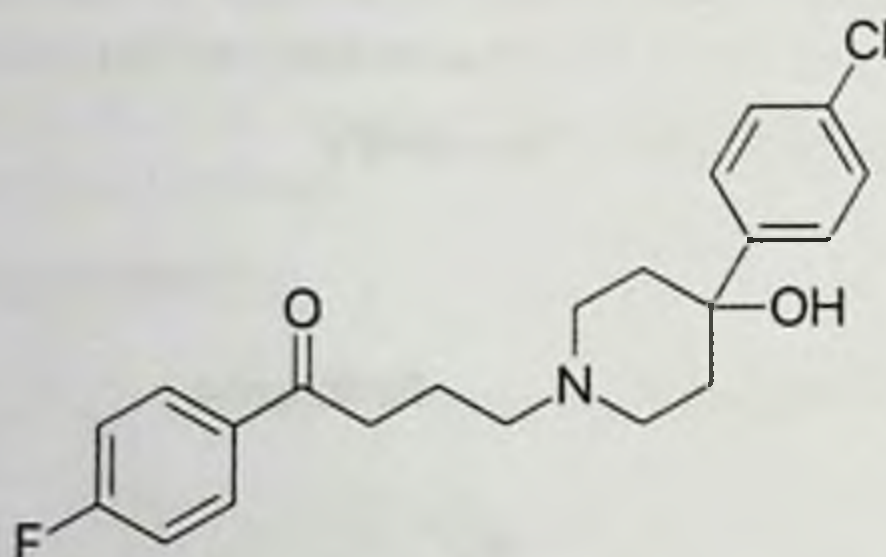


Fig. 8.8. 4-[4-(4-Chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone (as decanoate or lactate)

Droperidol (Dridol[®], Droleptan[®])

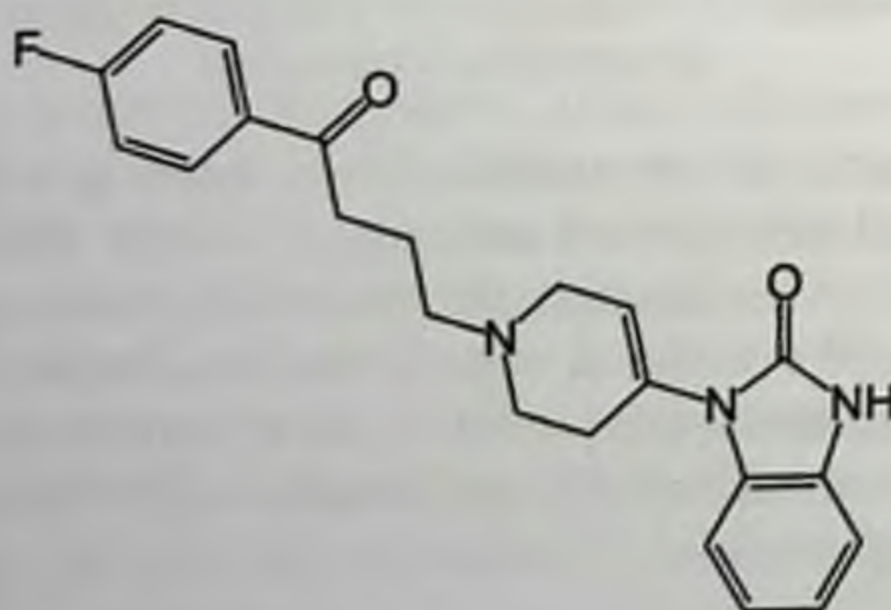


Fig. 8.9. 1-[1-[3-(p-Fluorobenzoyl)propyl]-1,2,3,6-tetrahydro-4-pyridyl]-2-benzimidazolinone

- ▶ Butyrophenone derivative. Has a rapid, potent but short-term action: after intravenous administration the effect occurs after 2–5 minutes reaching a maximum after 20–30 minutes and lasts 2–3 hours.
- ▶ Metabolized in the liver. Excreted as metabolites in the urine. $T_{1/2}$: 2 hours. For oral, intramuscular administration.

Trifluoperidol (Trisedyl[®])

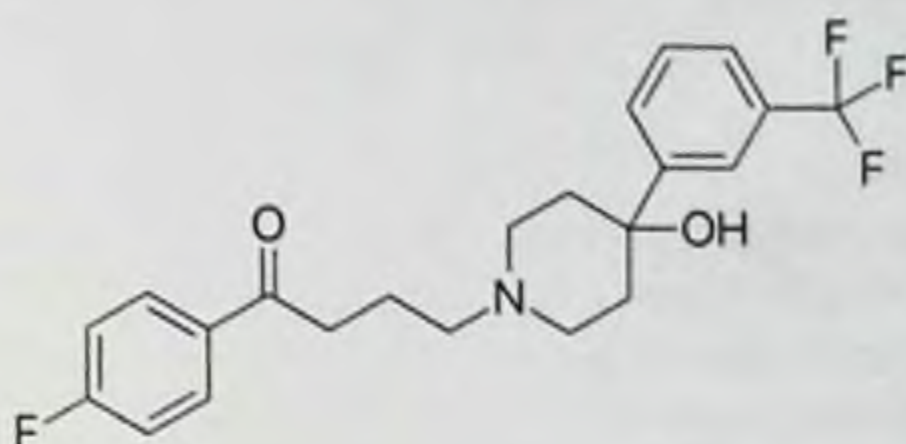


Fig. 8.10. 1-(4-Fluorophenyl)-4-[4-hydroxy-4-[3-(trifluoromethyl)phenyl]-1-piperidinyl]-1-butanone (and as hydrochloride)

- ▶ Butyrophenone derivative. Similar to haloperidol in its structure and action. It differs by the presence of a CF_3 group at the meta position of the phenyl nucleus (in piperidine) instead of a Cl atom at the para position of haloperidol. Its antipsychotic effect is 4-fold superior to haloperidol.
- ▶ For oral administration 2–4 times daily, for intramuscular administration.

Chlorprothixene (Truxal[®])

- ▶ Thioxanthene derivative. Inferior to phenothiazine derivatives in its antipsychotic action. Has antidepressant activity, moderate sedative and thymoleptic action (mood improvement, elimination of despair, lack of initiative, retardation, anxiety and fear). When taken orally, the effect occurs after 20 minutes. Bioavailability: 12%. Undergoes first-pass metabolism in the intestinal and hepatic walls. Crosses the placental barrier and is excreted into breast milk.
- ▶ Metabolized in the liver mainly by sulfoxidation and N-demethylation of the side chain, undergoes enterohepatic circulation. Excreted in the urine and bile. $T_{1/2}$: 16 hours. For oral administration 3–4 times daily, for intramuscular administration.

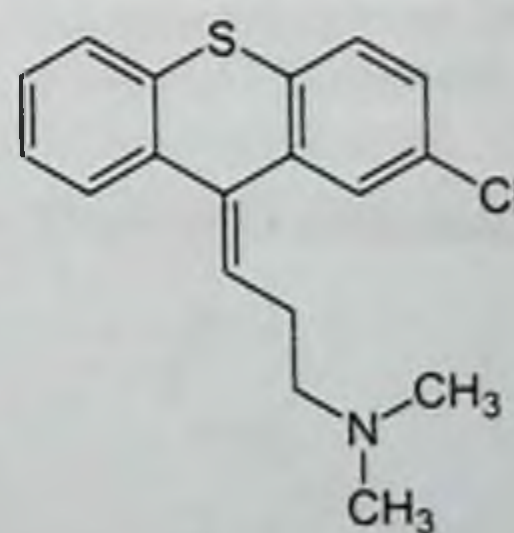


Fig. 8.11. (Z)-3-(2-Chloro-9H-thioxanthen-9-ylidene)-N,N-dimethyl-1-propanamine (and as hydrochloride)

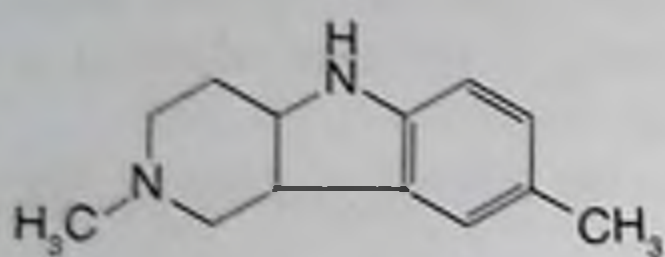


Fig. 8.12. 2,3,4,4a,5,9b-Hexahydro-2,6-dimethyl-1H-pyrido[4,3-b]indole

Dicarbine (Carbidinum⁺)

- ▶ Indole derivative. Antipsychotic action is combined with a moderate antidepressant effect. Bioavailability is low.
- ▶ Undergoes biotransformation in the liver to form inactive metabolites. Excreted mainly by the kidneys. For oral administration 3 times daily, for intramuscular administration.

Atypical neuroleptics

Unlike typical neuroleptics, they block D2 receptors of the nigrostriatal pathway and hypothalamus (lesser extent) for a short period of time. They are dopamine receptor antagonists in the limbic system and prefrontal cortex, and also block 5HT_{2A} receptors. Extrapyramidal and endocrine disorders are much less common. They have a high affinity for dopamine D₄ receptors. They vary in their psychotropic action and side effects.

Clozapine (Azaleptin⁺, Leponex⁺)

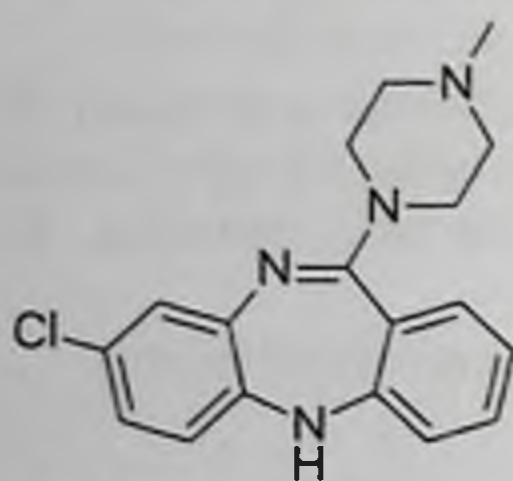


Fig. 8.13. 8-Chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine

- ▶ This dibenzodiazepine derivative is a tricyclic compound in chemical structure. High affinity for D₄, D₂ receptors (in the limbic system) and 5HT_{2A} receptors; high antipsychotic activity. Bioavailability: 50–60% (undergoes first-pass elimination), the maximum plasma concentration is reached within 2.5 hours. Crosses the BBB.
- ▶ Metabolized in the liver to inactive metabolites, excreted in the urine (50%) and bile (30%). T_{1/2}: 12 hours. For oral administration 1–2 times daily, for intramuscular administration.

Olanzapine (Zyprexa⁺)

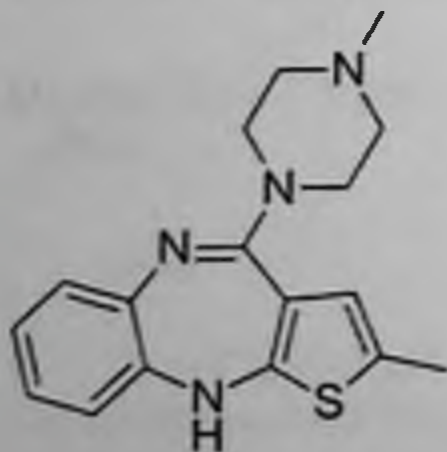


Fig. 8.14. 2-Methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine

- ▶ Thienobenzodiazepine derivative. Unlike clozapine, it contains a methylthienyl group instead of a phenyl group in the benzodiazepine nucleus. Maximum plasma concentration reached after 6 hours; 40% of the dose undergoes first-pass metabolism. Crosses the BBB and placental barrier.
- ▶ Metabolized in the liver by oxidation and glucuronidation, mediated by cytochrome P450. Excreted in the urine as metabolites. T_{1/2}: 29–55 hours. For oral administration once daily.

Quetiapine (Seroquel®)

- ▶ Atypical neuroleptic, dibenzothiazepine derivative. Quetiapine and its active metabolite N-desalkylquetiapine (norquetiapine) interact with a wide range of neurotransmitter receptors in the brain. They show a higher affinity for 5HT₂ receptors (compared to D₁ and D₂ receptors), also have a high affinity for H₁ receptors and α_1 -AR, and are less active towards α_2 -AR. Metabolized in the liver with the involvement of cytochrome P450 to form the active metabolite N-desalkylquetiapine.
- ▶ T_{1/2}: about 7 hours, excreted in the urine (73%) and bile (21%) as inactive metabolites. For oral administration 2 times daily.

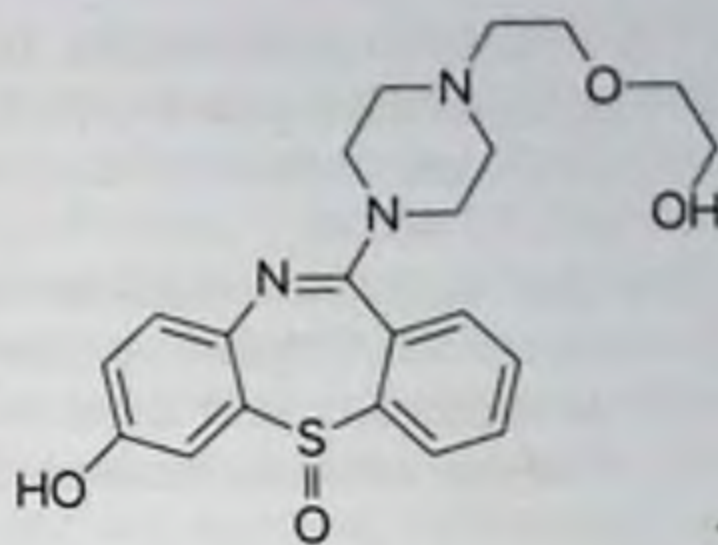


Fig. 8.15. 2-[2-(4-Dibenzo[b,f][1,4]thiazepin-11-yl-1-piprazinyl)ethoxy]ethanol (and as hemifumarate)

Sulpiride (Eglonyl®)

- ▶ Has a substituted benzamide in its chemical structure. It has a characteristic regulatory effect on the CNS: it combines moderate antipsychotic activity with antidepressant properties and a slight sedative effect, but if patients are anergic and lethargic, it produces mild stimulation; has thymoleptic and anxiolytic effects. Has a cytoprotective effect on the mucous membrane of the GI tract. Bioavailability: 25–35% (first-pass effect), maximum plasma concentration after oral and parenteral administration is 4.5 hours and 0.5 hours, respectively.
- ▶ Marginally metabolized in the liver, excreted mainly unchanged in the urine. T_{1/2}: 7 hours. For oral administration twice daily, for intramuscular administration.

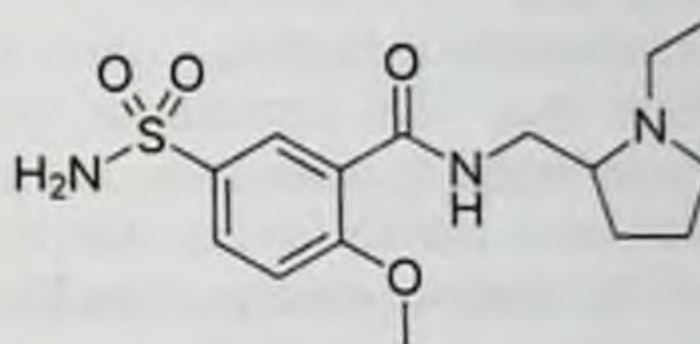


Fig. 8.16. 5-(Aminosulfonyl)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methoxybenzamide

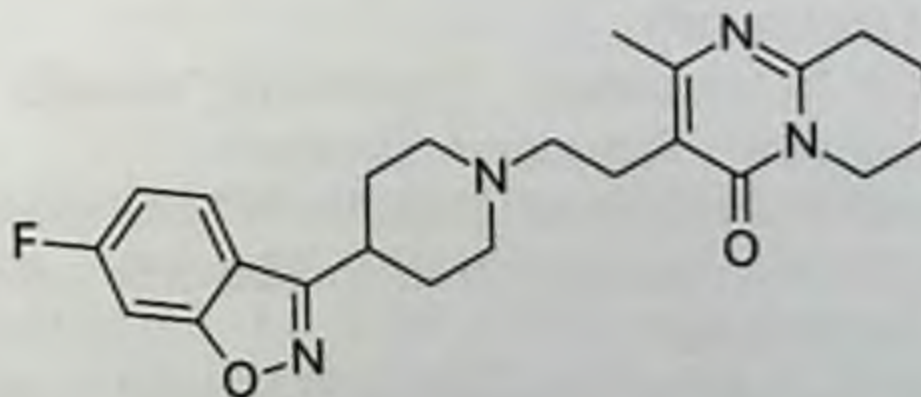
Risperidone (Rispolept®)

Fig. 8.17. 3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

- ▶ Benzisoxazole derivative. The main difference from other products is that it has a higher affinity for 5-HT₂ than for D₂ receptors, and a more gradual occupancy of D₂ receptors. Bioavailability: 70%; maximum plasma concentration achieved in 1–2 hours.
- ▶ The main biotransformation pathway is hydroxylation to form the active metabolite 9-hydroxyperidone. Excreted in the urine (70%) and bile (15%). T_{1/2} of risperidone and the active metabolite is 3 hours and 24 hours, respectively. For oral administration once or twice daily.

TRANQUILIZERS (ANXIOLYTICS, ATARACTICS, ANTI-ANXIETY DRUGS)

The term “tranquilizers” first appeared in 1957 (from the Latin *tranquillare* — “to calm”).

The development of the first drug products dates back to the 1950s. The use of anxiolytics began with the introduction of meprobamate into clinical practice in 1955 and chlordiazepoxide in 1959. One year later, diazepam appeared on the pharmaceutical market. To date, tranquilizers comprise more than 100 drug products. More than 3000 compounds have been synthesized in the most popular series of benzodiazepine derivatives, and over 40 of them are used in clinical practice. These substances mainly have an anxiolytic (tranquilizing) effect: relaxation, elimination of psychic tension, anxiety, fear. Most anxiolytics also have a sedative effect.

Classification

1. Benzodiazepine derivatives
 - Short-acting (T_{1/2}: less than 6 hours)
 - Midazolam (Dormicum[®]).
 - Intermediate-acting (T_{1/2}: 6–24 hours)
 - Oxazepam (Nozepam[®], Tazepam[®])
 - Alprazolam (Xanax[®])
 - “Daytime” tranquilizers
 - Medazepam (Mezapam[®], Rudotel[®])
 - Tofisopam (Grandaxin[®])
 - Long-acting (T_{1/2}: 24–48 hours)
 - Diazepam (Seduxen[®], Relanium[®], Sibazon[®])
 - Bromdihydrochlorphenylbenzodiazepine (Phenazepam[®])
2. Products of a non-benzodiazepine structure (daytime tranquilizers)
 - Bicyclic bisurea derivative
 - Tetramethyltetraazabicyclooctandione (Mebicar[®], Adaptol[®])
 - Azaspirodecanedione derivative
 - Buspirone (Spitomin[®])
 - Mercaptobenzimidazole derivative
 - Fabomotizole (Afobazol[®])

Mechanism of action of benzodiazepines: Anxiolytics derived from benzodiazepine are agonists of benzodiazepine receptors associated as allosteric centers with GABA_A receptors in the neurons of the cerebral cortex, hippocampus, amygdala, striatum, thalamus, hypothalamus, cerebellum, reticular formation, and spinal cord. By activating benzodiazepine receptors, they act as modulators, i.e., increase the binding of GABA to GABA_A receptors. As a result, Cl⁻ channels in the neuronal membrane open more frequently, membrane hyperpolarization occurs, and inhibition develops. The effects of anxiolytics occur only in the presence of GABA and if the GABA_A receptors are not blocked. Differences in the pharmacological effects of individual anxiolytics are related to the variable structure of benzodiazepine and GABA_A receptors.

Pharmacological effects

- ▶ Anxiolytic: prevent the formation of a dominant focus of negative emotions, reduce their autonomic and endocrine accompaniment, cause inhibition of the cerebral cortex, which is manifested by decreased anxiety, fear, and emotional tension
- ▶ Sedative: suppress the ascending reticular activating system; cause drowsiness, decreased alertness, concentration, and responsiveness
- ▶ Muscle relaxant: reduce the effect on polysynaptic spinal reflexes (interneurons of the lateral horns)
- ▶ Anticonvulsant: associated with action on receptors in the hippocampus
- ▶ Potentiating: with hypnotics, anesthetics, narcotic analgesics
- ▶ Hypnotic: rapid onset of sleep, prolongation of sleep time
- ▶ Anterograde amnesia (a loss of memory for events occurring after drug ingestion)
- ▶ Stabilizing of autonomous nervous system: inhibition of neurons in the limbic-reticular complex (central regulation of the autonomic nervous system). Decreased autonomic manifestations of anxiety (fluctuating blood pressure, tachycardia, excessive sweating, GI disorders, etc.)

Specifics of individual products

Diazepam (Seduxen⁺, Sibazon⁺, Relanium⁺)

- ▶ Long-acting benzodiazepine derivative. Bioavailability: 75%. Maximum blood concentration: 0.5–2.0 hours (when taken orally), 0.5–1.5 hours (when administered intramuscularly). It crosses the BBB, placental barrier and is excreted into breast milk.
- ▶ Undergoes biotransformation (98–99%) in the liver to form active metabolites: desmethyldiazepam (nordiazepam), oxazepam and temazepam. Excreted mainly in the urine (0.5–2.0% unchanged, about 70% as metabolites) and bile (about 10%). T_{1/2}: 30–50 hours.

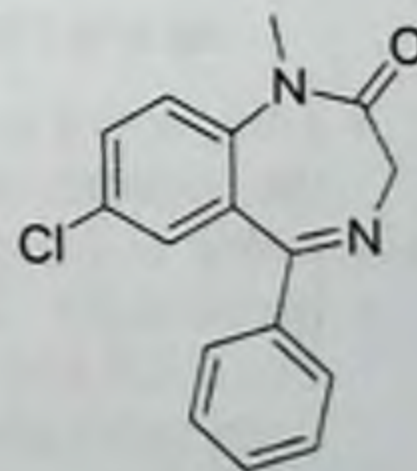


Fig. 8.18. 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

For oral administration 1–2 times daily, for intramuscular, intravenous administration.

Therapeutic indications: neurotic and stress-related disorders having emotional stress, anxiety, fear, increased irritability; sleep disorders; withdrawal syndrome (alcohol, narcotic analgesics); premedication; ataralgia (often in combination with fentanyl analgesics); epilepsy (as part of combination therapy); status epilepticus, tetanus (intravenously); spastic states of central origin and in musculoskeletal disorders with skeletal muscle tension; cardiovascular diseases (essential hypertension, angina, etc.).

Side effects: lethargy, somnolence, increased fatigue, ataxia, lack of emotions, slow reaction rate and decreased alertness, paradoxical reactions (acute agitation, anxiety, nightmares, inappropriate behavior), anterograde amnesia; elevated liver transaminases and alkaline phosphatase; menstrual disorders, diminished libido; addiction, drug dependence, withdrawal syndrome, aftereffect syndrome (muscle weakness, decreased daytime performance); injection site reactions (thrombosis, phlebitis, formation of infiltrates); with rapid intravenous administration — circulatory collapse, respiratory failure; teratogenic effects.

Restrictions related to the patient's occupation.

Contraindications: severe hepatic and/or renal impairment; myasthenia gravis, cerebral and spinal ataxia; drug or alcohol dependence (except when treating withdrawal symptoms); severe heart and respiratory failure; pregnancy, breastfeeding

Bromdihydrochlorphenylbenzodiazepine (Phenazepam⁺)

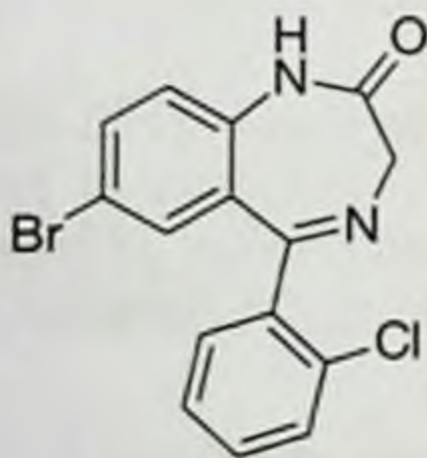


Fig. 8.19. 7-Bromo-5-(2-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one

- ▶ Long-acting benzodiazepine derivative. It is superior to other tranquilizers in the strength of its anxiolytic effect. Maximum blood concentration reached within 1–2 hours when taken orally.
- ▶ Metabolized in the liver, excreted mainly as metabolites in the urine. $T_{1/2}$: 6–18 hours. For oral administration 2–3 times daily, for intramuscular, intravenous administration.

Midazolam (Dormicum[®])

- ▶ Short-acting benzodiazepine derivative. Bioavailability: 90%, maximum blood concentration within 2 hours. Onset in 15 minutes with intramuscular administration and 5 minutes with intravenous administration.
- ▶ Undergoes biotransformation in the liver by hydroxylation with the involvement of cytochrome P450 isoenzyme. Excreted in the urine as glucuronic conjugates (less than 1% excreted unchanged). $T_{1/2}$: 1.5–3.0 hours. For oral, intramuscular, intravenous administration.

Additional therapeutic indications: induction of anesthesia (intravenously)

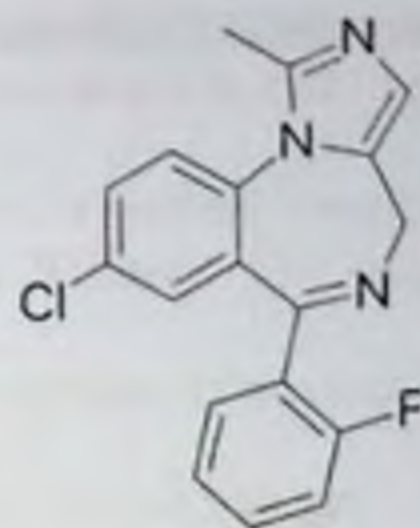


Fig. 8.20. 8-Chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine (as hydrochloride or maleate)

Medazepam (Mezapam[®], Rudotel[®])

- ▶ Intermediate-acting benzodiazepine derivative. Has pronounced anxiolytic effect with almost no sedative, hypnotic, muscle relaxant or anticonvulsant effects. It does not disrupt performance, thus is known as a “daytime tranquilizer”. Bioavailability: 50–75%, maximum blood concentration within 1–2 hours. Crosses the BBB, placental barrier, and is excreted into breast milk.
- ▶ Metabolized in the liver by hydroxylation, N-demethylation, oxidation to form active metabolites (oxazepam, desmethylnedazepam, diazepam). Excreted as metabolites conjugated with glucuronic acid in the urine (63–85%) and bile (15–37%). $T_{1/2}$ (including metabolites): 20–176 hours. For oral administration 2–3 times daily.

Therapeutic indications: neurotic and stress-related disorders

Side effects: dyspepsia, allergic reactions

Contraindications: pregnancy, breastfeeding

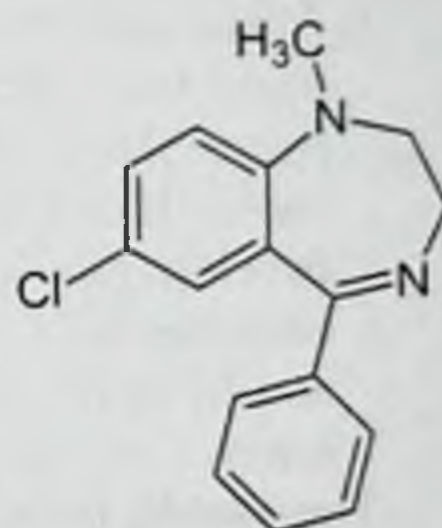


Fig. 8.21. 7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine (as hydrochloride)

Tetramethyltetraazabicyclooctandione (Mebicar[®], Adaptol[®])

- ▶ Tetramethyltetraazabicyclooctandione derivative. A “daytime tranquilizer” with a moderate anxiolytic activity. Bioavailability: 77–80%; maximum blood concentration within 30 min.
- ▶ Excreted mainly in the urine (55–70%) and bile unchanged within 24 hours. For oral administration 2–3 times daily.

Therapeutic indications: neurotic and stress-related disorders

Side effects: dyspepsia, allergic reactions

Contraindications: pregnancy, breastfeeding

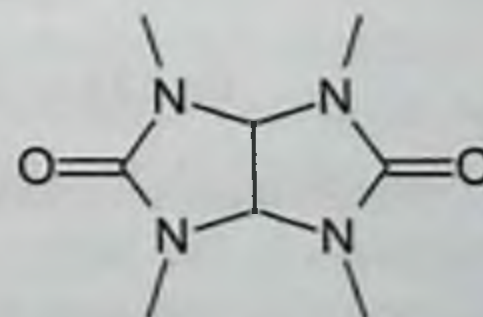


Fig. 8.22. 2,4,6,8-Tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione

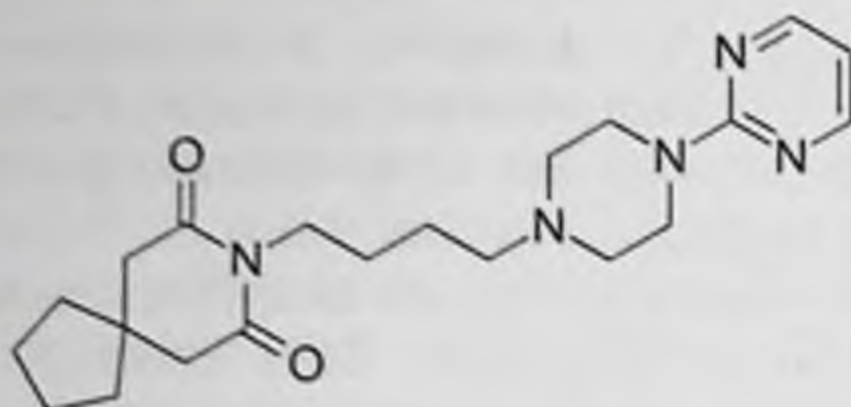
Buspirone (Spitomin⁺)

Fig. 8.23. 8-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4,5]decane-7,9-dione (and as hydrochloride)

Mechanism of action: Has a high affinity for pre- (agonist) and postsynaptic (partial agonist) serotonin $5HT_{1A}$ receptors. Reduces the synthesis and release of serotonin, the activity of serotonergic neurons, including in the dorsal raphe nucleus. The active metabolites of buspirone have an adrenergic effect: the associated general mood improvement explains the antidepressant effect. It has no affinity for benzodiazepine receptors and does not affect GABA binding. It is a daytime tranquilizer.

- ▶ Azaspirodecanedione derivative. Pronounced anxiolytic effect. Maximum blood concentration reached within 40–90 minutes. Bioavailability: 4%. It is hydroxylated and dealkylated during first-pass metabolism. The N-dealkylated metabolite 1-pyrimidinyl-piperazine is pharmacologically active. The effect develops gradually over 7–14 days and reaches its maximum after 4 weeks.
- ▶ Metabolized by the liver. Excreted mainly as metabolites in the urine (29–63%) and bile (18–38%). $T_{1/2}$ of buspirone: 2–3 hours, $T_{1/2}$ of active metabolite: 4.8 hours. For oral administration 2 or 3 times daily.

Therapeutic indications: neurosis, vegetative-vascular dystonia

Side effects: dizziness, headache, restlessness

Contraindications: severe hepatic, renal impairment; pregnancy, breastfeeding

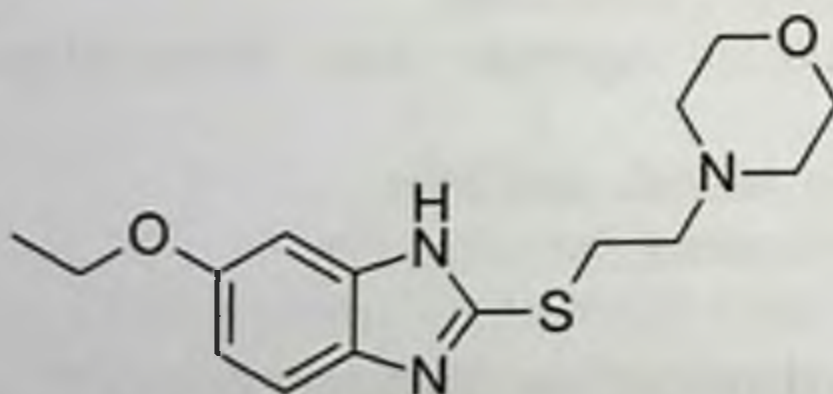
Fabomotizole (Afobazol⁺)

Fig. 8.24. 4-[2-[(6-ethoxy-1H-benzimidazol-2-yl)sulfanyl]ethyl]morpholine

Mechanism of action: Selective non-benzodiazepine anxiolytic. By acting on ω_1 receptors in the brain neurons, it restores the sensitivity of GABA/benzodiazepine receptors to endogenous inhibitory mediators. Increases the bioenergetic potential of neurons and has a neuroprotective effect. The action is mainly a combination of its anxiolytic and stimulating effects. It restores impaired cognitive functions. It is a daytime tranquilizer.

- ▶ Mercaptobenzimidazole derivative. Subject to first-pass effect. The therapeutic effect occurs on Day 5–7 of treatment with the maximum achieved by the end of Week 4.
- ▶ Metabolized in the liver by hydroxylation and oxidation. Excreted mainly as metabolites in the urine and partially with bile. $T_{1/2}$: 8 hours. For oral administration 3 times daily.

Therapeutic indications: neurosis, anxiety disorders in cardiovascular, respiratory, digestive diseases, neurasthenia, adjustment disorders

Side effects: allergic reactions

Contraindications: pregnancy; breastfeeding, children (under 18 years of age)

SEDATIVES

Derived from the Latin word *sedatio* — “soothing”. They have a general calming effect on the CNS, reduce the severity of reactions to various external stimuli and daily activity. They enhance inhibition and weaken excitation in the cerebral cortex, promote the onset of natural sleep, do not cause muscle relaxation, ataxia, psychological or physical dependence.

Classification

1. Bromine products
 - Potassium bromide
 - Sodium bromide
2. Herbal products
 - Preparations of valerian, motherwort, passionflower, peony
3. Combined agents
 - Corvalol* (peppermint leaf oil, phenobarbital, ethylbromisovalerate)
 - Novo-Passit*
 - Persen* (valerian root and rhizome extract, lemon balm extract, peppermint leaf extract)

Therapeutic indications: neurosis, irritability, insomnia

Bromides

Due to their slow elimination, they accumulate and can provoke chronic bromide intoxication (bromism). This is manifested by general lethargy, apathy, memory impairment; skin lesions are typical. The irritant effect of bromides leads to mucositis, which is accompanied by cough, rhinitis, conjunctivitis, diarrhea. Treatment of bromism: product discontinuation, acceleration of bromide elimination (intravenous sodium chloride, saluretics).

Herbal products

Preparations of valerian (infusion, tincture, extract) contain essential oil, valeric acid, borneol, organic acids, and some alkaloids.

Preparations of motherwort (infusion, tincture)—prepared from quinquelobate motherwort and cardiac motherwort—contain essential oil, alkaloids, saponins, tannins.

Combined agents

Corvalol* (peppermint leaf oil, phenobarbital, ethylbromisovalerate)

Ingredients: ethyl ester of α -bromoisovaleric acid, phenobarbital, sodium hydroxide (to convert phenobarbital to soluble phenobarbital sodium), peppermint oil, ethanol

Novo-Passit*

Ingredients: guaifenesin and extracts of hawthorn, hops, St. John's wort, lemon balm, passionflower, elderberry, and valerian

Persen* (valerian root and rhizome extract, lemon balm extract, peppermint leaf extract)

Ingredients: extracts of valerian rhizomes, lemon balm, peppermint

9. PSYCHOTROPIC DRUGS WITH STIMULATORY ACTION: STIMULANTS, ANTIDEPRESSANTS, ANALEPTICS

STIMULANTS

This is a class of psychotropic drugs that increases mental and physical performance (especially when fatigue), improves one's ability to perceive external stimuli (enhanced vision and hearing; faster reactions), elevates mood, relieves fatigue and temporarily reduces the need for sleep.

Amphetamine was first synthesized in 1887 by L. Edeleanu, a Romanian chemist in Germany, as a racemic mixture. The psychoactive properties of amphetamine were discovered in 1929 by G. Alles, an American biochemist. Amphetamine (phenamine^v) is not used in modern medical practice.

Caffeine in its pure form was first obtained in 1828 by French chemists and pharmacists P. Pelletier and J. Cavantu. In 1832, its composition was established by German chemists F. Wöhler, C. H. Pfaff, and J. Liebig. The structure of caffeine was elucidated near the end of the 19th century by H. E. Fischer who was also the first to synthesize it completely. He was awarded the Nobel Prize in chemistry in 1902, in part for this work. The physiological effects of caffeine on the CNS were studied by I. P. Pavlov and colleagues who showed that it enhances and regulates excitation processes in the cerebral cortex.

Sidnocarb was synthesized in 1971 by M. D. Mashkovsky, one of the founders of Soviet pharmacology. Pharmacologists and psychiatrists Y. A. Aleksandrovsky, G. Y. Avrutsky, A. B. Smulevich participated in its clinical research.

Adamantylbromophenylamine (Ladasten*) was invented at V. V. Zakusov Research Institute of Pharmacology in the 1970s. The idea behind this drug was to create a medication with actoprotective action. This drug was first synthesized under the guidance of Professor B.

M. Pyatin, and further researched by Professor I. S. Morozov. This drug has been shown to have both psychostimulant and immunostimulant properties.

Under the influence of psychostimulants, the cortical neurons generate nerve impulses whose frequency is optimal for a flexible response to afferent signals. Emotional responses and motivation improve due to activation of the midbrain reticular formation and non-specific thalamic nuclei, accompanied by an increase

in excitation processes in the cerebral cortex; the inhibitory influence of the nigrostriatal pathway on the spinal cord becomes weaker. These drugs mobilize functional and energy reserves, which allows one to continue doing intense activities for a short period of time.

Classification

1. Phenylalkylamines

- Amphetamine (Phenamine[®]) (excluded from the Russian State Register of Medicinal Products due to pronounced side effects and a high risk of drug dependence, has toxicological significance)

2. Sydnimine derivatives

- Mesocarb (Sydnocarb[®])
- Feprosidine[®] (Sydnophen[®]) (excluded from the Russian State Register of Medicinal Products)

3. Methylxanthines

- Caffeine (Caffeine sodium benzoate[®])

4. Adamantane derivative

- Adamantylbromphenylamine (Ladasten[®])

Therapeutic indications: diseases accompanied by depression of CNS function, cardiovascular and respiratory systems (infectious diseases, poisoning with narcotic analgesics, hypnotics, etc.), asthenic syndrome; enhancement of mental and physical performance, prevention of somnolence; anxiety with asthenic syndrome (adamantylbromphenylamine); asthenic depression (feprosidine); cerebral vasospasm, including migraine (caffeine); moderate hypotension (caffeine); enuresis; narcolepsy; respiratory disorders (periodic breathing, idiopathic central sleep apnea, asphyxia) (caffeine); restoration of adequate breathing after general anesthesia (caffeine)

Side effects: irritability, tremor, restlessness, tachypnea (caffeine), insomnia; tachycardia, arrhythmias, increased BP; nausea, vomiting; exacerbation of stomach ulcers (caffeine); atropine-like effects (sydnophen)

Contraindications: Hypertension, decompensated heart failure; psychomotor agitation, epilepsy, insomnia; pregnancy, breastfeeding; pediatric age (under 18 years) [adamantylbromphenylamine (Ladasten[®])]

Specifics of individual products by group

Phenylalkylamines

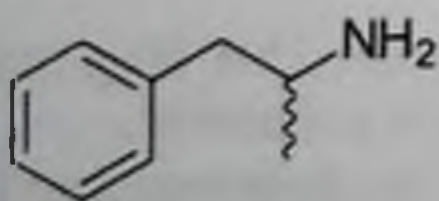


Fig. 9.1. (±)-α-Methylbenzeneethanamine (as a phosphate and sulfate)

Amphetamine (Phenamine[®])

Amphetamine was included in the list of narcotic drugs, psychotropic substances and their precursors prohibited for circulation in the Russian Federation pursuant to Decree No. 486 of the Russian Federation dated 30 June 2010.

Mechanism of action: increased catecholamine release, especially dopamine and norepinephrine, from presynaptic terminals. Normal function of dopaminergic synapses results in dopamine being released into the synaptic cleft by exocytosis of dopamine-containing vesicles. This is followed by dopamine reuptake into the cell: the dopamine active transporter transports dopamine from the synaptic cleft into the cytoplasm, while the vesicular monoamine transporter transports dopamine from the cytoplasm into the vesicle. When amphetamine enters the cell, these transporters start working in the opposite direction, transporting dopamine from the vesicle into the cytoplasm and then into the synaptic cleft. As a result, the dopamine concentration in the synaptic cleft increases, although the normal (vesicular) mechanism of neurotransmitter release decreases. Norepinephrine release due to amphetamine has a similar mechanism to that described above. The released catecholamines stimulate their respective receptors in the CNS. In addition, neuronal uptake of norepinephrine and dopamine is reduced.

Amphetamine activates the limbic system, striatum, thalamus, hypothalamus, reticular formation, and stimulates adrenaline release from the adrenal glands. The excitatory effect is associated with its stimulating effect on the ascending reticular activating system of the brain stem as well as on cortical neurons.

Pharmacological effects

- ▶ Psychostimulant: increases mental and physical performance, reduces the need for sleep, elevates mood
- ▶ Analeptic effect: directly stimulates the respiratory center, mainly in cases of respiratory depression
- ▶ Anorexigenic effect: suppresses the hunger center (lateral hypothalamic nuclei) and activates the satiety center (ventromedial hypothalamic nuclei)
- ▶ Peripheral α - and β -adrenergic activity: constricts peripheral blood vessels, increases and accelerates heart rate, elevates blood pressure, relaxes the bronchial muscles, induces mydriasis
- ▶ Increases glucose, pyruvate, lactate, fatty acids levels in blood; induces metabolic acidosis, promotes macroergic energy expenditure
- ▶ Activates glycogenolysis and lipolysis, increasing glucose and free fatty acids delivery to tissues and their utilization but dissociating oxidation and phosphorylation
- ▶ Increases oxygen demand in organs, disrupts ATP synthesis.

Side effects: euphoria, tolerance, cumulation, drug dependence (psychological and physical), anorexia, insomnia, tachycardia, hypertension, schizophrenia-like psychosis

Sydnonimine derivatives

Mechanism of action: In contrast to amphetamine (phenamine), they exert more potent action on noradrenergic brain structures than on dopaminergic one and to a lesser extent, influence the release of catecholamines from various neuronal depots. In addition to their effect on neuronal norepinephrine uptake, they also increase the synthesis of dopamine from tyrosine. These neurochemical actions differentiate in their clinical efficacy and tolerability from amphetamine.

Pharmacological effects: The psychostimulant effect develops gradually (no abrupt initial activating effect) and lasts for a long time. These drugs do not cause euphoria or motor agitation; no peripheral adrenergic effects (increased BP, tachycardia). No residual weakness or sleepiness are observed.

Mesocarb (Sydnocarb[®])

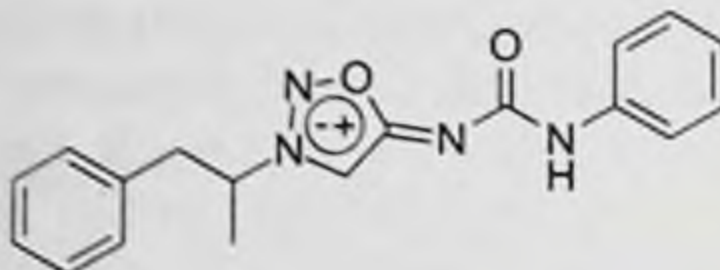


Fig. 9.2. N-Phenylcarbamoyl-3-(β-phenylisopropyl)-sydnonimine

- ▶ Its chemical structure is similar to that of amphetamine (phenamine[®]), since it contains a phenylisopropyl radical but no free amino group; the nitrogen atom corresponding to the amino group nitrogen in amphetamine (phenamine[®]) is a part of the heterocyclic system, sydnonimine, substituted in the amino group by a phenylcarbamoyl radical in sydnocarb.
- ▶ Metabolized in the liver by C-hydroxylation of the benzene ring of the phenylcarbamoyl radical and the aliphatic chain of the phenylisopropyl substituent to form the metabolite α-oxysydnocarb. Excreted in the urine (60 %), bile (30 %), exhaled air (10 %). For oral administration 1–2 times daily.

Feprosidnine[®] (Sydnophen[®])

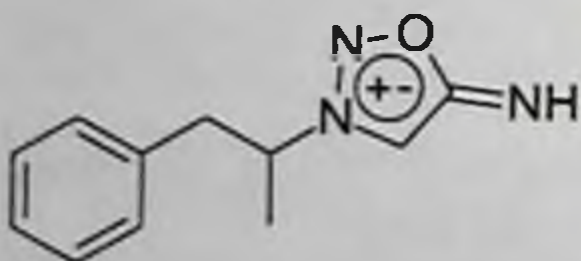


Fig. 9.3.3-(β-Phenylisopropyl)-sydnonimine hydrochloride

- ▶ Compared with sydnocarb, its CNS stimulating effect is significantly less. The psychostimulant effect is combined with a moderate antidepressant action (reversibly inhibits type MAO-A). Crosses the BBB.
- ▶ Biotransformation: in the liver, excreted in urine. For oral administration.

Methylxanthines

Caffeine is an alkaloid found in tea leaves (about 2 %), coffee seeds (1–2 %), and kola nuts. It can also be synthesized.

Mechanism of action: Neurochemical mechanism: competitive blockade of adenosine receptors (A₁, A₂), with the purine nucleoside adenosine acting as its endogenous agonist (the structural similarity between caffeine and adenosine contribute to this), which reduces excitation in the brain, so its replacement by caffeine has a stimulating effect.

Administration of high doses results in PDE inhibition, leading to accumulation of intracellular cAMP, which increases glycogenolysis, lipolysis, and other metabolic processes in different organs and tissues, including muscle tissue and the CNS; also increases gastric secretion.

Chronic use of caffeine may lead to the formation of new adenosine receptors in brain cells, thereby gradually reducing the effects of caffeine. Abrupt discontinuation of caffeine results in adenosine occupying all available receptors, which can lead to increased inhibition with fatigue, somnolence, depression, etc.

Pharmacological effects:

- ▶ Psychostimulant: directly stimulates the cerebral cortex, i.e., stimulates mental activity, increases mental and physical performance, motor activity, shortens reaction time, activates conditioned reflexes. The CNS effect depends on the dose of caffeine — stimulates at low doses (0.05–0.10 g) and depresses at high doses. The average dose for adults is 0.05–0.10 g per intake 2–3 times daily. For those with a “weak” nervous system in Pavlov's typology, excitation is achieved by administering small doses of caffeine; high doses are required for those with a “strong” nervous system (Table 9.1).
- ▶ Analeptic effect: direct stimulating action on the respiratory and vasomotor centers. Increases the frequency and depth of breathing, which is particularly evident during respiratory depression.
- ▶ Acts on the spinal cord at high doses; enhances spinal reflexes by facilitating interneuronal transmission of excitation.
- ▶ Direct stimulating action on the myocardium: increases cardiac contractile force and heart rate (especially at high doses), induces arrhythmia, increases myocardial oxygen demand; excitation of the vagal nerve results in bradycardia. The final effect depends on the predominance of a certain type of action.
- ▶ Direct action on vascular smooth muscle cells (due to PDE blockade) causes a decrease in vascular tone. Dilates coronary vessels, renal vessels, skeletal muscle vessels, but constricts cutaneous and mucosal blood vessels, and blood vessels in the abdominal organs; tones cerebral vessels. Caffeine increases vascular tone by stimulating the vasomotor center. Increases BP in hypotension. Reduces platelet aggregation.
- ▶ Exerts myotropic spasmolytic action on the bronchi, bile ducts.
- ▶ Increases diuresis, which is associated with inhibition of electrolyte reabsorption in renal tubules and increased glomerular filtration due to renal vasodilation.
- ▶ Other effects: activates glycogenolysis, gluconeogenesis (hyperglycemia), activates lipolysis (increased content of free fatty acids in plasma), increases adrenaline release from chromaffin cells of the adrenal medulla (at high doses), increases secretion from the gastric glands.

Table 9.1. Effects of methylxanthines (caffeine) and adenosine

Focus of action	Methylxanthines	Adenosine
CNS	Excitation	Depression
Catecholamines release	Increased	Decreased
Heart rate and cardiac contractile force	Increased	Decreased
Renal blood flow and renin release	Increased	Decreased
Histamine release from mast cells	Decreased	Increased
Adipose tissue lipolysis	Increased	Decreased

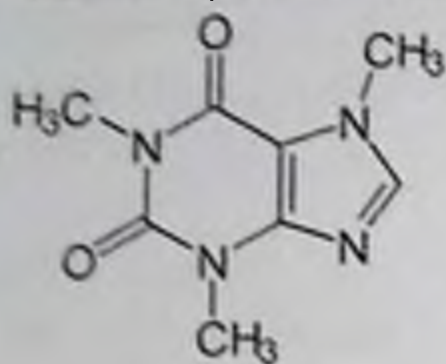
Caffeine (Caffeine sodium benzoate[†])

Fig. 9.4.
1,3,7-Trimethylxanthine
(and as a sodium
benzoate)

- ▶ Crosses the BBB and placental barrier. Peak plasma concentrations are reached in 50–75 min following oral administration.
- ▶ More than 90 % is metabolized in the liver: 80 % of the dose is metabolized to paraxanthine, 10 % is metabolized to theobromine, and about 4 % is metabolized to theophylline. These compounds are demethylated to monomethylxanthinates and then to methylated uric acids. Caffeine and its metabolites are excreted in the urine (with 1–2 % excreted as unchanged substance). $T_{1/2}$: 5–10 hours. For oral administration 2–3 times daily or subcutaneous administration.

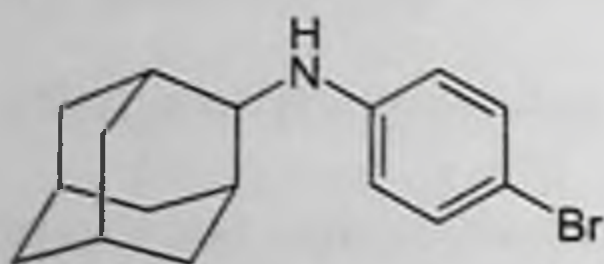
Adamantane derivatives

Fig. 9.5. N-(2-Adamantyl)-N-(2-bromophenyl)amine

Adamantylbromophenylamine (Ladasten[†])

Mechanism of action: Increases synthesis and Ca^{2+} -dependent processes of dopamine release from presynaptic terminals; blocks dopamine reuptake and enhances biosynthesis due to expression of the tyrosine hydroxylase gene. Neuronal catecholamine reserves are not depleted because dopamine synthesis increases.

Restores GABA reception disrupted by stress and decreases expression of the gene encoding the GABA transporter protein responsible for reuptake of GABA from the synaptic cleft. This reduction in gene expression subsequently reduces GABA content in the synaptic cleft, which enhances GABA transmission and helps increase ligand binding by the GABA-benzodiazepine-chloride ionophore complex.

Reduces excessive lipid peroxidation activity, which contributes to maintaining the integrity and barrier function of cellular and mitochondrial membranes.

Pharmacological effects

- ▶ Psychostimulant: increases mental and physical performance, slows the onset of fatigue, accelerates recovery under normal conditions as well as conditions complicated by hypoxia and hyperthermia, improves mnemonic processes.
- ▶ Anxiolytic effect: exerts modulating action on the GABA-benzodiazepine receptor complex.
- ▶ Immunostimulant effect occurs due to the optimization of neuroimmune interaction through central regulatory mechanisms: dopamine activation, influence of cytokines through cytokine-mediated signaling pathways of neuroimmunomodulation.
- ▶ Actoprotective effect: enhances the body's ability to withstand physical stress without increasing oxygen demand.

The drug has no addictive potential; it has no hypnotic or muscle relaxing properties, does not cause hyperstimulation or exhaustion of the body's functional capabilities: does not induce excessive or depleting activation of the sympathoadrenal system.

ANTIDEPRESSANTS

Antidepressants are psychotropic drug products used to treat depression.

Desynchronization, i.e., disruption of biological rhythms, plays an important role in the pathogenesis of depression. A decrease in monoamines, serotonin and norepinephrine occurs in the emotional centers of the limbic system (hippocampus, amygdala) and prefrontal cortex. Monoaminergic systems regulate mood, cognitive functions, endocrine secretion, and circadian rhythms. The hippocampus controls mood, learning, memory, concentration. The amygdala is responsible for emotional control, while the prefrontal cortex is responsible for mood, memory, decision making and initiative.

Antidepressants became a separate pharmacological class in the 1950s with the discovery of the synthetic drugs iproniazid and imipramine which exert thymoleptic action. The first synthetic antidepressants were introduced into medical practice in the mid-1950s. In the 1960s, selective MAO inhibitors and selective serotonin reuptake inhibitors appeared. In the 1990s, more selective drugs were synthesized that had fewer side effects.

The first original Soviet tricyclic antidepressant was azaphen, which was developed at the All-Union Chemical Pharmaceutical Research Institute by M. N. Shchukina, studied by M. D. Mashkovsky and authorized for use in 1970. Pirlindole (Pyrazidol*) was developed at the All-Union Chemical Pharmaceutical Research Institute by M. D. Mashkovsky and N. I. Andreeva and authorized for use in 1975.

Main focus of antidepressant action

Antidepressants cause serotonin and norepinephrine to accumulate in the brain: some block the breakdown of these neurotransmitters (norepinephrine, serotonin, dopamine), while others block their reuptake by the presynaptic membrane (Fig. 9.6).

Classification

I. MAO inhibitors

1. Non-selective irreversible (MAO-A and MAO-B inhibitors)
 - Nialamide (Nuredal[®]) (excluded from Russian State Register of Medicinal Products)
2. Selective reversible (MAO-A inhibitors)
 - Moclobemide (Aurorix[®])
 - Pirlindole (Pyrazidol*)

II. Monoamine reuptake inhibitors

1. Non-selective serotonin and norepinephrine reuptake inhibitors (tricyclic antidepressants)
 - Imipramine (Imizine[®], Melipramin*)
 - Amitriptyline (Amyzol*, Amineurin[®])
 - Pipofezine (Azaphen*)
2. Selective
 - A. Serotonin reuptake inhibitors
 - Fluoxetine (Prozac*, Framex[®])
 - Sertraline (Zoloft*)

- Fluvoxamine (Avoxine[®], Fevarin[®])
- B. Norepinephrine reuptake inhibitors
- Maprotiline (Ludiomil[®])

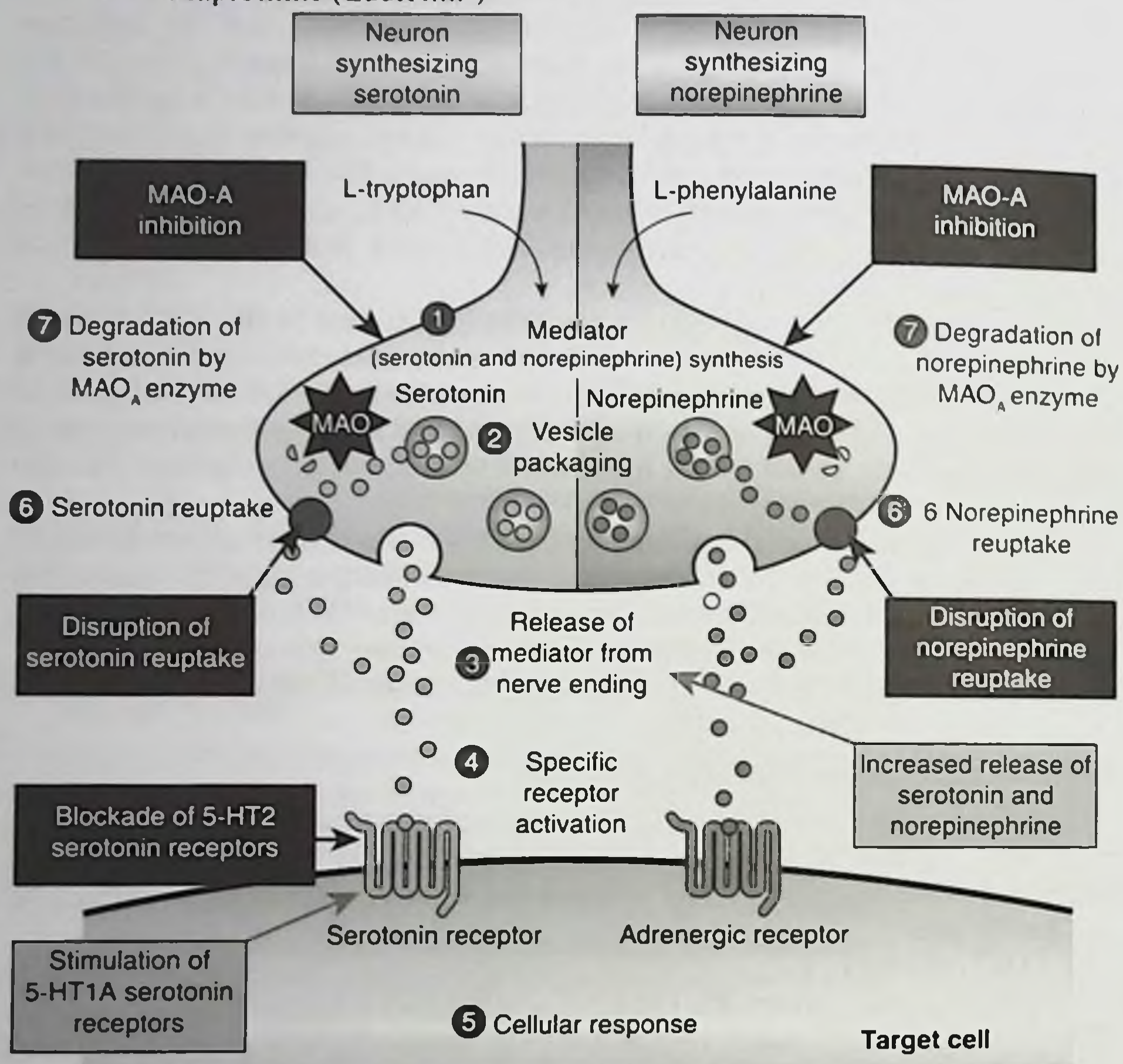


Fig. 9.6. Basic molecular mechanisms of antidepressant action in the context of the monoamine hypothesis of depression (Brunton L., et al., 2011): 1 — neurotransmitters (serotonin and norepinephrine) are synthesized in nerve cells and used by the cells to transmit signals to each other. The essential amino acids L-tryptophan and L-phenylalanine are building blocks for their synthesis; 2 — following synthesis, mediators are packed into special granules, i.e. vesicles, in which they travel to nerve endings (synapses) and are deposited; 3 — after a cell receives a certain stimulus, mediators are released from the nerve ending into the synaptic cleft; 4 — the mediator binds to special protein formations on the surface of the receiving cell, i.e. receptors (serotonin and adrenergic receptors in this case); 5 — after binding, the mediator stimulates the receptor in question, which alters metabolic processes inside the cell and, as a result, changes (enhances or inhibits) its function; 6, 7 — after performing its function, 80 % of the mediator is taken back into the nerve cell, where a portion of the mediator is destroyed by monoamine oxidase A, and a portion is repackaged into vesicles for reuse. Reuptake of the mediator significantly reduces the energy cost of synthesizing it from amino acids.

Specifics of individual products by group

Monoamine oxidase inhibitors

Mechanism of action: MAO inhibitors block MAO, an enzyme that causes oxidative deamination and inactivation of monoamine neurotransmitters that contribute to the transmission of nerve impulses in the CNS. There are two known forms of MAO — A and B — which differ by their target substrates. MAO-A causes deamination mainly of norepinephrine, adrenaline, dopamine, and serotonin, while MAO-B causes deamination of phenylethylamine; both oxidize tyramine. Blockade of MAO-A is necessary for the antidepressant effect.

MAO inhibitors slow the inactivation of serotonin and norepinephrine, letting these neurotransmitters accumulate, and potentiate their activating effect on receptors in the prefrontal cortex, limbic system, hypothalamus, reticular formation.

Nialamide (Nuredal[®])

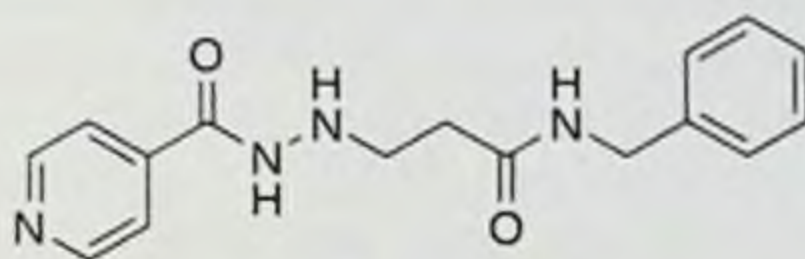


Fig. 9.7. 2-[2-(Benzylcarbamoyl)-ethyl]-hydrazide isonicotinic acid

- ▶ Isonicotinic acid hydrazide derivative. The antidepressant effect occurs in 7–14 days.
- ▶ Metabolized in the liver (predominantly by acetylation), excreted in the urine.

Mechanism of action: The drug non-selectively and irreversibly inhibits MAO, inhibits the oxidative deamination of norepinephrine and serotonin, contributing to their accumulation in brain tissue. At least 2 weeks is required for enzyme resynthesis.

Pharmacological effects:

- ▶ Thymoanaleptic effect (from the Greek thymos, meaning “soul, mood”; ana, meaning “upward movement”; lepticos, meaning “able to perceive”): improves altered mood, restores lost interest in life and optimism, increases activity in depressed patients.
- ▶ Potentiating effect: applies to analgesics, antihypertensive agents, etc.

Side effects: tyramine or cheese syndrome: hypertensive crisis and other complications occurring with the simultaneous consumption of tyramine-containing products (cheese, beer, smoked foods); restlessness, agitation, tremor, convulsions, insomnia; hepatotoxicity; tachycardia, BP reduction; dyspepsia, urinary retention

Moclobemide (Aurorix[®])

- ▶ Bioavailability: 40–80 %, undergoes first-pass metabolism in the liver. Maximum blood concentrations are reached in 1 hour.
- ▶ Metabolized in the liver by oxidation. Excreted in the urine

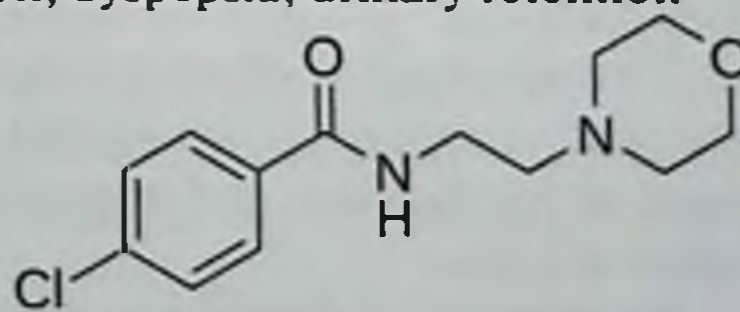


Fig. 9.8. 4-Chloro-N-(2-morpholinoethyl)-benzamide

predominantly as metabolites (with less than 1 % excreted as unchanged drug). $T_{1/2}$: 1–4 hour. For oral administration 2–3 times daily.

Mechanism of action: The drug selectively and reversibly inhibits MAO-A, slows the metabolism of serotonin (predominantly), norepinephrine, and dopamine, causing their accumulation in the synaptic cleft. The drug poorly blocks mAChRs. The optimal antidepressant effect develops when 60–80 % of MAO is inhibited by the end of the first week of treatment; a pronounced activating effect is observed in the first days of administration.

Pharmacological effects

- ▶ Antidepressant effect: reduces symptoms of depression, such as dysphoria, lethargy, inability to concentrate; relieves symptoms of social anxiety disorder.
- ▶ Psychostimulant effect: alleviates psychomotor retardation, improves mental well-being.

Therapeutic indications: depression of various types, social anxiety disorder, anxious depression resistant to tricyclic antidepressants

Side effects: insomnia, agitation (excessive motor activity and extreme emotional excitement coupled with restlessness), irritability, confusion, paresthesia, blurred vision, dry mouth, nausea, dyspepsia, allergic reactions

Contraindications: pregnancy, breastfeeding

Pirlindole (Pyrazidol*)

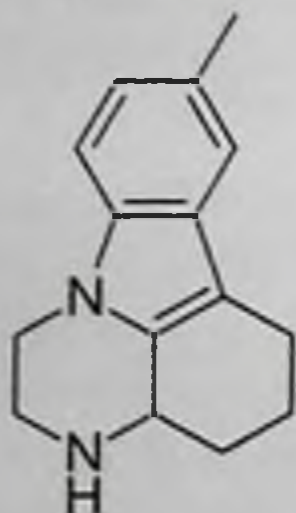


Fig. 9.9. 1,10-Trimethylen-8-methyl-1,2,3,4-tetrahydropyrazino[1,2a]-indole hydrochloride

- ▶ Tetracyclic compound, indole derivative. Maximum plasma concentrations are reached in 2–8 hours. Bioavailability: 20–30 % (first-pass effect). Crosses the blood-tissue barriers, including the BBB, resulting in high concentrations in the brain.
- ▶ Almost completely biotransformed in the liver and included in the enterohepatic circulation. Excreted in the urine (50–70 % of metabolites) and the bile (25–45 % of metabolites). $T_{1/2}$: 1.7–3.0 hours. For oral administration twice daily.

Mechanism of action: The drug selectively and reversibly inhibits MAO-A, blocks deamination of serotonin and norepinephrine and, to a lesser extent, that of tyramine. It partially inhibits monoamine reuptake, potentiates the effects of the norepinephrine precursor L-3,4-dioxyphenylalanine (L-DOPA) and the serotonin precursor 5-hydroxytryptophan. The drug stimulates adrenergic and serotonergic structures. It upregulates synaptic transmission in the CNS. Overall, the use of pyrazidol results in significant upregulation of synaptic transmission in the CNS. The drug does not block mAChRs.

Pharmacological effects: Antidepressant with a regulatory effect on the CNS: at low doses, produces psychostimulant effects in apathy, anergic depression (persistent sense of hopelessness and impending doom); at high doses, exerts sedative action in agitated states.

Therapeutic indications: depression of various types, predominantly with psychomotor retardation and asthenic disorders, anxious-depression or delirious

components; alcohol withdrawal syndrome; Alzheimer's disease (in combination therapy)

Untoward effects: tremor, tachycardia, dizziness, allergic reactions

Contraindications: hepatitis, blood disorders

Monoamine reuptake inhibitors

Imipramine (Imizine[®], Melipramin[®])

- ▶ Dibenzazepin derivative. Maximum plasma concentrations are reached in 1–2 hours following oral administration and in 30–60 min following intramuscular administration. Bioavailability: 29–77 %; crosses the blood-tissue barriers, including the BBB.
- ▶ Undergoes biotransformation in the liver: one of the metabolites (desmethylinipramine) exerts antidepressant activity. Excreted predominantly in the urine. $T_{1/2}$: 4–24 hours. For oral administration 3–4 times daily, for intramuscular administration.

Mechanism of action: The drug inhibits the uptake of monoamine neurotransmitters (norepinephrine, dopamine, serotonin) at presynaptic nerve endings, increasing their levels in the synaptic cleft and enhancing their physiological activity. It also blocks α_1 ARs (which increases norepinephrine release) and serotonin ($5HT_{1A-1D}$) receptors. The inhibitory effect of serotonin on the limbic system (amygdala) may be one of the important mechanisms of the antidepressant action of imizine[®]. The drug blocks mAChRs.

Pharmacological effects: Antidepressant effect with psychostimulant effect and, to a lesser extent, a sedative effect.

Therapeutic indications: asthenic-depressive disorder, depression (endogenous, involutional, menopausal, reactive, alcohol-induced); depressive moods in psychopathy and neurosis; panic disorders, enuresis

Side effects: atropine-like effects (increased IOP, tachycardia, obstipation, difficulty urinating, etc.); orthostatic hypotension; leukopenia, agranulocytosis; agitation, hallucinations, insomnia; headache, tremor, paresthesia, coordination disorders; hepatotoxicity; galactorrhea, decreased libido; photosensitization

Contraindications: glaucoma, prostate adenoma, intestinal and bladder atony, tachycardia; hepatic/renal impairment; decompensated heart failure; schizophrenia, epilepsy; pregnancy, breastfeeding

Amitriptyline (Amyzol[®], Amineurin[®])

- ▶ Dibenzocycloheptadine derivative. Its structure is different from that of imipramine: the nitrogen atom in the central part of the tricyclic system is replaced by a carbon atom. Bioavailability: 30–60 %. Maximum blood concentrations are reached in 2.0–7.7 hours, crosses the blood-tissue barriers, including the BBB, placental barrier, excreted into breast milk.
- ▶ Undergoes biotransformation in the liver (demethylation, hydroxylation, N-oxidation) to form active (nortriptyline, 10-hydroxyamitriptyline)

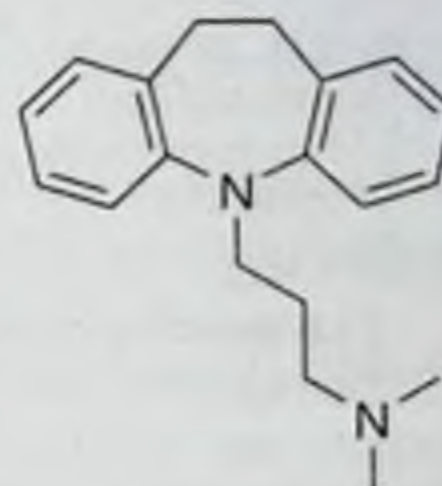


Fig. 9.10. N-(3-Dimethylaminopropyl)-iminodibenzyl hydrochloride

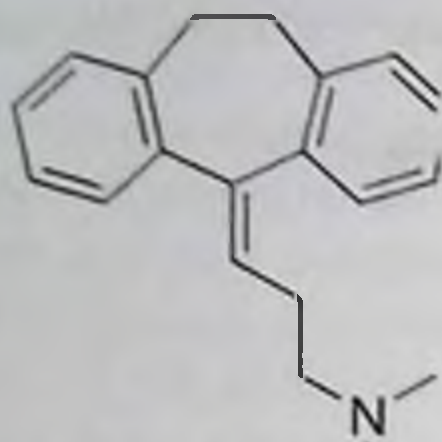


Fig. 9.11. 3-Dimethylaminopropylidene)-10,11-dihydrodibenzocyclohepten

and inactive metabolites. Excreted in the urine (predominantly as metabolites). $T_{1/2}$: 10–26 hours. For oral administration 2–3 times daily; for intramuscular, intravenous administration.

Mechanism of action: The drug inhibits the uptake of neurotransmitters (norepinephrine, serotonin) at presynaptic nerve endings, causes accumulation in the synaptic cleft, and increases postsynaptic impulse generation. It normalizes adrenergic and serotonergic transmission, rebalancing these systems which are disrupted in depressive states; chronic use reduces the functional activity (desensitization) of β -adrenergic and serotonin receptors in the brain. The drug blocks mAChRs.

Pharmacological effects: Antidepressant and sedative effects, analgesic effect.

Therapeutic indications: depression of various types (especially with marked anxiety and agitation), including endogenous, involutional, reactive and neurotic; depression after brain injury; enuresis, chronic pain syndrome (of neurogenic origin), prophylaxis of migraine

Side effects: atropine-like effects (increased IOP, urinary retention, obstipation, tachycardia, etc.); ataxia, increased fatigue, irritability, somnolence, peripheral neuropathy, difficulty concentrating; agranulocytosis, leukopenia, eosinophilia, thrombocytopenia; elevated liver transaminase levels; galactorrhea, impaired glucose tolerance

Contraindications: glaucoma, prostate adenoma, intestinal and bladder atony, decompensated heart failure, blood disorders, pregnancy, breastfeeding

Pipofezine (Azaphen*)

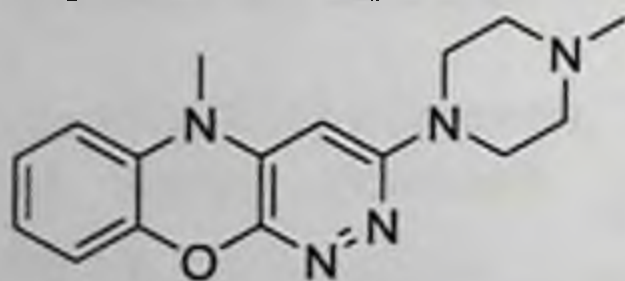


Fig. 9.12. 2-(4-Methyl-1-piperazinyl)-10-methyl-3,4-diazaphenoxazine dihydrochloride

- ▶ Bioavailability: 80 %. Maximum blood concentrations are reached in 2 hours.
- ▶ Metabolized in the liver to form inactive metabolites. Excreted in the urine. $T_{1/2}$: 16 hours. For oral administration twice daily.

Mechanism of action: The drug non-selectively inhibits the reuptake of serotonin and norepinephrine.

Pharmacological effects: Antidepressant and sedative effects.

Therapeutic indications: mild and moderate depression

Untoward effects: headache, dizziness, nausea, vomiting

Contraindications: hepatic and/or renal impairment, pregnancy, breastfeeding

Fluoxetine (Prozac*, Framex[®])

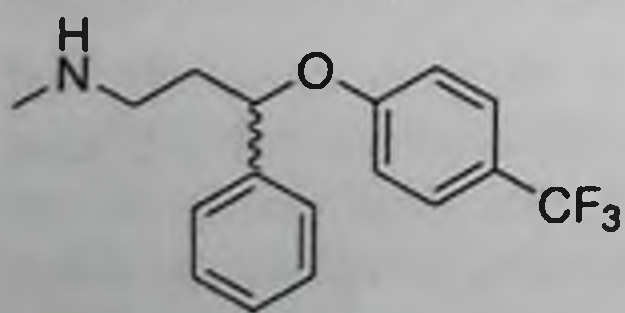


Fig. 9.13. (RS)-N-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine

- ▶ Phenoxypropylamine derivative. Maximum blood concentrations are reached in 6–8 hours. Bioavailability: more than 60 %, crosses the BBB.
- ▶ Metabolized in the liver by demethylation, one of its metabolites (norfluoxetine) exerts antidepressant activity. Excreted in the urine as metabolites (80 %) and in the bile (15 %), predominantly as glucuronides.

$T_{1/2}$ for fluoxetine is 1–3 days, $T_{1/2}$ for norfluoxetine is 7–15 days. For oral administration twice daily.

Mechanism of action: The drug selectively inhibits the neuronal uptake of serotonin, increasing its concentration in the synaptic cleft, thus enhancing and prolonging its action at postsynaptic receptor sites. In addition to enhancing serotonergic transmission through a negative feedback loop, it inhibits the neurotransmitter's circulation. Chronic use lowers the activity of $5HT_1$ receptors. The drug poorly blocks mAChRs.

Pharmacological effects: Antidepressant and psychostimulant effects, anorexigenic effect.

Therapeutic indications: depression of various types (especially accompanied by fear), including cases of resistance to other antidepressants; obsessive-compulsive disorder (obsessive-compulsive neurosis); bulimia

Side effects: anxiety, tremor, nervousness, insomnia; diarrhea, poor appetite; decreased appetite, decreased libido; rare: atropine-like effects

Contraindications: glaucoma, bladder atony, benign prostatic hyperplasia; severe renal impairment; seizure disorders, epilepsy; pregnancy, breastfeeding; children below the age of 18 years

Fluvoxamine (Avoxine⁺, Fevarin⁺)

- ▶ Bioavailability: 53 % (due to first-pass effect). Maximum plasma concentrations are reached in 3–8 hours.
- ▶ Undergoes demethylation and deamination in the liver to form inactive metabolites. Excreted predominantly in the urine (94 %). $T_{1/2}$: 15–20 hours. For oral administration once daily.

Mechanism of action: The drug selectively inhibits serotonin uptake from the synaptic cleft, blocking the reuptake pump in the presynaptic membrane. It enhances serotonergic transmission, has a high affinity for σ_1 -receptors, acting as their agonist.

Pharmacological effects: Antidepressant with balanced (neither sedative nor activating) effects, neuroprotective, anxiolytic effects.

Therapeutic indications: depression of various types, obsessive-compulsive disorder

Untoward effects: increased excitability, insomnia, tremor, dyspepsia

Contraindications: hepatic impairment, pregnancy, breastfeeding

Sertraline (Zoloft⁺)

- ▶ Bicyclic naphthylamine derivative. Forms the active metabolite N-desmethylertraline during the first pass through the liver. Maximum blood concentrations are reached in 6–8 hours.
- ▶ Undergoes biotransformation in the liver (deaminated, hydroxylated) and glucuronide

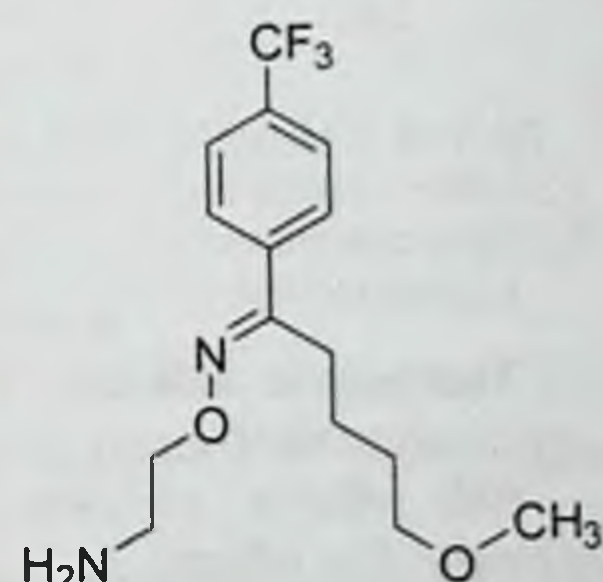


Fig. 9.14. (E)-5-Methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone-O-(2-aminoethyl) oxime (as a maleate)

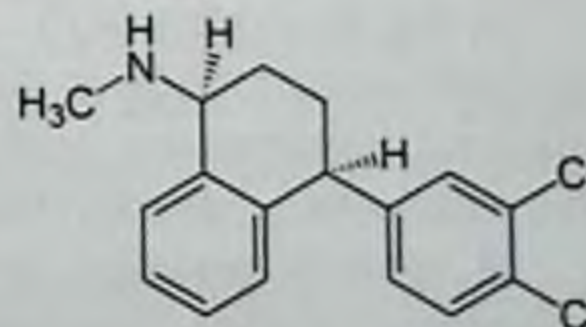


Fig. 9.15. (11S,4S)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine (as a hydrochloride)

conjugation. Excreted equally (40–45 %) in the urine and bile, with 12–14 % excreted as unchanged drug. $T_{1/2}$: 22–36 hours. For oral administration once daily.

Mechanism of action: The drug inhibits the reuptake of serotonin, increases serotonergic transmission, resulting in subsequent inhibition of adrenergic activity in the locus ceruleus.

Pharmacological effects: Antidepressant with balanced (neither sedative nor activating) effects and predominant anxiolytic properties.

Therapeutic indications: depression of various types (including those accompanied by anxiety), obsessive-compulsive disorder, social anxiety

Untoward effects: somnolence, tremor, diarrhea, dyspepsia

Contraindications: pregnancy, breastfeeding

Maprotiline (Ludiomil®)

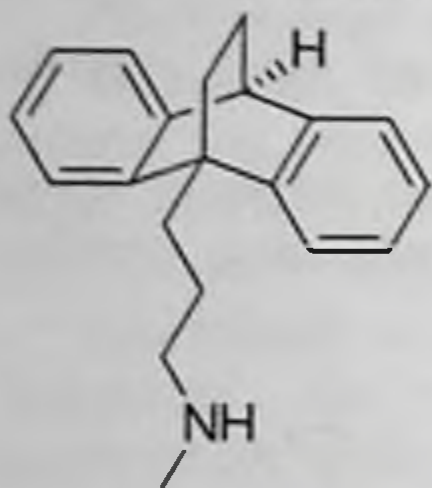


Fig. 9.16. N-Methyl-9,10-ethanoanthracene-9(10H)-propanamine (as a hydrochloride)

► Tetracyclic compound. Bioavailability: 66–70 %.

► Metabolized in the liver to form the active metabolite desmethylnmaprotiline. Excreted mainly as metabolites in the urine and partially in the bile. $T_{1/2}$: 43–45 hours. For oral administration 1–3 times daily; for intramuscular, intravenous administration.

Mechanism of action: The drug inhibits the neuronal uptake of norepinephrine (predominantly) by presynaptic neurons of the cerebral cortex with insignificant inhibition of serotonin reuptake. The drug blocks mAChRs.

Pharmacological effects: antidepressant and sedative effects, anxiolytic effect

Therapeutic indications: depression accompanied by fear, irritability, apathy; psychosomatic disorders caused by depression or fear

Side effects: somnolence, headache, tremor, dyspepsia, muscle weakness, atropine-like effects

Contraindications: epilepsy, glaucoma, prostate adenoma; severe liver/kidney disease; pregnancy, breastfeeding

ANALEPTICS

Analeptics (from the Greek *analēptikos*, meaning “restorative”) are drugs that exert an excitatory action on the respiratory and vasomotor centers of the medulla oblongata, stimulating the vital functions of respiration and blood circulation.

At the beginning of the 20th century, advances were made in understanding how synaptic transmission in the autonomic ganglia occurs. In the 1930s, the analeptic alkaloid lobeline was widely used; in 1937, the analeptic cytitone was created. Nowadays they have lost their clinical relevance.

In medical practice, two forms of camphor are used: a natural, right-rotating camphor obtained from the camphor tree, and a synthetic, left-rotating camphor obtained from fir oil. P. G. Golubev proposed a method for obtaining synthetic camphor in 1903. In 1934, left-rotating camphor was synthesized from fir oil by

borneol dehydrogenation. Left-rotating camphor was introduced into practice by N. V. Vershinin, who developed a drip method to infuse Siberian camphor in patients who were in shock. A. S. Saratikov found that the cardiotonic action of camphor is caused by increased sensitivity of cardiac ARs to norepinephrine and adrenaline, slower oxidation of these catecholamines, and improved myocardial bioenergetics.

Classification by mechanism of action

1. Direct-acting
 - Caffeine (Caffeine sodium benzoate[•]) (acts predominantly on cerebral cortex)
 - Bemegride (Megimide[•], Agipnon[•], Etimid[•])
2. Reflex-acting
 - Lobeline (Lobeline hydrochloride[•])
 - Cytisine (Cytiton[•])
3. Mixed-acting
 - Nikethamide (Cordiamine[•])
 - Camphor (Camphor[•])
 - Sulfocamphocaine[•] (procaine, sulfocamphoric acid)

Classification by chemical structure

1. Trimethylxanthines (purines)
 - Caffeine (Caffeine sodium benzoate[•])
2. Glutarimides
 - Bemegride (Megimide[•], Agipnon[•], Etimid[•])
3. Alkylated acid amides
 - Nikethamide (Cordiamine[•])
4. Bicyclic ketones
 - Camphor (Camphor[•])

Therapeutic indications:

- ▶ mild poisoning with general anesthetics, narcotic hypnotics — barbiturates (bemegride)
- ▶ heart failure, circulatory disorders and decreased breathing during surgical interventions and the postoperative period
- ▶ decreased vascular tone and breathing in patients with infectious diseases.

Side effects: increased CNS excitability, restlessness, insomnia; muscle twitching; tonic-clonic (grand mal) seizures (dose-dependent effect); hypertension, arrhythmias; nausea, vomiting; infiltrates at the injection sites (camphor)

Contraindications: psychomotor agitation; epilepsy; CAD, essential hypertension

Mechanism of action: The drugs have different affinity for individual CNS structures: nikethamide, bemegride, camphor predominantly act on the medulla oblongata; caffeine also stimulates the medulla oblongata, but its predominant effects are on the cerebral cortex. Analeptics stimulate the respiratory and vasomotor centers by lowering their excitation threshold, which increases their sensitivity to humoral and neural stimuli:

- ▶ facilitate neuronal depolarization by increasing the permeability of sodium and calcium channels
- ▶ increase the lability of nerve centers and after-discharge frequency
- ▶ shorten the latent period of reflexes

- ▶ exhibit antagonism with inhibitory mediators of the CNS: bemegride reduces the action of GABA, caffeine reduces the action of adenosine.

They increase the sensitivity of respiratory center neurons to carbon dioxide, H^+ ions, and to reflex stimuli from the carotid body. The stimulating effect on respiration is most pronounced when the respiratory center's functions are inhibited and it is less reactive to physiological stimuli (CO_2).

By toning the vasomotor center, they increase the tone of resistance and capacitance vessels, increase venous return to the heart, increase cardiac output, BP, and myocardial oxygen demand.

The drugs can be arranged in the following order of analeptic activity: bemegride > nikethamide (Cordiamine[®]) > camphor.

Analeptics have a narrow therapeutic range: increasing the dose results in generalization of excitation processes in the CNS, increasing spinal reflex excitability.

The most dangerous complication is tonic-clonic seizures; for this reason, analeptics are called "seizure-inducing poisons". Seizures occur because of facilitated transmission of nerve impulses between neurons, shortened recovery cycle, spread of excitation, and prolongation of trace processes (e.g., residual effects). Consequently, they are administered at doses sufficient to restore respiration, blood circulation with mild to moderate inhibition of these functions.

Pharmacological effects:

Stimulating effects:

- ▶ on the respiratory center, resulting in increased respiratory rate and depth
- ▶ on the vasomotor center (especially when its tone is reduced)

Characteristics of individual drugs

Caffeine (Caffeine sodium benzoate[®])

The drug stimulates the cerebral cortex, respiratory and vasomotor centers of the medulla oblongata, which restores the cerebral, respiratory, and circulatory functions, especially when they are affected by CNS depression.

See "Psychostimulants".

Lobeline (Lobeline hydrochloride[®]), Cytisine (Cytiton[®])

The drugs stimulate nAChRs of the sinocarotid zone; the impulses reach the medulla oblongata via afferent pathways, reflexively increasing the activity of respiratory and vasomotor center neurons.

These drugs are not effective when the respiratory reflex is inhibited (e.g., by barbiturates).

See "Nicotinic agonists".

Bemegride (Megimide[®], Agipnon[®], Etimid[®])

- ▶ Glutarimide, direct-acting analeptic. Antagonizes the inhibitory action of hypnotics (particularly barbiturates) and general anesthetics on the

CNS Superior antagonistic activity to other analeptics [caffeine, nikethamide (Cordiamine[®]), camphor]. Stimulates the vasomotor center to a lesser extent.

- ▶ The drug is slowly administered intravenously, 5–10 mL of 0.5 % solution; if the effect is insufficient or absent, injections are repeated at intervals of 2–3 min until reflexes are restored, breathing becomes deeper or completely normalized, pulse and BP return back to normal.

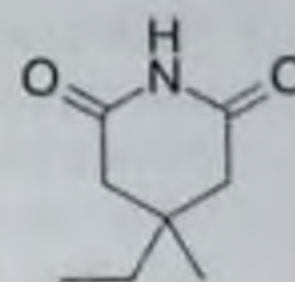


Fig. 9.17. 4-Ethyl-4-methyl-2,6-piperidinedione

Nikethamide (Cordiamine[®])

- ▶ Nicotinic acid diethylamide solution 25 %, mixed-acting analeptic.
- ▶ Undergoes rapid metabolism in the liver to form inactive metabolites. Excreted mainly in the urine. For oral administration 2–3 times daily; for subcutaneous, intramuscular, intravenous administration.

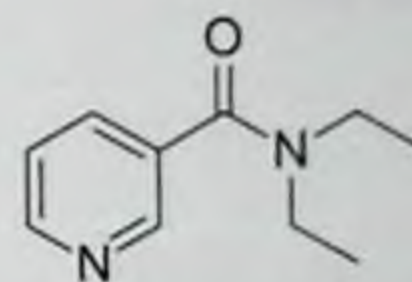


Fig. 9.18. N,N-Diethyl-3-pyridinecarboxamide

Camphor (Camphor[®])

- ▶ Terpene ketone. The toning effect is due to the presence of an oxo group. The molecule contains two asymmetric carbon atoms at the branching rings, so it has two optically active isomers: the natural right-rotating D-stereoisomer and the semisynthetic left-rotating L-isomer. Its moderate analeptic action is inferior to other drugs in this group.
- ▶ Mixed-acting analeptic: irritation of the subcutaneous tissue receptors contributes to reflex excitation of the medulla oblongata centers; after absorption, the respiratory and vasomotor centers are activated directly. The respiratory center's sensitivity to carbon dioxide and H⁺ ions increases; the vasomotor center's activity is reduced. For subcutaneous, topical administration.

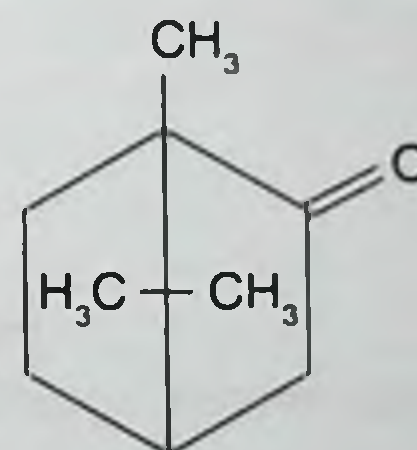


Fig. 9.19. 1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one

Additional pharmacological effects.

- ▶ Cardiotonic effect: sensitizes cardiac β ARs to norepinephrine and adrenaline, inhibits oxidation of catecholamines, increasing the release of amino acids with antioxidant properties from red blood cells.
- ▶ Stimulates glycolysis and aerobic oxidation, increases the conjugation of oxidation and phosphorylation, increases the cardiac synthesis of ATP, creatine phosphate and glycogen, moderately increases the heart's oxygen demand but also expands the coronary vessels to ensure adequate oxygen delivery.
- ▶ Narrows dilated blood vessels of the abdominal organs, activating the vasomotor center, but dilates the cerebral and coronary vessels due to spasmolytic action.
- ▶ Antiplatelet effect: increases microcirculation

- ▶ While showing superficial activity, it is adsorbed on the membranes of tissue cells and capillaries, weakening the damaging effect of inflammatory mediators and protein breakdown products.
- ▶ When excreted partially through the respiratory tract, increases bronchial gland secretion, mucociliary clearance.
- ▶ When used topically — irritating, analgesic effects.

Sulfocamphocaine

Complex compound of sulfocamphoric acid and procaine. For subcutaneous, intramuscular, intravenous administration. The onset of action is faster than that of camphor.

10. BRONCHODILATORS, ANTIHISTAMINES

BRONCHODILATORS

Theophylline (1,3-dimethylxanthine) is a natural alkaloid that was first isolated in 1888. In 1912, its bronchodilator effect was demonstrated by P. Trendelenburg, a German physician. Long-acting forms were created in the 1970–1980s.

Zileuton[®] and zafirlukast were introduced to the US pharmaceutical market in 1996, montelukast was introduced in 1998.

Classification

I. Drugs that affect afferent nerves

1. Adrenergic agonists (AA)

- $\alpha_1\alpha_2\beta_1\beta_2$: Epinephrine (Adrenaline hydrochloride-Vial[®])
- $\beta_1\beta_2$: Isoprenaline (Isadrine[®], Novodrine[®], Euspiran[®]), orciprenaline (Asthmopent[®], Alupent[®])
- β_2 : Fenoterol (Berotec[®]), salbutamol (Ventolin[®]), formoterol (Foradil[®]), salmeterol (Serevent[®])

2. MRA: ipratropium bromide (Atrovent[®]), tiotropium bromide (Spiriva[®])

II. Combination bronchodilators: Berodual, Symbicort[®] (budesonide, formoterol), Seretide[®] (salmeterol, fluticasone), Ditec[®] (cromoglicic acid, fenoterol)

III. Antispasmodics (purines, methylxanthines)

- Aminophylline (Euphylline[®]), Theophylline[®]
- Long-acting forms of theophylline: First generation: Theotard[®], Retaphyl[®], Theopec[®]
- Second generation: Euphyllong[®], Uniphyl[®]

IV. Leukotriene modifiers

1. 5-lipoxygenase inhibitors: Zileuton[®] (Zyflo[®])

2. Leukotriene receptor antagonists [cysteinyl leukotriene receptor (CysLT₁R) antagonists]

- Zafirlukast (Accolate[®]), Montelukast (Singulair[®])

For AA, MRAs and combination bronchodilators, see “Adrenergic agonists”, “Cholinergic blockers”.

Specifics of individual products by group

Methylxanthines (purines)

Mechanism of action:

- ▶ Blocks adenosine receptors (A_1 and A_2 , P_1 receptors) on bronchial smooth muscle cells, which inhibits the bronchoconstrictor effect of adenosine. Also inhibits the release of histamine from mast cells.
- ▶ Inhibits PDE III, IV at high doses (i.e., theophylline plasma concentration 100 $\mu\text{g/mL}$), but even a small degree of PDE inhibition is functionally significant. Inhibition of PDE III results in increased cAMP concentrations in myofibrils and intracellular redistribution of Ca^{2+} ions with a decrease in their concentrations in the cytosol and mitochondrial uptake. Inhibition of PDE IV results in suppression of the functions of mast cells, eosinophils and T cells. The drugs suppress the high molecular fraction of adenylylated PDE only when the latter's activity is high. This is the fraction that is increased during an asthma attack.
- ▶ Inhibits the transport of Ca^{2+} ions through the slow channels of smooth muscle cell membranes, reducing its release from intracellular depots.

Pharmacological effects:

- ▶ Bronchodilator effect: relaxes large and medium bronchi, relaxes bronchioles 0.5 to 1.0 mm in diameter, increases pulmonary ventilation.
- ▶ Stimulates mucociliary transport by increasing bronchial gland secretions and ciliary epithelium activity.
- ▶ Anti-inflammatory effect: stabilizes the membranes of mast cells and inhibits the release of inflammatory mediators, reduces bronchial mucosal edema and formation of free oxygen radicals by neutrophils and macrophages; inhibits the synthesis and release of cytokines from monocytes and macrophages (interleukin-1, tumor necrosis factor α).
- ▶ Excites the respiratory center, improves respiratory mechanics and increases ventilation by contraction of respiratory muscles (including the diaphragm).
- ▶ Vasodilator effect: dilates blood vessels of the systemic circuit, reducing TPR, BP; dilates pulmonary blood vessels, reducing pressure in the pulmonary circuit; reduces hypercapnia and increases oxygen saturation
- ▶ Diuretic effect: improves renal blood flow and increases filtration, reduces tubular reabsorption of Na^+ ions
- ▶ Increases heart rate and cardiac contractile force, increase conduction, including AV conduction (reflex response and direct myocardial stimulation)
- ▶ Relaxes the smooth muscles of internal organs
- ▶ Inhibits platelet aggregation

Aminophylline (Euphylline⁺)

- ▶ Theophylline (80 %) with 1,2-ethylenediamine (20 %). The action is based on the theophylline portion of the drug. Ethylenediamine increases the spasmolytic activity and helps the drug dissolve in water, ensuring its parenteral administration. Exhibits bronchodilator properties at concentrations

of 10–20 µg/mL; concentrations exceeding 20 mg/mL are toxic. Excreted into breast milk, crosses the placental barrier.

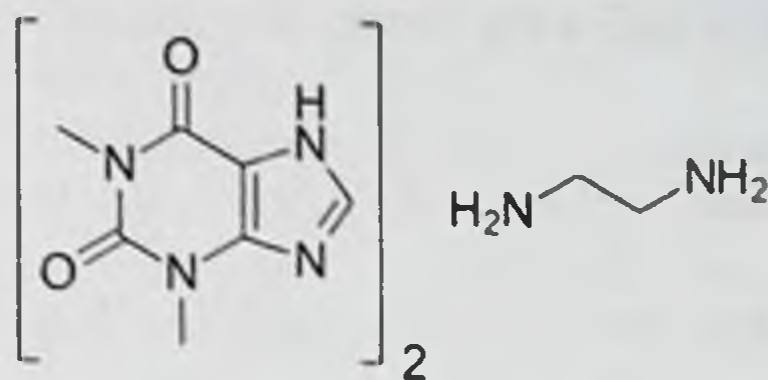


Fig. 10.1. 3,7-Dihydro-1,3-dimethyl-1H-purine-2,6-dione (theophylline) with 1,2-ethylenediamine (2:1)

- ▶ About 90 % is metabolized in the liver, releasing theophylline, which undergoes metabolism with cytochrome P450 isoenzymes. Metabolites are excreted in the urine, with 7–13 % excreted as unchanged drug. $T_{1/2}$: 5–10 hours. For intravenous or intramuscular administration.

Therapeutic indications: management of broncho-obstructive syndrome such as asthma, COPD; hypertension in the pulmonary circuit

Side effects: tachycardia, hypotension, more frequent angina attacks, dizziness, headache, insomnia, agitation, tremor, nausea, vomiting, diarrhea, tenderness at the injection site, exfoliative dermatitis

Contraindications: hypotension, paroxysmal tachycardia, extrasystoles, myocardial infarction; epilepsy; stomach and duodenal ulcers, hyperacid gastritis; hepatic/renal impairment; pregnancy, breastfeeding

Theophylline⁺

Natural alkaloid (found in cocoa beans) with low solubility. Bioavailability: over 90 %, maximum plasma concentrations are reached in 6 hours. Crosses the BBB, excreted into breast milk.

Metabolized in the liver with cytochrome P450 isoenzymes to form 1,3-dimethyluric acid (pharmacologically active), 1-methyluric acid, and 3-methylxanthine. Excreted in the urine as metabolites. $T_{1/2}$: 6–12 hours. For oral administration 2–4 times daily.

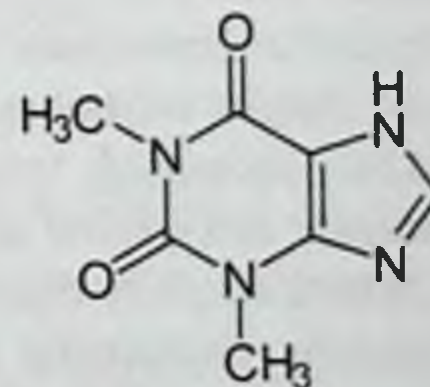


Fig. 10.2. 3,7-Dihydro-1,3-dimethyl-1H-purine-2,6-dione (1,3-Dimethylxanthine)

Theopec⁺, Euphylong⁺

- ▶ Long-acting forms of theophylline with delayed release of the active substance. While they have the pharmacological properties of theophylline, they are integrated into a polymer carrier to ensure metered release of theophylline in the gastrointestinal tract, with therapeutic levels of theophylline in the blood being reached 3–5 hours following administration. Bioavailability: 92–94 %.
- ▶ Duration of action: up to 12 hours for Theopec, up to 24 hours for Euphylong. Circadian rhythms affect the pharmacokinetics. The absorption rate of the morning dose is higher than that of the evening dose, so the peak daytime concentration occurs at 10 a.m. and the peak nighttime concentration at 2 a.m.

- ▶ **Advantages:** the frequency of administration is 1–2 times a day, making it more convenient and increasing compliance; stable theophylline blood concentrations are maintained, which makes the therapeutic effect easier to predict; prevention of asthma attacks.
 - ▶ **For oral administration:** twice daily for Theopec, once daily for Euphyllong.
- Therapeutic indications:** broncho-obstructive syndrome of various types, hypertension in the pulmonary circuit.
- Side effects, contraindications:** see “Aminophylline (Euphylline[®])”.

Leukotriene modifiers

Leukotrienes are a group of highly active lipid substances formed in the body from arachidonic acid.

There are two subgroups: cysteinyl leukotrienes — LTC₄, LTD₄, LTE₄ contain peptide residues in the side chain, which are powerful bronchoconstrictors; the second group includes LTB₄ that contains hydroxyl groups. LTC₄, LTD₄, LTE₄ modulate specific G protein-coupled receptors — CysLTRs (cysteinyl-leukotriene receptors). There are two types of CysLTRs. Type 1 receptors (CysLT₁ receptors) are present in bronchial smooth muscle cells, macrophages, and other pro-inflammatory cells (including eosinophils and some myeloid stem cells). The interaction of leukotrienes with CysLT₁ receptors defines their main effect (bronchospasm); binding of leukotrienes with CysLT₂ receptors leads to changes in vascular tone and permeability. Together with histamine and PGs, leukotrienes are classified as early-phase mediators of immediate hypersensitivity reactions. The action of histamine results in immediate and short-term bronchospasm, while leukotrienes cause delayed and longer bronchospasm (1000 times more potent than histamine). Leukotrienes cause increased vascular permeability, increased mucosal gland secretion and cellular infiltration of the airway mucosa, and bronchial remodeling. Remodeling is characterized by mass death of epithelial cells, a large number of mucous plugs in the bronchi, thickening of the basal membrane, hypertrophy and hyperplasia of goblet cells and serous glands, hypertrophy of bronchial smooth muscles.

5-lipoxygenase inhibitors

Mechanism of action: They selectively and reversibly inhibit 5-lipoxygenase (antagonist of 5-lipoxygenase-activating protein) and reduce formation of cysteinyl leukotrienes: LTE₄, LTC₄, LTD₄, and LTB₄ (Fig. 10.3).

Pharmacological effects:

- ▶ **Bronchodilator effect:** reduces bronchial reactivity, decreases the degree and rate of bronchoconstriction following contact with bronchoconstrictors, prevents bronchospasm
- ▶ **Anti-inflammatory effect:** reduces vascular permeability, airway mucosal edema

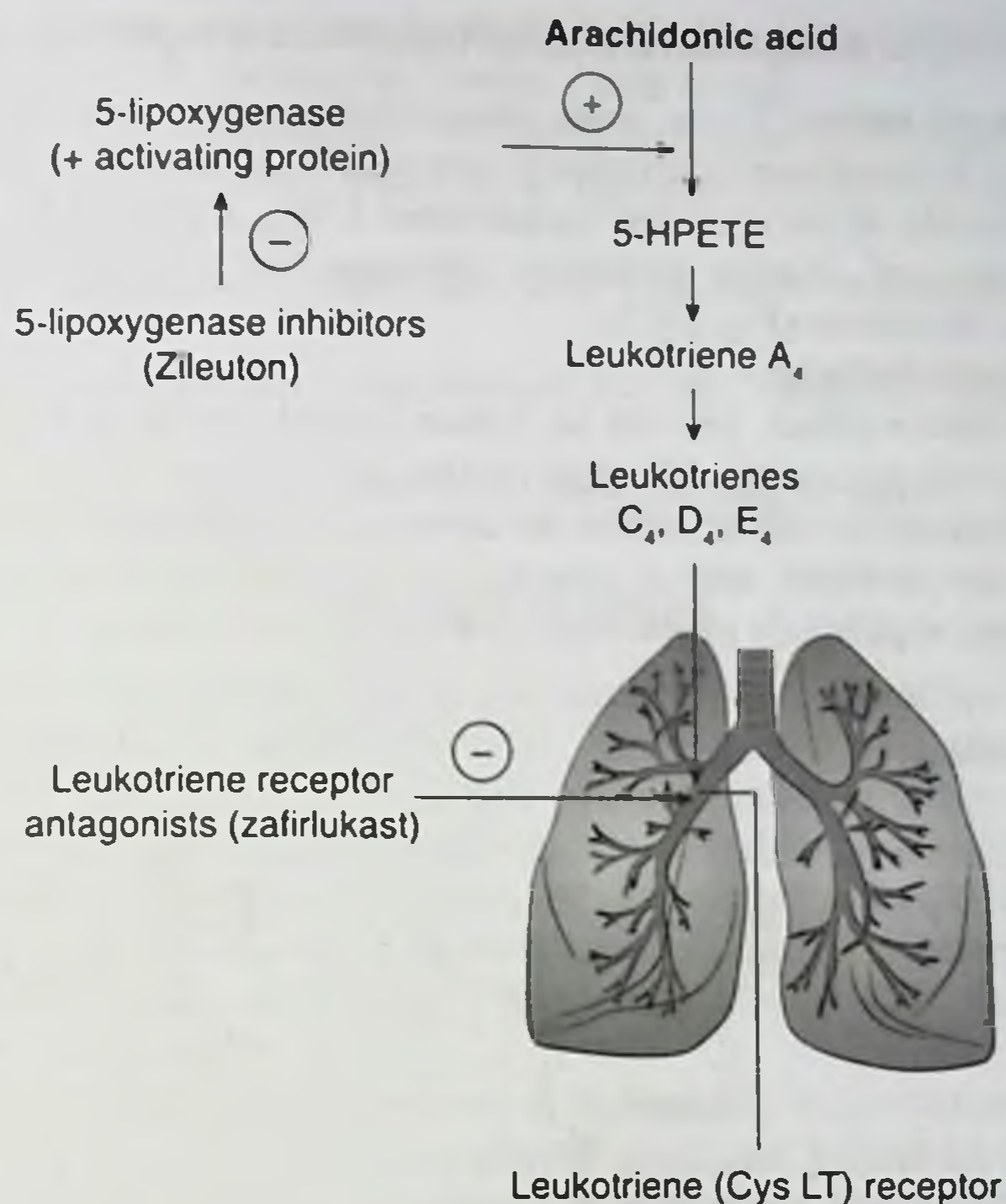


Fig. 10.3. Focus of action on the leukotriene system (Kharkevich D. A., 2021)

Zileuton[®] (Zyflo[®])

- ▶ Maximum blood concentrations are reached in 1.7 hours, dietary fat stimulates absorption. Onset of action: 2 hours, duration of action: 5 hours.
- ▶ Glucuronides are formed during the first pass through the liver. Zileuton and its N-dehydroxylated metabolite are metabolized by cytochrome P450 isoenzymes: CYP1A2, CYP2C9, and CYP3A4.

CYP1A2 inhibitor. Metabolites are excreted in the urine and in the bile: 95.5 % and 2.2 %, respectively. T_{1/2}: 2.5 hours. For oral administration 4 times daily.

Therapeutic indications: prophylaxis of bronchospasms

Side effects: elevated liver transaminase levels, myalgia, sleep disorders, fatigue, dizziness, nausea, vomiting, obstipation

Contraindications: 3-fold increase in liver transaminase levels, pregnancy, breastfeeding

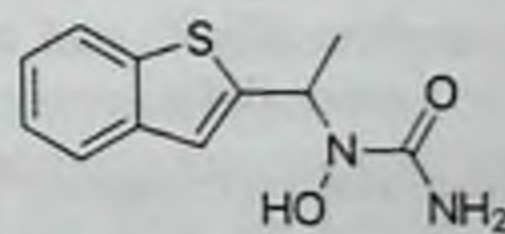


Fig. 10.4. N-[1-(1-benzothien-2-yl) ethyl]-N-hydroxyurea

Leukotriene receptor antagonists (cysteinyl leukotriene receptor antagonists)

Mechanism of action: These drugs competitively and reversibly block airway epithelial CysLT₁ receptors and prevent contraction of bronchial smooth muscles under the influence of the cysteinyl leukotrienes LTC₄, LTD₄, and LTE₄, the most potent mediators of chronic persistent inflammation that maintains bronchial hyperreactivity in asthma (Fig. 10.3).

Pharmacological effects:

- ▶ Bronchodilator effect: prevent or reduce bronchospasm induced by physical exertion, cold air, various allergens (pollen, etc.).
- ▶ Anti-inflammatory effect: inhibit the action of inflammatory mediators, reduce vascular permeability, airway mucosal edema, penetration of eosinophils into the airways, superoxide production by alveolar macrophages.

Zafirlukast (Accolate[®])

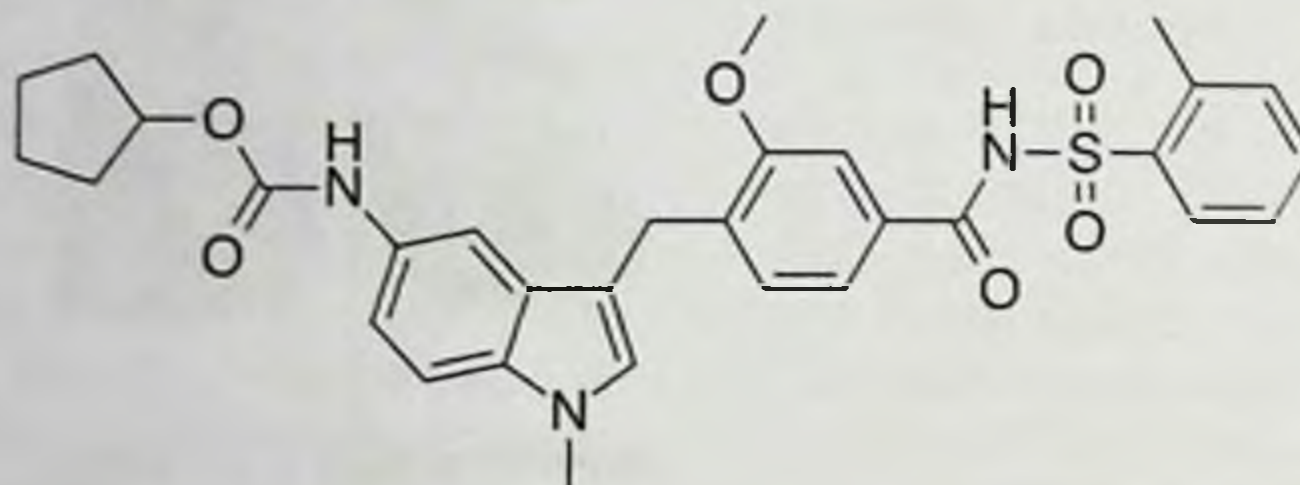


Fig. 10.5. Cyclopentyl 3-[2-methoxy-4-[(o-tolylsulfonyl)carbamoyl]benzyl]-1-methyl-1H-indol-5-ylcarbamate

- ▶ Maximum blood concentrations are reached in 3 hours, food intake decreases absorption by 40 %.
- ▶ Undergoes biotransformation, inhibits microsomal enzymes. Excreted in the bile (89 %) and urine (about 10 %). T_{1/2}: 10 hours. For oral administration twice daily.

Montelukast (Singulair[®])

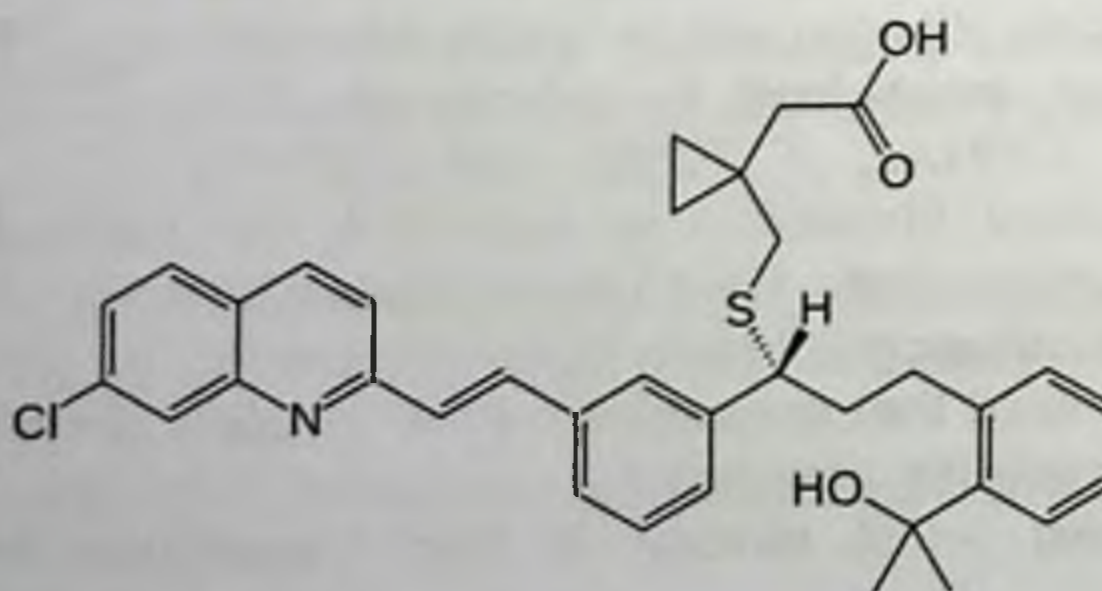


Fig. 10.6. (R,E)-2-(1-((1-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(2-hydroxypropan-2-yl)phenyl)propylthio)methyl)cyclopropyl)acetic acid

- ▶ Absorption does not depend on food intake, bioavailability: 70 %; the bronchodilator effect occurs in 2 hours. Long-acting.
- ▶ Undergoes biotransformation in the liver, does not inhibit cytochrome P450 (CYP) isoenzymes. Excreted in the bile. $T_{1/2}$: 2.5–5.5 hours. For oral administration once daily.

Therapeutic indications: prophylaxis and long-term treatment of mild and moderate asthma

Side effects: increased liver transaminase activity, headache, nausea, vomiting, dyspepsia

Contraindications: hepatic impairment, liver cirrhosis, pregnancy, breastfeeding

ANTIHISTAMINES

Histamine was first isolated and synthesized in 1907; histamine (H_1) receptors were discovered in 1937. French scientist H. Halpern introduced the antihistamines phenbenzamine[®] and pyrilamine[®] (highly toxic, production stopped) into clinical practice in the early 1940s and diphenhydramine (Dimedrol[®]) and promethazine in the late 1940s. In 1957, D. Bovet, a Swiss physiologist and pharmacologist, was awarded the Nobel Prize for his discovery of antihistamines for the treatment of allergies. Second-generation antihistamines were synthesized in the 1980s. Fexofenadine was authorized for sale in 1996.

Histamine (imidazolyl-2-ethylamine), a biologically active substance, is present in many tissues. It exerts a variety of physiological and pathological effects and is normally released locally. It is a mediator of immediate hypersensitivity reactions and inflammatory reactions, plays a role in the secretion of gastric juice. Histamine is formed by decarboxylation of the amino acid L-histidine with the involvement of histidine decarboxylase. Following its formation, it is deposited or inactivated through the involvement of methyltransferase or diamine oxidase. The bulk of tissue histamine is bound in the granules of mast cells or basophils; it can be found outside mast cells in various tissues, including the brain, where it functions as a neurotransmitter. The bound form of histamine is biologically inactive. In immediate hypersensitivity reactions, as well as in cases when histamine liberators (substances that increase the release of histamine, such as morphine) are introduced into the body, the amount of free histamine increases.

The main receptor subtypes interacting with histamine are receptors H_1 – H_3 . The location and main effects of stimulating H_1 receptors are shown in Table 10.1.

H_2 receptors regulate the secretory activity of the gastric glands, cardiac activity, and lipid metabolism.

Table 10.1. Histamine H_1 receptors

Preferential location	Effects caused by stimulation
Bronchial smooth muscles	Increased tone
Intestinal smooth muscles	Increased tone
Heart	Inhibition of AV conduction

Arterial smooth muscles	Decreased tone
Venous smooth muscles	Increased tone
Capillaries	Increased permeability
CNS neurons	Regulation of sleep-wake cycles

Both types of receptors are present in blood vessels. In this regard, both H_1 and H_2 receptors are involved in the development of histamine-induced hypotension. Both types of histamine-sensitive receptors are found in the CNS. H_1 receptors are mainly concentrated in the CNS, on the presynaptic membrane of nerve endings and mast cell membranes. H_2 receptors are highly expressed in the bone marrow and regulate the release of neutrophils from the bone marrow.

H_1 receptor antagonists are nitrogenous bases containing an aliphatic side chain (like in a histamine molecule) of substituted ethylamine, which produces the antihistamine activity.

Classification

- ▶ First generation
 - Ethanolamines: diphenhydramine (Dimedrol*), clemastine (Tavegil*)
 - Ethylenediamines: chloropyramine (Suprastin*)
 - Phenothiazines: promethazine (Diprazin*, Pipolphen*)
 - Quinuclidines: quifenadine (Phencarol*)
 - Tetrahydrocarbolines: mebhydrolin (Diazolin*)
- ▶ Second generation: loratadine (Claritin*), cetirizine (Zyrtec*), ebastine (Kestin*)
- ▶ Third generation: fexofenadine (Telfast*), desloratadine (Aerius*), levocetirizine (Xyzal*)

Specifics of individual products by group

First generation

Mechanism of action: Binding to the receptor causes slower phospholipase C activation, which results in decreased formation of inositol trisphosphate and diacylglycerol from phosphatidylinositol; as a result, the release of Ca^{2+} ions from intracellular depots slows. Decreased release of Ca^{2+} ions from intracellular organelles into the cytoplasm in various types of cells leads to a decrease in the proportion of activated enzymes mediating the effects of histamine in these cells. These drugs have a significantly lower affinity for H_1 receptors than histamine, so they cannot displace histamine previously bound to the receptor. However, they can block unoccupied or released receptors, and when their concentration decreases, they are displaced by histamine from the complex with the receptors. These drugs are not selective: they affect other receptors (ACh receptors, serotonin receptors, ARs) and ion channels.

Pharmacological effects:

- ▶ Antihistamine effect: reduce capillary permeability, prevent tissue edema, prevent allergic reactions, reduce spasm of the bronchial and intestinal smooth muscles.

- ▶ Sedative effect: due to blockade of H_1 receptors in the brain region that consists of histaminergic neurons (tuberomammillary nucleus of the posterior hypothalamus) which synthesize, transport, and release histamine, and the histamine receptors it acts on. The sedative effect is also associated with blockade of central serotonin receptors and ACh receptors. These drugs block 50–90 % of histamine receptors in the CNS.
- ▶ Potentiating effect: applies to sedatives, hypnotics, general anesthetics, narcotic and non-narcotic analgesics.
- ▶ Antiemetic effect: associated with central cholinergic blocking action, reduction of vestibular receptor stimulation and inhibition of labyrinthine function.
- ▶ Vasodilator effect: due to blockade of α_1 ARs.
- ▶ Local anesthetic effect: due to decreased permeability of membranes for Na^+ ions.

Disadvantages: CNS depression; short duration of therapeutic action (1.5–6.0 hours); low bioavailability (due to first-pass elimination) and incomplete binding to H_1 receptors (30 %), resulting in the need for high therapeutic doses and frequent administration; lack of selectivity; tolerance.

Advantages: availability of parenteral forms to be administered in allergic reactions that require emergency care.

Therapeutic indications: immediate hypersensitivity reactions: urticaria, hay fever, vasomotor rhinitis, allergic conjunctivitis; angioedema (in combination therapy); as a component in the lytic cocktail; premedication; vomiting in pregnancy, Ménière's disease, motion sickness; insomnia. Not very effective in anaphylactic shock — the drug of choice is epinephrine.

Side effects: tachycardia, hypotension; dry mucous membranes, increased sputum viscosity; somnolence, decreased concentration and performance; obstipation, urinary retention; numb oral mucosa

Contraindications: intestinal atony, bladder atony, prostate adenoma, angle-closure glaucoma, pregnancy, breastfeeding

Given the sedative effect, there are restrictions related to the patient's occupation.

Diphenhydramine (Dimedrol*)

- ▶ Ethanolamine derivative. Marked antihistamine activity; lipophilic, crosses the BBB: exhibits sedative, hypnotic, potentiating, antiemetic action; exerts local anesthetic action, relaxes smooth muscles. Blocks neuronal AChRs of the autonomic ganglia, mAChRs.
- ▶ Bioavailability: 50 %, duration of action: 4–6 hours. Metabolized in the liver to form benzohydrol conjugated with glucuronic acid, excreted in the urine. $T_{1/2}$: 4–10 hours. For oral administration 1–3 times daily, for intramuscular, intravenous, topical administration.

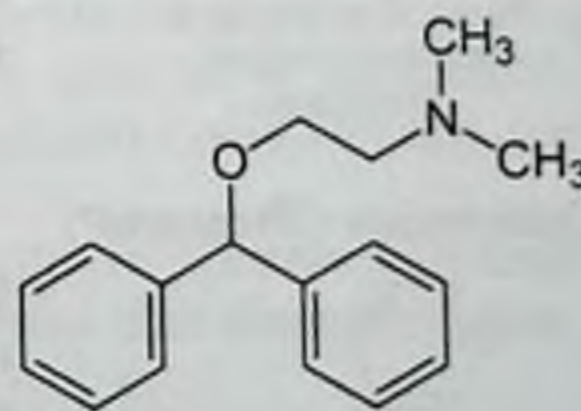


Fig. 10.7. 2-(Diphenylmethoxy)-N,N-dimethylethanamine (and as a hydrochloride))

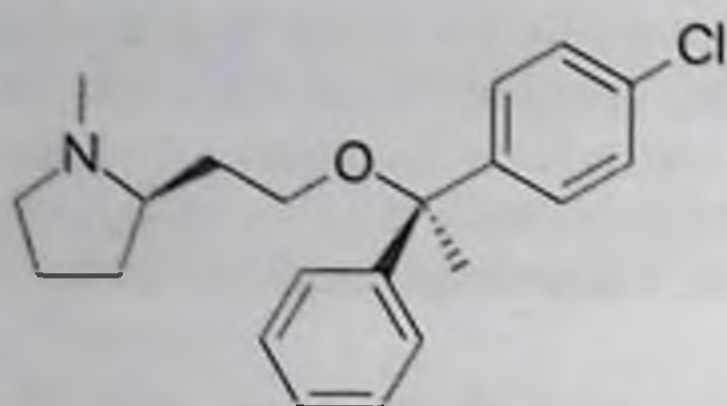


Fig. 10.8. (2R)-2-(2-((R)-1-(4-Chlorophenyl)-1-phenylethoxy)ethyl)-1-methylpyrrolidine (E)-butenedioate

Clemastine (Tavegil*)

Ethanolamine derivative, crosses the BBB. Its structure and pharmacological properties are similar to those of diphenhydramine (Dimedrol*), but its antihistamine activity is superior and it is longer acting (8–12 hours following a single dose); excreted in the urine predominantly as metabolites. For oral administration twice daily, for intramuscular, intravenous administration.

Chloropyramine (Suprastin*)

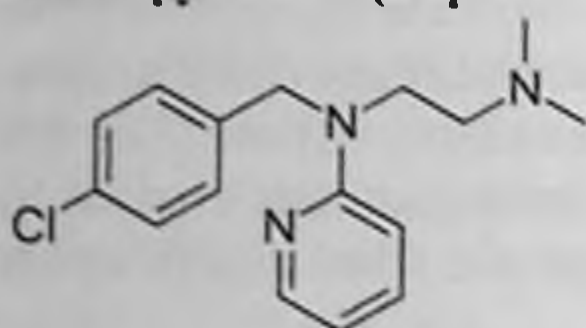


Fig. 10.9. N-[(4-Chlorophenyl)methyl]-N',N'-dimethyl-N-2-pyridinyl-1,2-ethanediamine (and as a hydrochloride)

- ▶ Ethylenediamine derivative; crosses the BBB. Exhibits anticholinergic and myotropic spasmolytic activity. Duration of action: 4–6 hours.
- ▶ Metabolized in the liver, excreted predominantly as metabolites in the urine. For oral administration 3–4 times daily, for intramuscular, intravenous administration.

Promethazine (Diprazin*, Pipolphen*)

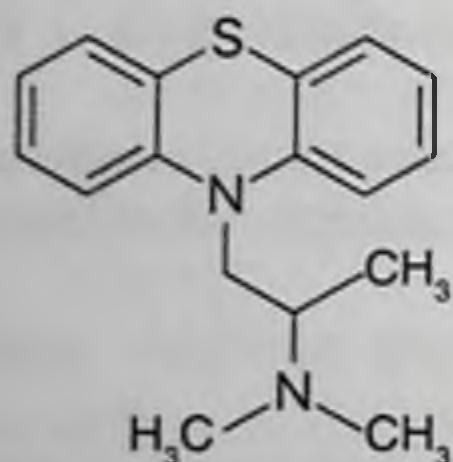


Fig. 10.10. N,N,α-Trimethyl-10H-phenothiazine-10-ethanamine (as a hydrochloride or camsylate)

- ▶ Phenothiazine derivative, crosses the BBB. Its structure and some of its pharmacological properties are similar to those of aminazine. Marked adrenergic blocking, sedative effect; decreases body temperature, prevents and relieves vomiting; exhibits moderate peripheral and central cholinergic blocking action. Duration of action: 4–6 hours.
- ▶ Metabolized in the liver to form promethazine sulfoxides, N-desmethyldiprazin. Metabolites are excreted in the urine, in the bile. $T_{1/2}$: 7–14 hours. For oral administration 3–4 times daily; for intramuscular, intravenous administration.

Quifenadine (Phencarol*)

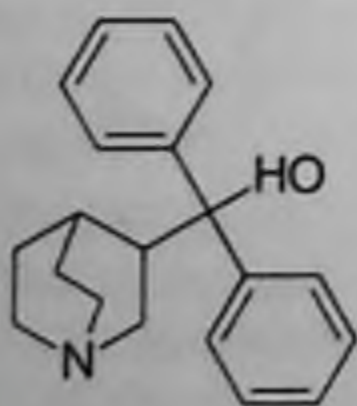


Fig. 10.11. α,α-Diphenyl-3-quinuclidinemethanol (and as a hydrochloride)

- ▶ Quinuclidine derivative, has low lipophilicity thus it does not easily cross the BBB and does not have a depressing effect on the CNS, “daytime” antihistamine. It also decreases the content of histamine in tissues by activating diamine oxidase that inactivates histamine. Does not exhibit adrenergic and cholinergic blocking activity. Bioavailability: 45 %, duration of action: 4–6 hours.
- ▶ Metabolized in the liver, excreted in the urine, in the bile. For oral administration 2–3 times daily; for intramuscular administration.

Mebhydrolin (Diazolin[®])

- ▶ Tetrahydrocarboline derivative, does not cross the BBB, "daytime" antihistamine. Bioavailability: 40–60 %. The drug poorly blocks mAChRs. A hepatic microsomal enzyme inducing drug.
- ▶ Undergoes biotransformation in the liver by methylation, excreted in the urine. Duration of action: 48 hours. $T_{1/2}$: 4 hours. For oral administration 1–2 times daily.

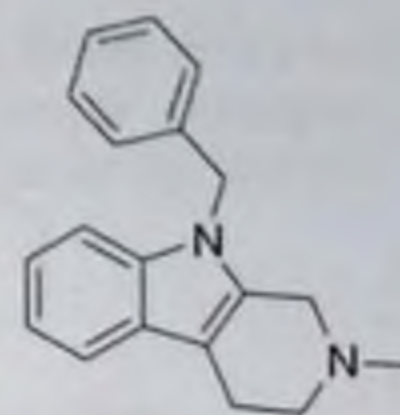


Fig. 10.12. 2,3,4,5-Tetrahydro-2-methyl-5-(phenylmethyl)-1H-pyrido[4,3-b]indole

Second generation

Mechanism of action: The drugs exhibit a high affinity for H_1 receptors; at high concentrations, histamine does not displace these drugs from the receptors.

Pharmacological effects:

- ▶ Antihistamine effect.
- ▶ Anti-inflammatory effect: inhibit the expression of nuclear factor κB regulating gene, which regulates the production of most proinflammatory cytokines and is activated via H_1 receptors even in the absence of histamine. These drugs suppress the activity of the nuclear factor κB , which stabilizes the membranes of mast cells, reduces the expression of adhesion molecules, suppresses the release of interleukin-8 induced by eosinophils, granulocyte-macrophage colony-stimulating factor.

Advantages

- ▶ Selective binding to H_1 receptors and no effect on other receptors.
- ▶ No sedative effect and no effect on cognitive functions at therapeutic doses due to poor penetration through the BBB, which is due to their lipophobicity, electrostatic charge and removal from the CNS by transport proteins (P-glycoprotein). These drugs bind to less than 20 % of central H_1 receptors.
- ▶ Duration of action: up to 24 hours, administered once daily. High bioavailability (90–95 %), absorption does not depend on food intake. Most of these drugs are metabolized: they produce an effect only after metabolism in the liver with the involvement of the CYP3A4 isoenzyme P450 to form active compounds; cetirizine is the only exception: it enters the body as an active substance and does not undergo metabolism.
- ▶ No tolerance during chronic use, which means they can be prescribed for long-term treatment; therapeutic effect may persist for 1 week after discontinuation.

Disadvantages

- ▶ Cardiotoxic effect: can block calcium channels on cardiac myocytes, which is associated with QT prolongation and cardiac rhythm disturbances (dose-dependent effect).
- ▶ No parenteral forms available.

Loratadine (Claritin[®])

- ▶ Tricyclic compound. Inhibits the release of histamine and LTC_4 from mast cells. Has anti-allergic, anti-exudative actions; relieves smooth muscle spasm.

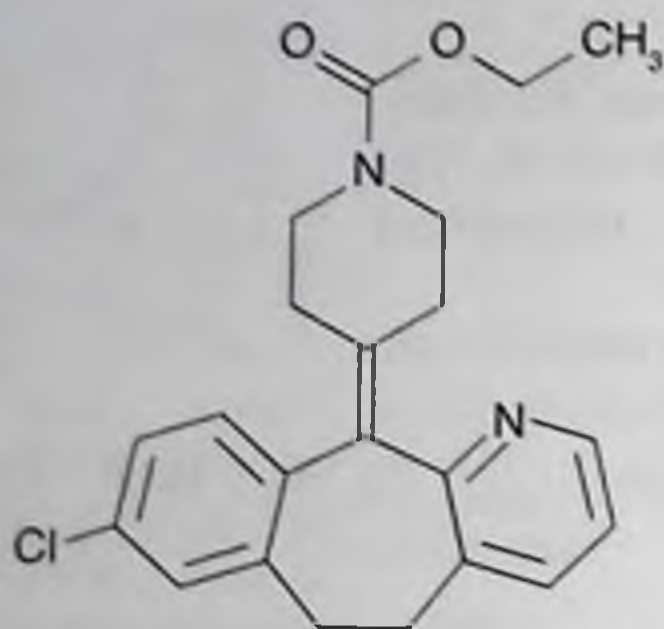


Fig. 10.13. 4-(8-Chloro-5,6-dihydro-11H-benzo-[5,6] cyclohepta [1,2-b]pyridin-11-ylidene)-1-piperidine-carboxylic acid ethyl ester

- ▶ Onset of action occurs in 30 min, reaches its maximum in 8–12 hours and lasts 24 hours.
- ▶ Biotransformation occurs in the liver by the cytochrome P450 system (predominantly CYP3A4 and to a lesser extent CYP2D6) to form the active metabolite descarboethoxyloratadine. Excreted in the urine and in the bile as hydroxylated metabolites and/or conjugates. $T_{1/2}$ of loratadine: 8.4 hours, $T_{1/2}$ of the active metabolite: 28 hours. For oral administration once daily.

Cetirizine (Zirtek[®])

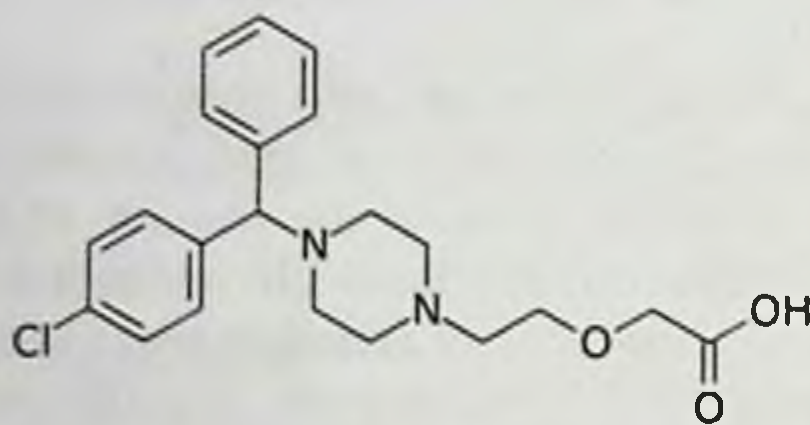


Fig. 10.14. [2-[4-[(4-Chlorophenyl) phenylmethyl]-1-piperazinyl]ethoxy]acetic acid (as a hydrochloride)

- ▶ Piperazine derivative, racemic mixture of L- and R-enantiomers, with the R-enantiomer levocetirizine having physiological activity.
- ▶ Maximum blood concentrations are reached in 1 hour.

Metabolized in small amounts by O-dealkylation to form an inactive metabolite, excreted in the urine (70 %) predominantly as unchanged drug. $T_{1/2}$: 4–10 hours. The action persists for up to 3 days after discontinuation. For oral administration once daily.

Ebastine (Kestin[®])

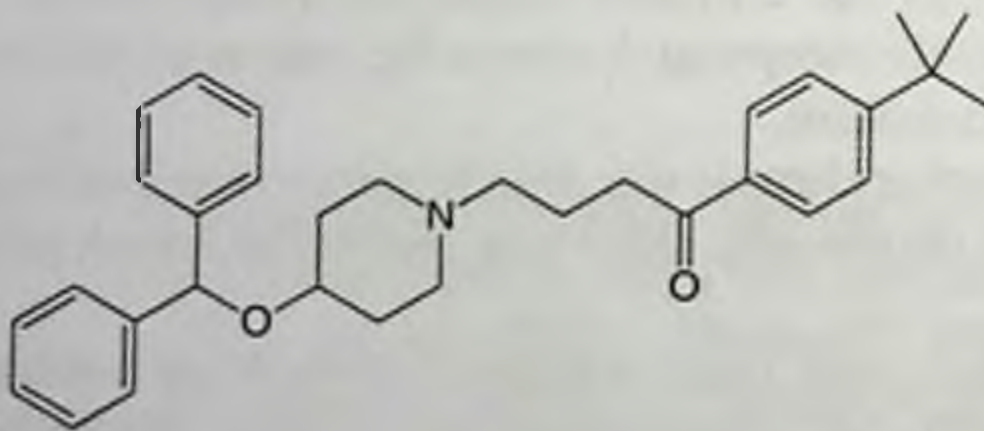


Fig. 10.15. 1-[4-(1,1-Dimethylethyl)phenyl]-4-[4-(diphenylmethoxy)-1-piperidinyl]-1-butanone

- ▶ Prevents histamine-induced smooth muscle spasms and increased vascular permeability. Does not affect the QT interval. Bioavailability: 90–95 %, the onset of action occurs in 1 hour and lasts 48 hours.

- ▶ Almost completely metabolized in the liver to form the active metabolite carebastine. 66 % of the drug is excreted in the urine as conjugates, $T_{1/2}$: 15–19 hours. The effect lasts 72 hours after treatment due to the action of the active metabolite. For oral administration once daily.

Third generation

Pharmacological effects: antihistamine effect, anti-inflammatory effect.

The active metabolites of second-generation drugs have better efficacy than third-generation drugs. However, third-generation drugs are better able to inhibit the early- and late-phase mediators of the allergic cascade, have a better safety profile, exert predictable effects and do not depend on cytochrome P450 enzymes. They do not produce cardiotoxic effects or sedation. Dose adjustment is not required in patients with hepatic or renal impairment.

Fexofenadine (Telfast*)

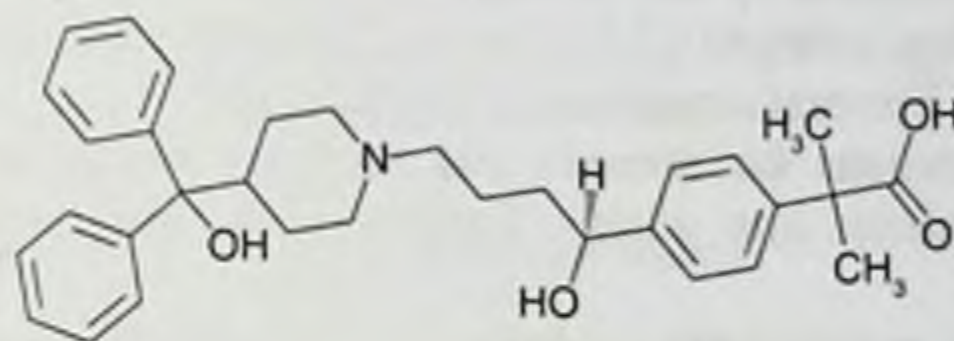


Fig.10.16.(±)-4-[1-Hydroxy-4-[4-(hydroxyphenylmethyl)-1-piperidinyl]butyl]- α,α -dimethylbenzeneacetic acid (and as a hydrochloride)

- ▶ Racemic mixture of two pharmacologically active isomers of the active metabolite terfenadine. Apart from blockade of H_1 receptors, it stabilizes the membranes of mast cells, preventing the release of histamine and other allergic mediators. The effect occurs in 1 hour, reaches its maximum in 6 hours, and lasts 24 hours.
- ▶ Not metabolized by the cytochrome P450 system, excreted in the bile (80 %) and urine (11 %). $T_{1/2}$: 14 hours. For oral administration twice daily.

Desloratadine (Aerius*)

- ▶ Inhibits the cascade of allergic inflammatory reactions, including the release of proinflammatory cytokines, interleukin-4, -6, -8, -13, production of superoxide anions by activated polymorphonuclear neutrophils, adhesion and chemotaxis of eosinophils, expression of adhesion molecules. Active metabolite of loratadine, maximum blood concentrations are reached in 3 hours.
- ▶ Metabolized in the liver by hydroxylation to form 3-OH-desloratadine and glucuronidation. Excreted predominantly as metabolites in the urine, also in the bile. $T_{1/2}$: 27 hours. For oral administration once daily.

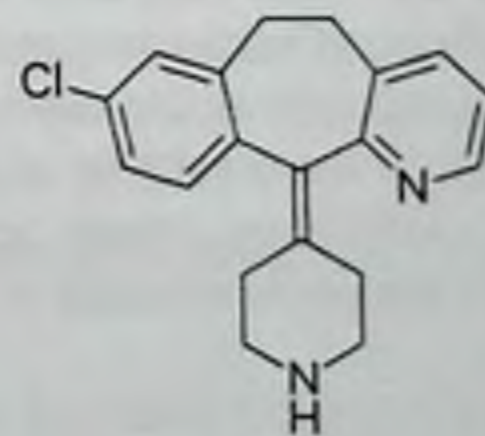


Fig. 10.17. 8-Chloro-6,11-dihydro-11-(4-piperidinyliden)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

Levocetirizine (Xyza®)

- ▶ Active R-enantiomer of cetirizine racemic compound. Bioavailability is absolute.

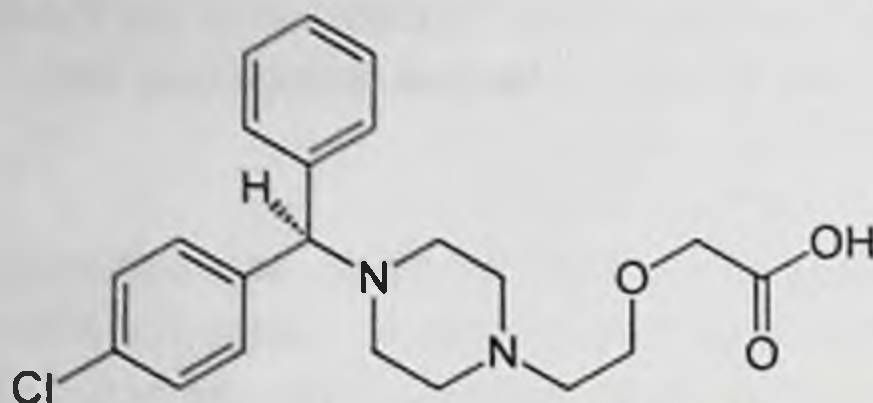


Fig. 10.18. 2-(2-[4-[(R)-(4-Chlorophenyl)(phenyl)methyl]piperazin-1-yl]ethoxy)acetic acid

- ▶ The extent of metabolism is less than 14 %; metabolic pathways include aromatic oxidation, N- and O-dealkylation, and taurine conjugation; dealkylation pathways are mediated by the cytochrome P450 isoenzyme CYP3A4; aromatic oxidation involves multiple CYP isoforms. Excreted predominantly in the urine. $T_{1/2}$: 8–9 hours. For oral administration once daily.

Therapeutic indications for second- and third-generation drugs: seasonal and perennial allergic rhinitis and allergic conjunctivitis, pollinosis, allergic contact dermatitis

Untoward effects: somnolence, tachycardia (dose-dependent effect in second-generation drugs), headache, dyspepsia

Contraindications: pregnancy, breastfeeding

Mast cell stabilizers

- ▶ Cromoglicic acid (Sodium cromoglicate^o, Intal[®])
- ▶ Nedocromil sodium (Taled[®])
- ▶ Ketotifen (Zaditen[®], Asthafen^o)

Mechanism of action: The drugs inhibit PDE activity and increase cAMP concentration inside the cell, prevent the opening of calcium channels and the entry of Ca^{2+} ions into mast cells; inhibit calcium-dependent cell degranulation and the release of histamine, platelet-activating factor, leukotrienes, lymphokines, and other biologically active substances that induce allergic and inflammatory reactions. They reduce the sensitivity of mast cells to the action of degranulation agents.

Combined, these actions prevent mast cell degranulation and the release of spasmogenic substances (Fig. 10.19).

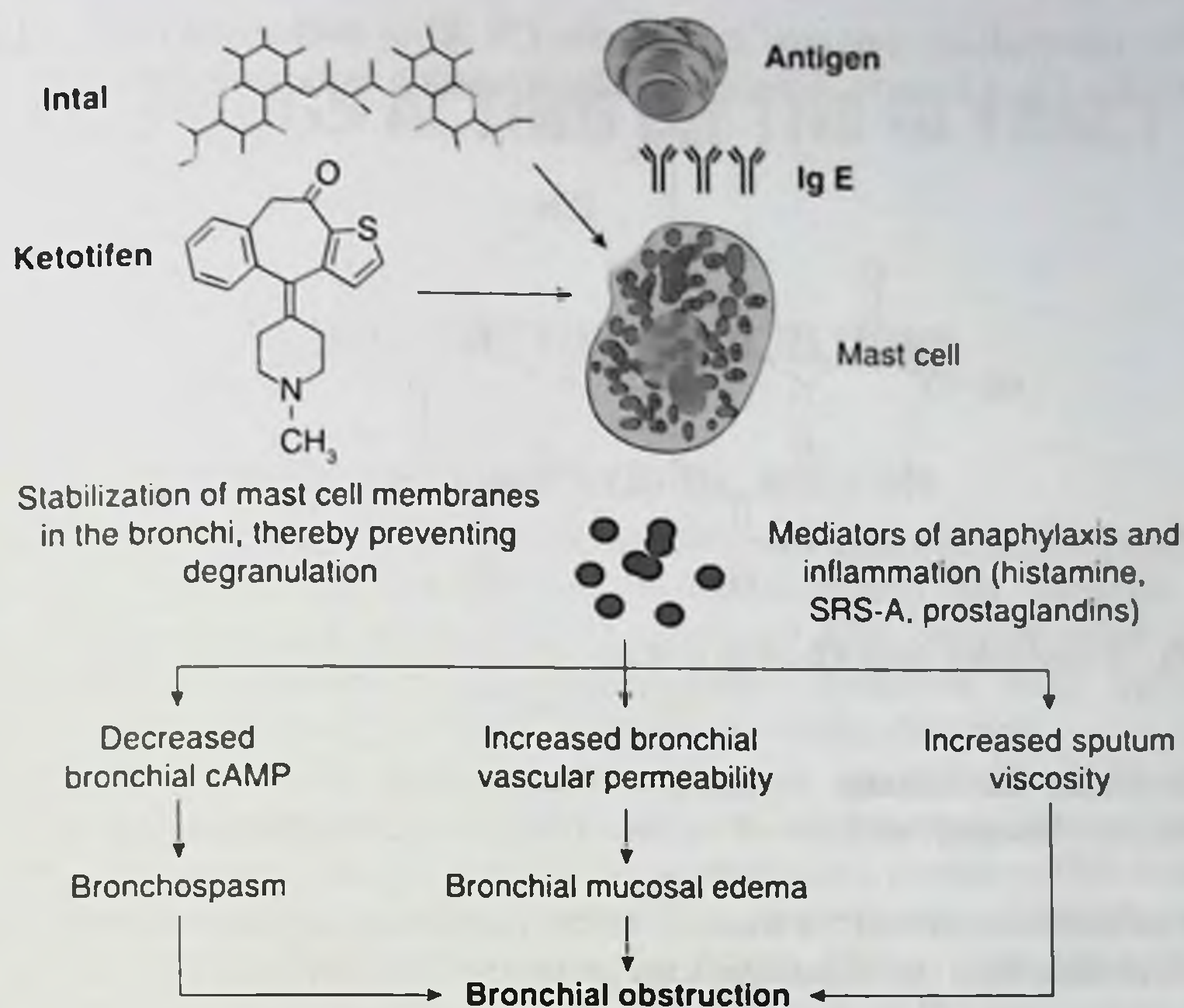


Fig. 10.19. Mechanism of action for mast cell stabilizers

Pharmacological effects: anti-allergic effect, anti-inflammatory effect

Specifics of individual products

Cromoglicic acid (Sodium cromoglicate[®], Intal[®])

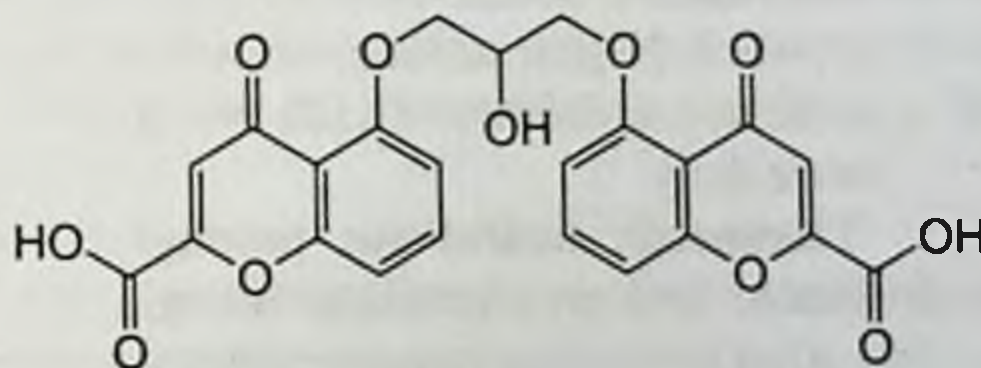


Fig. 10.20. 5,5'-[(2-Hydroxy-1,3-propanediyl)bis(oxy)]bis[4-oxo-4H-1-benzopyran-2-carboxylic acid (and as a disodium salt)

- ▶ When administered by inhalation, up to 90 % of the drug is deposited in the trachea and large bronchi; the effect develops in 2-4 weeks.
- ▶ Does not undergo metabolism, excreted in the urine and bile. $T_{1/2}$: 1.0–1.5 hours. Administered by inhalation 4 times daily (aerosol, solution, inhalation capsules).

Nedocromil sodium (Tailed[®])

- ▶ When administered by inhalation, the effect develops by the end of the first week. Its anti-inflammatory activity is 4–10 times higher than that of sodium cromoglicate.

- ▶ Not metabolized, excreted in the urine (70 %) as unchanged drug and in bile (30 %). $T_{1/2}$: 3.5 hours. Administered by inhalation twice daily (aerosol).

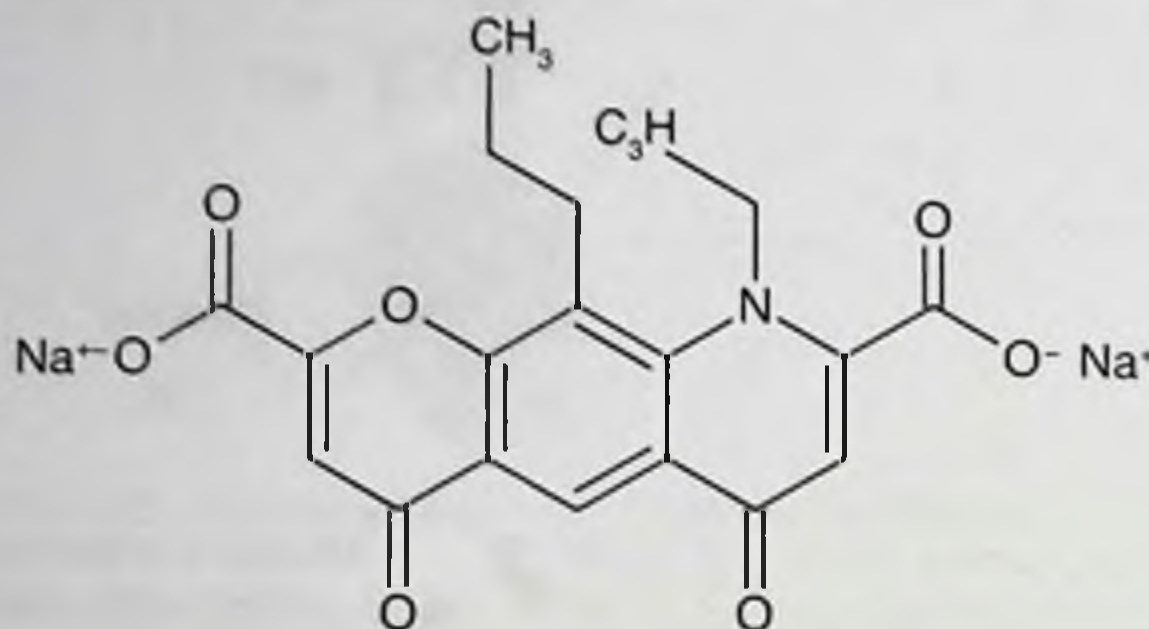


Fig. 10.21. 9-Ethyl-6,9-dihydro-4,6-dioxo-10-propyl-4H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid disodium salt

Therapeutic indications: respiratory diseases with reversible obstruction (in combination therapy): asthma of various types, bronchospasm caused by various factors

Side effects: irritation of the mucous membrane, cough, dry mouth, hoarseness

Contraindications: status asthmaticus, pregnancy, breastfeeding

Ketotifen (Zaditen[®], Asthafen[®])

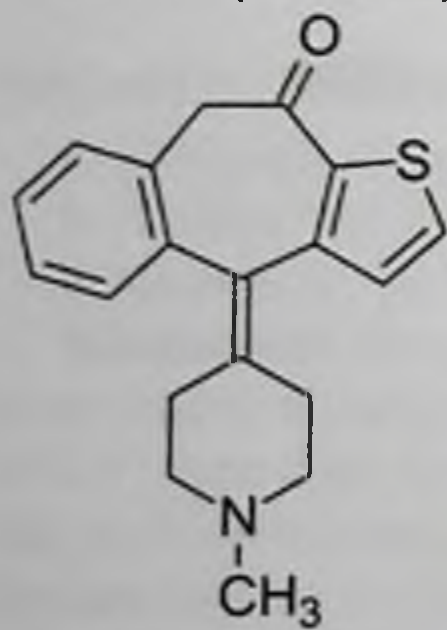


Fig. 10.22. 4,9-Dihydro-4-(1-methyl-4-piperidyl)-10H-benzo[4,5]cyclohepta[1,2-b]thiophen-10-one (as a fumarate)

- ▶ Its action consists of stabilizing the membranes of mast cells and blocking H₁ receptors. Bioavailability: 50 % due to the first-pass effect; maximum blood concentrations are reached in 2–4 hours, crosses the BBB, excreted into breast milk.
- ▶ Metabolized in the liver to form the inactive metabolite ketotifen-N-glucuronide; excreted predominantly in the urine as metabolites. $T_{1/2}$: 21 hours. For oral administration twice daily.

Therapeutic indications: prophylaxis of asthma attacks, treatment and prophylaxis of allergic rhinitis, conjunctivitis, and other immediate hypersensitivity reactions

Side effects: somnolence, fatigue, lethargy, thrombocytopenia

Contraindications: pregnancy, breastfeeding

Given the sedative effect, there are restrictions related to the patient's occupation.

11. DRUGS ACTING ON THE GI TRACT

DRUGS AFFECTING GI SECRETIONS

Antisecretory drugs, gastroprotectants, antacids

This is a group of drug products for treating acid-related disorders (gastroesophageal reflux disease, chronic gastritis, chronic duodenitis, gastric and duodenal ulcers, gastric and duodenal erosions and ulcers associated with administration of non-steroidal anti-inflammatory drugs, Zollinger–Ellison syndrome, etc.). *Helicobacter pylori* (*H. pylori*) is the most common cause of acid-related disorders.

The main stimulators of gastric acid secretion are histamine, gastrin and acetylcholine, which act through specific cellular receptors on the basement membrane of parietal cells: histamine (H_2), gastrin (G) and muscarinic receptors (M). Activation of these receptors in parietal cells increases the concentration of cAMP and Ca^{2+} ions, which activates tubulovesicles containing H^+/K^+ -ATPase (Fig. 11.1). The most important endogenous inhibitors of gastric acid secretion are PG and somatostatin.

Gastric mucosa protective factors

1. Mucus-bicarbonate barrier: Bicarbonates secreted by gastric and intestinal epithelial cells act as a buffer that maintains a neutral pH at the surface of the epithelium.
2. Epithelium regeneration: The resistance of the gastric and duodenal mucosa largely depends on the integrity and continuous renewal of the apical membrane of enterocytes. Repair of the gastric mucosa through epithelial cell division is promoted by PG, epidermal growth factor and TGF α (transforming growth factor- α).
3. Adequate blood flow
4. Immune protection: Secretory IgA that has a protective function when it comes to the mucous membranes.
5. PGs (cytoprotective agents): The gastric mucosa produces PGE $_2$ and PGI $_2$, which support the gastroduodenal mucosa's resistance due to their ability to inhibit gastric acid secretion, stimulate the production of mucus and the alkaline component of gastric juice, increase blood flow in the mucosa and its regenerative ability.

Mode of action: reduce gastric acid secretion (antisecretory drugs: proton pump inhibitors, histamine H_2 blockers, MRAs) increase the gastric mucosa's resistance to damaging factors (gastroprotectants) neutralize gastric acid (antacids) *H. pylori* eradication.

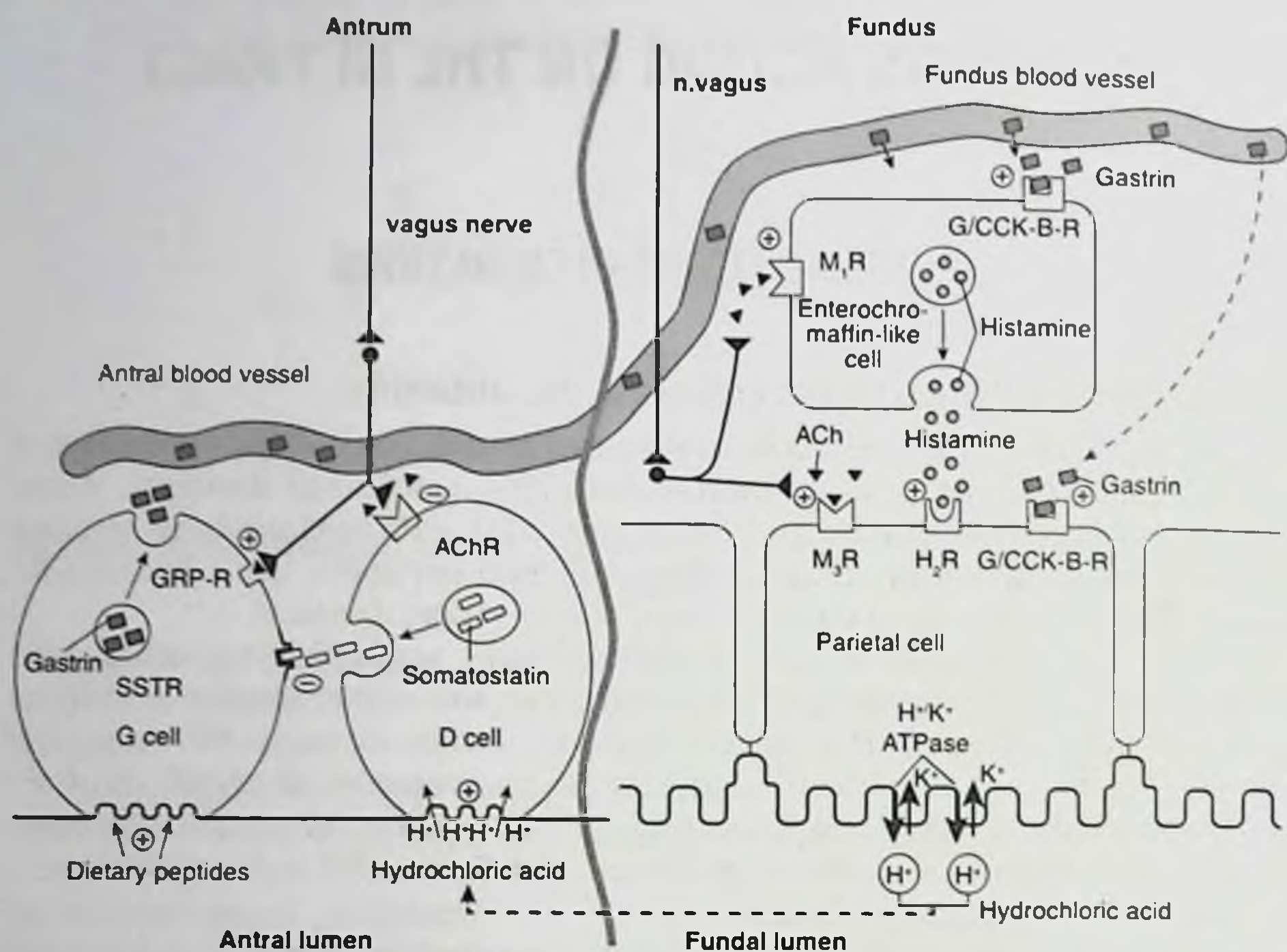


Fig. 11.1. Schematic of how gastric acid secretion is controlled by parietal cells in the stomach (Katzung B.G., 2009): GRP-R — gastrin releasing peptide receptors; AChR — acetylcholine receptors; SSTR — somatostatin receptor; G/CCKB-R — gastrin cholecystikinin B receptor; H₂-R — H₂ histamine receptor; M₁-R — muscarinic receptor 1; M₃-R — muscarinic receptor 3

Antisecretory drugs

Drug product groups: proton pump inhibitors (PPIs) (H⁺/K⁺-ATPase blockers), H₂ blockers, muscarinic receptor antagonists (MRAs).

Proton pump inhibitors (H⁺,K⁺-adenosine triphosphatase blockers)

These drug products reduce gastric acid secretion by blocking H⁺/K⁺-ATPase in the parietal cells of the gastric mucosa.

The first product in the PPI group, omeprazole under the trade name Losec, was synthesized in 1978 in Sweden by a group of researchers led by I. Östholm. Advances in the development of antisecretory drugs have led to a decrease in the number of surgeries in patients with peptic ulcers, in particular, vagotomy. At the Yale Gastroenterology Conference in 1993, it was agreed that vagotomy was no longer considered the treatment of choice for peptic ulcers.

Classification

- ▶ First generation: Omeprazole (Omez[®], Losec[®])
- ▶ Second generation: Lansoprazole (Lanzap[®])
- ▶ Third generation: Pantoprazole (Controloc[®])

- ▶ Fourth generation: Rabeprazole (Pariet®)
- ▶ Fifth generation: Esomeprazole (Nexium®)
- ▶ Combination DPs: Omez D® (domperidone, omeprazole)

All PPIs are benzimidazole derivatives and have a single molecular core. The various PPIs differ only in their chemical radicals, which determine the latent period duration, the time of action, the pH selectivity, and drug interactions with other concomitant products (Fig. 11.2). First-to-fourth-generation PPIs are 1:1 racemic mixtures of the R- and S-isomers, while fifth-generation PPIs are the S-isomer (which has higher bioavailability due to a smaller first-pass effect).

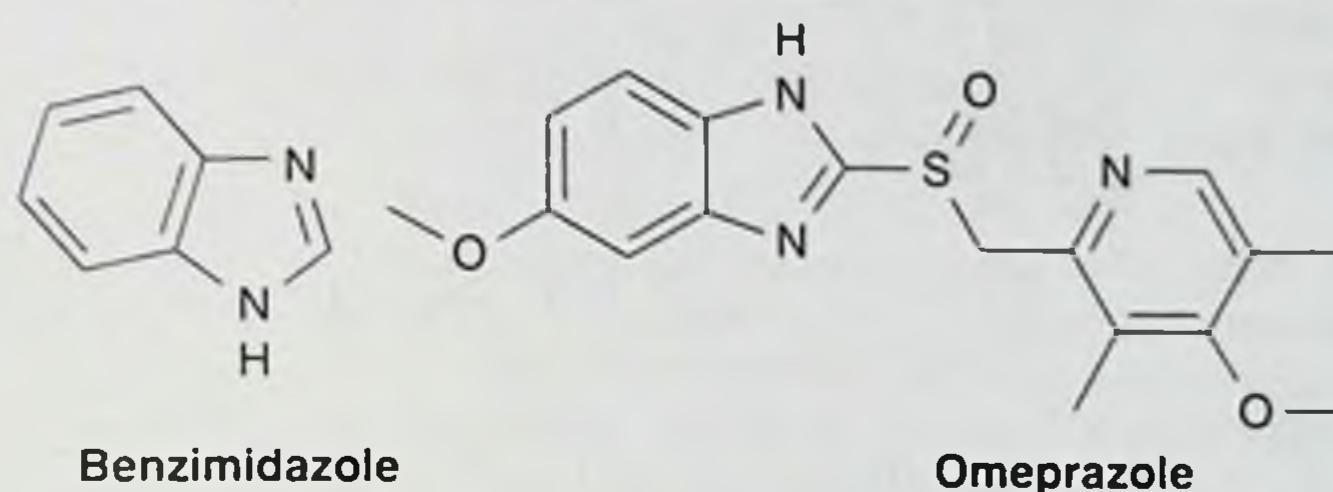


Fig. 11.2. Structural formulas of benzimidazole and omeprazole

Mechanism of action.

Hydrogen-potassium adenosine triphosphatase (H^+/K^+ -ATPase) is a proton pump that plays an important role in gastric acid secretion. H^+/K^+ -ATPase transports the H^+ ion from the parietal cell cytoplasm to the gastric cavity through the apical membrane in exchange for the K^+ ion transported inside the cell. In this case, both cations are transported against the electrochemical gradient. The energy source for this transport is hydrolysis of the ATP molecule. Along with H^+ ions, Cl^- ions are transported into the lumen of the stomach by active transport against the gradient. K^+ ions entering the cell leave it along the concentration gradient together with Cl^- ions through the apical membrane of parietal cells. H^+ protons are formed in equivalent quantities with HCO_3^- ions during the dissociation of carbonic acid H^2CO^3 with the involvement of the carbonic anhydrase enzyme. HCO_3^- ions passively move into the blood along the concentration gradient through the basolateral membrane in exchange for Cl^- ions. Thus, gastric acid is secreted into the lumen of the stomach with the involvement of H^+/K^+ -ATPase in the form of H^+ and Cl^- ions, and K^+ ions move from the interior to the exterior through the membrane. PPIs are weak-base prodrugs. The nitrogen on the pyridine ring of these compounds is able to bind the H^+ proton in an acidic environment. Protonation of the pyridine ring leads to intramolecular rearrangement when another ring is formed between the benzimidazole group and the pyridine ring, which includes a sulfur atom. The resulting sulfenamide ring is a highly reactive compound capable of interaction with the SH groups of proteins, in particular with the SH groups of the proton pump (Fig. 11.3). To convert the prodrug into a drug, the stomach's environment must be a sufficiently acidic.

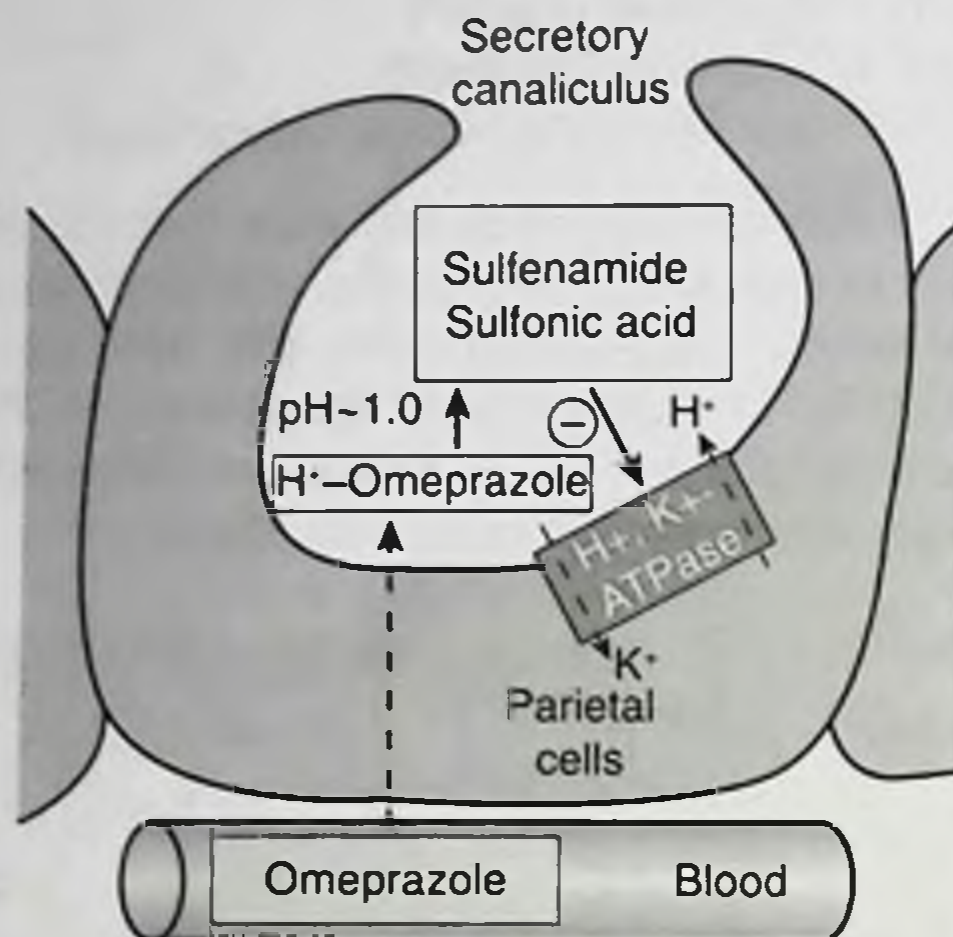


Fig. 11.3. Inhibitory effect of omeprazole metabolites on the proton pump ($H^+/K^+-ATPase$) of gastric parietal cells (Kharkevich D.A., 2021)

Stages of PPI action (Fig. 11.4)

1. Intestinal absorption with penetration into the systemic circulation. Oral tablets or granules containing PPIs have an acid-resistant coating that dissolves in a slightly alkaline environment. That is why they pass intact through the lumen of the stomach with its acidic contents. The coating of tablets or granules quickly disintegrates in a slightly alkaline environment of the small intestine, after which PPIs are absorbed and enter the bloodstream.
2. High PPI concentration in the canaliculi of parietal cells.
3. Proton binding in the acidic environment of the canaliculi. Once in an acidic environment, PPIs bind a proton, become charged and then lose their ability to cross membranes. PPIs selectively accumulate in intermembrane spaces where they are protonated, mainly in the canaliculi of parietal cells, where the pH is approximately 2.0. during digestion.
4. Conversion from prodrug to drug (PPI activation by acid).
5. Covalent binding to SH groups of the proton pump, leading to its inhibition.

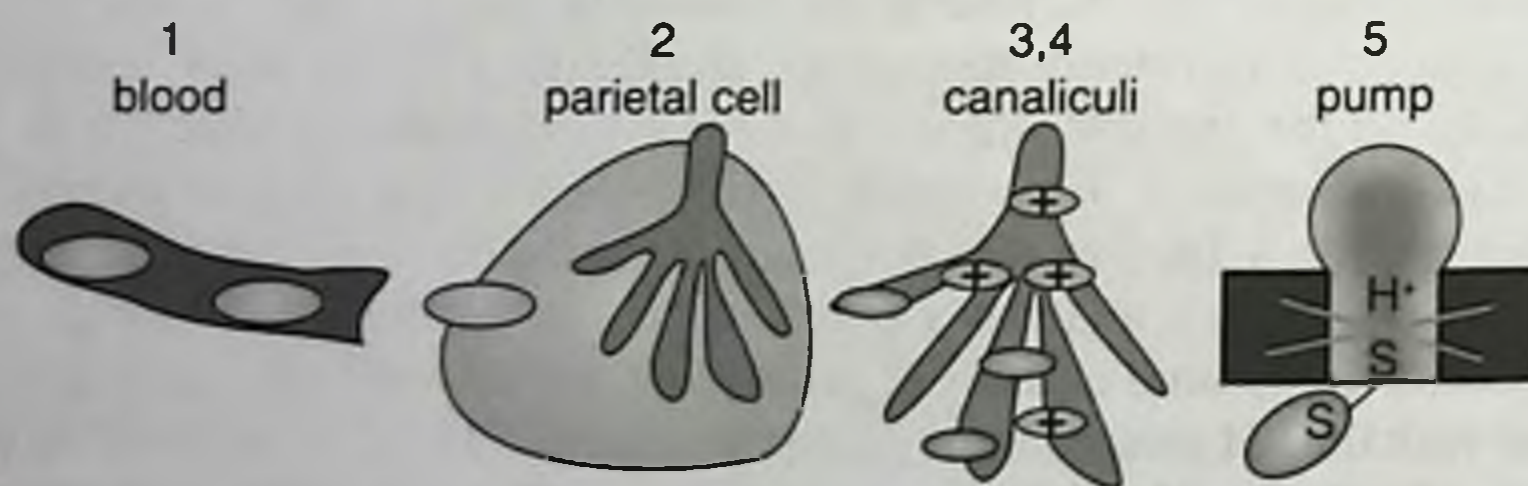


Fig. 11.4. Main stages of action of proton pump inhibitors (Lopina O.S., 2016)

Conversion of prodrugs (PPI) into DPs and inhibition of proton pumps, from highest to lowest:

esomeprazole > rabeprazole > lansoprazole > omeprazole > pantoprazole

Features of PPIs: PPIs occupy a central position among anti-ulcer agents. Their antisecretory activity is significantly higher than other DPs that reduce gastric acid secretion. The duration of a PPIs effective antisecretory action is determined by the fact that all blocked H^+/K^+ -ATPases are replaced in the cell with new ones in 72–96 hours (and half of the H^+/K^+ -ATPases are replaced in 30–48 hours), which is much more than the time of action of any other anti-ulcer agent. Since they have anti-*Helicobacter* activity, they are an integral component of *H. pylori* eradication schemes. They reduce basal and stimulated secretion, regardless of the nature of the stimulus. They are characterized by a high level of activation in an acidic environment. Unlike H_2 blockers, there is no rebound effect.

The widespread use of omeprazole led to the emergence of the term “omeprazole resistance” in modern gastroenterology. Resistance to omeprazole means the pH in the body of the stomach is maintained below 4.0 for more than 12 hours with daily pH monitoring after a double standard dose of the product. The resistance to PPI in adults from 25.7 % to 42.4 % on the first day of dosing, and from 5.6 % to 27.8 % on the 4th day.

Nocturnal acid breakthrough is a nocturnal decrease in pH below 4.0 for at least 1 hour, which occurs in 70% of patients, including healthy patients, regardless of a PPI. This phenomenon is explained by the fact that in the evening, at the time of the PPI dosing, not all patients have all H^+/K^+ -ATPases in the active state and PPIs do not affect non-activated H^+/K^+ -ATPases. Since the PPI elimination time is about 1.0–1.5 hours, the PPI is already eliminated by the time H^+/K^+ -ATPases are activated, thus H^+/K^+ -ATPases activated at night begin to secrete hydrochloric acid. Nocturnal acid breakthrough is not associated with the resistance to some PPIs.

Therapeutic indications: treatment and prevention of gastric and duodenal ulcers; eradication therapy for *H. pylori* with gastric and duodenal ulcers (in combination therapy only); NSAID-associated gastric and duodenal ulcers; stress ulcers, gastroesophageal reflux; Zollinger–Ellison syndrome

Side effects: dyspepsia, elevated liver transaminases, headache, dizziness, sleep disturbances, edema, impotence, alopecia, acne, allergic reactions.

Contraindications: severe renal and/or hepatic impairment, pregnancy, breastfeeding, allergic reactions

Specifics of individual products

Omeprazole (Omez⁺, Losec⁺)

The antisecretory effect occurs within 1 hour after oral administration, reaching a maximum in 2 hours. Bioavailability: 30–40%. It is an inhibitor of the cytochrome P450 isoenzyme, CYP2C19. $T_{1/2}$: 0.5–1.0 hours. Metabolized in the liver with the involvement of the CYP2C19 enzyme system. Excreted in the urine (70–80%) and bile (20–30%). For oral administration (once daily), for intravenous administration.

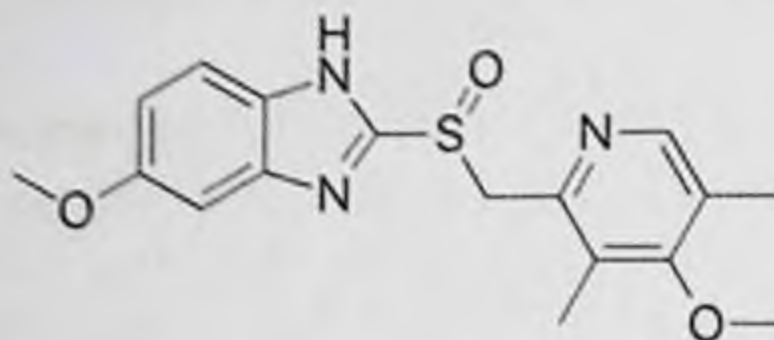


Fig. 11.5. (RS)-5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]-1H-benzimidazole

Lansoprazole (Lanzap[®])

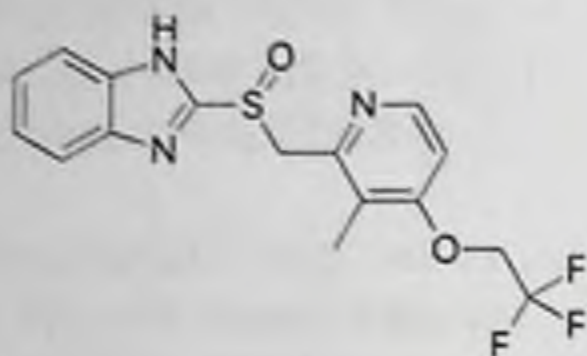


Fig. 11.6. (RS)-2-[(3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methylsulfinyl]-1H-benzimidazole

Food intake reduces absorption and bioavailability, but the inhibitory effect on gastric secretion is the same with or without food. The inhibitory effect increases over the first 4 days of administration. After discontinuation, acidity remains below 50% of the basal level for 39 hours. $T_{1/2}$: 1.3–1.7 hours, excreted in the urine as metabolites (14–23%) and in the feces. For oral administration once daily.

Pantoprazole (Controloc[®])

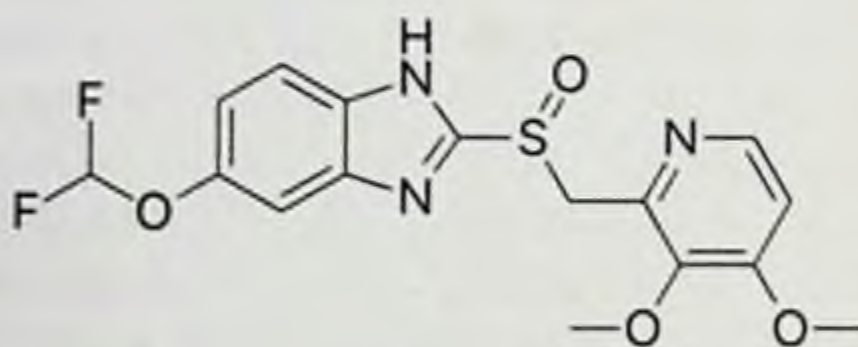


Fig. 11.7. (RS)-5-(Difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methylsulfinyl]-3H-benzimidazole

The therapeutic effect after a single dose occurs rapidly and lasts 24 hours. Bioavailability: 65–77%, antacids or food intake do not affect the product's bioavailability. $T_{1/2}$: 0.9–1.9 hours. Excreted predominantly in the urine (82%) as metabolites. For oral administration 1–2 times daily, for intravenous administration.

H₂ blockers

These drug products reduce gastric acid secretion by blocking H₂ receptors in the parietal cells of the gastric mucosa.

H₂ blockers are similar to histamine in their chemical structure but differ in a heavy aromatic portion or a change in aliphatic radicals (Fig. 11.8). Cimetidine contains an imidazole heterocycle as the molecule base, ranitidine belongs to furan derivatives, famotidine and nizatidine are thiazole derivatives.

At the beginning of the 20th century, the English pharmacologist and physiologist H. Dale (Fig. 11.9) and the English chemist G. Barger discovered a previously unknown biologically active substance that was later identified as β -imidazolyethylamine and named histamine. A few years later, in animal experiments, H. Dale found that the administration of histamine contributed to the development of peptic ulcers by increasing gastric secretion.

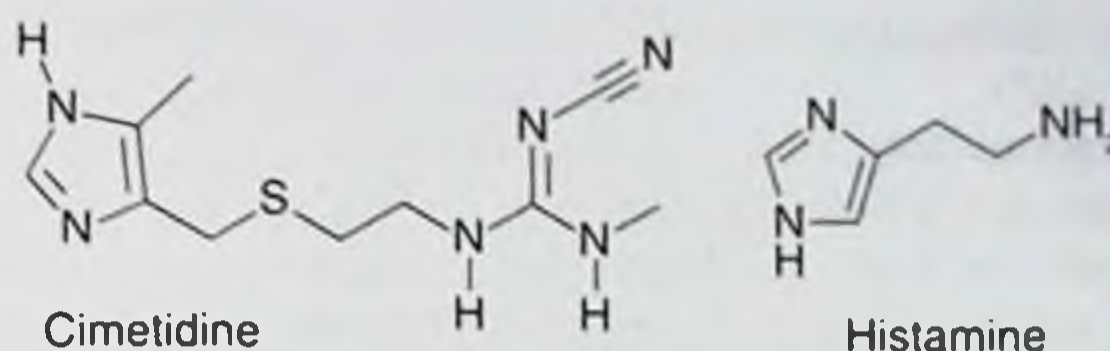


Fig. 11.8. Comparison of the structural formula of histamine and cimetidine



Fig. 11.9. Henry Hallett Dale (June 9, 1875 – July 23, 1968) was an English pharmacologist and physiologist who was awarded the 1936 Nobel Prize in Physiology or Medicine for studying acetylcholine (jointly with O. Loewi)

In 1972, the Scottish pharmacologist J. Black (Fig. 11.10), after having tried more than 700 different structures, found that a burimamide compound containing an imidazole ring in the side chain acts on gastric receptors (later named H_2 receptors). J. Black was awarded the Nobel Prize in 1988 for identifying H_2 receptors and developing DPs that block them.

Cimetidine appeared in 1975, ranitidine in 1979, famotidine in 1984, and nizatidine in 1987. H_2 blockers immediately became the gold standard for treating acid-related disorders (and ranitidine was the best-selling prescription product by 1988) and remained so until the advent of PPIs.

Classification

- ▶ First generation: cimetidine (excluded from the Russian State Register of Drug Products)

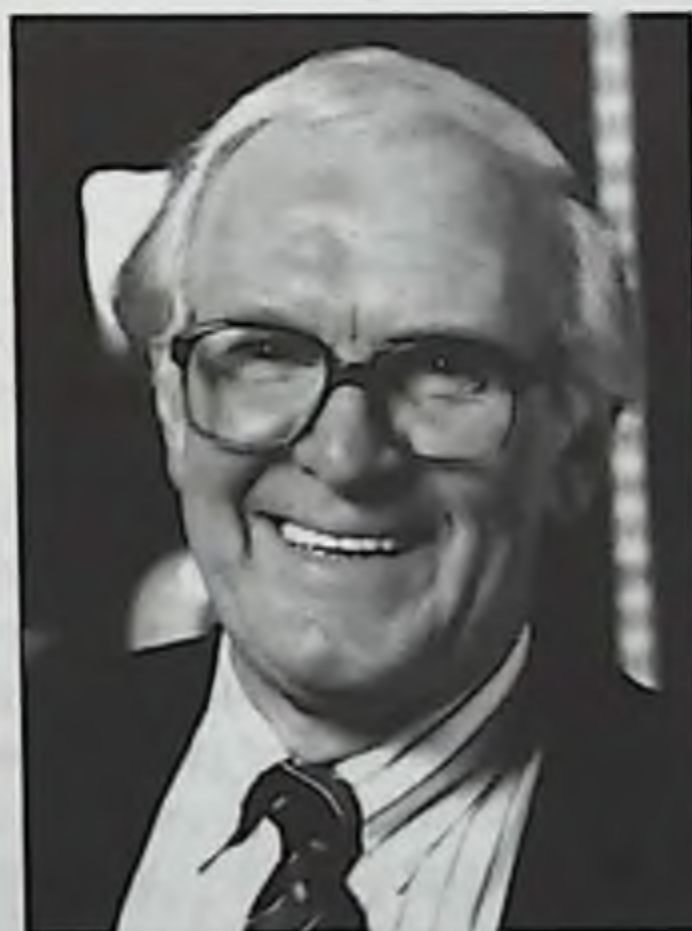


Fig. 11.10. James Whyte Black (June 14, 1924 – March 22, 2010) was a Scottish pharmacologist. Studies by Black led to the advent of a new class of anti-ulcer agents — histamine H_2 receptor antagonists — as well as the beta-blocker ANAPRILIN® (Propranolol). He was awarded the 1988 Nobel Prize in Physiology or Medicine

- ▶ Second generation: ranitidine (Zantac[®], Rantac[®], Rintid[®]), ranitidine bismuth citrate (Pylorid[®])
- ▶ Third generation: famotidine (Quamatel[®])
- ▶ Fourth generation: nizatidine (Axid[®])
- ▶ Fifth generation: roxatidine (Roxan[®])

The H_2 receptor is an integral membrane protein, one of the four histamine receptors, which belongs to the group of rhodopsin-like G-protein-coupled receptors. It is activated by binding histamine, bound to adenylate cyclase through the G-protein, a stimulator of cAMP generation, which activates protein kinase A. H_2 receptors are located on the parietal (aka oxyntic, delomorphous) cells of the stomach, vascular smooth muscles, neutrophils, mast cells, heart, uterus, CNS (caudate nucleus, cerebral cortex, hippocampus, dentate nucleus of the cerebellum). Activation of the H_2 receptor stimulates gastric juice secretion (the goal of antihistamines acting on H_2 receptors in peptic ulcer and gastroesophageal reflux disease).

Mechanism of action: Competitive antagonist of H_2 receptors in the parietal cells, which is accompanied by a decrease in basal and stimulated gastric secretion, inhibition of pepsin production.

Features of H_2 blockers: They cross the blood-tissue barriers well, including the placental one, but not the BBB due to low lipophilicity. They are excreted predominantly unchanged, mainly in the urine (Table 11.1).

Table 11.1. Pharmacokinetics of H_2 blocker

Parameter	Cimetidine	Ranitidine	Famotidine	Roxatidine
Bioavailability, %	60–80	50–60	30–50	90–100
T _{1/2} , hours	2	2	3.5	6
Therapeutic concentration, ng/mL	500–600	100–200	20–40	200
Inhibition of acid secretion, %	50	70	70	70
Renal excretion, %	50–70	50	50	50

Therapeutic indications: esophageal ulcers, gastroesophageal reflux, gastric and duodenal ulcers, Zollinger–Ellison syndrome, prevention of stress ulcers, pancreatitis (famotidine)

Side effects (mainly for first-generation and second-generation products):

- ▶ abdominal pain, diarrhea occurs due to the antisecretory action — suppression of hydrochloric acid secretion increases the stomach's pH preventing the conversion of pepsinogen into pepsin, which is involved in the breakdown of food proteins; decreased production of gastric juice and blockade of pancreatic H_2 receptors reduce the secretion of digestive enzymes from the pancreas and bile
- ▶ antiandrogenic effect: associated with the ability of H_2 blockers to displace endogenous testosterone from binding to receptors; this is observed with long-term use and manifests as increased blood prolactin levels, the development of galactorrhea, amenorrhea; gynecomastia, impotence, decreased number of spermatozoa
- ▶ inhibition of hepatic microsomal enzymes; hepatotoxicity evidenced by elevated aminotransferases and decreased blood flow in the liver

- ▶ headache, anxiety, fatigue, depression, hallucinations, confusion: associated with blockade of H_2 receptors in the CNS
- ▶ cardiotoxicity: associated with blockade of myocardial H_2 receptors, accompanied by sick sinus syndrome, arrhythmias, CAD aggravation
- ▶ nephrotoxicity: increased serum creatinine levels
- ▶ inhibition of the Castle's intrinsic factor production and decreased absorption of vitamin B_{12} , leuko- and thrombocytopenia
- ▶ rebound syndrome (withdrawal syndrome): when H_2 blockers are abruptly discontinued, acidity increases and, as a result, the disease is exacerbated
- ▶ allergic reactions.

Contraindications: pregnancy, breastfeeding, allergic reactions

Some of the basic characteristics of H_2 blockers are worse than proton pump inhibitors, without surpassing them in others. However, PPIs have a number of disadvantages, including a high percentage of patients being resistant to certain PPIs and a risk of nocturnal acid breakthrough; therefore, H_2 blockers are preferable to PPIs in a number of patients.

Specifics of individual products

Cimetidine

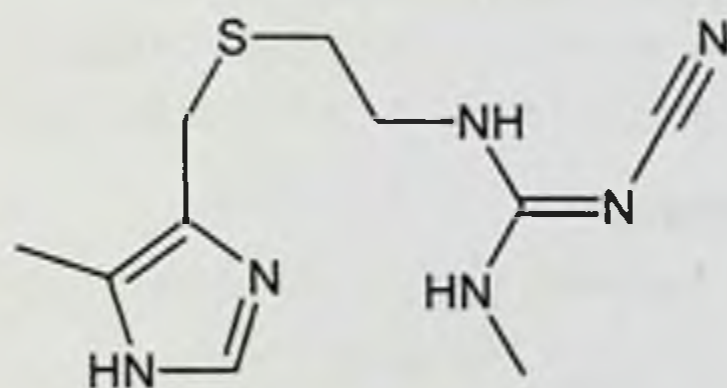


Fig. 11.11. N-Cyano-N'-methyl-N'-[2-[[[(5-methyl-1H-imidazol-4-yl)methyl]thio]ethyl]guanidine

Excluded from the Russian State Register of Drug Products.

- ▶ Its activity, selectivity and time of action are inferior to ranitidine (5–10-fold). After oral administration, the therapeutic effect persists for 4–5 hours.
- ▶ Currently not used in clinical practice due to side effects and low efficacy.

Ranitidine (Zantac[®], Rantac[®], Rintid[®])

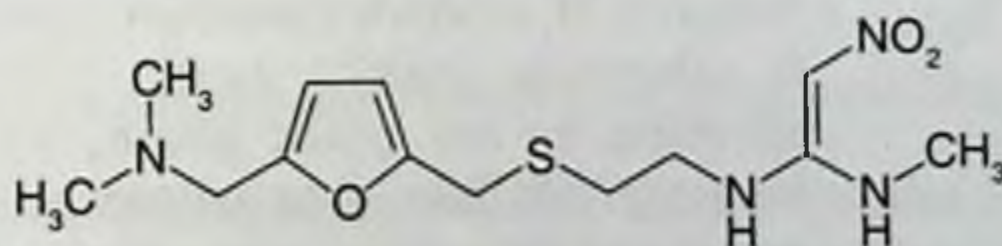


Fig. 11.12. N-2-5-(Dimethylamino)methylfurfuryl-thio-ethyl-N'-methyl-2-nitro-1,1-ethylenediamine

Has nearly no antiandrogenic effect but slightly affects the activity of hepatic microsomal enzymes. Bioavailability: 50% (first-pass effect). Time of action: up to 10–12 hours. Metabolized in the liver to form desmethyl ranitidine and S-oxyranitidine. $T_{1/2}$: 2–3 hours. Excreted mainly in the urine. For oral, intravenous, intramuscular administration.

Ranitidine bismuth citrate (Pylorid[®])

Fixed-dose combination of ranitidine (base), trivalent bismuth and citrate in a weight ratio of 81:64:55 that dissociates into separate components in the stomach. It has a combined effect: ranitidine blocks H₂ receptors in the parietal cells of the stomach and inhibits basal (day and night) and stimulated gastric acid secretion, while bismuth citrate has a protective (astringent) effect on the gastric mucosa and bactericidal effect on *H. pylori*. For oral administration.

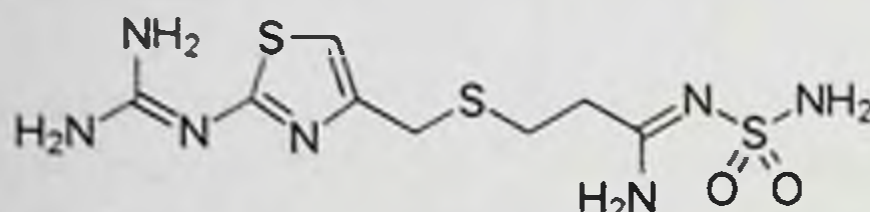
Famotidine (Quamatel[®])

Fig.11.133-[(2-[(Diaminomethylidene)amino]-1,3-thiazol-4-yl)methyl)sulfanyl]-N-sulfamoyl-propanimidamide

It is more active than ranitidine, a single oral dose suppresses secretion for 10–12 hours. No antiandrogenic effect. It does not affect hepatic microsomal enzymes. It does not change serum gastrin levels. Bioavailability: 40–45%. Metabolized in the liver to form S-oxide. T_{1/2}: 2.5–4 hours. Excreted mainly in the urine: 27–40% unchanged. For oral and intravenous administration.

Fourth- and fifth-generation H₂ blockers, nizatidine and roxatidine, are comparable in their efficacy and frequency of side effects to famotidine.

Muscarinic receptor antagonists

They inhibit gastric acid secretion by preventing ACh-mediated stimulation of the vagal nerve fibers.

Classification

1. Muscarinic receptor antagonists: atropine (Atropine sulfate[®]), metocinium iodide (Methacin[®]), platyphylline (Platyphylline hydrotartrate[®])
2. M₁ selective antagonists: pirenzepine (Gastrozepin[®])

MRAs, due to a weak effect on gastric acid secretion and multiple atropine-like effects on other systems and organs, are rarely used to treat gastric disorders in current practice.

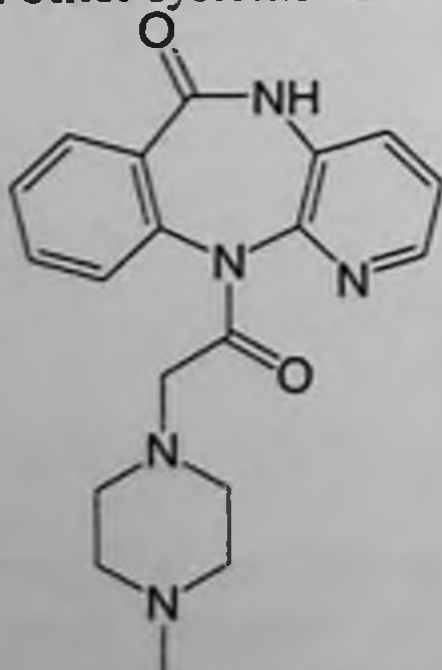


Fig. 11.14. 5,11-Dihydro-11-[(4-methyl-1-piperazinyl)acetyl]-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one (as a dihydrochloride)

Pirenzepine (Gastrozepin[®])

- ▶ Selective M₁ receptor antagonist. Unlike typical blockers, it selectively inhibits gastric acid and pepsinogen secretion by the gastric glands, without significantly blocking mAChRs of the salivary glands, heart, smooth muscles of the eye and other organs.
- ▶ Bioavailability: 20–30%, decreases when taken with food. Insignificant amounts are metabolized in the liver. T_{1/2}: 10–12 hours. Excreted in the urine (10%), the rest is excreted in bile. For oral, intramuscular, intravenous administration.

Mechanism of action: It blocks M_1 receptors at the level of intramural ganglia and turns off the vagus nerve's ability to stimulate gastric secretion.

For side effects and contraindications, see section "Cholinergic blockers".

Gastroprotectants

A group of drug products that act directly on the gastric mucosa and prevent it from being damaged by chemical or physical factors (acids, bases, enzymes, etc.).

Classification

1. Drug products that help protect the mucous membrane (ulcerative surface):
sucralfate (Venter*), bismuth tripotassium dicitrate (De-Nol*)
2. Drug products that enhance the protective function of the mucosal barrier and its resistance to damaging factors: misoprostol (cytotec*), rebamipide

Specifics of individual products

Sucralfate (Venter*)

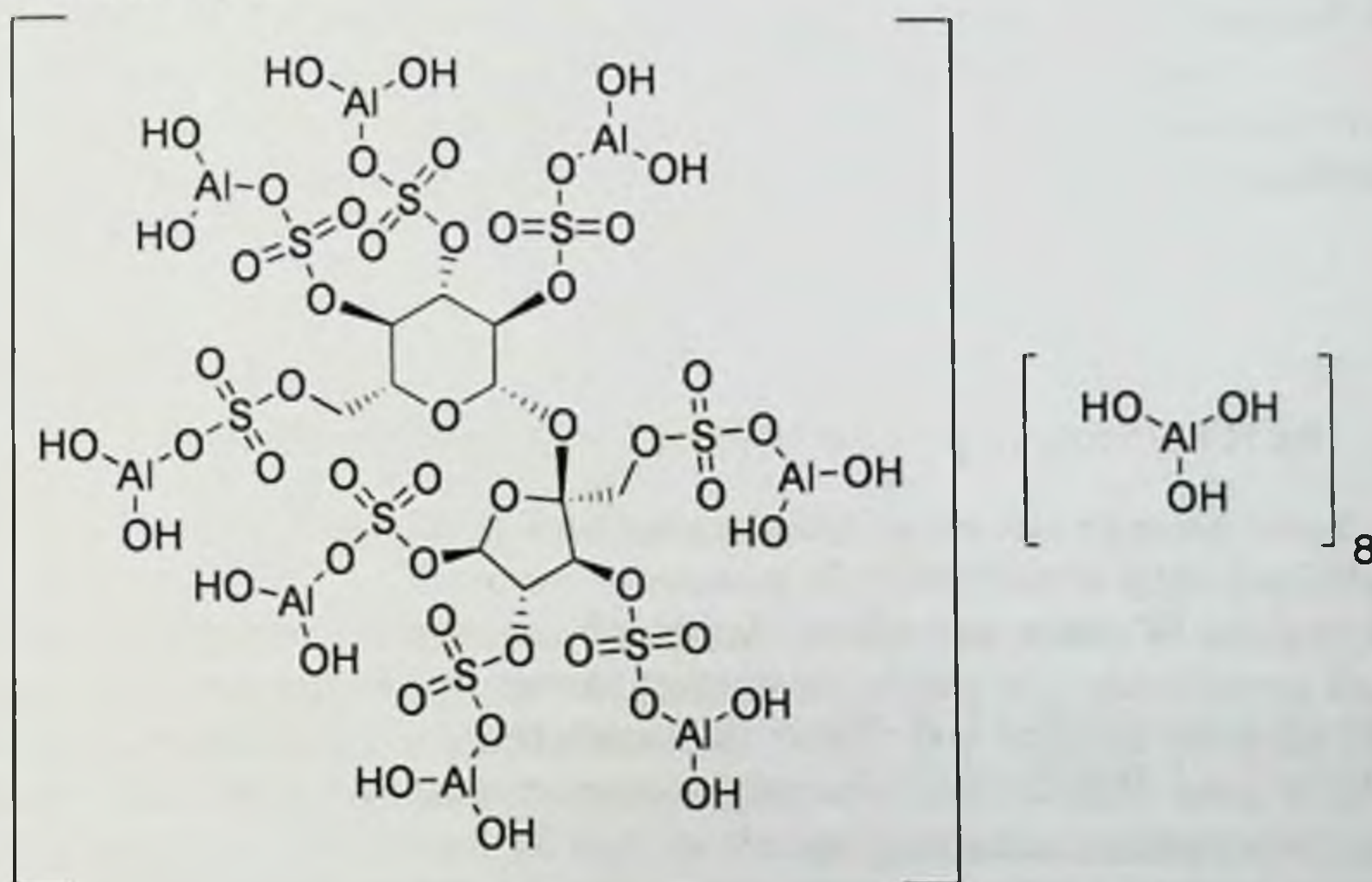


Fig. 11.15. β -D-Fructofuranosyl- α -D-glucopyranoside octakis(hydrogen sulfate) aluminum complex

- Sulfated disaccharide, aluminum sucrose sulfate complex. It has some chemical similarity to heparin sodium but lacks its anticoagulant properties.
- Bioavailability: 5%, not metabolized, excreted unchanged mainly in bile. For oral administration 3–4 times daily, 30 min – 1 hour before meals.

Mechanism of action: In the acidic environment of the stomach (at pH below 4.0), it dissociates into aluminum and sucrose sulfate; the former denatures mucus proteins and the latter binds to them, becomes fixed on the necrotic masses of the ulcerative lesion, and forms a protective film, which acts as a barrier to pepsin, hydrochloric acid and refluxed bile. It adsorbs bile acids, waste products of the gastrointestinal

microflora, reduces the local inflammatory process. The protective layer remains intact for up to 8 hours in the stomach and about 4 hours in the duodenum.

Therapeutic indications: gastric and duodenal ulcers, reflux esophagitis, hyperacid gastritis

Side effects: dry mouth, nausea, obstipation, allergic reactions

Contraindications: dysphagia, gastrointestinal obstruction, gastrointestinal hemorrhage, severe renal impairment, allergic reactions

Bismuth tripotassium dicitrate (De-Nol[®])

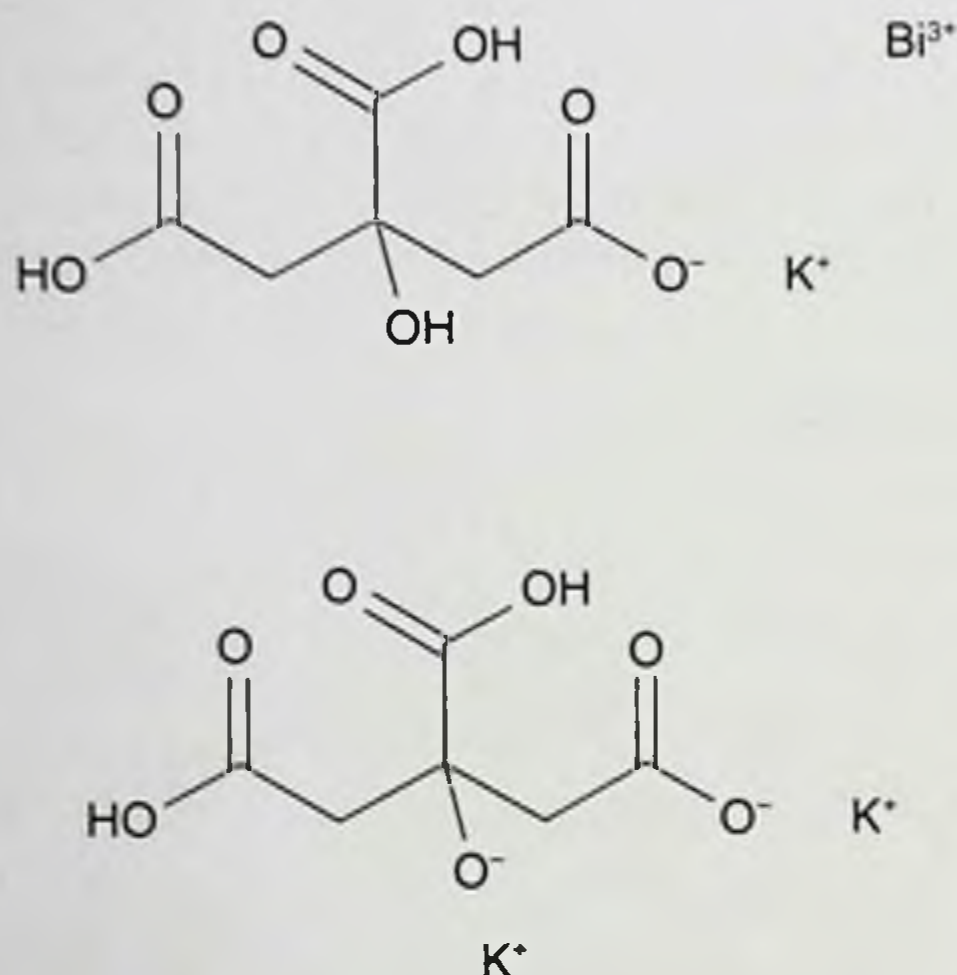


Fig. 11.16 Bismuth (III) potassium 2-hydroxy-1,2,3-propanetricarboxylate (salt 1:3:2)

Colloidal bismuth subcitrate. Not absorbed from the GI tract, excreted in bile. For oral administration 4 times daily, 30 minutes before meals.

Mechanism of action and effects. At pH 4.0 and below (gastric juice), insoluble bismuth oxychloride and citrate precipitate; chelate compounds are formed with a protein substrate to cover and protect the ulcer's surface (this polymer glycoprotein complex is more effective than normally secreted mucus) from acid, pepsin and bile. It coagulates proteins and kills *H. pylori*.

- ▶ Promotes the healing of peptic ulcers, restores the protective function of the gastric mucosa and preserves barrier integrity.
- ▶ Stimulates PGE₂ synthesis (increases mucus production) and bicarbonate secretion, improves the quantitative and qualitative characteristics of gastric mucus and mucin production.
- ▶ Leads to the accumulation of epidermal growth factor in the defect area.

Therapeutic indications: exacerbated gastric and duodenal ulcers, including those associated with *H. pylori*; exacerbated chronic gastritis and duodenitis, including those associated with *H. pylori*.

Side effects: dark stool, darkening of the tongue

Contraindications: severe renal impairment, pregnancy, breastfeeding, allergic reactions

Misoprostol (Cytotec®)

Synthetic analog of PGE₁, cytoprotective agent. The effect occurs in 30 minutes and lasts at least 3–6 hours. $T_{1/2}$: 20–40 minutes, excreted in the urine (80%) and bile (15%). For oral administration 2–4 times daily.

Mechanism of action and effects. It binds to PGE receptors in the parietal cells, inhibits the basal, stimulated and nocturnal secretion of gastric juice and hydrochloric acid, enhances bicarbonate and mucus production, improves blood flow and has a cytoprotective effect. It increases the gastric mucosa's resistance and prevents the development of erosions and ulcers; promotes the healing of peptic ulcers. It has a weak stimulating effect on the smooth muscles of the GI tract.

Therapeutic indications: prevention of NSAID-associated gastric ulcer, treatment of exacerbation of gastric and duodenal ulcers

Side effects: dyspepsia, flatulence, nausea, vomiting, diarrhea, abdominal pain, dysmenorrhea, allergic reactions, dizziness, headache, asthenia, fatigue

Contraindications: CAD, hypertension; cerebrovascular diseases; hepatic and renal disorders; hormone-dependent tumors; suspected ectopic pregnancy; breastfeeding, children under 18 years of age, allergic reaction

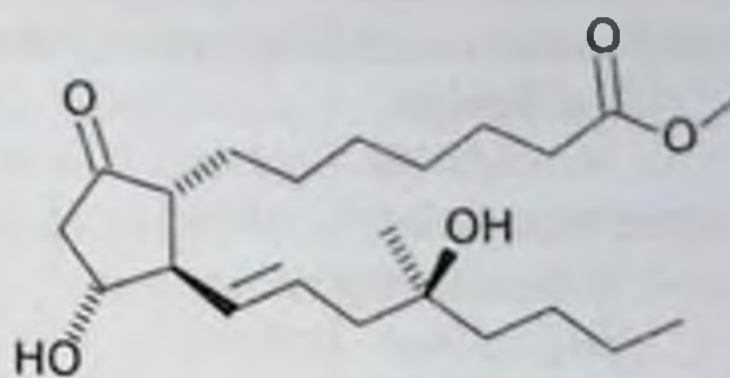


Fig. 11.17 Methyl-7-((1R,2R,3R)-3-hydroxy-2-((S,E)-4-hydroxy-4-methyloct-1-enyl)-5-oxocyclopentyl)heptanoate

Rebamipide (Rebagit®)

- ▶ 2-(1H)-quinolinone derivative, increases PGE₂ in the gastric mucosa and gastric juice. $T_{1/2}$: 60 min. For oral administration 3 times daily.
- ▶ Has a cytoprotective effect on the gastric mucosa versus the damage caused by ethanol, acids and bases, NSAIDs.
- ▶ Promotes the activation of enzymes that accelerate the biosynthesis of high-molecular glycoproteins and increases the amount of mucus on the stomach wall surface. Improves blood supply to the gastric mucosa,
- ▶ activates its barrier function, alkaline secretion of the stomach, enhances the proliferation and metabolism of gastric epithelial cells, removes hydroxyl radicals from the mucous membrane and inhibits superoxides produced by polymorphonuclear leukocytes and neutrophils in the presence of *H. pylori*, protects the gastric mucosa from bacterial damage.

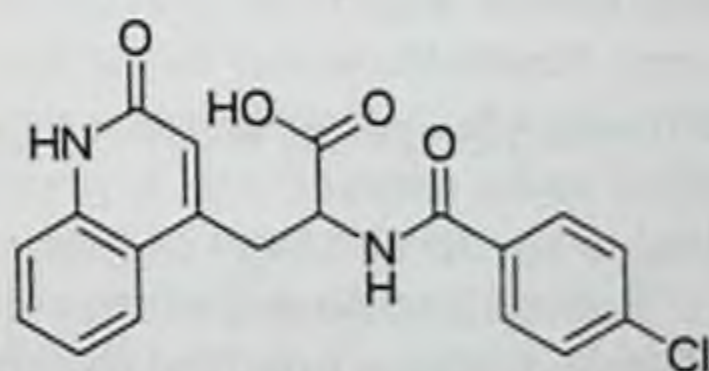


Fig. 11.18 2-[(4-Chlorobenzoyl)amino]-3-(2-oxo-1H-quinoline-4-yl)propanoic acid

Antacids

Antacids (from the Greek *anti* “against”, from the Latin *acidum* “acid”) are drug products that neutralize hydrochloric acid, thus decreasing the irritating effect of gastric juice on the mucous membrane and relieving pain.

Antacids have a rapid but short-lived effect; they are usually prescribed in combination with DPs that inhibit GI secretions and motility.

Classification

1. Absorbable (systemic): sodium bicarbonate (NaHCO_3), calcium carbonate (Vitacalcin[®]) (CaCO_3), magnesium oxide (Magnesia[®]) (MgO)
2. Non-absorbable (non-systemic, topical): aluminum hydroxide [$\text{Al}(\text{OH})_3$], magnesium hydroxide [$\text{Mg}(\text{OH})_2$], aluminum phosphate (Phosphalugel[®], Alfogel[®]) (AlPO_4)
3. Combination: Rennie[®], Gattart[®], Tums[®], Andrews antacid[®] (calcium carbonate, magnesium carbonate); Bourget mixture[™] (sodium bicarbonate, sodium sulfate, sodium phosphate); Gastric[™] (calcium carbonate, magnesium hydroxide); Almagel[®], Maalox[®] (algedrate, magnesium hydroxide); Almagel A[®] (algedrate, benzocaine, magnesium hydroxide); Almagel Neo[®] (algedrate, magnesium hydroxide, simethicone); Gastal[®] (aluminum hydroxide, magnesium carbonate, magnesium hydroxide); Gestid[®]

Mechanism of action: They interact with hydrochloric acid to rapidly relieve symptoms (pain, heartburn and discomfort) and reduce discharge of acid into the duodenum, bind a large volume of acid. They reduce the acidity of the stomach contents to a pH range of 4.0–5.0 (in this range, almost all H^+ ions are bound, their concentration decreases by 2–3 orders of magnitude compared to baseline); at this level, the protease activity of gastric juice is significantly decreased.

Absorbable (systemic) antacids: They rapidly decrease the stomach's acidity after administration, but since they have short time of action and a significant number of side effects, absorbable antacids are now considered less preferable to non-absorbable ones. Neutralization of hydrochloric acid is accompanied by the production of carbon dioxide, which provokes gastroesophageal reflux and also stretches the stomach. They often cause rebound acid hypersecretion. Bicarbonate absorption into the blood can lead to the development of systemic alkalosis.

Rebound acid hypersecretion: an increase in acid production after discontinuation of drug products intended to reduce acidity in the GI tract. It is due to stimulated gastrin production by G-cells, as well as a direct effect of Ca^{2+} cations on parietal cells. It often occurs with administration of absorbable antacids as a reaction to overly rapid gastric alkalization, which activates gastric acid secretion. Some time after dosing, the gastric acidity increases and can reach 1/3 of the maximum discharge.

Non-absorbable antacids. While their effect takes longer to develop than absorbable ones, their time of action is longer and reaches 2.5–3.0 hours. They have the ability to buffer the secreted gastric acid and are able to maintain acidity within 3.0–4.0 pH during this time. They can adsorb pepsin, helping to reduce the proteolytic activity of gastric juice. They bind lysolecithin and bile acids that damage the gastric mucosa. They have an enveloping, moderate cytoprotective effect associated with increased PG levels in the gastric mucosa, stimulation of bicarbonate secretion, and increased production of gastric mucus glycoproteins.

Therapeutic indications: symptomatic treatment of gastric and duodenal ulcers (exacerbation phase), acute or chronic (exacerbation phase) gastritis with normal or increased secretion, reflux esophagitis, duodenitis, enteritis

Side effects:

- ▶ **Magnesium-containing:** diarrhea (increased GI motility), hypermagnesemia, which can cause hypotension, decreased muscle tone, bradycardia and impaired respiratory function
- ▶ **Aluminum-containing:** obstipation (due to inhibition of GI motility), hypophosphatemia, osteoporosis, osteomalacia, hypercalcemia, nervous system dysfunction (encephalopathy), nephropathy, myopathy [excessive therapeutic doses of aluminum-containing antacids can lead to aluminum accumulation in the body (risk of severe side effects occurs when the aluminum blood concentration is more than 100 µg/mL), accompanied by damage to the bone tissue, the brain (Alzheimer's disease) and the development of nephropathy], aluminum directly disrupts bone tissue mineralization, has a toxic effect on osteoblasts, affects the function of the parathyroid glands and inhibits the synthesis of the active metabolite of vitamin D₃. Aluminum phosphate is less toxic than aluminum hydroxide since it is more resistant to dissolution and since neutral complexes can form in the presence of acidic food.
- ▶ **Calcium-containing:** systemic alkalosis, rebound phenomenon; hypercalcemia; delayed excretion of phosphorus (leads to an increase in the content of insoluble calcium phosphate and the development of nephrocalcinosis)

Specifics of individual products

Sodium hydrogen carbonate (NaHCO_3), calcium carbonate (Vitacalcin®) (CaCO_3)

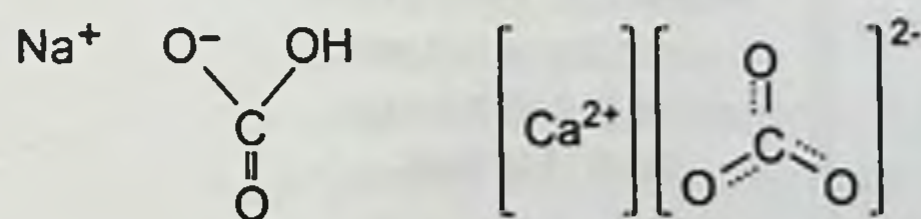


Fig. 11.19

- ▶ Rapidly neutralizes hydrochloric acid to produce carbon dioxide
- ▶ Time of action: 5 minutes to 1 hour when taken while fasted and up to 3 hours when taken with food.

Sodium bicarbonate has a negative effect on water-salt metabolism; therefore, edema, blood pressure increase, signs of heart failure may occur during treatment, which limits its use in patients with concomitant cardiovascular pathology and in the elderly.

Magnesium oxide (MgO)

- ▶ The effect lasts about 30 minutes when taken while fasted and up to 3–4 hours when taken with food.

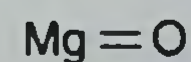


Fig. 11.20

- ▶ When interacting with HCl, magnesium chloride and water are produced. The neutralization reaction proceeds more slowly. Its neutralization ability is 4-fold superior to sodium bicarbonate. Carbon dioxide is not released, and there is no secondary secretion. It acts in the intestines as a laxative.

Aluminum hydroxide [$\text{Al}(\text{OH})_3$]

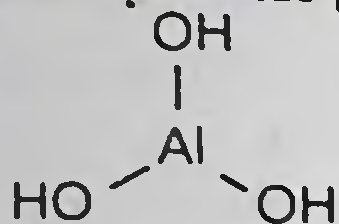


Fig. 11.21

It neutralizes hydrochloric acid to form aluminum chloride; the reaction stops at pH 4.0 even with an excess of the product.

Magnesium hydroxide [$\text{Mg}(\text{OH})_2$]

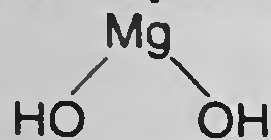


Fig. 11.22

It neutralizes hydrochloric acid in the stomach and reduces pepsin activity. Its action is not accompanied by secondary hypersecretion of hydrochloric acid and changes in acid-base balance.

Combined antacids

Almagel⁺, Maalox⁺ (algedrate, magnesium hydroxide)

Combination DP containing aluminum hydroxide and magnesium hydroxide (Fig. 11.23).

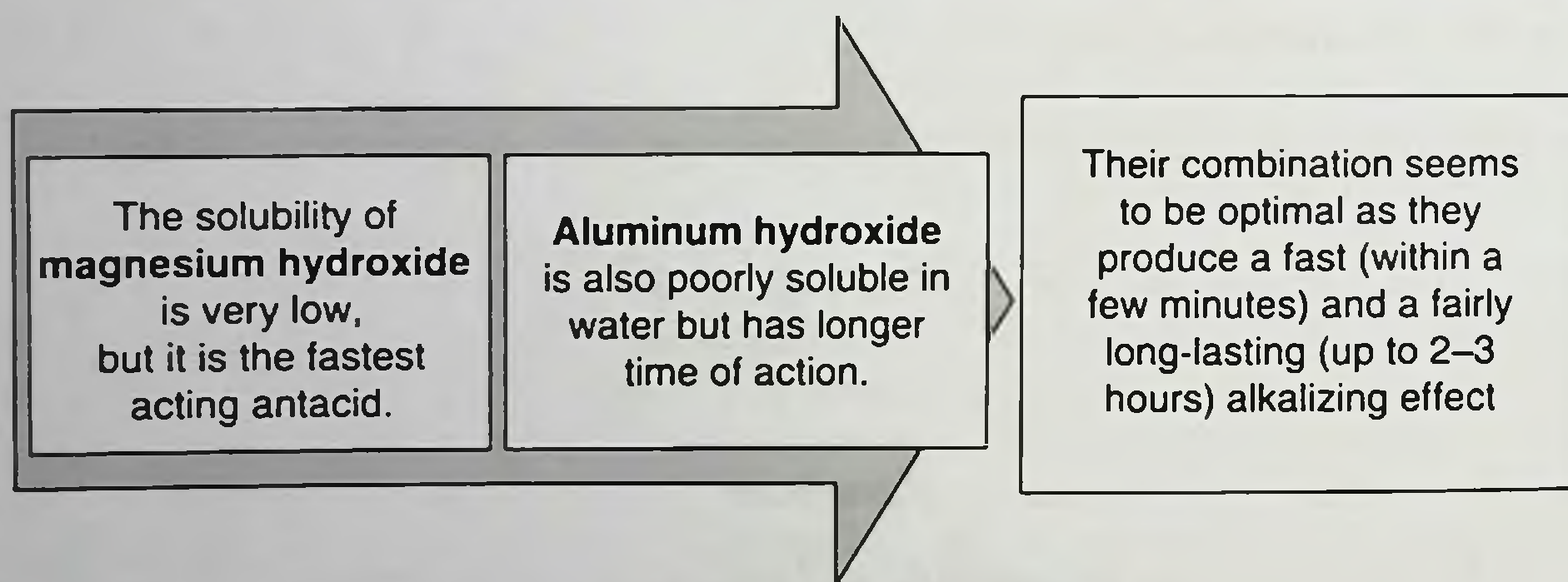


Fig. 11.23. Composition of Maalox and its effects

Rennie⁺ (calcium carbonate, magnesium carbonate)

Combination DP containing calcium carbonate and magnesium carbonate. Produces fast and long-term neutralization of excess hydrochloric acid of gastric juice, thereby protecting the gastric mucosa. A positive effect is achieved within 3–5 minutes.

DRUGS AFFECTING GI MOTILITY

Emetics and antiemetics

Vomiting is a physiological defense mechanism that helps the body to expel toxic substances from the stomach. Vomiting is regulated by the vomiting center in the lateral reticular formation of the brainstem next to the chemoreceptor trigger zone in the area postrema, in the rhomboid fossa, as well as the solitary tract nucleus of the vagus nerve. Stimuli from the vomiting center are mediated by the cerebral cortex and the vestibular system, which is important in the pathogenesis of reflex vomiting and vomiting due to motion sickness. The implementation of the gag reflex, regardless of its origin, involves the neurotransmitters dopamine, histamine, ACh, endogenous opiates, serotonin, GABA and substance P (Fig. 11.24).

Emetics

A group of drug products that cause vomiting reflexively or by acting on the vomiting center.

The pharmacological effects of a naturally occurring analogue of apomorphine[®] in the blue lotus (*N. caerulea*) were known to the ancient Egyptians and the Mayans. The modern medical history of apomorphine[®] begins with its synthesis by Finnish chemist A. E. Arppe in 1845 from morphine and sulfuric acid. In 1965, A. N. Ernst (Netherlands) discovered that apomorphine[®] was a powerful dopamine receptor stimulant. In 1817, the alkaloid emetine was isolated from the root of ipecacuanha. In 1895, N. N. Tokarev in the I. P. Pavlov laboratory was the first to investigate the emetic effect of the alkaloid emetine and later established the reflexive nature of its action.

Classification

1. Central action: apomorphine hydrochloride (excluded from the Russian State Register of Drug Products)
2. Peripheral action: copper sulfate, zinc sulfate
3. Reflexive action: preparations of thermopsis, ipecacuanha

Therapeutic indications: acute poisoning with toxic substances or poor-quality food (rapid removal of stomach contents when it is impossible to perform gastric lavage)

Contraindications: unconsciousness; poisoning with substances that damage the mucous membrane (e.g., gasoline, kerosene, turpentine, acids, bases, phenol and other substances, since their droplets can enter the respiratory tract during vomiting), pregnancy, breastfeeding

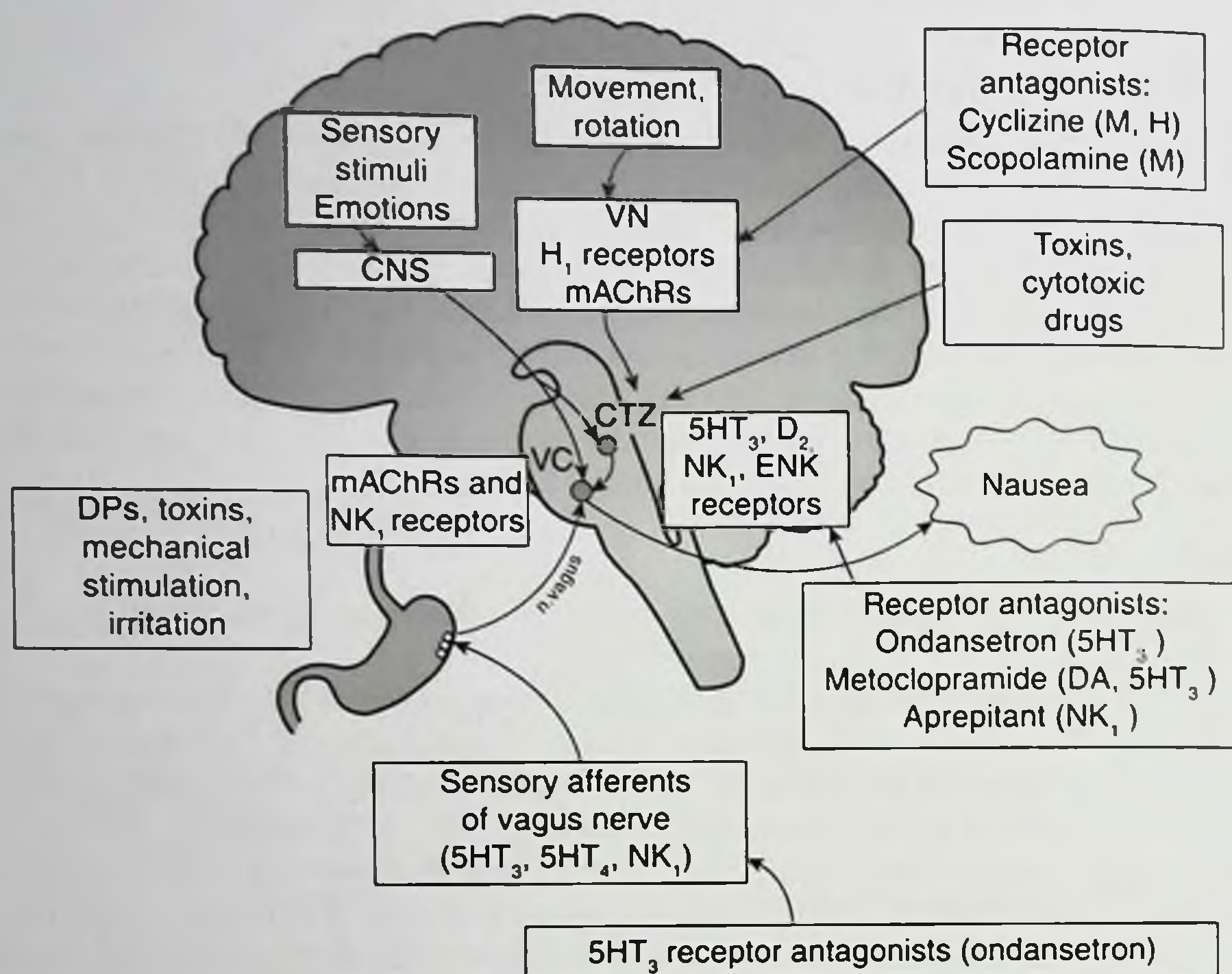


Fig. 11.24. Neuronal pathways and receptors involved in the control of nausea and vomiting (Waller D., 2018). The chemoreceptor trigger zone contains serotonin $5HT_3$ receptors, D_2 receptors, and opiate receptors; the solitary tract nucleus has opiate and H_1 receptors, mAChRs, and $5HT_3$ receptors. NK_1 receptors (neurokinin-1 receptors), whose endogenous ligand is substance P, are located in the abdominal part of the *vagus nerve*, *solitary tract nucleus* and *area postrema*

Specifics of individual products

Apomorphine[®] (Apokinon[®])

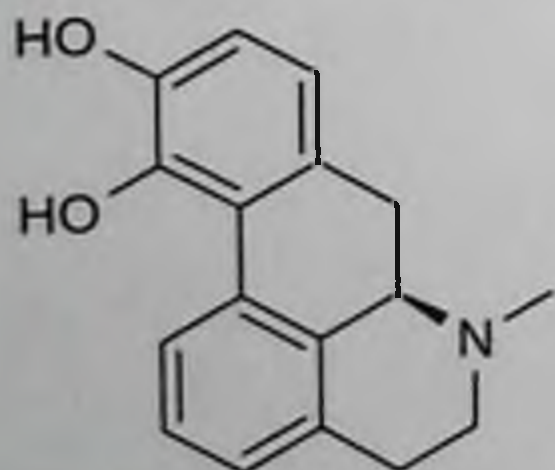


Fig. 11.25. (6aR)-6-Methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline-10,11-diol

Excluded from the Russian State Register of Drug Products. A semi-synthetic alkaloid derived from morphine after treating it with hydrochloric acid. It crosses the BBB, has an effect on the central dopaminergic system. It has a weak analgesic activity and an inhibitory effect on the respiratory center.

Mechanism of action: Stimulates dopamine (D_2) receptors in the chemoreceptor trigger zone of the medulla oblongata.

Copper sulfate

Inorganic compound, copper salt of sulfuric acid (copper sulfate). For oral administration, 15–50 mL dose of a 1% solution.

Mechanism of action: When taken orally, it irritates the gastric mucosa and reflexively induces vomiting.

Side effects: epigastric pain, allergic reactions

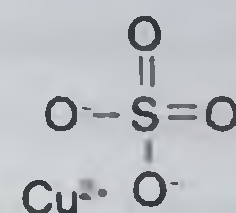


Fig. 11.26

Zinc sulfate

Zinc sulfate, zinc salt of sulfuric acid. For oral administration at a dose of 100–300 mg once daily.

Mechanism of action: Irritates the gastric mucosa and reflexively induces vomiting.

Side effects: dyspepsia, epigastric pain, allergic reactions

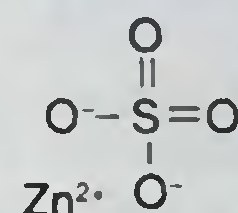


Fig. 11.27

Antiemetics

Antiemetics (from the Latin *emesis* “vomiting”) are drug products that suppress or reduce the gag reflex by acting on the trigger zone receptors or peripheral receptors of the GI tract.

In the middle of the 20th century, the key role of dopamine, histamine and serotonin receptors in gag reflex physiology was established. In the late 1930s, antihistamines were synthesized and found to be highly effective in motion sickness. By the 1950s, histamine receptor antagonists — tripeleennamine and diphenylhydramine — were proposed as antiemetics. In the early 1950s, the first highly effective antipsychotic — chlorpromazine (Aminazin[®]) — appeared and its antiemetic properties were revealed. In 1974, a D² receptor antagonist — domperidone — was synthesized. Metoclopramide was first synthesized by French scientists L. Justin-Besançon and Ch. Laville in 1964 while working to improve the antiarrhythmic properties of procainamide. In 1989, serotonin 5HT₃ receptor antagonists — ondansetron (Latan[®]), tropisetron and granisetron — were synthesized.

Classification

1. Muscarinic antagonists: scopolamine (scopolamine hydrobromide[®])
2. H₁ receptor antagonists: promethazine (diprazine[®], Pipolphen[®]), diphenhydramine (Dimedrol[®])
3. Dopamine receptor antagonists
 - A. Selective
 - Prokinetics: metoclopramide (Ceruleal[®], Reglan[®]), domperidone (Motilium[®], Motilak[®])
 - Thiethylperazine (Torecan[®])
 - B. Non-selective: chlorpromazine (Aminazin[®]), perphenazine (Etaperazine[®]), haloperidol (Haloper[®], Galofen[®]).
4. Selective 5HT₃ receptor antagonists
 - First generation: ondansetron (Zofran[®], Emetron[®]), granisetron (Kytril[®]), tropisetron (Tropindol[®])
 - Second generation: palonosetron (Onicit[®])
5. Tachykinin (neurokinin) receptor antagonists: aprepitant (Emend[®])

Specifics of products by groups

Muscarinic antagonists

Scopolamine (scopolamine hydrobromide^u)

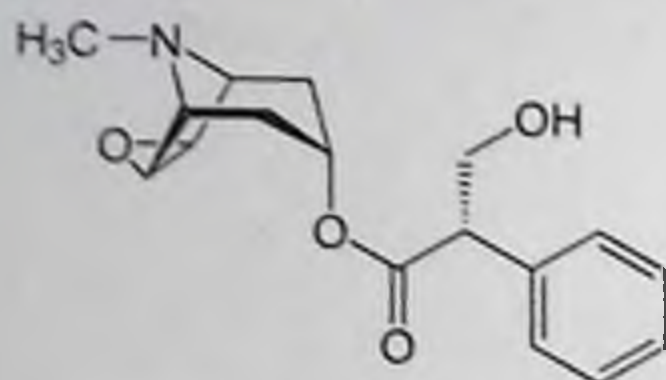


Fig. 11.28. (1*R*,2*R*,4*S*,7*S*,9*S*)-9-Methyl-3-oxa-9-azatricyclo[3.3.1.0^{2,4}]non-7-yl-(-)-(*S*)-3-hydroxy-2-phenylpropionate

- ▶ A scopine and tropic acid ester, an alkaloid contained along with atropine in plants of the nightshade family (*Atropa belladonna*, *Hyoscyamus*, *Datura*, *Scopolia*, etc.).
- ▶ Similar to atropine in its chemical composition and pharmacological action. Crosses the BBB. Has antiemetic, antispasmodic and sedative effects.

Therapeutic indications: prevention of vomiting in case of sea and air sickness, prevention of postoperative vomiting, prevention and relief of

attacks of Meniere's disease

H₁ receptor antagonists

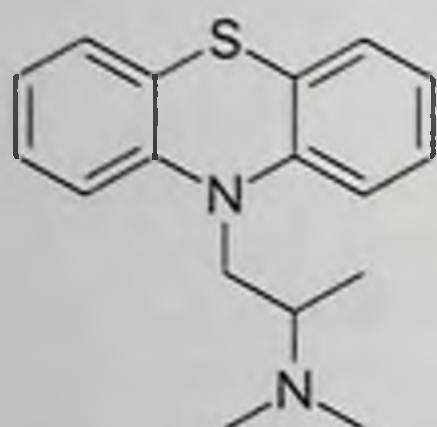


Fig. 11.29. N,N,α-Trimethyl-10H-phenothiazine-10-ethanamine (as hydrochloride or camsylate)

Promethazine (Diprazin^u, Pipolphen^{*})

A phenothiazine derivative, similar structure to aminazine and somewhat similar pharmacological properties. Well absorbed when taken orally, crosses the BBB and placental barrier. Bioavailability: 60–90%, time of action: 4–6 hours. It has antiemetic, sedative, hypnotic, potentiating, antiallergic, antimuscarinic, α-adrenergic blocking, local anesthetic effects. For oral, intramuscular, intravenous administration.

Mechanism of antiemetic action: It competitively blocks H₁ receptors and M₁ receptors of the vomiting center.

Therapeutic indications: prevention of sea and air sickness, Meniere's disease.

For side effects and contraindications, see section "Antihistamines".

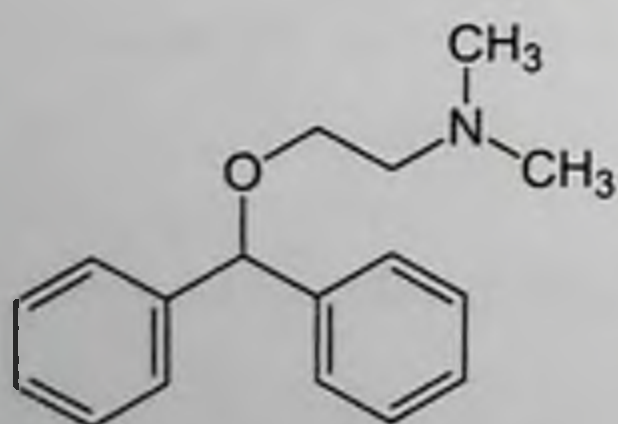


Fig. 11.30. 2-(Diphenylmethoxy)-N,N-dimethylethanamine (and as hydrochloride)

Diphenhydramine (Dimedrol^{*})

When taken orally, it is rapidly and well absorbed, crosses the BBB well. Bioavailability: 50%, T_{1/2}: 4–10 hours, time of action: 4–6 hours.

It has antiemetic, sedative, hypnotic, antiallergic, moderate antimuscarinic, antispasmodic, local anesthetic effects. For oral, intramuscular, intravenous, rectal administration.

Therapeutic indications: sea and air sickness, Meniere's syndrome, allergic diseases

For side effects and contraindications, see section "Antihistamines".

Dopamine receptor antagonists

Metoclopramide (Ceruleal[®], Reglan[®])

- ▶ Similar to sulpiride in its chemical structure. A D_2 receptor and $5HT_2$ receptor antagonist; at high doses it blocks $5HT_2$ receptors and has a direct stimulating effect on smooth muscles. It has antiemetic (not accompanied by general lethargy), anti-hiccup, prokinetic effects (has a regulatory effect on GI functions — the tone and motor activity of the digestive organs increase, but gastric secretion does not change).
- ▶ Bioavailability: 60–80%, $T_{1/2}$: 3–5 hours, crosses the
- ▶ BBB well. Rapidly absorbed after oral administration. Excreted mainly in the urine as unchanged drug and as conjugates within 24 hours. For oral, intravenous, intramuscular administration.

Mechanism of antiemetic action: It inhibits chemoreceptors of the brainstem trigger zone, reduces the sensitivity of the visceral nerves that transmit impulses from the pylorus and duodenum to the vomiting center. Through the hypothalamus and parasympathetic nervous system, it has a regulating and coordinating effect on the tone and motor activity of the upper GI tract (including the tone of the lower esophageal sphincter).

Therapeutic indications: postoperative vomiting, radiotherapy-induced vomiting, side effects of DPs (digitalis preparations, cytostatics, antibiotics, etc.), vomiting in pregnant women, functional digestive disorders (gastric atony and hypotonia, esophageal achalasia, gastroesophageal reflux disease, abdominal dyskinesia, postoperative intestinal paralysis), to hasten transit of the contrast material used for X-ray examination of the GI tract.

Side effects: extrapyramidal disorders, drowsiness, tinnitus, dry mouth, edema, depression, hyperprolactinemia, menstrual disorders, constipation, allergic reactions.

Contraindications: glaucoma, pheochromocytoma, epilepsy, parkinsonism, breastfeeding, gastrointestinal hemorrhage, mechanical intestinal obstruction.

Thiethylperazine (Torecan[®])

- ▶ Refers to phenothiazine derivatives. Unlike typical phenothiazine neuroleptics, it has no antipsychotic or sedative effects. It has antiemetic, anticholinergic, adrenergic blocking, potentiating (enhances the effects of tranquilizers, analgesics, β -AB, antihypertensive agents, alcohol) effects.
- ▶ Well absorbed when taken orally, crosses the BBB. $T_{1/2}$: 12 hours. It undergoes biotransformation in the liver. Excreted in the urine. For oral, intravenous, intramuscular, rectal administration.

Mechanism of antiemetic action: It blocks dopamine receptors (mainly D_2), inhibits the vomiting center and the chemoreceptor trigger zone in the rhomboid fossa.

Therapeutic indications: nausea and vomiting, after surgery, craniocerebral injuries, chemotherapy and radiotherapy, in gastrointestinal, hepatic and biliary

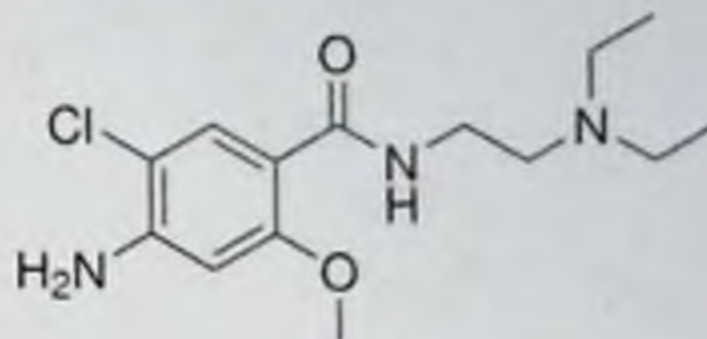


Fig. 11.31 4-Amino-5-chloro-N-(2-diethylaminostyl)-2-methoxybenzamide hydrochloride

disorders; sea and air sickness; dizziness of central and vestibular origin (concussion, atherosclerosis, vestibular and labyrinth disorders, Meniere's disease)

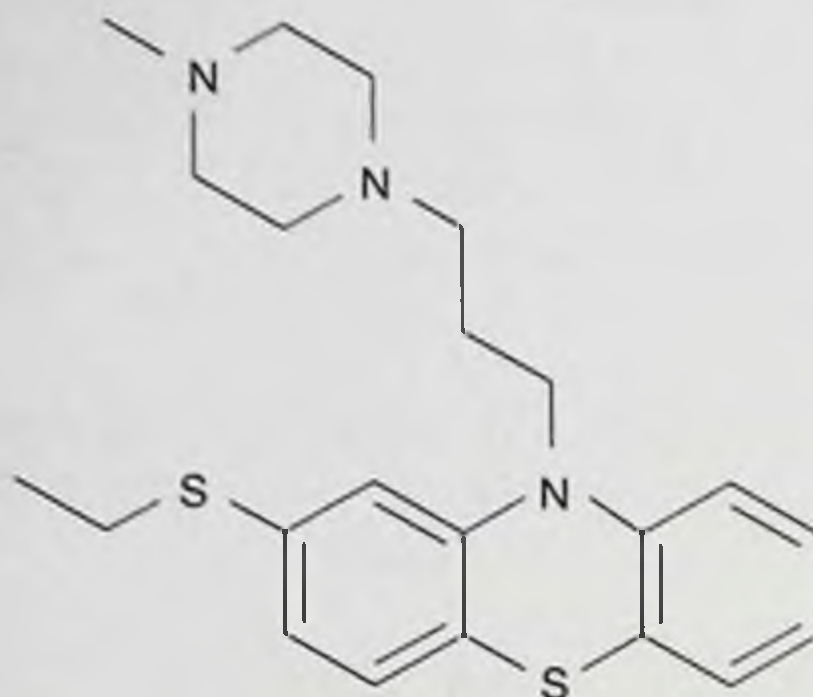


Fig. 11.32. 2-Ethylthio-10-[3-(1-methylpiperazinyl)-4-propyl]-phenothiazine dimaleate

Side effects: dry mouth, dizziness, xerostomia, peripheral edema, hepatic and renal impairment, agranulocytosis, allergic reactions, tachycardia

Contraindications: hepatic and renal impairment, angle-closure glaucoma, prostate enlargement, Parkinson's disease, pregnancy, breastfeeding

Domperidone (Motilium⁺, Motilak⁺)

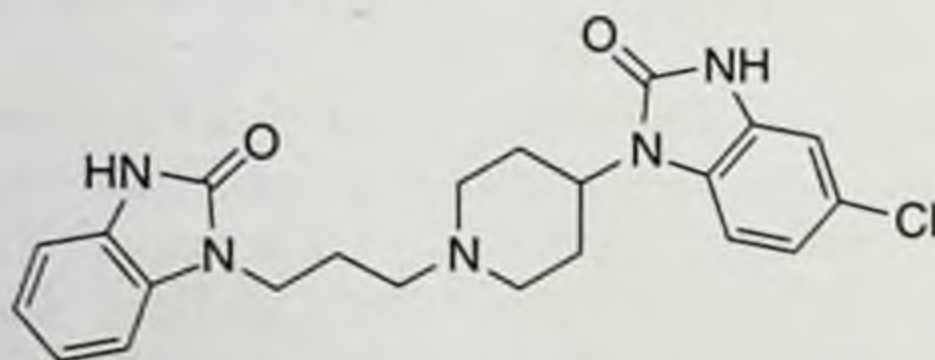


Fig. 11.33. 6-Chloro-3-[1-[3-(2-oxo-3H-benzimidazol-1-yl)propyl]piperidin-4-yl]-1H-benzimidazol-2-one

- ▶ Similar in structure to some antipsychotics of the butyrophenone group. Similar to metoclopramide in its action. A D_2 receptor antagonist. Poorly crosses the BBB and rarely causes extrapyramidal disorders. Has antiemetic, anti-hiccup and prokinetic effects.
- ▶ Rapidly absorbed in the GI tract. Bioavailability: about 15%. $T_{1/2}$: 7–9 hours. For oral administration.

Therapeutic indications: vomiting and nausea of various origins, functional gastroduodenal disorders

Side effects: increased serum prolactin levels, headache, dizziness, dry mouth, constipation

Contraindications: hyperprolactinemia, gastrointestinal hemorrhage, mechanical intestinal obstruction, gastric or intestinal perforation, pregnancy, breastfeeding

Perphenazine (Etaperazin⁺)

- ▶ An antipsychotic, a piperazine derivative of phenothiazine, blocks dopamine, histamine, serotonin, α -ARs and mAChRs.

- ▶ **Bioavailability:** 40%.
 $T_{1/2}$: 9–12 hours, not dose-dependent. It undergoes biotransformation in the liver to form inactive metabolites. Excreted mainly in the urine. For oral administration.

Therapeutic indications: nausea and vomiting of various etiologies, hiccups

For side effects and contraindications, see section "Antipsychotic agents".

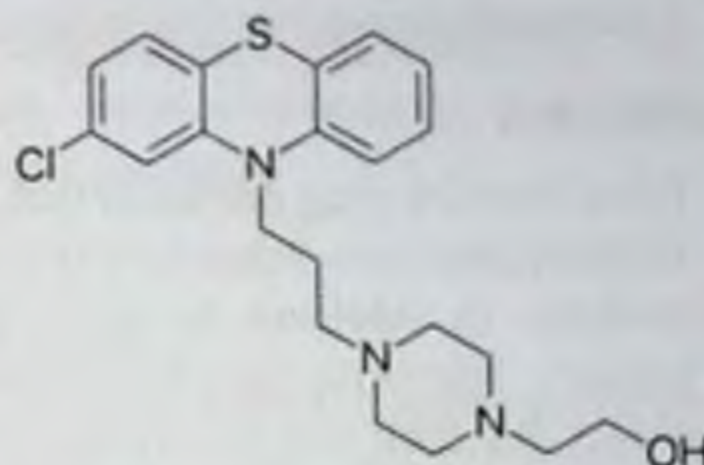


Fig. 11.34. 1-[4-(3-Chloro-10H-phenothiazin-2-yl)propyl]-10-piperazineethanol

Selective 5HT₃ receptor antagonists

Ondansetron (Zofran®, Emetron®)

- ▶ Selective antagonist of 5HT₃ receptors.
- ▶ Well absorbed from the GI tract, bioavailability: 60%. $T_{1/2}$: 3.0–5.5 hours. For oral, intravenous, intramuscular, rectal administration.

Therapeutic indications: prevention of nausea and vomiting during chemotherapy or radiotherapy, or during the postoperative period

Side effects: convulsions, transient visual disturbances, hot flashes

Contraindications: pregnancy, breastfeeding, allergic reactions

Tachykinin (neurokinin) receptor antagonists

Aprepitant (Emend®)

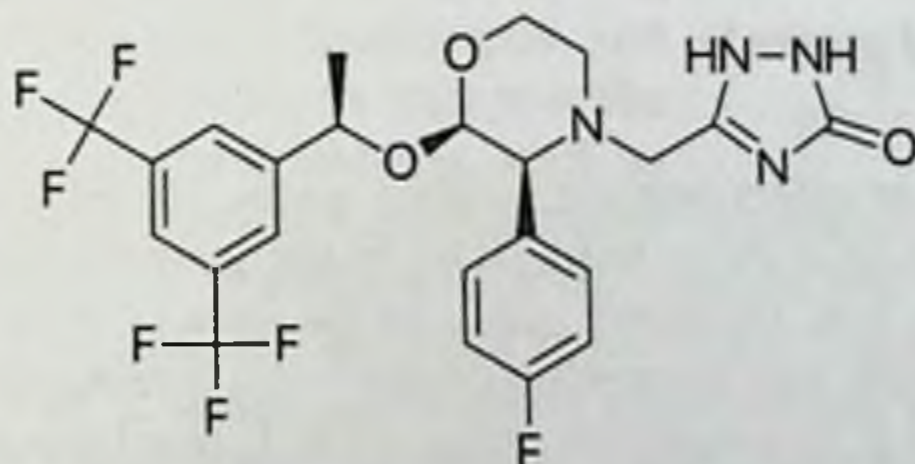


Fig. 11.36. 5-([(2R,3S)-2-((R)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy)-3-(4-fluorophenyl)morpholino]methyl)-1H-1,2,4-triazole-3(2H)-one

A selective high-affinity neurokinin-1 receptor antagonist (substance P) in the brain. Has a long-lasting central action. Bioavailability: 60–65%. $T_{1/2}$: 9–13 hours. For oral administration.

Therapeutic indications: prevention of nausea and vomiting caused by highly or moderately emetogenic antitumor agents (in combination with other antiemetics)

Side effects: hiccups, lack of energy or undue fatigue, constipation, headache, anorexia

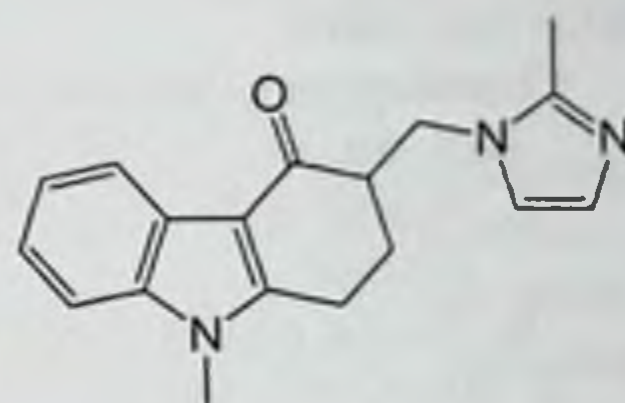


Fig. 11.35. (RS)-9-Methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-2,3-dihydro-1H-carbazol-4(9H)-one (as monohydrochloride dihydrate)

Contraindications: severe hepatic impairment, pregnancy, breastfeeding

Laxatives

Laxatives are drug products that stimulate bowel movements.

Constipation is a delay in bowel movements for more than two days with difficulty defecating. In addition to colon abnormalities and other organic diseases, such as tumors, hemorrhoids that require surgical correction, there are also functional disorders that lead to coprostasis, usually in the rectum and sigmoid colon. Treatment of constipation requires a trial of dietary modifications before administration of DPs. Most laxatives are administered at bedtime so that the period of increased peristalsis occurs in the morning. With systematic use, patients may build up tolerance. In this case, different products should be alternated. With long-term administration, water-salt metabolism disorders and colonic inertia may occur. In addition to these manifestations which are typical of laxatives as a group, individual products can cause other side effects.

Classification by mechanism and location of action

I. Bulk-forming laxatives (reduce water absorption)

A. Acting on the entire intestine: magnesium sulfate and sodium sulfate, macrogol (Forlax[®])

B. Acting mainly on the colon: lactulose (Duphalac[®]), sorbitol

II. Stimulant laxatives

A. Acting on the entire intestine: castor seed oil (Castor oil[®])

B. Acting mainly on the colon: preparations of buckthorn, rhubarb, senna; oxyphenisatine (Isapheninum[®]), bisacodyl[®], sodium picosulfate (Guttalax[®]), glycerol (Glycerin[®])

III. Stool softeners that contain mineral and vegetable oils (emollients): petrolatum (liquid paraffin), almond, fennel and other oils

Specifics of individual products

Magnesium sulfate

Epsom salt. It has an effect only when taken orally. The effect occurs in 4–6 hours. It is poorly absorbed (not more than 20%) in the jejunum and ileum, reabsorbed from bile, pancreatic and intestinal juice. In the case of malabsorption syndrome and high-fat food intake, the absorption of Mg^{2+} ions is reduced. It crosses the BBB, placental barrier, and is excreted into breast milk. It acts throughout the intestines.

Mechanism of laxative action: It dissociates in the GI tract to form ions that are poorly absorbed (Mg^{2+} , SO_4^{2-}). The osmotic pressure in the intestinal lumen increases, which prevents the absorption of the liquid part of the chyme and digestive juices. The volume of the intestinal contents increases which leads to the excitation of mechanoreceptors. In this case, intestinal peristalsis increases.

Therapeutic indications: acute constipation, chemical poisoning, preparation for endoscopic, X-ray examination of the GI tract, surgery

Side effects: nausea, vomiting, flatulence, spastic abdominal pain, thirst, electrolyte imbalance (undue fatigue, asthenia, confusion, arrhythmia, convulsions), hypermagnesemia in patients with renal impairment

Contraindications: severe chronic renal impairment, appendicitis, rectal hemorrhage, intestinal obstruction, dehydration, hypermagnesemia, pregnancy, breastfeeding, children under 18 years of age, allergic reactions

Macrogol (Forlax[®])

A synthetic drug product, a high molecular weight compound, a linear polymer. It acts throughout the intestines. The effect occurs in 24–48 hours. Not absorbed in the GI tract and does not undergo biotransformation. For oral administration.

Mechanism of action: It retains water molecules because of its hydrogen bonds. After oral administration of the product, the volume of intestinal contents increases, which leads to the excitation of mechanoreceptors. In this case, intestinal peristalsis increases.

Therapeutic indications: chronic constipation, preparation for diagnostic testing (endoscopic, X-ray) and colon surgeries

Side effects: bloating and/or pain, nausea, vomiting, allergic reactions

Contraindications: dehydration; gastric ulcer; advanced cancer or other colonopathy accompanied by extensive damage to the intestinal mucosa; intestinal obstruction; intestinal perforation or risk of intestinal perforation; severe inflammatory bowel disease (ulcerative colitis, Crohn's disease) or toxic megacolon; gastric emptying disturbances (including gastroparesis), allergic reactions

Lactulose (Duphalac[®])

A synthetic disaccharide. Absorption is low; less effective than macrogol. It acts mainly on the colon; the effect occurs 24–48 hours after dosing. As a prebiotic substance, it enhances the growth of beneficial bacteria such as bifidobacteria and lactobacilli, which in turn helps to suppress the growth of potentially pathogenic bacteria, such as *Clostridium* and *E. coli*, and provides a more favorable balance of intestinal microflora. It can inhibit the growth and reproduction of *Salmonella* and *Shigella*. It does not reduce vitamin absorption and does not build up tolerance. For oral administration.

Mechanism of action: It undergoes bacterial fermentation and hydrolysis in the colon, mainly by Bifidobacteria and Lactobacilli. Short-chain fatty acids that increase osmotic pressure and also have hypocholesterolemic and antiproliferative effects are the end-product of the drug metabolism. The osmolarity of short-chain fatty acids is lower than that of other osmotic laxatives, which, in combination with the location of action (only at the level of the colon), ensures the development of a rapid, but mild and predictable effect, without leading to excessive fluid loss. The breakdown of lactulose in the ileum is accompanied by the production of lactic, formic and acetic acids, which decreases the pH of the intestinal contents, suppresses the growth of ammonium-producing bacteria and reduces the flow of ammonia into the blood.

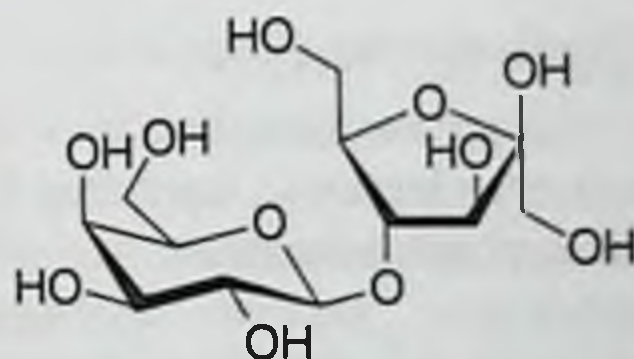


Fig. 11.37. 4-O-beta-D-Galactopyranosyl-D-fructose

Therapeutic indications: chronic constipation, hemorrhoids, postoperative period after colon and rectal surgery; hepatic encephalopathy — treatment and prevention of hepatic coma and precoma

Side effects: flatulence (occurs on Day 3–4 of drug administration and mostly resolves spontaneously or with a dose reduction), nausea, abdominal pain. Hypermnatremia when high doses are used to treat hepatic encephalopathy.

Contraindications: galactosemia, galactose and/or fructose intolerance, glucose-galactose malabsorption, intestinal obstruction, rectal hemorrhage, colostomy, ileostomy, appendicitis

Castor seed oil (Castor oil*)

Extracted from the castor bean seeds. The effect occurs 5–6 hours after oral administration, acts throughout the intestine. For oral administration.

Mechanism of action: Ricinoleic acid is formed from castor oil in the duodenum under the influence of lipase. It irritates the intestinal receptors, disrupts the transport of ions and delays the absorption of water, which increases intestinal motility and accelerates its emptying.

Therapeutic indications: acute constipation, bowel preparation before diagnostic procedures

Side effects: allergic reactions

Contraindications: acute abdomen, pregnancy, poisoning with fat-soluble substances (phosphorus, benzene, etc.), allergic reactions

Oxyphenisatine (Isapheninum[®])

An acetoxypheylmethane derivative, similar to phenolphthalein in its structure and action but less toxic. A prodrug. It acts mainly on the colon. The effect occurs in 8–12 hours. For oral administration.

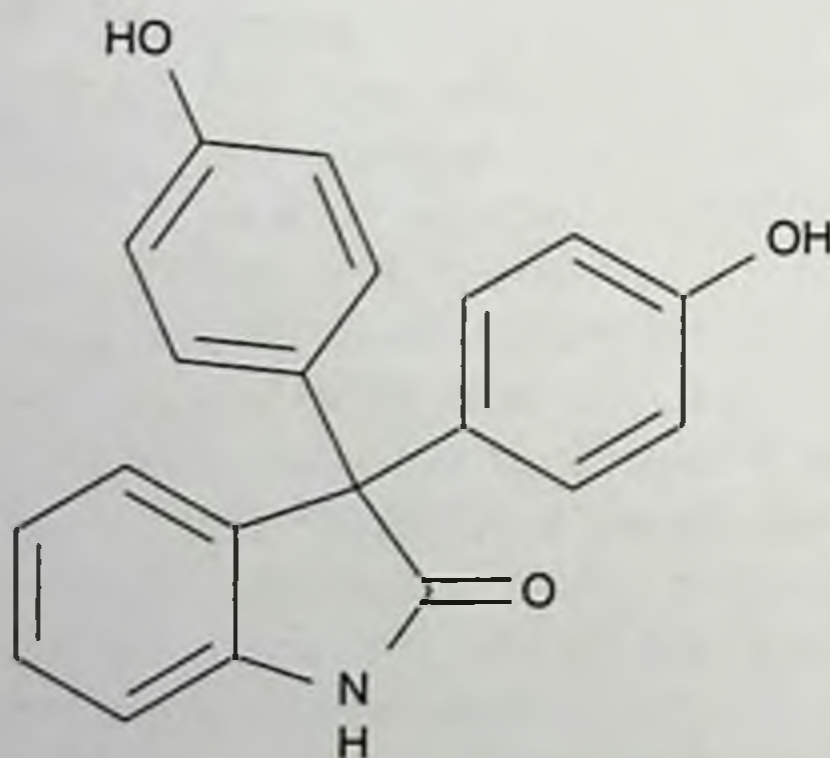


Fig. 11.38. 1,3-Dihydro-3,3-bis(4-hydroxyphenyl)-2H-indol-2-one

Mechanism of action: An active metabolite (dioxypheylisatin) is formed in the intestine under the influence of alkaline contents. It irritates the intestinal mucosa increasing its peristalsis.

Therapeutic indications: chronic constipation (including atonic)

Side effects: intestinal pain, nausea

Contraindications: spastic ileus, pregnancy, breastfeeding, allergic reactions

Bisacodyl*

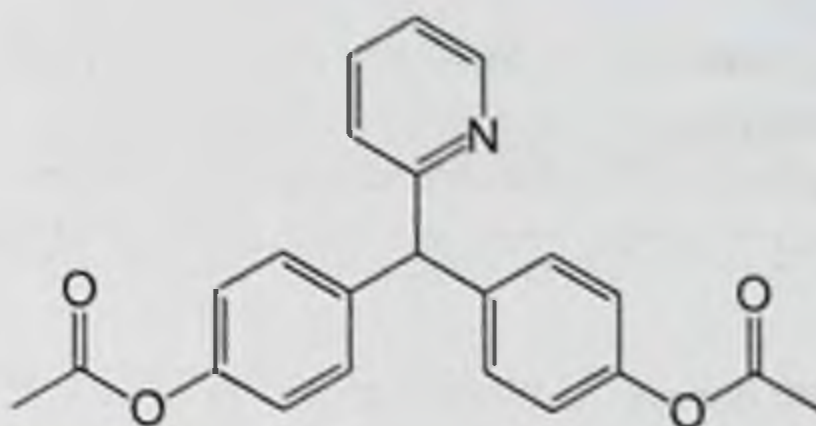


Fig. 11.39. 4,4'-Diacetoxydiphenylpyridyl-(2)-methane

An acetoxyphenylmethane derivative, similar to isapheninum in its chemical structure and action. It is barely absorbed from the GI tract. It acts mainly on the colon. With oral administration, a laxative effect occurs in 6–10 hours, with rectal administration, in 15–60 minutes.

Mechanism of action: It is degraded in the intestinal alkaline environment and irritates the mucosal receptors, increases the production of mucus in the colon, accelerates and enhances its peristalsis.

Therapeutic indications: chronic constipation of various origins; proctitis, anal fissures; purging during preoperative preparation, colon preparation for instrumented and X-ray examination.

Side effects: dyspepsia, flatulence, spastic epigastric or abdominal pain, water-electrolyte imbalance (muscle weakness, convulsions, decreased blood pressure); local irritation (for suppositories), allergic reactions

Contraindications: strangulated hernia, intestinal obstruction, spastic constipation, acute hemorrhoids, acute proctitis, inflammatory bowel diseases, peritonitis, abdominal pain of unknown origin, gastrointestinal hemorrhage, uterine hemorrhage, water-electrolyte imbalance, colon carcinoma (for suppositories), allergic reactions

Sodium picosulfate (Guttalax)

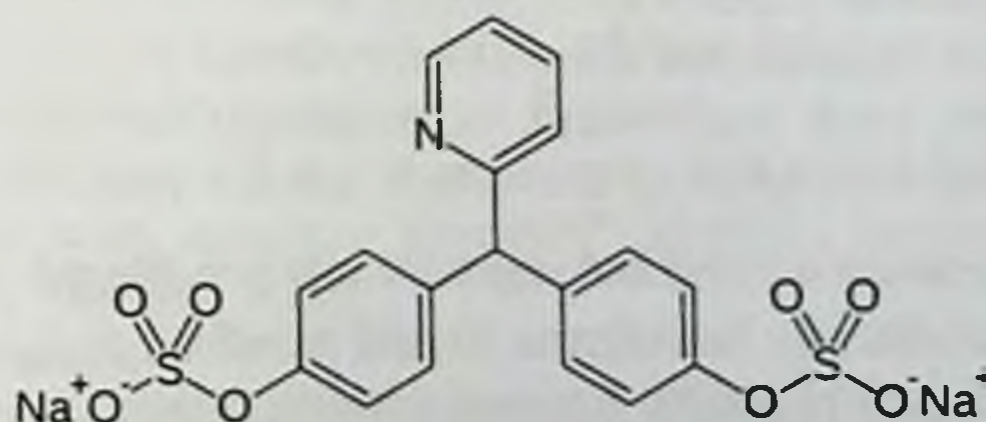


Fig. 11.40. Disodium (pyridin-2-ylmethylene)di-4,1-phenylene disulfate

A triarylmethane derivative; acts at the level of the colon, stimulates the natural process of evacuation from the lower GI tract, not absorbed. The effect occurs in 6–12 hours. For oral administration.

Mechanism of action: After bacterial digestion in the colon, it turns into bis-(p-hydroxyphenyl)-pyridyl-2-methane, which has a stimulating effect on the mucous

membrane, increasing peristalsis, and promoting the accumulation of water and electrolytes.

Therapeutic indications: constipation due to colonic atony and hypotonia; proctitis, anal fissures

Side effects: nausea, vomiting, abdominal cramps and pain, allergic reactions

Contraindications: mechanical intestinal obstruction, acute abdominal pain, including appendicitis; acute inflammatory bowel diseases; severe dehydration; lactase deficiency, lactose intolerance, glucose-galactose malabsorption; allergic reactions.

Herbal laxatives

Derived from senna leaves, rhubarb roots, buckthorn bark. Their action is associated with anthraglycosides, anthracene derivatives, mainly on the colon. The effect occurs in 8–12 hours.

Mechanism of action: Anthraglycosides are ester-like compounds, they release emodin and other anthracene derivatives after sugar elimination. Along with chrysophanic acid, they act on the intestinal interoceptors, stimulate peristalsis, mainly of the colon, which accelerates its emptying.

Therapeutic indications: spastic and atonic constipation of various etiologies, proctitis, anal fissures

Side effects: vomiting, abdominal pain, tenesmus, allergic reactions

Contraindications: intestinal obstruction, inflammatory bowel diseases, strangulated hernia, gastrointestinal hemorrhage, acute hemorrhoids, pregnancy, breastfeeding, allergic reactions

Rectal dosage forms of some laxatives

Glycerol suppositories

The effect occurs in 15–30 minutes; they are a relatively weak bowel movement stimulant.

Mechanism of action: Has a slight irritant effect on the rectal mucosa and reflexively stimulates intestinal contractility, promotes stool softening and its passage through the colon.

Therapeutic indications: chronic constipation of various origins

Side effects: rectal irritation and discomfort, catarrhal proctitis

Contraindications: renal impairment, appendicitis, hemorrhage, anal fissures, inflammatory diseases and tumors of the rectum, allergic reactions

Stool softeners that contain mineral and vegetable oils (emollients) — lubricants

Mineral and vegetable oils: petrolatum (liquid paraffin), almond, fennel, etc. The effect occurs 4–6 hours after dosing. For oral administration.

Mechanism of action: Most of them have both hydrophobic and hydrophilic properties, hence they retain water in the stool and increase their volume, which increases peristalsis. In addition to stool softening, they lubricate the intestinal walls, providing glide and facilitating the passage of chyme.

Therapeutic indications: chronic constipation of various origins

Side effects: nausea, abdominal pain

Contraindications: acute abdominal pain, mechanical intestinal obstruction, intestinal hemorrhage, pregnancy, poisoning with fat-soluble substances (phosphorus, benzene)

HEPATOPROTECTIVE AGENTS

A group of drug products whose action aims to restore homeostasis in hepatocytes, which helps to increase the liver's resistance to pathogenic factors, normalize its function and stimulate its repair and regeneration. They are used for hepatic disorders (acute and chronic hepatitis, dystrophy and cirrhosis, toxic lesions, including those associated with alcoholism), pathology of internal organs complicated by liver damage, and also as medical support when using DPs that affect the liver.

Classification by mechanism of action and use

- I. Drug products that act primarily on liver cytolysis manifestations and reduce fatty liver infiltration [Essentiale Forte N[®] (phospholipids)]
- II. Drug products that act primarily on cholestasis manifestations
 1. Ursodeoxycholic acid products: Ursosan[®], Ursofalk[®], etc. (ursodeoxycholic acid)
 2. Products containing S-adenosylmethionine: Heptral[®] (ademetionine), Remaxol[®] (inosine, meglumine, methionine, nicotinamide, succinic acid)
- III. Products with predominant detoxifying action
 1. Direct detoxifying action: Hepa-Merz[®] (ornithine), Glutargin[®], Glutargin alkoclean[®] (arginine glutamate), herbal and animal products
 2. Indirect detoxifying action (reduce the formation of endogenous toxins): lactitol
 3. Activating the formation of metabolites (have a predominantly detoxifying effect): Heptral[®] (ademetionine), balanced polyionic solution: Remaxol[®] (inosine, meglumine, methionine, nicotinamide, succinic acid)
 4. Accelerating the metabolism of toxicants: metadoxine
- IV. Products that prevent fibrosis and are used at the stage of liver cirrhosis
 1. Ursodeoxycholic acid products: Ursosan[®] (ursodeoxycholic acid)
 2. Products from the polyprenol group: Ropren[®]
 3. Products containing milk thistle flavonoids: milk thistle fruit extract (Carsil[®])
 4. Balanced polyionic solution: Remaxol[®] (inosine, meglumine, methionine, nicotinamide, succinic acid)

Classification by origin

- I. Herbal products: milk thistle containing silymarin [milk thistle fruit extract (Carsil[®], Legalon 70[®], Legalon 140[®]), Hepabene[®] (fume herb extract, milk thistle fruit extract), etc.], artichoke leaf extract (Chophytol[®]), pumpkin seed oil, Liv.52[®]
- II. Animal products: products derived from bovine liver extract (Sirepar[®], Hepadif[®])

- III. Products containing essential phospholipids: phospholipids (Essentiale Forte N[®], Essliver[®]), Phosphogliv[®] (glycyrrhizic acid, phospholipids)
- IV. Amino acids and their derivatives: ademetonine (Heptral[®]), ornithine (Hepa-Merz[®])
- V. Vitamins-antioxidants and vitamin-like products: group B and E vitamins
- VI. Products of different groups: acetylcysteine[®], ursodeoxycholic acid (Ursofalk[®]), thioctic acid (Berlithion 600[®], Berlithion 300[®], Thioctacid 600 T[®], Thioctacid HR[®]), Remaxol[®]

Herbal products

These contain a standardized extract of milk thistle flavonoids, the main component of which is silymarin.

Silymarin is a natural composition of biologically active substances from flavonolignans (silybin A, silybin B, isosilybin A, isosilybin B, silychristin, isosilychristin, silydianin), taxifolin and additional polyphenols and fatty acids (Fig. 11.41).

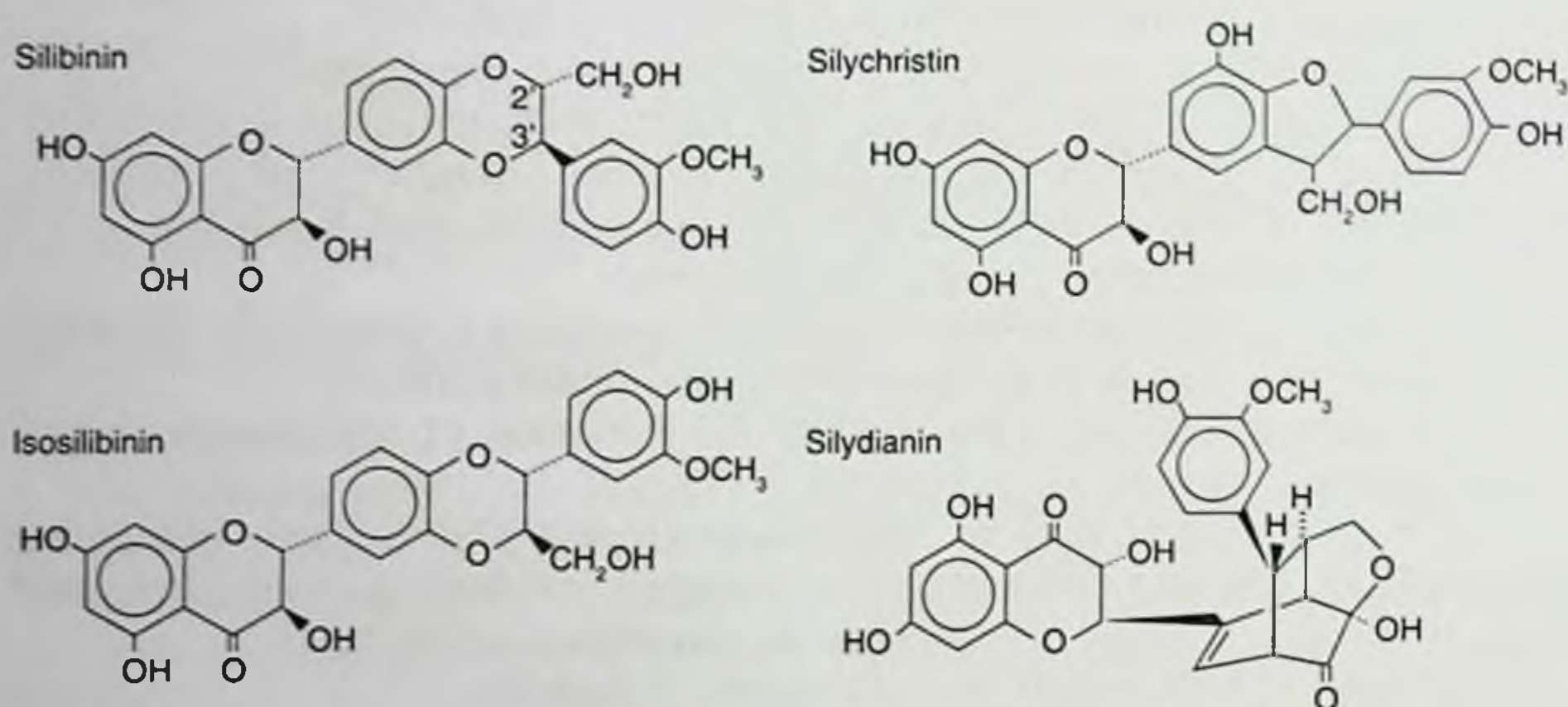


Fig. 11.41. Main components of silymarin

Mechanism of action: Stimulates the synthesis of proteins and phospholipids in the liver, has a membrane-stabilizing effect, and protects liver cells from toxins. Due to its phenolic structure, the components of silymarin can bind free radicals and have antioxidant properties. It stimulates the antioxidant defense system promoting an increase in reduced glutathione in the liver and accelerating the regeneration of damaged hepatocytes. The antifibrotic effect is due to an increase in the clearance of free radicals and direct suppression of collagen synthesis.

Milk thistle fruit extract (Silimar[®], Carsil[®], Legalon[®])

Contains silymarin. Does not accumulate in the body, bioavailability: 85%, $T_{1/2}$: 6–8 hours. For oral administration.

Pharmacological effects:

- ▶ detoxifying (the antitoxic effect of silymarin is seen in various types of poisoning: with the death cap mushroom (*Amanita phalloides*) toxins phalloidin and α -amanitin, lanthanides, carbon tetrachloride, galactosamine, thioacetamide and hepatotoxic virus FV3)
- ▶ cytoprotective (stops hepatotoxic substances from penetrating into the cell)
- ▶ antioxidant (binds free radicals, interrupts or prevents the pathophysiological process of lipid peroxidation, which is responsible for destruction of cell membranes)
- ▶ regenerative and membrane-stabilizing (stimulates regeneration of the glutathione system, one of the most important liver defense systems; stimulates the synthesis of proteins and phospholipids in damaged hepatocytes, helping to stabilize cell membranes; own proteins and phospholipids restore damaged hepatocyte structures; regenerative capacity improves and the regeneration of liver cells accelerates)
- ▶ hypocholesterolemia (reduces blood plasma levels of cholesterol and low-density lipoproteins)
- ▶ antifibrotic (inhibits collagenase and elastase in the liver, helping to reduce fibrosis)
- ▶ anti-inflammatory (blocks the 5-lipoxygenase pathway and has an inhibitory effect on the formation of leukotriene).

Therapeutic indications: complex therapy of chronic hepatitis, liver cirrhosis and toxic liver damage

Side effects: gastrointestinal disorders, allergic reactions

Contraindications: allergic reactions

Animal products

Hydrolysates of bovine liver extract containing cyanocobalamin, amino acids, low molecular weight metabolites (carnitine orotate, adenine hydrochloride, etc.).

Pharmacological effects: antioxidant, detoxifying, regenerative

Therapeutic indications: chronic hepatitis and liver cirrhosis, toxic and medicinal liver damage

Side effects: dyspepsia, allergic reactions.

Contraindications: active hepatitis (increases the manifestations of cytolytic, mesenchymal-inflammatory and immunopathological syndromes)

Products containing essential phospholipids

Phospholipids (Essentiale Forte N[®], Essliver[®])

A combination product that includes essential phospholipids, diglycerol esters of choline phosphoric acid and unsaturated fatty acids (linoleic — about 70%, linolenic, etc.). The raw material for the phospholipid fraction of this product is soybeans. Bioavailability: > 90%. $T_{1/2}$ of the choline component: 66 hours; $T_{1/2}$ of the linoleic component: 32 hours. For oral, intravenous administration.

The mechanism of action is associated with exogenous replenishment of cell wall phospholipids, stabilization of hepatocyte membranes and decrease in cytotoxicity,

protection of mitochondrial and microsomal enzymes from damage, a slowdown in synthesis and an increase in activity of collagenase.

Pharmacological effects: regenerative, membrane stabilizing, regulates the metabolism of lipids and proteins

Therapeutic indications: fatty liver disease (including in diabetes), acute and chronic hepatitis, liver cirrhosis, hepatic coma, toxic liver damage, psoriasis, radiation sickness

Side effects: dyspepsia, allergic reactions

Contraindications: allergy to legumes (peanuts, soybeans), phosphatidylcholine or other ingredients of the drug product

Amino acids and their derivatives

Ornithine (Hepa-Merz[®])

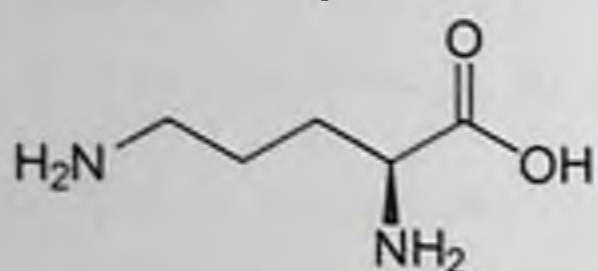


Fig. 11.42 L-Ornithine-L-aspartate
(2,5-diaminopentanoic acid)

Rapidly dissociates into ornithine and aspartate; its effect occurs within 15–25 minutes. L-ornithine is an amino acid that is not incorporated into proteins. It plays an important role in urea biosynthesis (intermediate product of arginine synthesis). For oral, intramuscular, intravenous administration.

Mechanism of action: Involved in the Krebs ornithine cycle (activates the cycle by restoring the activity of liver cell enzymes: ornithine carbamoyl transferase and carbamoyl phosphate synthetase). It promotes the production of insulin and growth hormone. It improves protein metabolism in diseases requiring parenteral nutrition. It helps to reduce asthenic, dyspeptic and pain syndromes, and normalize increased body weight (in steatosis and steatohepatitis).

Pharmacological effects: detoxifying (reduces elevated levels of ammonia, in particular, in case of hepatic disorders)

Therapeutic indications: acute and chronic hepatic diseases accompanied by hyperammonemia, hepatic encephalopathy (latent and severe), steatosis and steatohepatitis (of various origins)

Side effects: nausea, vomiting

Contraindications: severe renal impairment

Ademetionine (Heptral[®])

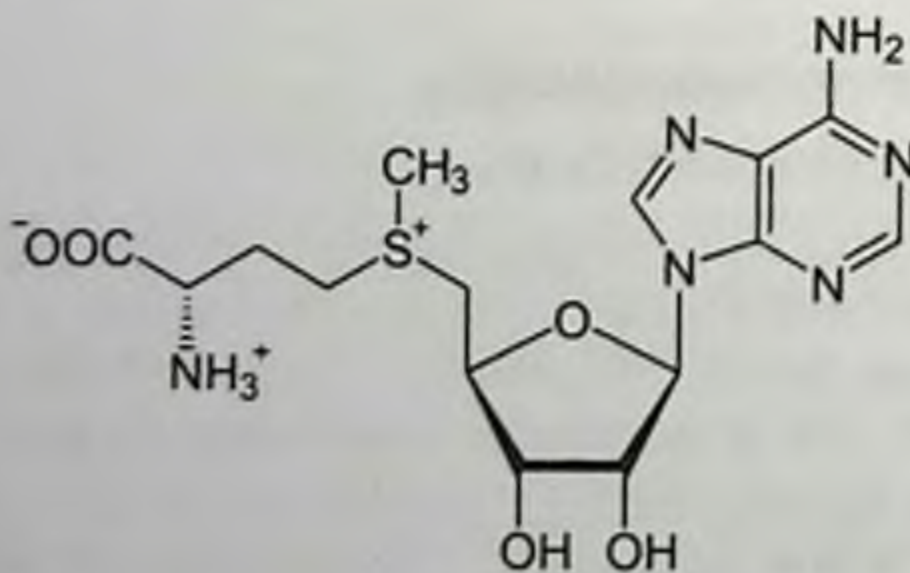


Fig. 11.43 S-Adenosyl-L-methionine

A coenzyme involved in methyl group transfer reactions, first described by G. Cantoni (USA) in 1952. It is involved in cellular metabolic pathways such as transmethylation, transsulfuration and aminopropylation. Well absorbed from the digestive tract. Bioavailability when taken orally: 5% (increased when taken on an empty stomach), when administered intramuscularly: 95%. $T_{1/2}$: 1.5–2.0 hours. Crosses the BBB. For oral, intravenous, and intramuscular administration.

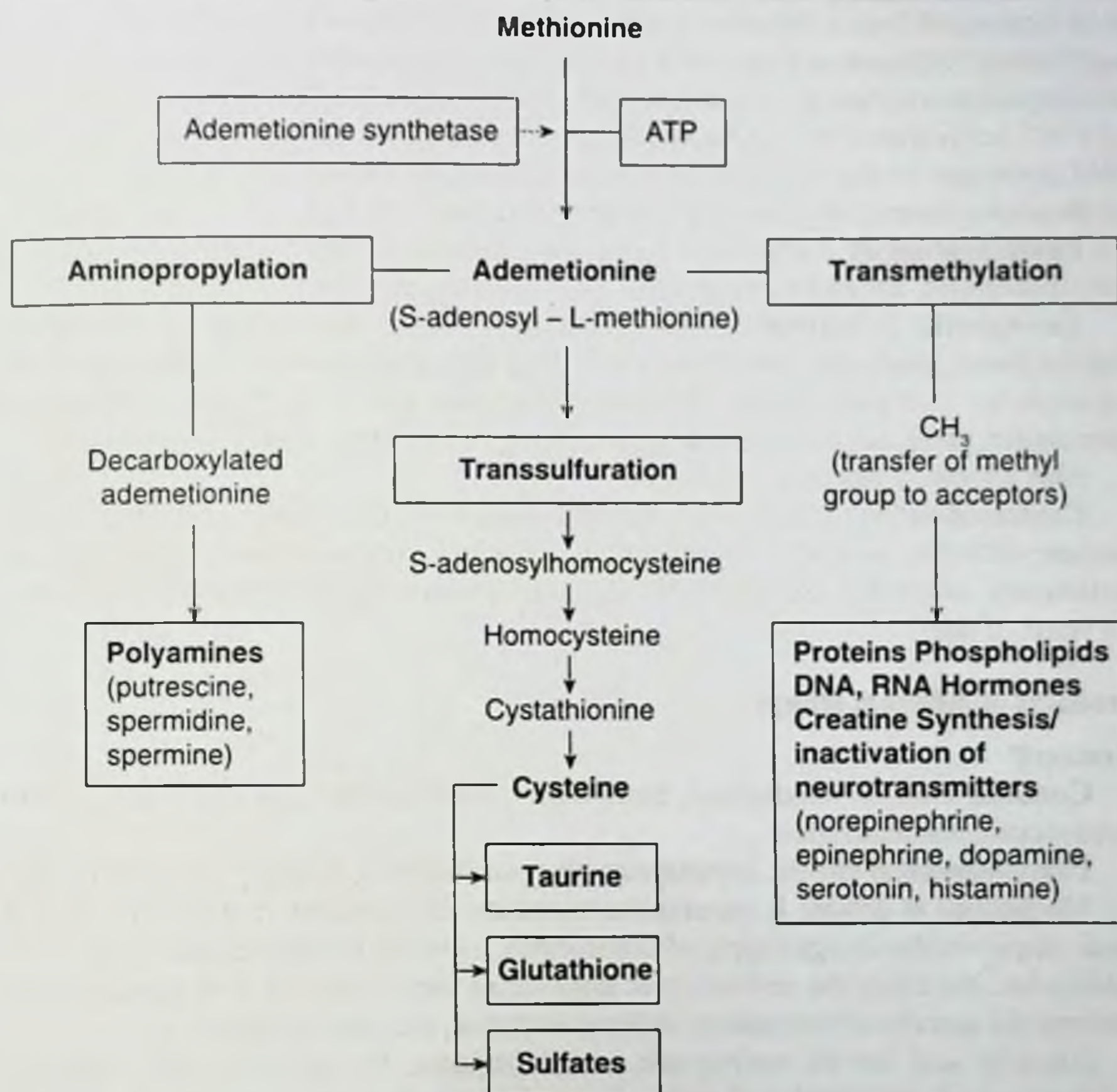


Fig. 11.44. Major metabolic pathways involving ademetionine

Mechanism of action: It compensates for ademetionine deficiency and stimulates its production in the body, primarily in the liver and brain. It is a precursor of physiological thiol compounds, cysteine, taurine, glutathione (ensures cellular redox homeostasis), CoA (Coenzyme A) in the transsulfuration pathway. After decarboxylation, it is involved in aminopropylation as a precursor of polyamines, putrescine (a stimulator of cell regeneration and hepatocyte proliferation), spermidine and spermine, which are part of the ribosome structure (Fig. 11.44). The anticholestatic effect is associated with an increase in the mobility and polarization of hepatocyte membranes due to stimulation of the phosphatidylcholine synthesis.

This improves the function of bile acid transport systems associated with hepatocyte membranes and promotes their passage into the biliary system. It increases the content of conjugated and sulfated bile acids in hepatocytes. Conjugation with taurine increases the solubility of bile acids and their removal from the hepatocyte. Sulfation enables renal elimination, facilitates passage through the hepatocyte membrane and excretion in bile. In addition, sulfated bile acids protect the membranes of liver cells from the toxic effects of non-sulfated bile acids (their high concentrations are present in hepatocytes in intrahepatic cholestasis). The antidepressant action is associated with ademetionine's effect on the metabolism of CNS neurotransmitters. Ademetionine-mediated transmethylation plays a key role in the synthesis/inactivation of the CNS neurotransmitters, norepinephrine, epinephrine, dopamine, serotonin, and histamine.

Pharmacological effects: hepatoprotective, detoxifying, antioxidant, anticholestatic, antidepressant

Therapeutic indications: intrahepatic cholestasis, liver damage of various origins (toxic, including alcoholic, viral, drug-induced), cirrhotic and precirrhotic conditions, encephalopathy, including that associated with liver impairment (alcoholic, etc.), depressive and withdrawal syndromes

Side effects: dyspepsia, headache

Contraindications: genetic disorders affecting the methionine cycle and/or causing homocystinuria and/or hyperhomocysteinemia (cystathionine β -synthetase deficiency, impaired cyanocobalamin metabolism); bipolar disorders, less than 18 years of age

Products of different groups

Remaxol*

Contains inosine, meglumine, methionine, nicotinamide and succinic acid. For intravenous administration.

Pharmacological effects: hepatoprotective, antihypoxic, detoxifying, antioxidant

Mechanism of action: It ensures the transition of anaerobic processes to aerobic ones, improves the energy supply of hepatocytes, increases the synthesis of energy-rich molecules, increases the resistance of hepatocyte membranes to lipid peroxidation, restores the activity of antioxidant defense enzymes, and reduces cytolysis.

Succinic acid has an antihypoxic action (supports the activity of the succinate oxidase unit of oxidation) and indirect antioxidant action (preserves the glutathione reduction pool). In addition to the antihypoxic action, succinate mediates its effects as a ligand through specific G-protein-coupled receptors (SUCNR1, GPR91) found on the cytoplasmic membrane. These receptors are located in many tissues: kidneys (epithelium of proximal tubules, cells of the juxtaglomerular apparatus), liver, spleen, blood vessels, brain (glial cells). Activation of these receptors by succinate, which is present in blood plasma and interstitial fluid, helps the cells adapt to inadequate or impaired oxygen utilization. Modulation of SUCNR1 activity through a change in the succinate concentration is one of the ways to control the secretion of metabotropic hormones or regulate the metabolic activity of various cells; in fact, succinate is said

to have hormone-like effects to a certain extent (in addition to its properties as an energy-producing substrate).

Nicotinamide activates nicotinamide adenine dinucleotide-dependent enzyme systems. This activates synthetic processes in hepatocytes and maintains their energy supply.

Methionine, under the influence of methionine adenosyltransferase, is converted into S-adenosylmethionine, which is subsequently involved in the synthesis of choline, lecithin, and other phospholipids. Experimental data have shown that the product increases endogenous S-adenosylmethionine in hepatocytes (see "Ademetionine" for the mechanism).

Inosine increases the total pool of purine nucleotides needed for the resynthesis of energy-rich molecules [ATP and GTP], second messengers (cAMP and cGMP) and nucleic acids. It suppresses xanthine oxidase activity, which leads to decreased production of highly active oxygen forms and compounds.

Therapeutic indications: acute and chronic hepatic disorders

Side effects: skin hyperemia, hot flashes, sore throat, dry mouth (with rapid administration), allergic reactions, nausea, headache, dizziness

Contraindications: individual intolerance to the product's constituents, pregnancy, breastfeeding

12. DRUGS ACTING ON BLOOD COAGULATION AND FIBRINOLYSIS

In 1897, Bayer scientists (F. Hoffman) synthesized acetylsalicylic acid. Clinical trials from the 1960s to the 1980s established its efficacy as an antiplatelet agent. In 1982, British pharmacologist J. Vane received the Nobel Prize for elucidating the mechanisms of action of aspirin. Pentoxifylline was synthesized in 1972 and has been used in Russia since 1977.

Heparin was discovered by J. McLean and W. H. Howell in 1916; it was first used in 1937 by Canadian surgeon G. Murray in clinical practice. Calciparine was created based on heparin sodium in 1966.

Warfarin was created in 1948, approved for clinical use in 1954, and authorized in the Russian Federation in 2001.

In 1933, American general practitioner and microbiologist W. S. Tillett discovered streptokinase. In 1987, alteplase[®] was approved for medical use.

Grouping of drugs

- I. Products used to treat and prevent thrombosis
 1. Reduction of platelet aggregation (antiplatelet agents)
 2. Reduction of blood coagulation (anticoagulants)
 3. Fibrinolytic (thrombolytic)
- II. Products that help stop bleeding (hemostatic agents)
 1. Increased blood clotting (for topical, systemic use)
 2. Antifibrinolytic
- III. Vasoprotective agents

PRODUCTS USED TO TREAT AND PREVENT THROMBOSIS

Antiplatelet agents

Classification

- I. Products that inhibit thromboxane activity (reduced TXA₂ synthesis)
 1. COX inhibitors: acetylsalicylic acid (Aspirin Cardio[®], Thrombo ASS[®])
 2. Thromboxane synthetase inhibitors: dazoxiben[®]
 3. Thromboxane synthetase inhibitors and thromboxane receptor antagonists: Ridogrel[®] (not on the Russian State Register of Drug Products)
- II. Products that increase prostacyclin activity
 1. By stimulating prostacyclin receptors: Epoprostenol[®] (Flolan[®], Veletri[®])
- III. Products that inhibit binding of fibrinogen to platelet glycoprotein (GP) IIb/IIIa receptors
 1. GP antagonists: abciximab (ReoPro[®]), tirofiban (Aggrastat[®])

2. By blocking platelet purine receptors and preventing adenosine diphosphate stimulation (GPs are not activated in this case): ticlopidine (Ticlid[®]), clopidogrel (Plavix[®])

IV. Products with different types of action: dipyridamole (Curantyl[®], Persantin[®])

Platelet aggregation is regulated by thromboxane and prostacyclin (Fig. 12.1). Both compounds are formed from cyclic endoperoxides, which are conversion products of arachidonic acid in the body, and act on thromboxane and prostacyclin receptors, respectively. TXA₂ (thromboxane A₂) is synthesized in platelets, increases platelet aggregation and causes vasoconstriction. Prostacyclin inhibits platelet aggregation and causes vasodilation. It is synthesized in vascular endothelial cells; the largest amount is contained in the vascular intima, also circulates in the blood. By stimulating prostacyclin receptors and the associated adenylate cyclase, prostacyclin increases cAMP in platelets and the vascular walls (the content of intracellular Ca²⁺ decreases).

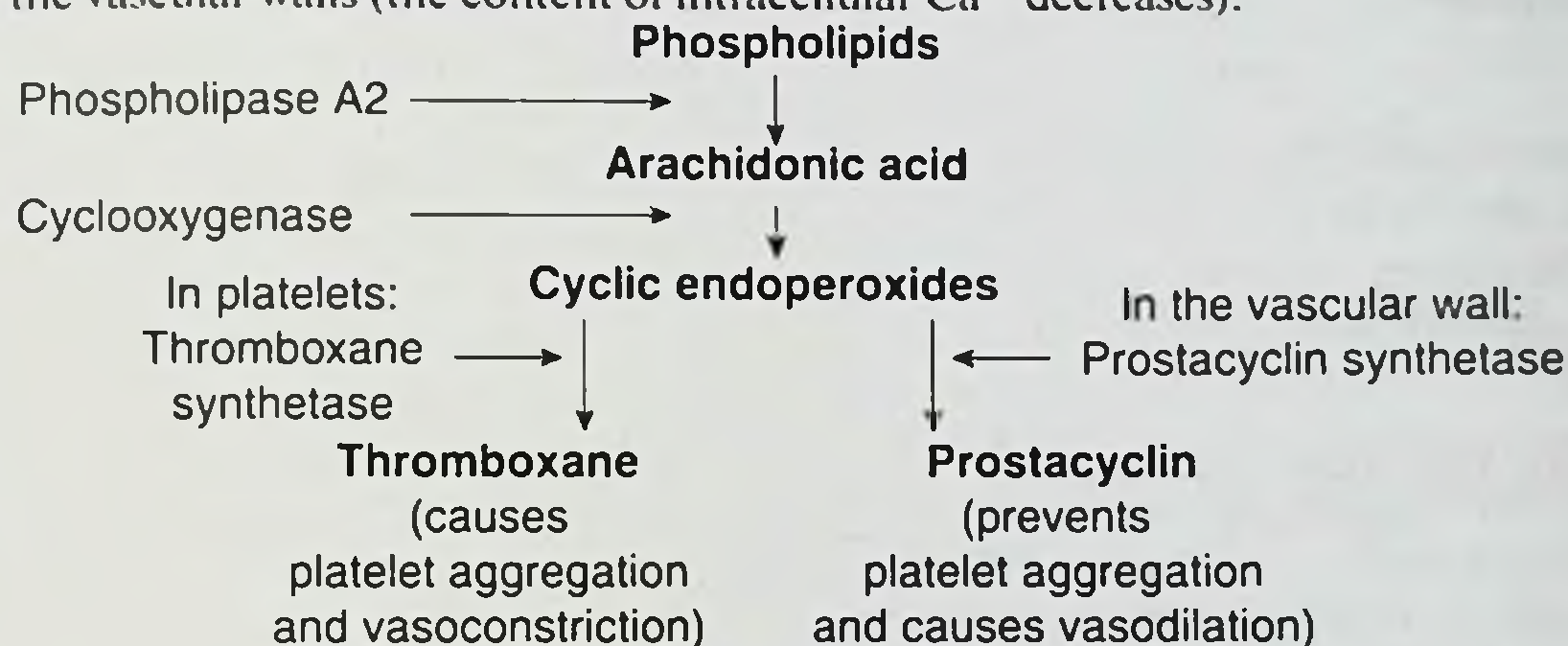


Fig. 12.1. Involvement of prostacyclin and thromboxane in platelet aggregation

Specifics of individual products

Acetylsalicylic acid (Aspirin Cardio[®], Thrombo ASS[®])

- ▶ Bioavailability: 50–68%, undergoes first-pass elimination in the intestinal wall and liver (deacetylated). Maximum blood concentrations are reached in 2 hours.
- ▶ The main metabolite is salicylic acid, which is metabolized in the liver to form salicylic acid phenolic glucuronide, salicyl glucuronide and gentisuric acid. Excreted in the urine unchanged (60%) and as metabolites. T_{1/2}: 2–3 hours.

For oral administration once daily.

Mechanism of action: At a dose of 75–300 mg/day, acetylsalicylic acid acetylates and inhibits platelet COX-1, while disrupting the synthesis of cyclic endoperoxides and TXA₂. Platelet COX is more sensitive than the analogous enzyme in the vascular wall. As a result, the antiplatelet effect prevails, which persists for several days since acetylsalicylic acid irreversibly inhibits platelet COX. After a single dose, the initial content of TXA₂ is restored in 7–10 days when new platelets from the bone marrow enter the bloodstream. Acetylsalicylic acid does not affect platelet adhesion. As a COX-2 inhibitor, it reduces the infiltration of mononuclear cells in blood vessels and the synthesis of inflammatory

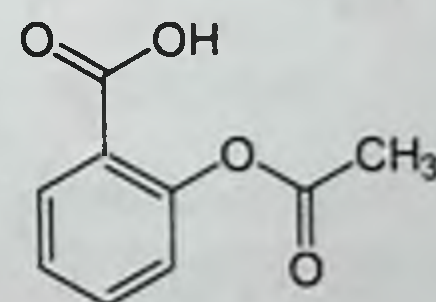


Fig. 12.2. 2-Acetoxybenzoic acid

mediators. It increases plasma fibrinolytic activity and reduces the concentration of vitamin-K-dependent coagulation factors (II, VII, IX, X).

Pharmacological effects (dose-dependent): antiplatelet, analgesic, hypothermic, anti-inflammatory

Therapeutic indications: unstable and stable angina; acute myocardial infarction, prevention of recurrent myocardial infarction; prevention of recurrent ischemic stroke; prevention of thrombotic complications after surgery or invasive vascular interventions

Side effects: hemorrhage of various locations, bronchospasm, ulcerogenic effect, thrombocytopenia, anemia

Contraindications: gastric and duodenal ulcers, asthma, bleeding diathesis, severe renal and/or hepatic impairment, decompensated heart failure, pregnancy, breastfeeding.

Dazoxiben[®]

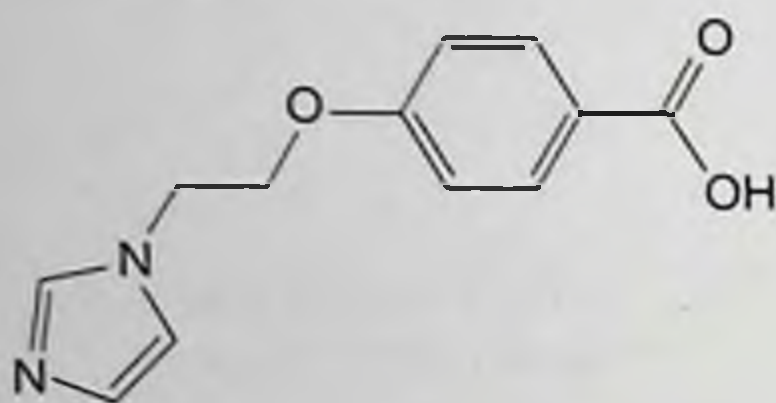


Fig. 12.3. 4-[2-(1H-imidazol-1-yl)ethoxy] benzoic acid

► An imidazole derivative that selectively blocks thromboxane synthetase: it competes with PGG_2 and PGH_2 for the active site of this enzyme; ultimately, the rate of TXA_2 formation drops sharply. Its efficacy is low because it induces the accumulation of pro-aggregating substances (PGG_2 and PGH_2 endoperoxides) formed in the cyclooxygenase pathway of arachidonic acid conversion, which stimulate thromboxane receptors.

Ridogrel[®]

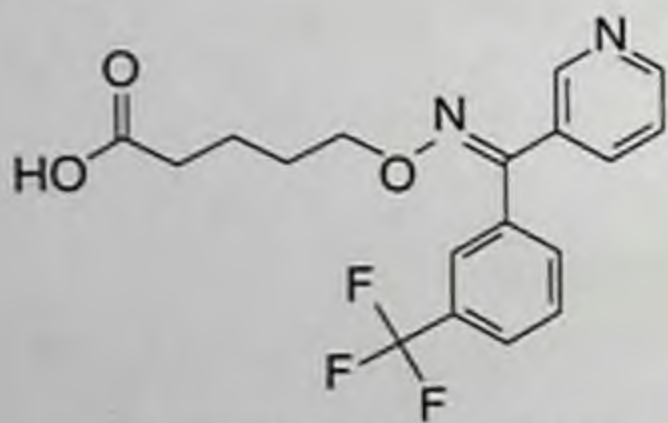


Fig. 12.4. 5-[(E)-[Pyridin-3-yl-[3-(trifluoromethyl)phenyl]methylidene] amino]oxypentanoic acid

Has a combined effect: deactivates thromboxane synthetase and acts as a receptor antagonist for TXA_2 . The product not only inhibits the production of thromboxane, but also blocks the proaggregatory effect of TXA_2 at the receptor level. It does not surpass the clinical efficacy of acetylsalicylic acid.

Epoprostenol[®] (Flolan[®], Veletri[®])

- PGI_2 (synthetic prostacyclin): stimulates prostacyclin receptors on platelets, increases the activity of adenylate cyclase and reduces the level of Ca^{2+} ions and platelet aggregation. It causes vasodilation and decreases blood pressure.
- It is rapidly hydrolyzed in the blood to metabolites, short-acting. Excreted in the urine (84%) and bile (4%). $T_{1/2}$: 3–6 min. For intravenous administration (infusion).

Therapeutic indications: hemodialysis, primary pulmonary hypertension, extracorporeal circulation

Side effects: hypotension, tachycardia, myalgia, nausea, vomiting, diarrhea

Contraindications: severe heart failure, pregnancy, breastfeeding

Abciximab (ReoPro®)

- ▶ A non-competitive antagonist of GP (glycoprotein) IIb/IIIa receptors. The DP consists of Fab fragments of mouse antibodies against glycoprotein IIb/IIIa, bound to the Fc fragment of human immunoglobulin.
- ▶ It has high and long-term affinity for platelet GP IIb/IIIa receptors. A steady-state concentration is maintained only by continuous IV infusion; once terminated the concentration decreases rapidly within 6 hours. The pronounced antiplatelet effect lasts up to 1 day. After intravenous infusion, partial blockade of receptors persists for 10 days. Excreted in the urine. $T_{1/2}$ in the 1st phase: 10 minutes, in the 2nd phase: 30 minutes. For intravenous administration (12–24 hour infusion).

Mechanism of action: Irreversibly binds to platelet GP IIb/IIIa receptors (changes the conformation of the Arg-Gly-Asp receptor binding site), prevents the binding of fibrinogen, von Willebrand factor and other adhesive molecules to these receptors, acting as a potent antiplatelet agent. The maximum antiplatelet effect is observed when at least 80% of GP IIb/IIIa receptors are occupied (Fig. 12.6).

Therapeutic indications: prevention of thrombosis after angioplasty, acute myocardial infarction, postinfarction and unstable angina

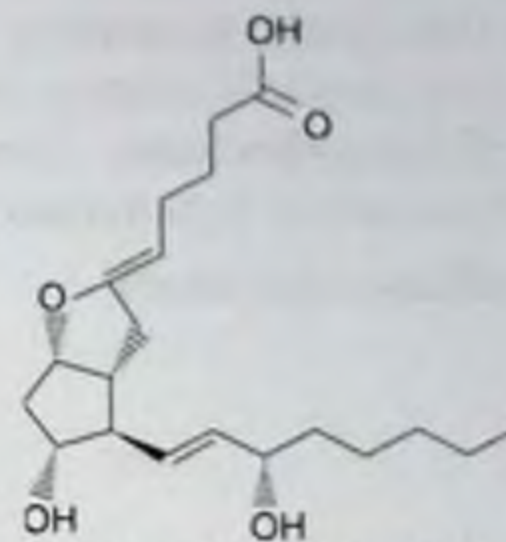


Fig. 12.5. (Z)-5-[(4R,5R)-5-Hydroxy-4-((S,E)-3-hydroxyoct-1-enyl)hexahydro-2H-cyclopenta[b]furan-2-ylidene]pentanoic acid

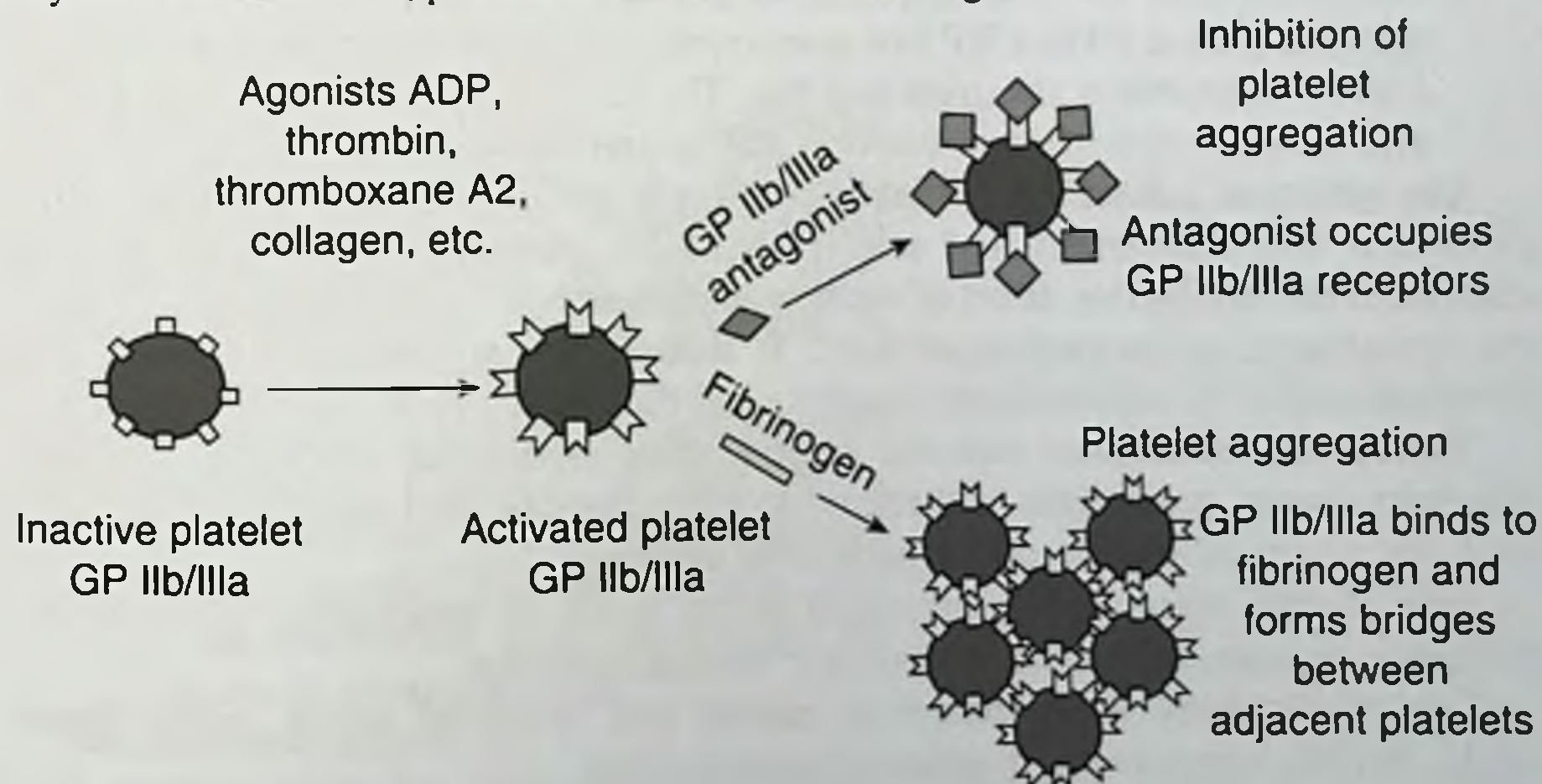


Fig. 12.6. Inhibition of platelet aggregation by platelet glycoprotein (IIb/IIIa) receptor antagonists (Bussel et al., 2000)

Side effects: hemorrhage; hypotension, bradycardia, AV block, thrombocytopenia, anemia, myalgia, nausea, vomiting, diarrhea

Contraindications: internal hemorrhage, bleeding diathesis, cerebrovascular disease, severe hypertension, renal and hepatic impairment, pregnancy, breastfeeding

Tirofiban (Aggrastat[®])

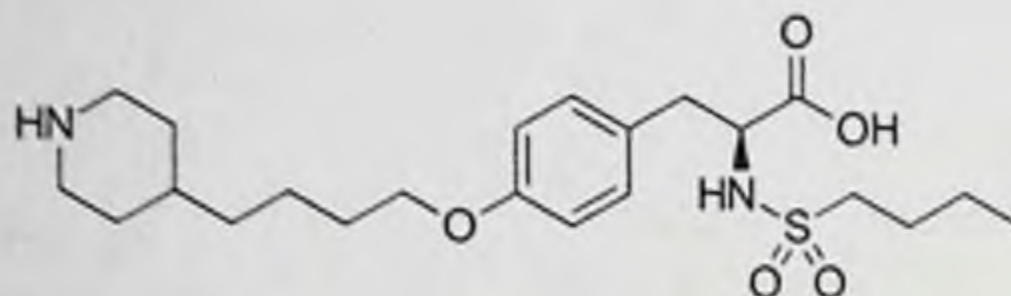


Fig. 12.7. N-(Butylsulfonyl)-4-[4-(piperidyl)butoxy]-L-phenylalanine hydrochloride

- ▶ A synthetic non-peptide GP IIb/IIIa receptor antagonist. It has a shorter time of action than abciximab: after the infusion is stopped, platelet aggregation is restored in 4–8 hours.
- ▶ Barely metabolized, excreted mainly unchanged in the urine (65%) and bile (25%). $T_{1/2}$: 2 hours. For intravenous administration.

Ticlopidine (Ticlid[®])

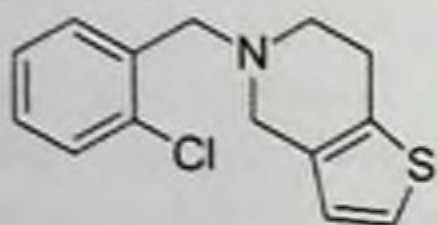


Fig. 12.8. 5-[(2-Chlorophenyl)methyl]-4,5,6,7-tetrahydrothieno-[3,2-c]pyridine (as hydrochloride)

- ▶ Thienopyridine derivative, platelet purine (P2Y₁₂) receptor antagonist. Bioavailability: 80–90%. The antiplatelet effect occurs 24–48 hours after oral administration, reaching a maximum after 3–5 days, and persists for 3 days after treatment discontinuation. Platelet aggregation induced by adenosine diphosphate returns to its baseline values in 4–8 days.

- ▶ Metabolized in the liver: four metabolites are formed under the influence of the cytochrome P450 CYP3A4 isoenzyme, one of which has pharmacological activity. Excreted in the urine and bile. $T_{1/2}$: 12–13 hours, extended to 4–5 days with a course of treatment. For oral administration twice daily.

Mechanism of action: The antiplatelet effect is due to the formation of an active metabolite that irreversibly and selectively blocks platelet P2Y₁₂ receptors. This eliminates the stimulating effect of adenosine diphosphate on platelets and decreases the cytoplasmic concentration of Ca^{2+} . It reduces the expression of GP IIb/IIIa receptors caused by adenosine diphosphate and their ability to bind to fibrinogen.

Therapeutic indications: unstable angina, acute myocardial infarction, transient ischemic attacks, prevention of thrombotic complications after cardiac and vascular surgeries, severe atherosclerosis of peripheral arteries

Side effects: hemorrhage, increased blood levels of atherogenic lipoproteins, thrombocytopenia, neutropenia; diarrhea, nausea, vomiting

Contraindications: exacerbation of gastric and duodenal ulcers, hemorrhagic stroke, hepatic impairment, pregnancy, breastfeeding

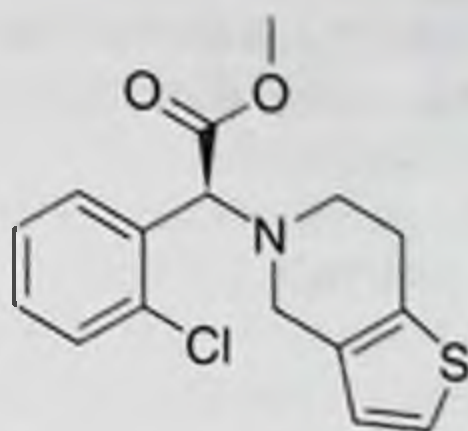
Clopidogrel (Plavix®)

Fig. 12.9. Methyl-(+)-(S)- α -(ortho-chlorophenyl)-6,7-dihydrothieno[3.2-c]pyridine-5(4H)-acetate

- ▶ Thienopyridine derivative, platelet P2Y₁₂ receptor antagonist. Bioavailability: 50%, maximum blood concentration: in 1 hour. With daily administration, the maximum antiplatelet effect occurs in 3–7 days. Long-acting. After product discontinuation, the effect persists for 7–10 days. Its activity is inferior to ticlopidine.
- ▶ It undergoes biotransformation in the liver in two ways: the first is hydrolysis with the formation of an inactive carboxylic acid derivative (85% of circulating metabolites); the second, through the cytochrome P450 system, is the formation of an intermediate metabolite (2-oxo-clopidogrel) and an active metabolite (thiol derivative of clopidogrel). $T_{1/2}$: 8 hours. Excreted in the urine (50%) and bile (46%). For oral administration once daily.

Mechanism of action: Like ticlopidine, it selectively and irreversibly blocks platelet P2Y₁₂ receptors, interacting with adenosine diphosphate, and eliminates the activation of GP IIb/IIIa receptors.

Therapeutic indications: prevention of thrombotic complications in patients with myocardial infarction, ischemic stroke, peripheral arterial occlusion

For side effects and contraindications, see Ticlopidine.

Dipyridamole (Curantyl®, Persantin®)

- ▶ Pyrimidine derivative, adenosine deaminase and PDE III inhibitor. Bioavailability: 37–66%, maximum blood concentration occurs in 60–75 min. About 20% of the dose is involved in enterohepatic circulation.
- ▶ Metabolized in the liver to form inactive glucuronides. Excreted in bile as a monoglucuronide and a small amount of diglucuronide. $T_{1/2}$: 20–40 min. For oral administration 3–4 times daily, for intravenous administration.

Mechanism of action:

- ▶ Inhibits PDE III and increases cAMP in platelets, which prevents their aggregation.
- ▶ Stimulates the release of prostacyclin by endothelial cells, inhibits the production of TXA₂.

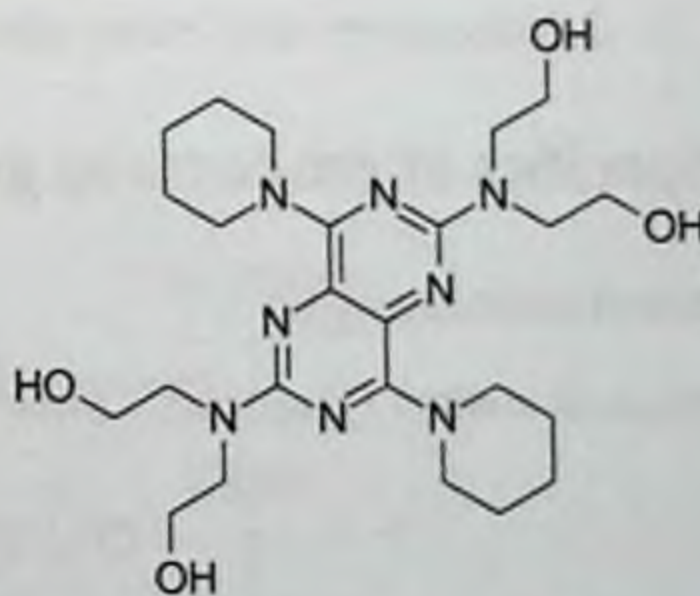


Fig. 12.10. 2,2',2,2'-[(4,8-Di-1-piperidinylpyrimido[5,4-d]pyrimidine-2,6-diyl)dinitrilo]tetrakis[ethanol]

- ▶ Inhibits adenosine deaminase and the reuptake of adenosine by erythrocytes (by affecting a special nucleoside transporter in the cell membrane) and increases its blood concentration. Adenosine stimulates adenylate cyclase and, in turn, cAMP in platelets, reduces cytoplasmic Ca^{2+} .

- ▶ Increases cAMP in vascular smooth muscle cells, reducing vascular tension.

It inhibits platelet adhesion more than aggregation.

Therapeutic indications: prevention of ischemic stroke and transient ischemic attacks in chronic cerebrovascular insufficiency; prevention of thromboembolic complications after peripheral vascular and cardiac surgery; progressive peripheral arterial occlusion

Side effects: hypotension, tachycardia, coronary steal syndrome, myalgia, thrombocytopenia, nausea, headache, dizziness

Contraindications: acute myocardial infarction, unstable angina, coronary artery atherosclerosis, pregnancy, breastfeeding

Anticoagulants

Classification

I. Direct anticoagulants

1. Indirect thrombin and factor Xa inhibitors: heparin sodium (Lioton 1000[®])
2. Indirect factor Xa inhibitors: nadroparin calcium (Fraxiparine[®]), enoxaparin sodium (Clexane[®])
3. Direct factor Xa inhibitors: rivaroxaban (Xarelto[®])
4. Direct thrombin inhibitors: bivalirudin (Angiomax[®], Angiox[®]), dabigatran etexilate (Pradaxa[®])

II. Indirect anticoagulants

1. 4-hydroxycoumarin derivatives: warfarin (Warfarex[®], Warfalan[®]), ethyl biscumacetate (Neodicoumarin[®], Pelentan[®])
2. Indandione derivative: phenindione (Phenylin[®])

Specifics of products by groups

Direct anticoagulants

Heparin sodium (Heparin[®], Lioton 1000[®])

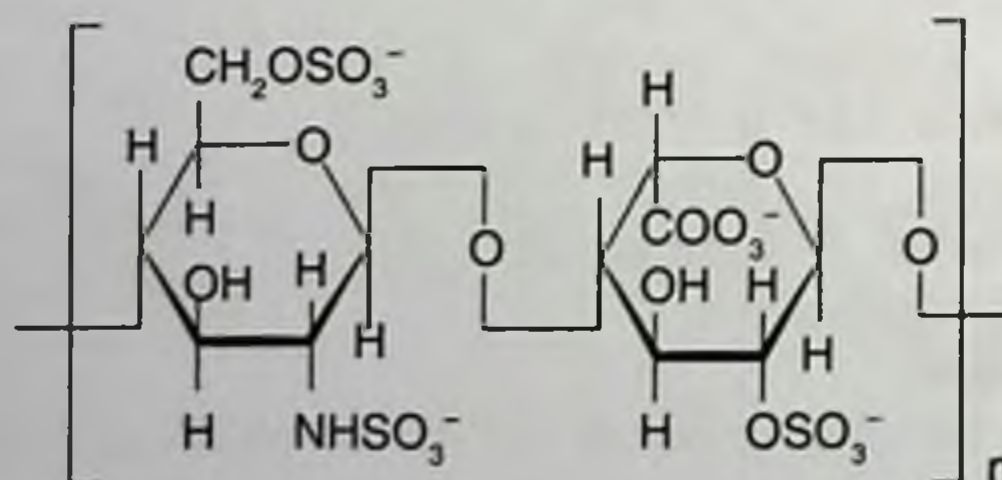


Fig. 12.11. Heparin structural formula

- ▶ Heparin sodium is a sodium salt of glycosaminoglycan containing sulfated and acetylated residues of D-glucosamine, D-glucuronic and L-iduronic acids.
- ▶ Indirect thrombin and factor Xa inhibitor. Bioavailability after subcutaneous administration is low (15–30%). It has a rapid but relatively short-term action. With intravenous administration, the effect occurs within 10–15 minutes, the time of action is 4–5 hours. With intramuscular administration, the effect occurs in 15–30 minutes and lasts up to 6 hours; with subcutaneous administration, the effect occurs in 40–60 minutes and lasts up to 8 hours. It poorly crosses the placental barrier; not excreted into breast milk.
- ▶ Metabolized in the liver with the involvement of N-desulfamidase and platelet heparinase, which is involved in the later stages of heparin metabolism. The involvement of platelet factor IV (anti-heparin factor) in metabolism and heparin binding to the macrophage system explains the rapid biological inactivation and short time of action. Excreted in the urine mainly as inactive metabolites. $T_{1/2}$: 1–2 hours. For intravenous, intramuscular, subcutaneous administration.

Mechanism of action: Due to the presence of a significant amount of negatively charged sulfate and carboxyl groups, the molecule has a negative charge, which facilitates the interaction of heparin sodium with proteins involved in blood clotting. Its sulfuric acid residues contribute to pronounced acidity. It inactivates thromboplastin, is an antithrombin III cofactor, causes conformational changes in its molecule and accelerates the complexing of antithrombin III with serine proteases of the coagulation system. This blocks thrombin, the enzymatic activity of activated factors IX, X, XI, XII, plasmin and kallikrein. It inhibits the transition of prothrombin to thrombin (Fig. 12.12).

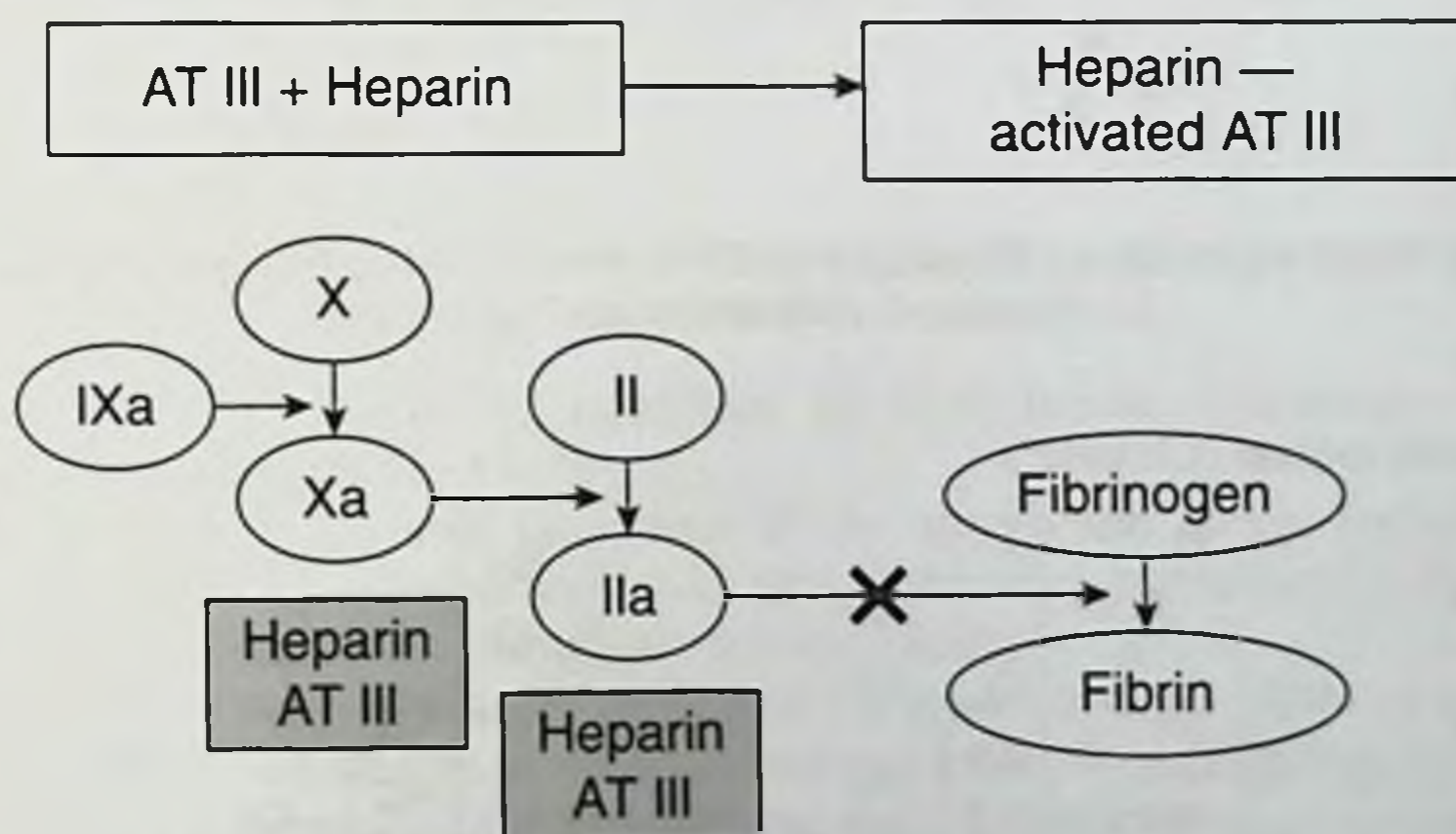


Fig. 12.12. Heparin mechanism of action

Pharmacological effects:

- ▶ anticoagulant: *in vivo* and *in vitro* activity
- ▶ antiplatelet: adsorbed to the endothelium and platelets, increases their negative charge, prevents platelet adhesion to the vascular endothelium and inhibits platelet aggregation

- ▶ anti-inflammatory (when applied topically): inhibits hyaluronidase
- ▶ hypolipidemic: lowers cholesterol and triglycerides by increasing lipoprotein lipase activity.

Therapeutic indications: deep vein thrombosis in the legs, pulmonary embolism, myocardial infarction, unstable angina, ischemic (thromboembolic) stroke, disseminated intravascular coagulation syndrome, extracorporeal circulation during cardiac surgery, hemoabsorption, hemodialysis

Side effects: hemorrhage, thrombocytopenia, with long-term use — alopecia, osteoporosis, soft tissue calcification, hypoaldosteronism, hyperkalemia

Contraindications: hemophilia, bleeding diathesis, hemorrhage at any location, gastric and duodenal ulcers (recurrence), subacute bacterial endocarditis, acute cardiac aneurysm, acute and chronic leukemia, aplastic and hypoplastic anemia, severe hepatic and/or renal disorders, cancer, cachexia, pregnancy

In case of overdose: antidote — protamine sulfate (1% solution by slow intravenous infusion at the rate of 0.1 mL per 100 IU of heparin sodium). The product has a positive charge, thus forming a neutral complex with heparin sodium.

Nadroparin calcium (Fraxiparine[®])

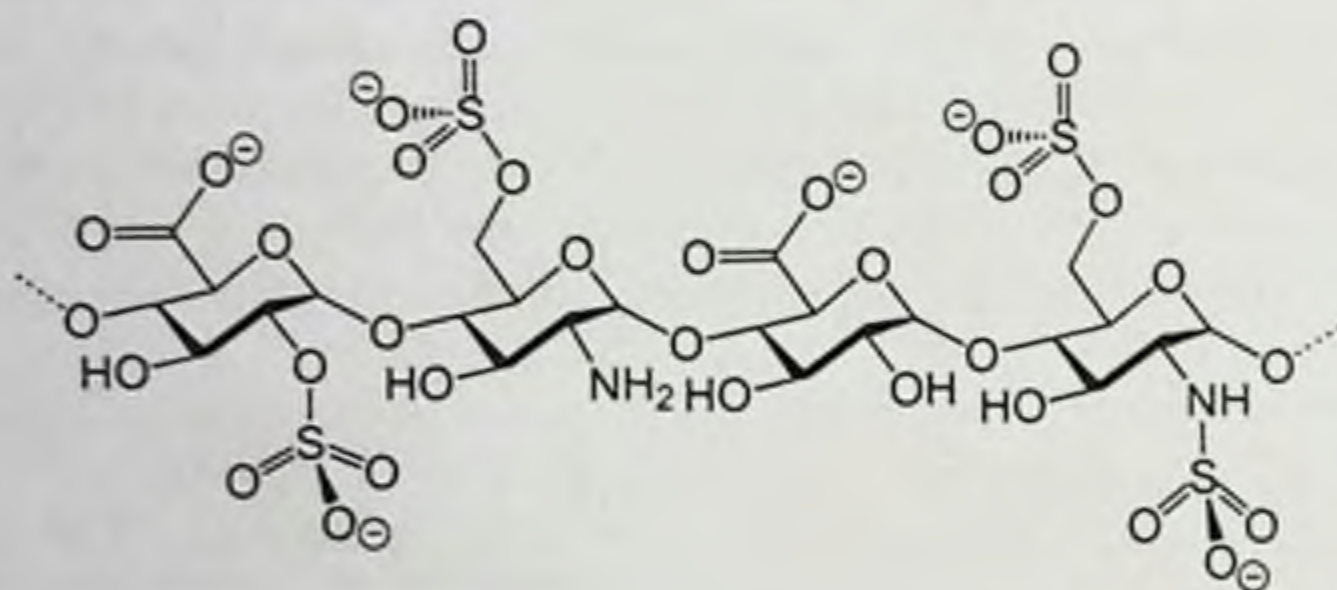


Fig. 12.13. 4S,6R)-6-[(2R,4R)-4,6-Dihydroxy-5-(sulfonatoamino)-2-(sulfonatooxymethyl)oxan-3-yl]oxy-3,4-dihydroxy-5-sulfonatooxan-2-carboxylate

Enoxaparin sodium (Clexane[®])

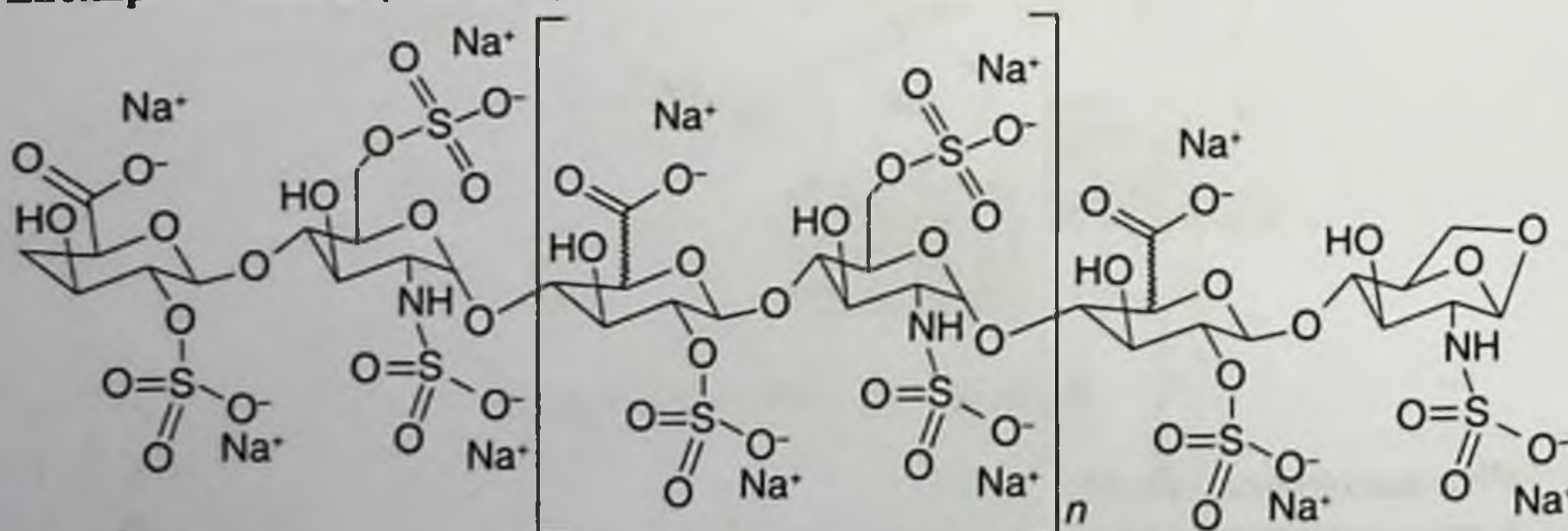


Fig. 12.14. 2-O-Sulfohexopyranosyluronic acid-(1->4)-2-deoxy-3-O-sulfo-2-sulfoamino-hexopyranosyl-(1->4)-2-O-sulfohexopyranosyluronic acid-(1->4)-2-acetamido-2-deoxy-6-O-sulfohexopyranose

Nadroparin calcium (Fraxiparine[®]) and enoxaparin sodium (Clexane[®]) are indirect factor Xa inhibitors (low molecular weight, fractionated heparins).

- ▶ They consist of heparin sodium fragments with an average molecular weight of 4000–5000 Da, obtained by fractionation, hydrolysis or depolymerization. Bioavailability when administered subcutaneously: 90%, time of action: 8–12 hours.
- ▶ $T_{1/2}$: 1.5–4.5 hours. For subcutaneous administration 1–2 times daily.

Mechanism of action: Unlike heparin sodium, they are better able to catalyze the inactivation of factor Xa, enhancing the blocking effect of antithrombin III on factor Xa (they have a more pronounced antithrombotic effect), do not have an inhibitory effect on thrombin — they show less anticoagulant activity, reducing the bleeding risk.

For therapeutic indications, see “Heparin sodium”.

Side effects: hemorrhage, thrombocytopenia

Contraindications: hemorrhagic tendency, including in gastric ulcer, thrombocytopenia, cerebrovascular disease, pregnancy

Rivaroxaban (Xarelto[®])

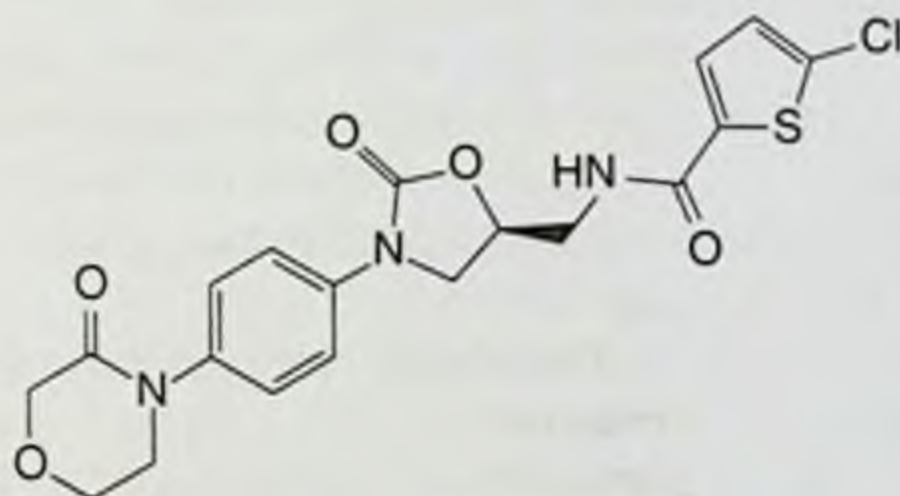


Fig. 12.15. (S)-5-Chloro-N-[[2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl] oxazolidin-5-yl]methyl]thiophene-2-carboxamide

- ▶ Bioavailability: 80–100%, regardless of food intake. Maximum plasma concentrations: after 2–4 hours.
- ▶ Metabolized in the liver (oxidation of the morpholine group, hydrolysis of amide bonds). Metabolites and unchanged rivaroxaban are excreted in the urine. $T_{1/2}$: 5–9 hours. For oral administration once daily.

Mechanism of action: Rivaroxaban is a highly selective direct inhibitor of factor Xa, which plays a central role in the coagulation cascade. By inhibiting factor Xa, it reduces thrombin formation. Activity does not require a cofactor (e.g., antithrombin III). It inhibits the activity of free factor Xa and prothrombinase. It has no direct effect on platelet aggregation but indirectly inhibits thrombin-induced platelet aggregation.

Therapeutic indications: prevention of venous thromboembolic complications after joint replacement, prevention of stroke and systemic thromboembolism in patients with atrial fibrillation, treatment and prevention of recurrent deep vein thrombosis and/or pulmonary embolism

Side effects: hemorrhage at various locations, posthemorrhagic anemia, elevated liver transaminases, hypotension

Contraindications: gastric and duodenal ulcers, cancers with a high risk of hemorrhage, hemorrhagic stroke, severe hepatic and/or renal disorders, pregnancy, breastfeeding, children under 18 years of age

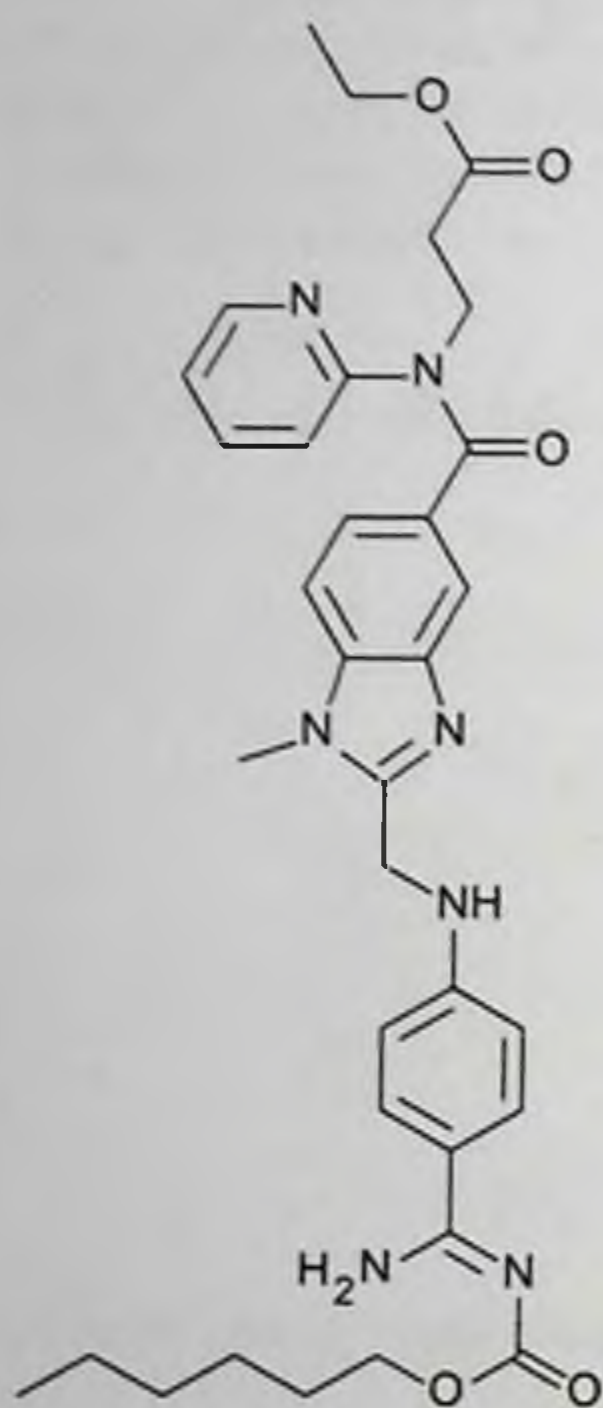


Fig. 12.16. Ethyl 3-[[2-[[4-(N'-hexyloxycarbonylcarbamidoyl)phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl] (pyridin-2-yl-amino)propanoate (as mesylate)

Dabigatran etexilate (Pradaxa*)

- ▶ Direct thrombin inhibitor. Dabigatran etexilate is completely converted by esterase-catalyzed hydrolysis to dabigatran, which is the major active metabolite in plasma. Maximum plasma concentrations: after 0.5–2.0 hours.
- ▶ Excreted in the urine (85%) and bile (6%). $T_{1/2}$: 12–14 hours. For oral administration 1–2 times daily.

Mechanism of action: A direct reversible thrombin inhibitor that binds hydrophobically to its active site. Since thrombin (serine protease) converts fibrinogen to fibrin during coagulation, inhibiting thrombin activity prevents clotting. Dabigatran has an inhibitory effect on free thrombin, fibrin clot-bound thrombin, and thrombin-induced platelet aggregation.

Therapeutic indications: prevention of venous thromboembolism after orthopedic surgery; prevention of stroke, systemic thromboembolism in atrial fibrillation; prevention of recurrent deep vein thrombosis and/or pulmonary embolism

Side effects: hemorrhage (gastrointestinal, urogenital), thrombocytopenia, posthemorrhagic anemia, nausea, diarrhea, hepatic impairment

Contraindications: coagulopathy, hemorrhage, hemorrhagic stroke, malignancies with a high risk of hemorrhage, hepatic disorders, pregnancy, breastfeeding, children under 18 years of age

Bivalirudin (Angiomax[®], Angiox*)

- ▶ A 20 amino acid peptide based on the structure of hirudin. It is rapidly distributed between plasma and extracellular fluid.
- ▶ Catabolized to its constituent amino acids, allowing these amino acids to be used in the body; metabolized by proteases, including thrombin. Excreted in the urine, 20% — unchanged. $T_{1/2}$: 35–40 min. For intravenous administration.

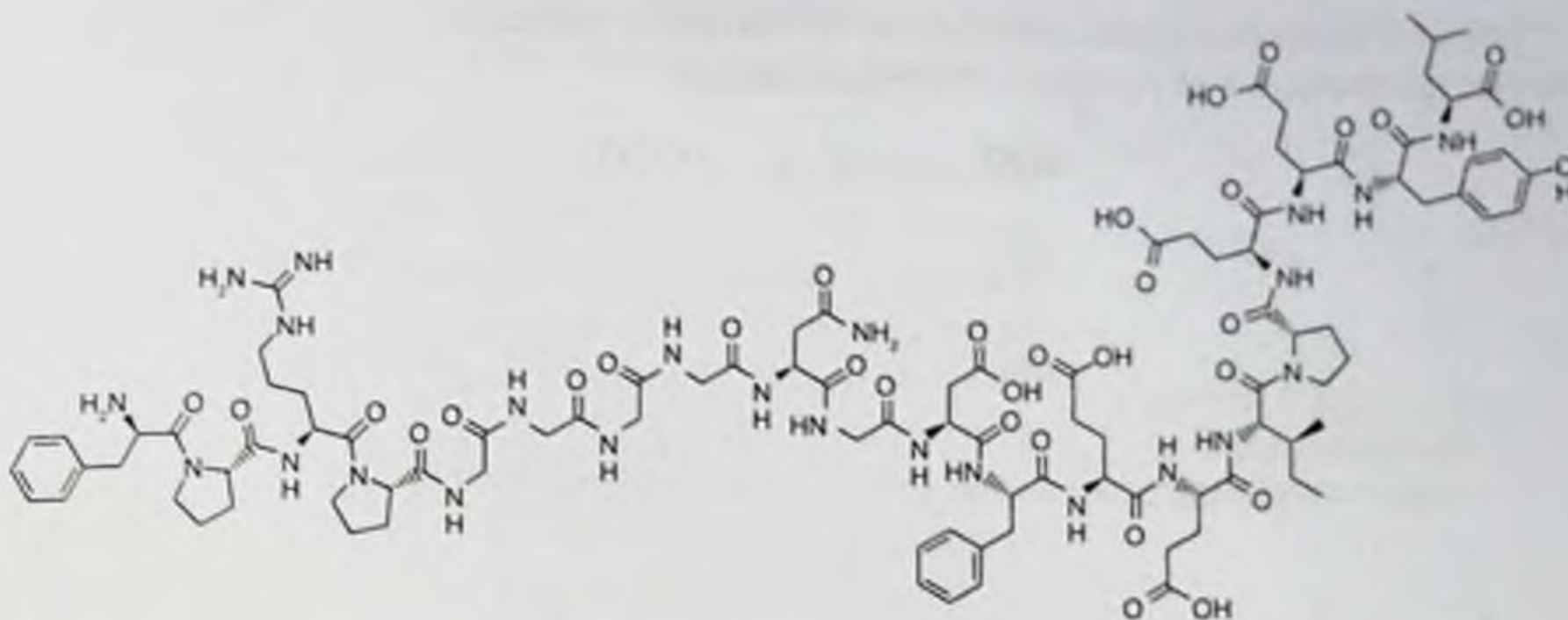


Fig. 12.17. Bivalirudin structural formula

Mechanism of action: Selective, reversible and direct thrombin inhibitor that binds to the catalytic site of thrombin as well as to the anion-binding site of both free and fibrin-bound thrombin. It inhibits all the reactions catalyzed and induced by thrombin, including thrombin formation, activation of coagulation factors V, VIII and XIII, platelet aggregation.

Therapeutic indications: percutaneous transluminal coronary angioplasty, unstable angina

Side effects: hemorrhage at various locations, low hemoglobin

Contraindications: hemorrhage, coagulopathy, hypertension, subacute bacterial endocarditis, severe renal impairment, pregnancy, breastfeeding, children under 18 years of age

Indirect anticoagulants

Mechanism of action: They inhibit the synthesis of vitamin K-dependent plasma proteins— factor II (prothrombin), factors VII, IX, X—in the liver. Vitamin K is needed for the formation of functionally complete factors as it acts as a coenzyme in the reaction of γ -carboxylation of glutamic acid residues. The reduced form of vitamin K, hydroquinone, exhibits co-enzyme activity. During the carboxylation reaction, vitamin K-hydroquinone is oxidized to form inactive vitamin K-epoxide. Indirect anticoagulants inhibit epoxide reductase and prevent the reverse transformation (reduction) of vitamin K-epoxide into active vitamin K-hydroquinone, which blocks the synthesis of factors II, VII, IX, X. Thus, they inhibit the synthesis of vitamin K-dependent plasma factors involved in hemostasis, causing the blood levels of prothrombin, factor VII, etc. to decrease (Fig. 12.18).

Therapeutic indications: treatment and prevention of deep vein thrombosis and thromboembolism (acute and recurrent DVT, pulmonary embolism), prevention of thromboembolic complications in patients with atrial fibrillation, heart valve damage or with prosthetic heart valves, secondary prevention of myocardial infarction and prevention of thromboembolic complications after myocardial

infarction, treatment and prevention of transient ischemic attacks and ischemic stroke, prevention of postoperative thrombosis

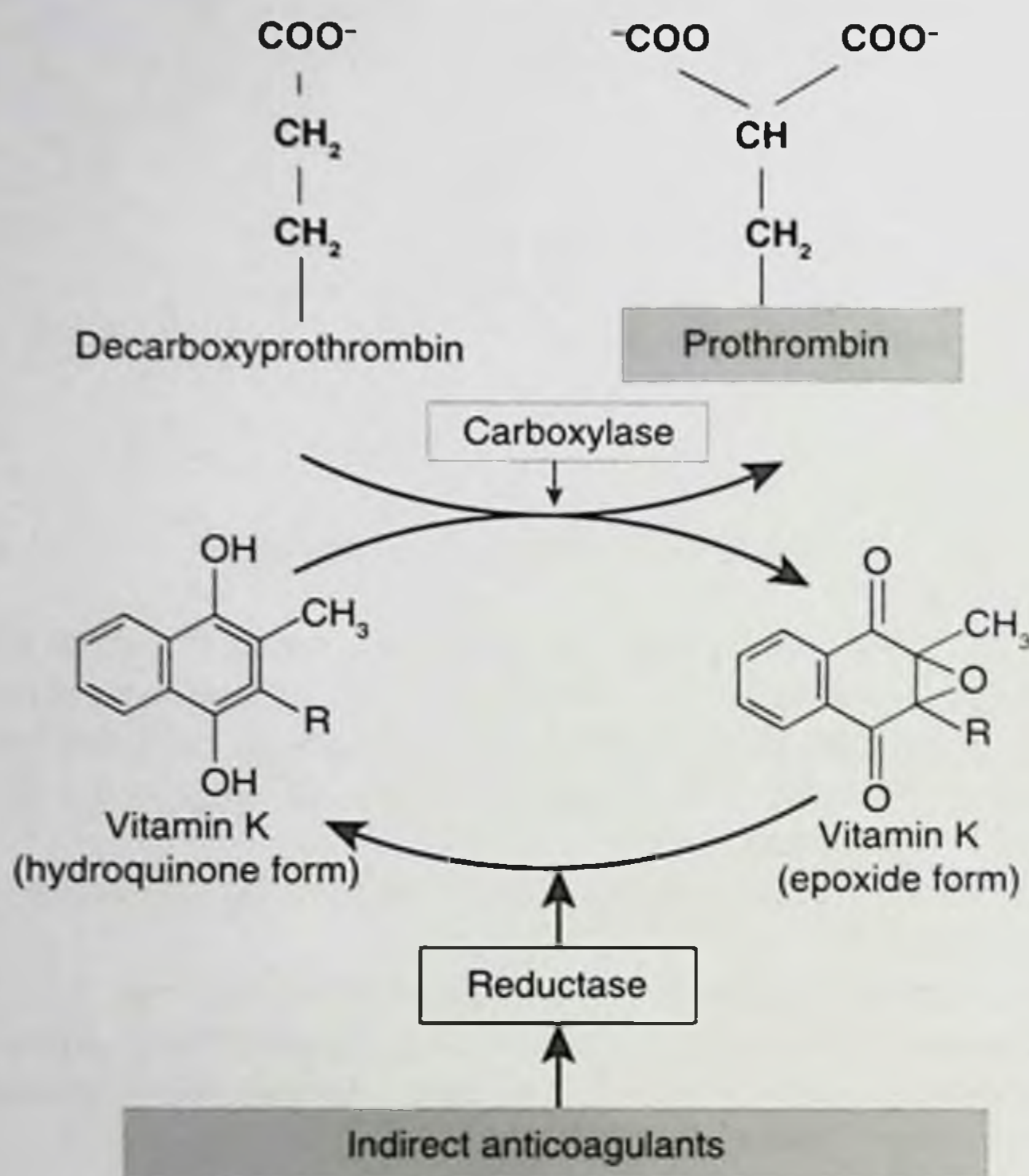


Fig. 12.18. Mechanism of action of indirect anticoagulants (Kharkevich D.A., 2021)

Side effects: cumulation, hemorrhagic syndrome, cholestatic hepatitis, elevated liver transaminases, nausea, vomiting, diarrhea, alopecia, fever, leukopenia, teratogenic effects

Contraindications: hematuria, bleeding diathesis, hemorrhagic stroke, hepatic and/or renal impairment, malignancies, gastric ulcer, duodenal ulcer, myocardial infarction, hypertension, pregnancy

Antidote for overdose with indirect anticoagulants: sodium menadione bisulfite (Vikasol[®]) in epoxide form activates a specific carboxylase that ensures the carboxylation of glutamic acid residues in the protein structure, which contributes to the synthesis of blood coagulation factors (II, VII, IX, X).

Warfarin (Warfarex[®], Warfalan[®])

- ▶ Indirect anticoagulant, a 4-hydroxycoumarin derivative; a racemic mixture of two active enantiomers, R- and S-configurations, each of which is excreted from the body through different routes. S-warfarin is 5-fold more potent than the R-isomer as an antagonist to vitamin K. The maximum plasma concentration is reached within the first 4 hours after administration. Crosses the placental barrier but not

excreted into breast milk. Bioavailability: about 95%, it takes about 4 days to achieve the maximum effect.

- ▶ Metabolized in the liver with the involvement of cytochrome P450 isoenzymes to form inactive hydroxylated metabolites (predominant metabolic pathway) and reductases to form reduced metabolites (warfarin alcohols), which have a minimal anticoagulant effect. The S-isomer is metabolized faster. Excreted mainly in the urine (92%) as inactive metabolites. $T_{1/2}$ of racemic warfarin: 40 hours. For oral administration once daily.

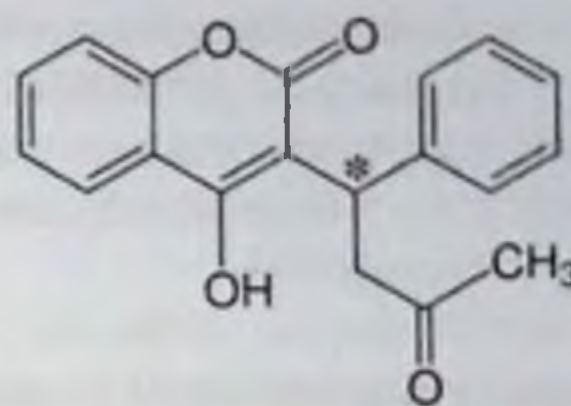


Fig. 12.19. 4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one

Ethyl biscum acetate (Neodicumarin[®], Pelentan[®])

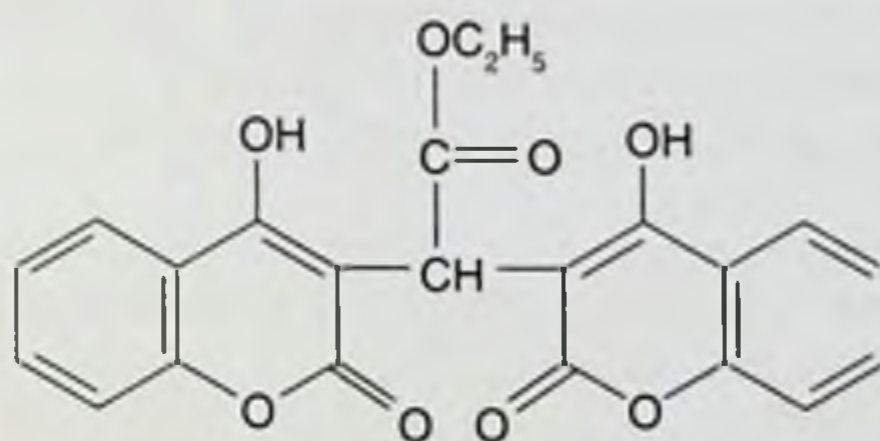


Fig. 12.20. 4-Hydroxy- α -(4-hydroxy-2-oxo-2H-1-benzopyran-3-yl)-2-oxo-2H-1-benzopyran-3-acetic acid ethyl ester

- ▶ Indirect anticoagulant, a 4-hydroxycoumarin derivative. The therapeutic effect occurs in 2–3 hours, reaching a maximum in 12–30 hours. It crosses the placental barrier and is excreted into breast milk.
- ▶ Metabolized in the liver, excreted in the urine as inactive metabolites. $T_{1/2}$: 2.5 hours. For oral administration 2–3 times daily.

Phenindione (Phenylin[®])

- ▶ Indirect anticoagulant, an indandione derivative. The concentration of blood coagulation factors decreases in 8–10 hours, reaching a maximum in 24–30 hours after administration. It crosses blood-tissue barriers, including the placental one.
- ▶ Metabolized in the liver with the involvement of cytochrome P450. Excreted in the urine unchanged and as metabolites. $T_{1/2}$: 6 hours. For oral administration 2–3 times daily.

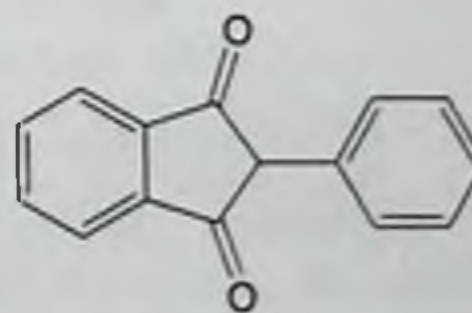


Fig. 12.21. 2-phenyl-1H-indene-1,3(2H)-dione

Fibrinolytic agents

Classification

- ▶ First generation: streptokinase (Kabikinase[®], Awelysin Braun[®]), streptodectase[®], urokinase (Purocin[®], Ukidan[®])

- ▶ Second generation: alteplase (Actilyse[®]), tenecteplase (Metalyse[®])

Fibrinolytic (thrombolytic) agents are activators of profibrinolysin. They are inactive when acting directly on fibrin strands, but when introduced into the body, they activate the endogenous fibrinolytic system (convert profibrinolysin to fibrinolysin).

Specifics of individual products

Streptokinase (Kabikinase[®], Awelysin Braun[®])

An enzyme derived from the culture of β -hemolytic streptococcus.

- ▶ With intravenous infusion, plasma fibrinogen levels decrease within 24–36 hours. The maximum therapeutic effect occurs in 45 minutes; hyperfibrinolysis gradually decreases but persists for several hours.
- ▶ It undergoes biotransformation in the liver by hydrolysis. Excreted in the urine. $T_{1/2}$ after intravenous administration of 1,500,000 IU: 1 hour; $T_{1/2}$ of streptokinase-plasminogen complex: 15–25 minutes; the complex is partially inactivated by anti-streptococcal antibodies. For intravenous drip (intra-arterial administration, if necessary).

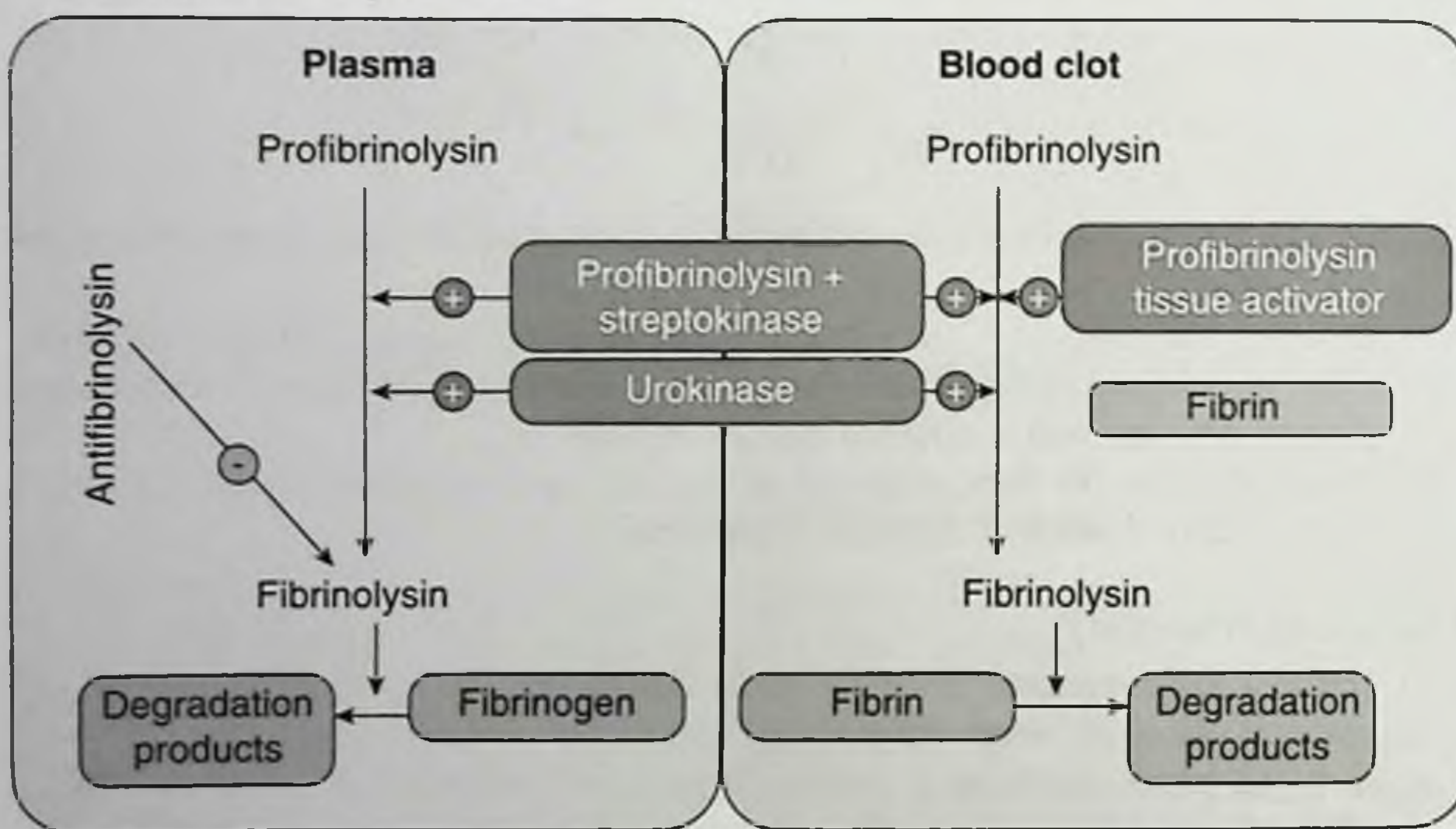


Fig. 12.22. Mechanism of action of fibrinolytics

Mechanism of action: Streptokinase does not have proteolytic activity; it is an activator of fibrinolysis. By interacting with plasminogen (profibrinolysin), it forms an activator complex that catalyzes the conversion of blood plasminogen and blood clots into plasmin (Fig. 12.22). Plasmin, having proteolytic enzymatic activity, causes lysis of fibrin strands in blood clots, inactivates fibrinogen, as well as factors V and VII. It dissolves blood clots, acting both on their surface and inside. Streptokinase is most effective on fresh fibrin clots up to 3 days (before contraction), restores the patency of thrombosed blood vessels. It activates not

only tissue fibrinolysis (the action is aimed at dissolving a blood clot, thrombolysis), but also systemic fibrinolysis (fibrinogen breakdown in the blood).

Therapeutic indications: pulmonary and peripheral embolism, deep and superficial vein thrombosis, acute myocardial infarction (during the first 12 hours), retinal vascular thrombosis

Side effects: bleeding and hemorrhage; pyrogenic reaction (fever, nausea, allergic reactions, including anaphylactic shock); with rapid intravenous administration: hypotension, arrhythmia; thromboembolism (due to mobilization of blood clot elements)

Contraindications: acute bleeding, bleeding diathesis, erosive and ulcerative gastrointestinal lesions, severe hypertension, septic endocarditis, cerebrovascular disease, active tuberculosis, pregnancy, breastfeeding

Streptodectase[®] is a streptokinase immobilized on a water-soluble polysaccharide matrix. Gradual biodegradation of the polysaccharide molecule ensures uniform and prolonged release. A single injection of the product increases fibrinolytic activity for 48–72 hours. For intravenous drip.

For therapeutic indications, side effects and contraindications, see “Streptokinase”.

Urokinase (Purochin[®], Ukidan[®])

- ▶ Proteolytic enzyme with the amino acid serine as an active site (serine protease). Urokinase administration decreases the levels of plasminogen and fibrinogen and increases fibrin and fibrinogen degradation products, which persist for 12–24 hours after infusion. It is inactivated by proteases (α 2-macroglobulin, α 1-antitrypsin, α 2-antiplasmin, antithrombin III).
- ▶ Metabolized in the liver. Inactive degradation products are excreted in the urine and bile. $T_{1/2}$: 10–20 min. For intravenous, intracoronary administration.

Mechanism of action: Unlike streptokinase, it is a direct plasminogen activator. The enzyme enters the blood clot and converts plasminogen into plasmin by hydrolysis of the arginine-valine bond. Plasmin destroys fibrin, dissolving the clot. Like streptokinase, it causes systemic activation of fibrinolysis, but its antigenic properties are less pronounced.

For therapeutic indications, side effects and contraindications, see “Streptokinase”.

Alteplase (Actilyse[®])

- ▶ Recombinant human tissue plasminogen activator, glycoprotein. After bolus injection, the plasma concentration of the active substance reaches 50% in 5 minutes, less than 10% in 20 minutes. The thrombolytic action of alteplase lasts about 4 hours.
- ▶ It undergoes biotransformation in the liver. About 80% of the dose is excreted in the urine as metabolites. $T_{1/2}$ from plasma: 4–5 minutes. For intravenous administration.

Mechanism of action: After intravenous administration, alteplase is inactive in the circulatory system. It binds to fibrin in the blood clot, activates clot-bound plasminogen, and cleaves it at the Arg561–Val562 peptide bond to form plasmin. Plasmin breaks cross-links between polymerized fibrin molecules, which dissolves the clot and opens thrombosed vessels. It causes systemic activation of profibrinolysin

to a much lesser extent than streptokinase and urokinase. Its thrombolytic efficacy is superior to streptokinase and urokinase and it has no antigenicity.

Therapeutic indications: myocardial infarction (in the first 6–12 hours), acute massive pulmonary embolism, acute ischemic stroke in the first 4.5 hours

Side effects: bleeding and hemorrhage; with rapid intravenous administration: hypotension, thromboembolism (due to mobilization of blood clot elements)

For contraindications, see "Streptokinase".

Tenecteplase (Metalyse[®])

- ▶ Recombinant tissue plasminogen activator, a derivative of natural tissue plasminogen activator. More stable and more fibrin-specific than alteplase.
- ▶ Metabolized in the liver, excreted in bile. $T_{1/2}$: 20 min. For intravenous administration.

For mechanism of action, therapeutic indications, side effects and contraindications, see "Alteplase".

PRODUCTS THAT HELP STOP BLEEDING (HEMOSTATIC AGENTS)

Classification

I. Coagulants

1. Topical coagulants: thrombin (Trombin[®]), Hemostatic collagen sponge[®] (boric acid, nitrofurazone, collagen)
 2. Systemic coagulants: sodium menadione bisulfite (Vikasol[®]), gelatin (Gelatinol[®]), human fibrinogen/human thrombin
 3. Herbal coagulants: water pepper herb, achillea herb, nettle leaf
- #### **II. Antifibrinolytic agents:** aminocaproic acid (ϵ -aminocaproic acid[®]), tranexamic acid (Tranexam[®], Cyklokapron[®]), aprotinin (Contrykal[®], Gordox[®]), Pantrypinum[®]

Specifics of individual products

Thrombin (Trombin[®])

Serine protease is an essential component of the human blood coagulation cascade and belongs to the hydrolase class of enzymes. It catalyzes the hydrolysis of peptide bonds formed by arginine and lysine residues, has limited substrate specificity. Its main function is the conversion of fibrinogen into fibrin.

Therapeutic indications (topical): surgical interventions on parenchymal organs (liver, lungs, spleen, kidney, etc.), gingival, nasal and other capillary bleeding, especially in Werlhof's disease, aplastic and hypoplastic anemia, hemophilia

Side effects: secondary infection

Contraindications: large vessel bleeding

Intravenous and intramuscular administration of thrombin is not allowed due to the risk of widespread vascular thrombosis.

Hemostatic collagen sponge* (boric acid, nitrofurazone, collagen)

The product has topical hemostatic and antiseptic effects, stimulates tissue regeneration. Upon contact with a bleeding surface, platelet adhesion and aggregation occur, which rapidly stops capillary and parenchymal bleeding.

Therapeutic indications (topical): capillary and parenchymal bleeding, trophic ulcers, bedsores

For side effects and contraindications, see "Thrombin".

Menadione sodium bisulfite (Vikasol*)

- ▶ Systemic coagulant; polycyclic aromatic ketone based on 1,4-naphthoquinone. A synthetic water-soluble analogue of vitamin K (vitamin K₃). Onset occurs in 8–24 hours after intramuscular injection.
- ▶ After metabolic activation, it is oxidized in the liver to the diol form. Excreted in the urine (up to 70%) and bile as metabolites.

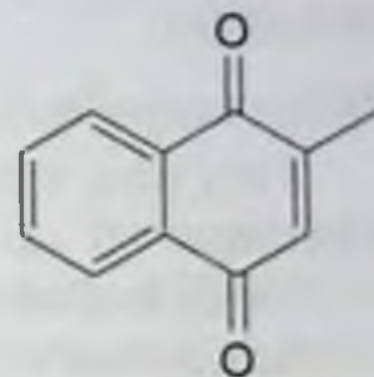


Fig. 12.23. 2-Methylnaphthalene-1,4-dione

For oral administration 2–3 times daily, for intramuscular administration.

Mechanism of action: As an epoxide, it activates carboxylases that ensure the carboxylation of glutamic acid residues in the polypeptide chains of proteins, which contributes to the synthesis of vitamin K-dependent plasma hemostasis factors II, VII, IX and X in the liver.

Therapeutic indications: hemorrhagic syndrome associated with hypoprothrombinemia; hypovitaminosis K (including in obstructive jaundice, hepatitis, liver cirrhosis, prolonged diarrhea); bleeding after injuries and surgical interventions; overdose of indirect anticoagulants; as a preventive measure for pregnant women, premature newborns

Side effects: hemolytic anemia, hemolysis in newborns with congenital glucose-6-phosphate dehydrogenase deficiency, hyperbilirubinemia, decreased blood pressure, tachycardia, change in taste

Contraindications: hypercoagulation, thromboembolism, hemolytic disease of the newborn, pregnancy, breastfeeding

Gelatin (Gelatinol*)

It contains amino acids: glycine, proline, methionine, cystine, etc.

For intravenous, intraarterial administration.

Therapeutic indications (as a plasma substitute): acute blood loss, surgical, hypovolemic shock, detoxification (in case of burns, etc.)

Side effects: proteinuria (1–2 days)

Contraindications: acute, chronic nephritis

Fibrinogen*

- ▶ Fibrinogen is a glycoprotein complex. The fibrinogen molecule is a dimer; each subunit has three types of polypeptide chains linked by disulfide bridges (SS bonds) into a single covalent structure.

- ▶ A systemic coagulant, compensates for fibrinogen deficiency. The conversion of fibrinogen to fibrin, which occurs under the influence of thrombin, is the final stage of the blood coagulation process, clot formation.

- For intravenous drip.

Therapeutic indications: hypo- and afibrinogenemia, bleeding in surgical, gynecological interventions, preoperative preparation of patients with hypofibrinogenemia

Side effects: hypercoagulation, thrombosis

Contraindications: thrombosis of various origins, hypercoagulation, myocardial infarction

Water pepper herb, achillea herb, nettle leaf

They have a hemostatic effect, reduce capillary permeability and increase blood clotting.

Nettle leaf contains vitamins K, C, carotene, etc. It is used as an infusion.

Achillea millefolium (commonly known as Yarrow) contains the alkaloid achillein, vitamin C, carotene. It is used as an infusion.

Water pepper contains flavonoids (including quercetin, rutin), tannins. It is used as an extract.

Therapeutic indications (oral, topical): heavy menstrual bleeding (in combination therapy), minor bleeding during the post-coagulation period of cervical erosion treatment.

Aminocaproic acid (ϵ -aminocaproic acid¹⁾)



Fig. 12.24. 6-aminohexanoic acid

- Fibrinolysis inhibitor; synthetic lysine analogue. With intravenous administration, the effect occurs in 15–20 minutes. Maximum blood concentration occurs within 2 hours.
- Metabolized in the liver, excreted in the urine — 40–60% unchanged. $T_{1/2}$: 4 hours. For intravenous administration.

Mechanism of action: It inhibits fibrinolysis by competitively saturating lysine-binding receptors, through which plasminogen (plasmin) binds to fibrinogen (fibrin). It suppresses the conversion of profibrinolysin to fibrinolysin by inhibiting the activator of this process, and also has a direct inhibitory effect on fibrinolysin, suppresses the activating effect of tissue kinases on fibrinolysis, neutralizes the effects of kallikrein, trypsin and hyaluronidase, and reduces capillary permeability.

Therapeutic indications: hemorrhage (hyperfibrinolysis, hypo- and afibrinogenemia); hemorrhage associated with increased fibrinolysis during surgery and other pathological conditions; fibrinolytic overdose; hemophilia, thrombocytopenic purpura, aplastic anemia

Side effects: hypotension (including orthostatic), hypercoagulation, nausea, diarrhea, acute renal impairment, convulsions

Contraindications: hypercoagulation (thrombosis, thromboembolism), coagulopathy due to disseminated intravascular coagulation, cerebrovascular disease, pregnancy, breastfeeding

Tranexamic acid (Tranexam[†], Cyklokapron¹⁾)

- Fibrinolysis inhibitor. Significantly more potent than aminocaproic acid; binds to both strong and weak binding sites in the plasminogen molecule. Superior efficacy to aminocaproic acid, acts longer. Bioavailability: 30–50%.

Antifibrinolytic concentration in various tissues persists for 17 hours, and up to 7–8 hours in plasma. It crosses the BBB, placental barrier, excreted into breast milk.

- ▶ It undergoes minimal biotransformation. Excreted in the urine, with more than 95% unchanged, during the first 12 hours. For oral administration 2–4 times daily, for intravenous administration.

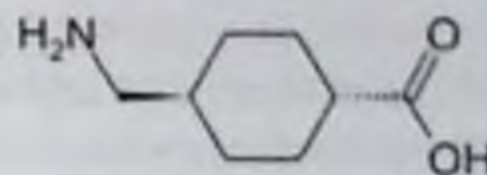


Fig. 12.25. Trans-4-(aminomethyl)cyclohexanecarboxylic acid

Aprotinin (Contrykal[®], Gordox[®]), Pantrypinum[®]

- ▶ Single-chain polypeptide containing 58 amino acids that blocks the kallikrein-kinin system. Inhibits both total proteolytic activity and the activity of individual proteolytic enzymes. It is a polyvalent inhibitor of proteases (including plasmin, kininogenase, trypsin, chymotrypsin, kallikrein, including activating fibrinolysis). Reduces fibrinolytic activity in blood, inhibits fibrinolysis and has a hemostatic effect in coagulopathy.
- ▶ Excreted in the urine as inactive metabolites, the initial $T_{1/2}$ is 0.3–0.7 hours, the final $T_{1/2}$ is 5–10 hours. For intravenous administration.

VASOPROTECTIVE AGENTS

Drug products that normalize metabolic processes in the vascular wall, reduce the permeability of the vascular wall and improve microcirculation.

Specifics of individual products

Ethamsylate (Dicynone[®])

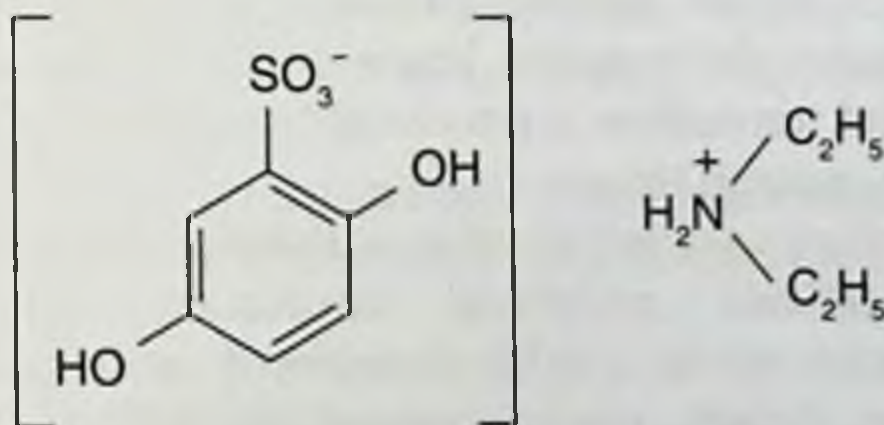


Fig. 12.26. 2,5-Dihydroxybenzenesulfonic acid with diethylamine

- ▶ The hemostatic effect with intravenous administration occurs in 5–15 minutes, reaching a maximum in 1–2 hours, the time of action is 4–6 hours. When taken orally, the maximum effect occurs in 3 hours. After a course of treatment, the effect persists for 5–8 days. Crosses the placental barrier.
- ▶ Excreted in the urine (unchanged) and bile. $T_{1/2}$ after intramuscular administration is 2.1 hours, 1.9 hours after intravenous administration, 3.7 hours after oral administration. For oral administration 3 times daily, for intramuscular, intravenous, subconjunctival, retrobulbar administration.

Mechanism of action: Stimulates the production of platelets and their release from bone marrow. Activates the production of tissue thromboplastin (factor III) at the site of damage to small vessels, reduces the production of prostacyclin PGI₂ in the vascular

endothelium, increases platelet adhesion and aggregation. Increases the formation rate of the primary clot and enhances its contraction. Having anti-hyaluronidase activity, it promotes the production of mucopolysaccharides in the vascular wall, increases capillary resistance, normalizes their permeability, reduces the release of fluid and diapedesis of blood cells from the vascular bed, improves microcirculation.

Therapeutic indications: prevention and arrest of capillary and parenchymal bleeding during dental, urological, ophthalmic, otorhinolaryngological surgery; intestinal, renal, pulmonary hemorrhage; secondary hemorrhage in thrombocytopenia; hemorrhagic vasculitis, bleeding diathesis; diabetic microangiopathy; intracranial hemorrhage

Side effects: hypotension, nausea, heartburn, lower extremity paresthesia

Contraindications: thrombosis, history of thromboembolism, porphyria, pregnancy, breastfeeding

Pentoxifylline (Trental[®])

- ▶ Purine derivative. Maximum concentration when taken orally occurs in 1 hour. It undergoes first-pass metabolism in the liver to form two main pharmacologically active metabolites: 1-5-hydroxyhexyl-3,7-dimethylxanthine and 1-3-carboxypropyl-3,7-dimethylxanthine. Bioavailability is low. Excreted into breast milk.

- ▶ Excreted in the urine as water-soluble metabolites (more than 90%) and bile (less than 4%). $T_{1/2}$: 0.5–1.5 hours. For oral administration 2–3 times daily, for intravenous administration.

Mechanism of action: It inhibits PDE, stabilizes cAMP and reduces intracellular Ca^{2+} concentrations. It blocks adenosine receptors. It reduces platelet aggregation, increases their resistance to deformation, improves the rheological properties of blood, inhibits thrombosis and normalizes microcirculation. It has a vasodilating effect and improves the oxygen supply to tissues.

Pharmacological effects: angioprotective, antiplatelet, vasodilating

Therapeutic indications: peripheral circulation disorder, dyscirculatory encephalopathy, ischemic stroke, trophic disorders of organs and tissues, acute central retinal artery occlusion, diabetic neuropathy and angiopathy

Side effects: tachycardia, angina attacks, visual disturbances, scotoma, convulsions, dyspepsia, intestinal atony, decreased blood pressure (when administered intravenously)

Contraindications: acute myocardial infarction, major bleeding, cerebral and retinal hemorrhage, severe arrhythmias, coronary and cerebrovascular atherosclerosis, pregnancy and breastfeeding

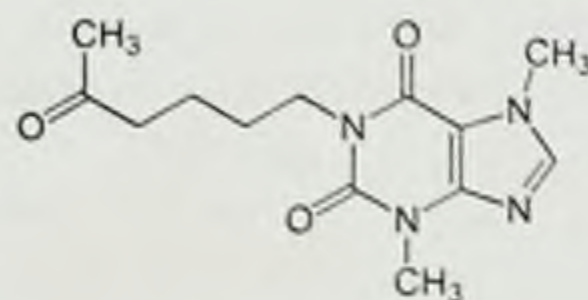


Fig. 12.27. 3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1H-purine-2,6-dione

Troxerutin (Troxevasin[®]), Rutoside (Venoruton[®])

- ▶ Vasoprotective, flavonoid (a semi-synthetic rutin derivative). Absorption after oral administration: 10–15%, maximum plasma concentration reached in 2 hours.
- ▶ Metabolized in the liver. Partially excreted unchanged in the urine (20–22%) and bile (60–70%). For oral, topical administration.

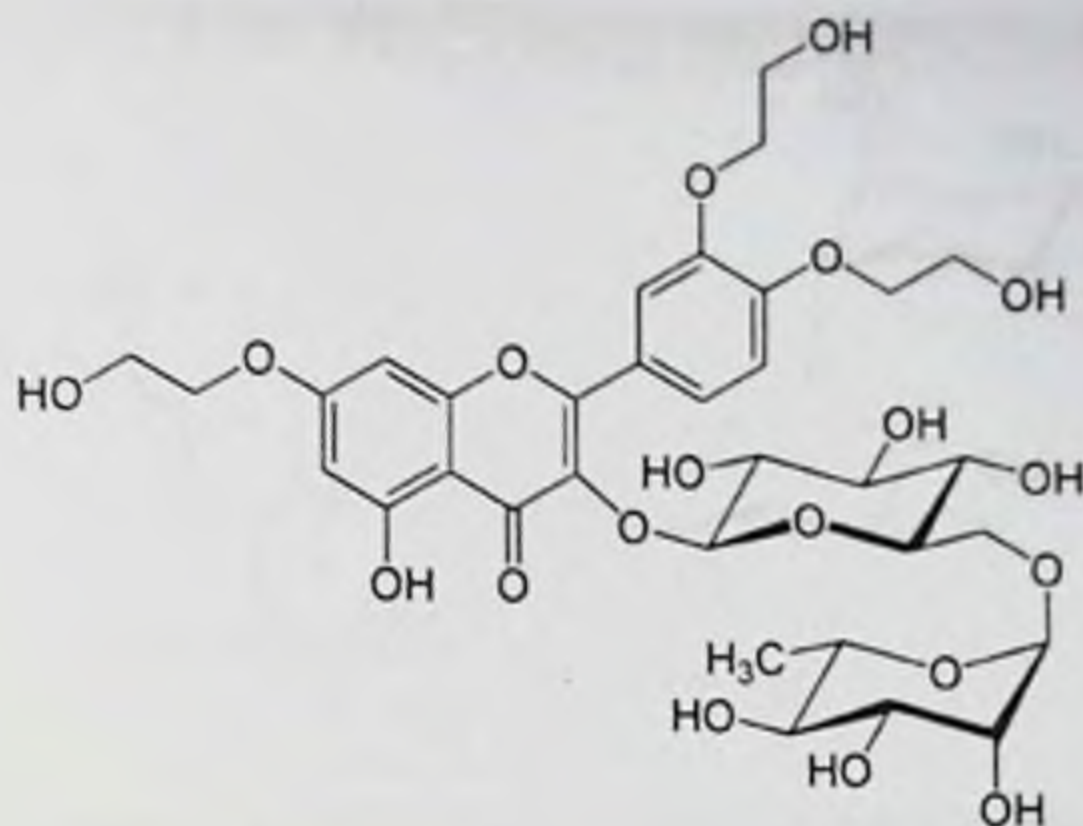


Fig. 12.28. 2-[3,4-bis(2-Hydroxyethoxy)phenyl]-5-hydroxy-7-(2-hydroxyethoxy)-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxychromen-4-one

Mechanism of action: Acts mainly on the capillaries and veins.

Involved in redox processes, blocks hyaluronidase, stabilizes hyaluronic acid at cell membranes, reduces capillary permeability and increases their tone. Increases vascular wall density, reduces plasma exudation and diapedesis of blood cells, reduces inflammation in the vascular wall. Inhibits aggregation and increases the degree of erythrocyte deformability.

Pharmacological effects: venotonic, angioprotective, anti-inflammatory, antioxidant

Therapeutic indications: varicose veins, chronic venous insufficiency, trophic disorders in chronic venous insufficiency, bleeding diathesis, capillary toxicosis, diabetic microangiopathy, retinopathy

Side effects: gastrointestinal erosions and ulcers, nausea, diarrhea, heartburn

Contraindications: gastric and duodenal ulcers, exacerbated chronic gastritis, pregnancy, breastfeeding

Ascorutin[®] (ascorbic acid, rutoside)

Combination product: ascorbic acid is involved in the regulation of redox processes, blood clotting, and healing processes; rutoside reduces the permeability and fragility of capillaries, strengthens the vascular wall by reducing swelling and inflammation. It has an antiplatelet effect, which improves microcirculation.

Therapeutic indications: in combination therapy for varicose veins, trophic disorders and skin ulcers, chronic venous insufficiency, hemorrhagic diathesis

Side effects: dyspepsia, headache

Contraindications: congenital fructose intolerance, glucose-galactose malabsorption, sucrase/isomaltase deficiency; pregnancy (1st trimester), children under 18 years of age

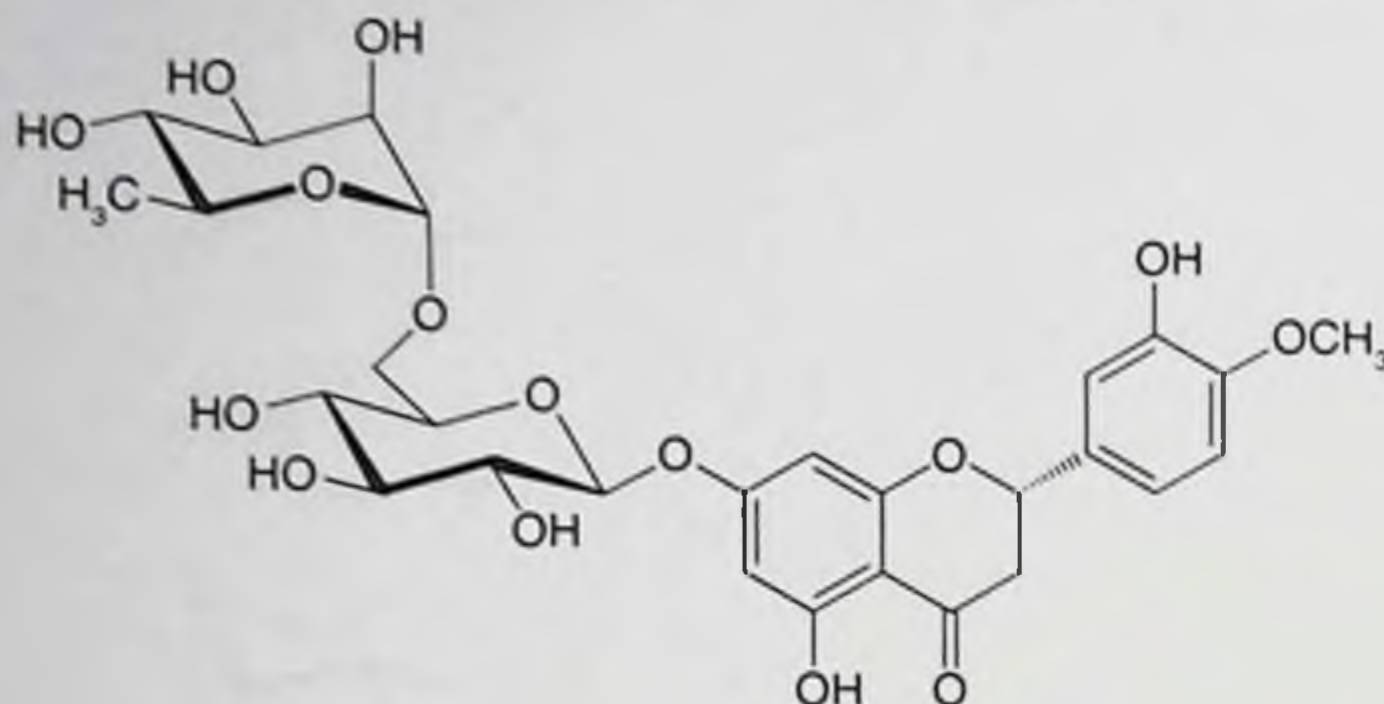
Detralex* (diosmin, flavonoids calculated with reference to hesperidin)

Fig. 12.29. Diosmin structural formula (5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-7-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxychromen-4-one)

- ▶ A venotonic, venoprotective agent that contains diosmin and hesperidin. Hesperidin is a flavone compound similar to rutin and quercetin in its structure and action. Diosmin also has a flavone structure (rhamnoglucoside), similar to hesperidin (substituted by a sugar radical). The product reduces vein compliance and venous stasis, reduces capillary permeability and increases their resistance, improves microcirculation and lymphatic outflow.
- ▶ For oral administration twice daily.

Therapeutic indications: chronic venous insufficiency in the legs, exacerbation of hemorrhoids

Side effects: dyspepsia, nausea, vomiting

Contraindications: hypersensitivity to the drug product's ingredients

Aescusan* (horse chestnut seed extract, thiamine hydrochloride), Venoplant*

- ▶ Horse chestnut fruit extract contains flavonoids (similar to rutin in their nature), saponins, thiamine, escin, etc.
- ▶ It decreases the concentration of lysosomal enzymes, resulting in less breakdown of mucopolysaccharides in capillary walls. It reduces vascular permeability, preventing the filtration of low molecular weight proteins, electrolytes and water into the intercellular space. It has anti-exudative and venotonic effects.
- ▶ For oral administration 3 times daily.

Therapeutic indications: venous congestion, varicose veins, hemorrhoids, leg ulcers

13. DRUGS AFFECTING HEMATOPOIESIS

Grouping of drugs

- I. Drugs affecting erythropoiesis
 - A. Stimulating agents
 - B. Suppressive agents
- II. Drugs affecting leukopoiesis
 - A. Stimulating agents
 - B. Suppressive agents

ERYTHROPOIESIS STIMULATING AGENTS

Classification

1. Drugs used mainly for hypochromic anemia
 - Drugs containing iron, cobalt or erythropoietin
2. Drugs used mainly for hyperchromic anemia
 - Cyanocobalamin (vitamin B₁₂, Cobamamide*)
 - Folic acid [vitamin B₉ (B_c), Folacin*]

Iron is an essential micronutrient that is contained in hemoglobin and myoglobin. Iron is involved in various mitochondrial metabolic processes including respiration. It participates in detoxification (as a part of cytochrome P450) and immune function. It also regulates the activity of some CNS enzymes. Iron is an important component or cofactor in 75 or so enzymes. Iron depletion (discrepancy between iron supply and needs) leads to the development of iron-deficiency anemia.

Iron has been used to treat iron-deficiency anemia since ancient times. Physicians in ancient Greece offered gave iron to their patients to treat fatigue and gain strength of Ares, the Greek god of war. Ancient roman doctor Celsus (1st century) recommended to his patients with splenomegaly to drink water in which the blacksmith had occasionally dipped his red hot iron. Hippocrates and Dioskuridis prescribed wine in which iron objects had been soaking. Therapeutic use of iron was introduced by the English physician Thomas Sydenham (1624–1689) for the treatment of anemia.

In 1832, French physician Pierre Blaud recommended iron supplement pills containing ferrous sulfate and potassium carbonate. In the 18th century, Count Alexey Petrovich Bestuzhev-Ryumin proposed using a solution of ferric chloride

in ethanol and ethyl ether in drops as a tonic and stimulant. In 1989, Epogen was introduced into clinical practice. There have been enormous advances in understanding the role and metabolism of iron in biological systems and many researchers continue to work towards finding optimal dosage forms of iron.

Pharmacokinetics of iron

Iron in food usually exists in the ferric (Fe^{3+}) state bound by a protein or organic salts. Iron is released from food during digestion by hydrochloric acid. It is predominantly absorbed in the duodenum. Dietary ascorbic acid is known to enhance iron absorption because it is effective at reducing the ferric form to the ferrous form (Fe^{2+}), which can enter the intestinal mucosa. Daily food intake contains approximately 15–20 mg of iron, but only 10% of this amount is absorbed.

Iron absorption by the intestine usually exceeds the amount of iron needed by the body. Once inside the enterocytes, iron can be stored there or transported into circulation; this transport is dependent on apoferritin synthesis. Apoferritin binds to iron in enterocytes, transforms into ferritin and then is stored in enterocytes. This process limits the transport of iron from the intestinal cells into circulation. When the body has enough iron, the rate of apoferritin synthesis increases. Mucosal cells shed into the intestinal lumen eliminate excess iron from the body. In cases of iron deficiency, apoferritin is barely synthesized in enterocytes. Iron entering the blood from enterocytes transports transferrin.

Transferrin is a glycoprotein that is synthesized in the liver and binds only oxidized iron (Fe^{3+}).

Transferrin interacts with specific cell membrane receptors. This interaction forms the Ca^{2+} -calmodulin-PKC (protein kinase C) complex in the cell cytosol, which phosphorylates the transferrin receptor and induces the formation of endosomes. The ATP-dependent proton pump in the endosome membrane creates an acidic environment within the endosome. The acidic environment of the endosome promotes iron release from transferrin. The apotransferrin-receptor complex is then recycled to the surface of the plasma membrane. At the extracellular fluid's neutral pH, apotransferrin changes its conformation, separates from the receptor and enters the blood plasma. From there, it can re-bind iron ions and participate in a new cycle of iron transport into the cell.

Iron in the cell is used to synthesize iron-containing proteins or is deposited in ferritin.

Ferritin is an oligomeric protein with a molecular weight of 500 kDa. It consists of heavy (21 kDa) and light (19 kDa) polypeptide chains that make up 24 protomers. Ferritin heavy chains oxidize Fe^{2+} to Fe^{3+} . Iron in the hydroxyphosphate form is located in the center of the sphere, the shell of which is formed by the protein part of the molecule. It is transferred inside and released out through the channels penetrating the protein shell of apoferritin; however iron can also be deposited in the protein part of the ferritin molecule. Ferritin is found in almost all tissues, but the greatest amounts are found in the liver, spleen and bone marrow. Iron metabolism in the body is summarized in Fig. 13.1.

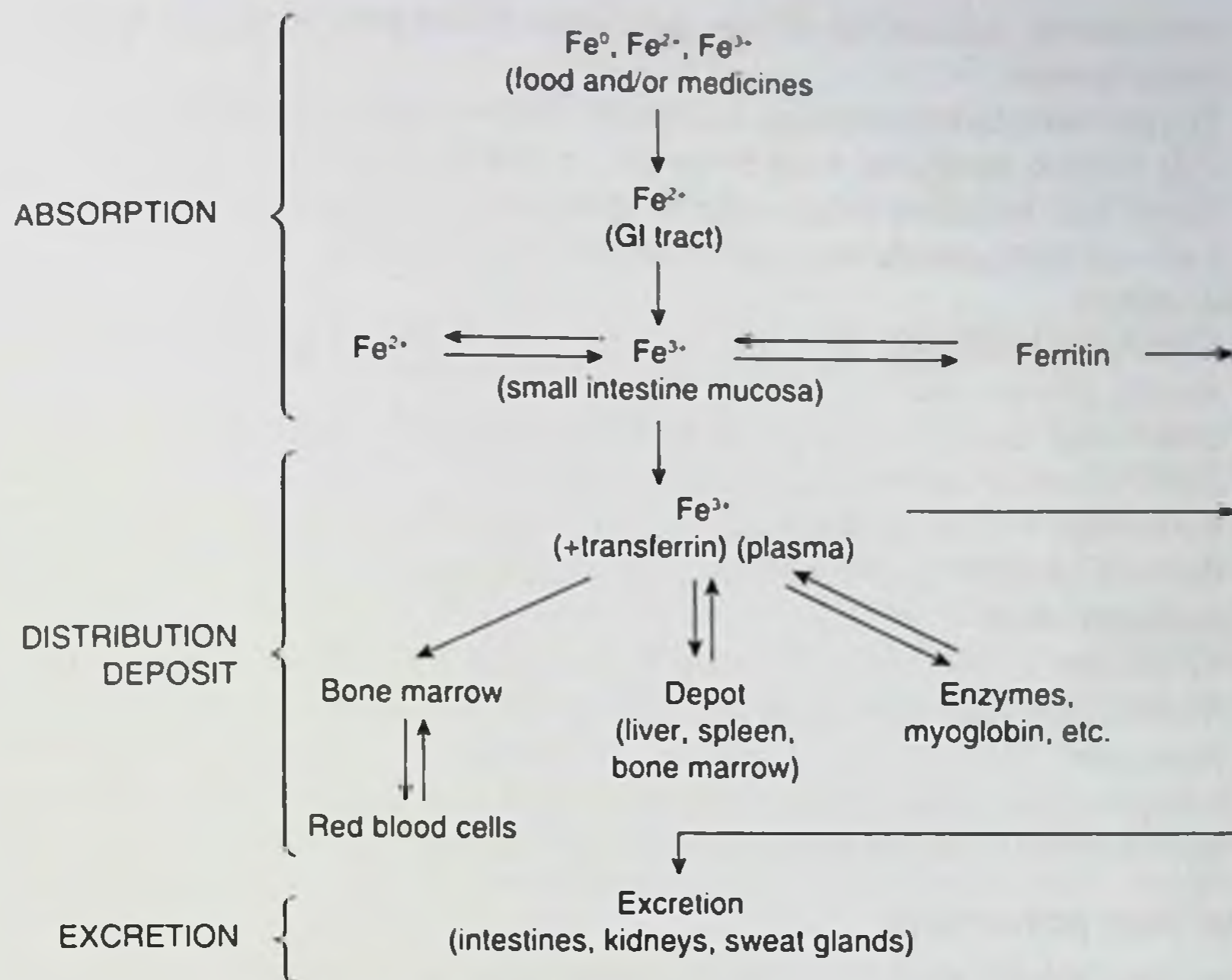


Fig. 13.1. Pharmacokinetics of iron (Kharkevich D.A., 2021)

Drugs used mainly for hypochromic anemia

Classification of iron supplements

I. For oral administration:

- Bivalent iron preparations (Fe^{2+}): iron gluconate, iron sulfate (Tardiferon[®]), iron fumarate (Ferronat[®])
- Trivalent iron preparations (Fe^{3+}): Ferlatum[®], iron lactate, iron (III)-hydroxide polymaltose (Ferrum Lek[®], Maltofer[®])

II. For parenteral administration:

- Trivalent iron preparations (Fe^{3+}): iron (III)-hydroxide sucrose complex (Likferr100[®], Velferrum[®], Venofer[®]), iron (III)-hydroxide polymaltose (Maltofer[®], Ferrum Lek[®])

III. Fixed combinations of iron with other drugs

- For oral administration: Sorbifer Durules[®], Ferroplex[®] (ferrous sulfate, ascorbic acid), Ferretab comp[®] (ferrous fumarate, folic acid), Ferlatum Fol[®], Totema[®] (iron gluconate, manganese gluconate, copper gluconate), Fenules[®] (multivitamins, minerals)
- For parenteral (intravenous) administration: Fercoven[®] (iron saccharate[®], cobalt gluconate[®])

Therapeutic indications

- For oral administration: iron-deficiency anemia (insufficient intake from food, chronic blood loss, iron malabsorption due to GI disorders), anemia of

prematurity, prevention of iron deficiency during pregnancy, lactation and in blood donors

- ▶ For parenteral administration: treatment of all forms of iron-deficiency conditions that require rapid iron replenishment, including severe iron deficiency due to blood loss; impaired intestinal iron absorption; conditions in which treatment with oral iron preparations are ineffective or not feasible

Side effects

- ▶ Common: headache, dizziness, fatigue, skin hyperemia; metallic taste in the mouth; allergic reactions
- ▶ Oral forms: nausea, vomiting, heartburn, constipation/diarrhea, epigastric pain, dark colored urine or stools, teeth staining
- ▶ Parenteral forms: paresthesia, arterial hypotension, feeling of heat, facial flushing, pain at the injection site, phlebitis, abscess

Contraindications

- ▶ All dosage forms: hemochromatosis, hemosiderosis, impaired iron utilization mechanisms (lead poisoning, sideroblastic anemia, thalassemia)
- ▶ Parenteral forms: first trimester of pregnancy, hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu syndrome), acute kidney infections, uncontrolled hyperparathyroidism, severe liver disease

Acute iron poisoning

Parenteral administration of iron preparations in patients with reduced transferrin levels causes poisoning due to an increase in free iron levels in the blood and increased formation of free radicals (oxidative stress). Iron from the blood enters tissues and cells, especially the liver, causing damage. Free iron is a capillary poison. Toxic concentrations of Fe^{3+} damages the endothelium, causes massive hemolysis, catalyzes lipid peroxidation in mitochondria with high levels of polyunsaturated fatty acids, thereby damaging mitochondrial membranes and disrupting the Krebs cycle and electron transport. Increased vascular permeability leads to plasma release into tissues (hematocrit and blood viscosity increase) and to diapedesis of erythrocytes into the lumen of the stomach and intestines, into the brain tissue (stroke), etc.

Clinical presentation

Facial flushing, surge of blood into the head and chest, hypotension, tachycardia, heartburn, back pain, bloody vomiting and diarrhea, hematuria. In severe cases: signs of hepatic, renal and cardiovascular insufficiency.

Treatment

- ▶ Antidote — deferoxamine (Desferal[®])
- ▶ Sodium bicarbonate is used to create an alkaline environment (pH above 5.0–6.0) in the stomach, which allows ferrous (bivalent) iron to shift to an oxidized form. Sodium bicarbonate is used for this purpose.
- ▶ Hemodialysis is used for patients with renal impairment
- ▶ Symptomatic treatment

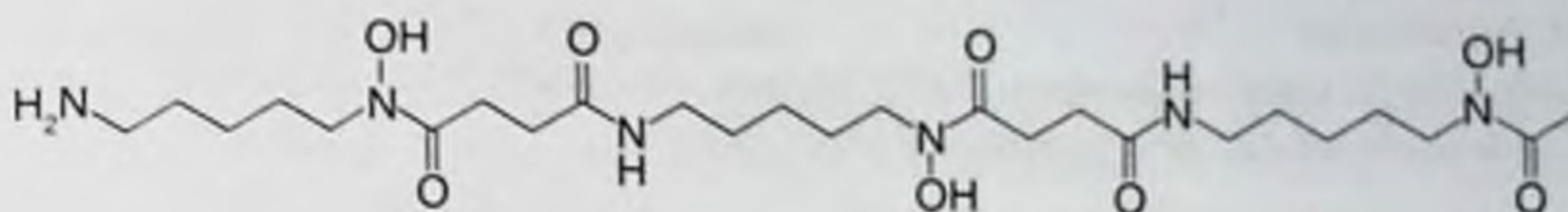
Deferoxamine (Desferal[®])

Fig. 13.2. N'-[5-(Acetylhydroxyamino)pentyl]-N-[5-[3-(5-aminopentylhydroxycarbonyl)propanoylamino]pentyl]-N-hydroxy-butane diamide

Hydroxamic acid derivative, complexing agent, actinomycete metabolite.

Rapidly absorbed and distributed after parenteral administration. Metabolized in the liver by transamination, oxidation, decarboxylation and N-hydroxylation. Excreted in the urine and bile. For intravenous, intramuscular, subcutaneous administration.

Mechanism of action: It forms a stable complex mainly with Fe^{3+} ions, preventing it from participating in future reactions: it binds iron of ferritin and hemosiderin (but not transferrin), does not interact with the iron of cytochrome, myoglobin and hemoglobin.

Therapeutic indications: acute iron poisoning

Side effects: dizziness, convulsions; dyspeptic symptoms, hepatic impairment; arterial hypotension, collapse, thrombocytopenia; renal impairment, allergic skin reactions, irritation at the injection site

Contraindications: anuria, first trimester of pregnancy, breastfeeding

Cobalt preparations**Coamid⁺**

- ▶ A complex of cobalt with nicotinic acid amide. It stimulates hematopoiesis, promotes iron absorption in the body and stimulates its transformation (formation of protein complexes, hemoglobin synthesis), regulates erythropoietic activity. It stimulates amino acid synthesis, increases the content of polysaccharides, DNA and RNA in tissues, and increases the levels of certain enzymes (succinate dehydrogenase, alkaline phosphatase and cytochrome oxidase). For oral and subcutaneous administration.

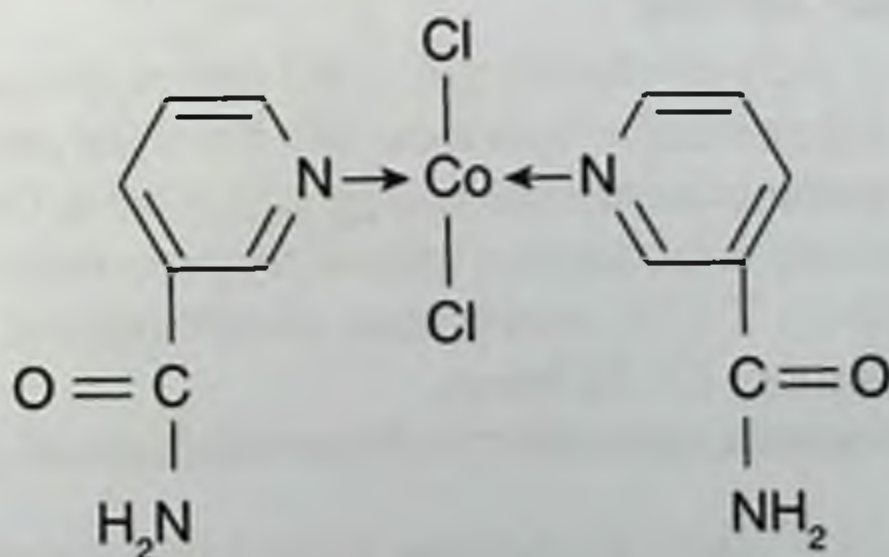


Fig. 13.3. Dichloronicotinamide-cobalt

- ▶ It is a constituent of multivitamin products (Complivit, Oligovit, etc.).

Therapeutic indications: hypochromic, hypoplastic anemia, anemia in chronic renal impairment

Side effects: nausea, dizziness, facial redness, tachycardia, blood pressure decrease

Contraindications: decompensated heart failure

Erythropoietin preparations

Erythropoietin is a glycoprotein and growth factor that regulates erythropoiesis. It stimulates the proliferation and differentiation of erythroid precursor cells. It promotes the release of reticulocytes from the bone marrow into the blood. The production of erythropoietin is stimulated by tissue hypoxia and is impaired in chronic renal disorders.

Epoetin alfa (Epocrin[®], Eprex[®])

- ▶ Recombinant human erythropoietin. It specifically stimulates erythropoiesis, activates mitosis and maturation of erythrocytes from erythrocyte precursor cells, increases hemoglobin and hematocrit, improves tissue blood supply and heart function. Its composition and biological properties are identical to the native human erythropoietin. Bioavailability after subcutaneous administration: 25–40%. $T_{1/2}$ for intravenous administration: 5–6 hours, $T_{1/2}$ for subcutaneous administration: 16–24 hours. For intravenous and subcutaneous administration.

Therapeutic indications: anemia due to chronic kidney disease, hemodialysis, HIV infection during treatment with zidovudine, cytostatic chemotherapy, in premature newborns

Side effects: flu-like symptoms (fever, headache, myalgia); allergic reactions (skin rash, urticaria, pruritus); hypertension, thrombocytosis; local reactions (hyperemia, burning, tenderness at the injection site); decreased serum levels of ferritin, serum indicators of iron metabolism; in patients with uremia — hyperkalemia and hyperphosphatemia

Contraindications: partial red cell aplasia after previous therapy with any erythropoietin, uncontrolled hypertension, inability to conduct adequate anticoagulant therapy, myocardial infarction within 1 month after the event, unstable angina or increased risk of deep vein thrombosis and thromboembolism, porphyria

Epoetin beta (Recormon[®], Epostim[®])

Epoetin beta is β -(1-165)-erythropoietin, a 165 amino acid glycoprotein that, as a mitogenic factor and differentiation hormone, promotes the production of red blood cells from partially determined erythropoiesis precursor cells. Genetically engineered recombinant erythropoietin is identical to human erythropoietin in its amino acid and carbohydrate composition. $T_{1/2}$ for intravenous administration: 4–12 hours, $T_{1/2}$ for subcutaneous administration: 13–28 hours.

For therapeutic indications, side effects and contraindications, see Epoetin alfa.

Drugs used mainly for hyperchromic anemia

Cyanocobalamin (vitamin B₁₂, Cobamamide)

- ▶ Vitamin B₁₂ is involved in carbohydrate, protein, and lipid metabolism. It stimulates tissue regeneration, regulates hematopoiesis, liver and nervous system functions, activates the blood coagulation system, and lowers blood cholesterol. In the body (mainly the liver), it converts into the cofactor cobamide, which is part of numerous enzymes, including the reductase that reduces folic acid to tetrahydrofolic acid. Cobamide is involved in the transfer of methyl and other one-carbon fragments and therefore is necessary to form deoxyribose and DNA, creatine, methionine (a donor of methyl groups) for the synthesis of the lipotropic factor choline, to convert methylmalonic acid into succinic acid, which is part of myelin, and to utilize propionic acid. It promotes the accumulation of compounds containing sulfhydryl groups in erythrocytes, which explains their higher tolerance to hemolysis.

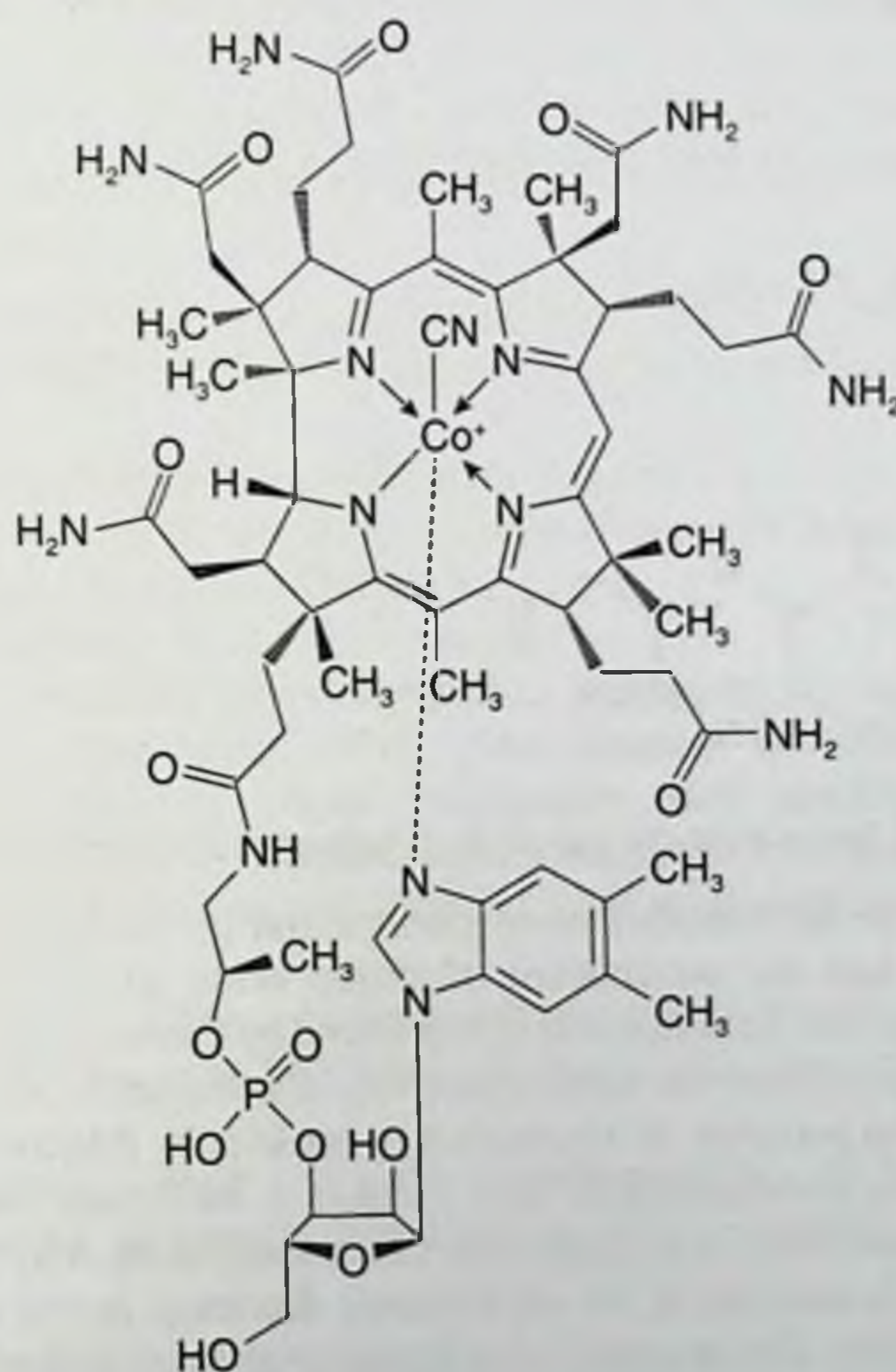


Fig. 13.4. α -(5,6-Dimethylbenzimidazolyl)cobamide cyanide

- ▶ It is absorbed mainly in the small intestine. It binds to a special intrinsic factor in the ileum, becoming impervious to intestinal microorganisms. The complex

in the small intestine wall transfers vitamin B₁₂ to the receptor, which transports it into the cell (receptor activity depends on the structure and function of the mucous membrane supported by folic acid, as well as on the presence of Ca²⁺ ions and the pH). In the blood, vitamin B₁₂ binds to transcobalamins I and II, which transport it to tissues. It is deposited mainly in the liver, then excreted from the liver in bile into the intestine and reabsorbed. Excreted predominantly in the urine. For subcutaneous, intramuscular, intravenous administration.

Therapeutic indications:

- ▶ Anemia with vitamin B₁₂ deficiency (Addison–Biermer anemia, alimentary macrocytic anemia, etc.), as part of combination therapy for anemia (including iron-deficiency, posthemorrhagic, aplastic anemia)
- ▶ Chronic hepatitis, liver cirrhosis, hepatic impairment, alcoholism
- ▶ Gastric and intestinal pathology with vitamin B₁₂ malabsorption (gastric or small bowel resection, Crohn's disease, malabsorption syndrome)

Side effects: agitation, cardialgia, tachycardia, headache, dizziness, allergic reactions

Contraindications: thromboembolism, polycythemia vera, erythrocytosis, pregnancy, breastfeeding, allergic reactions

Folic acid [vitamin B₉ (B_c), Folacin*]

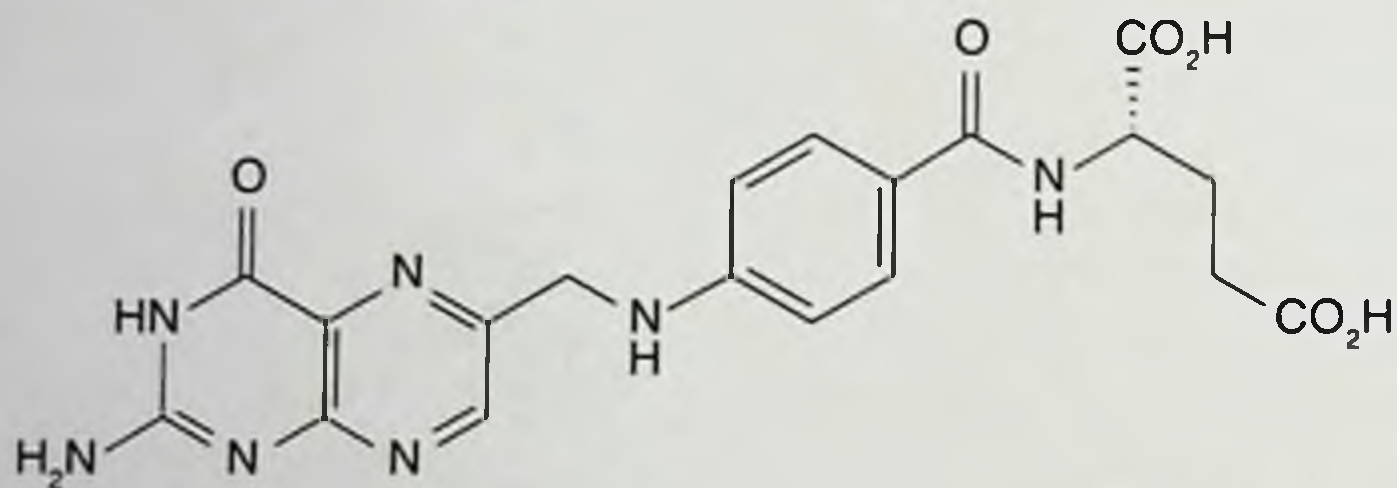


Fig. 13.5. (2S)-2-[[4-[(2-Amino-4-oxo-1H-pteridin-6-yl)methylamino]benzoyl]amino]pentanedioic acid

- ▶ It is involved in the metabolism of purines and pyrimidines, the synthesis of nucleic acids and the metabolism of amino acids (glycine, methionine and histidine). After oral administration, it is bound by Castle's intrinsic factor in the stomach and absorbed in the upper part of the duodenum. It is almost completely bound to plasma proteins. It is activated in the liver by dihydrofolate reductase, converting into tetrahydrofolic acid, which is necessary for maturation of megaloblasts and their transformation into normoblasts. The maximum blood concentration is reached in 30–60 minutes. Excreted in the urine unchanged and as metabolites. For oral administration.

Therapeutic indications: treatment and prevention of all types of anemia due to folic acid deficiency, including insufficient intake from food, malabsorption, increased requirements (pregnancy, lactation, hemolytic anemia, hyperthyroidism, exfoliative dermatitis or chronic infections)

Side effects: nausea, bloating, bitter taste in mouth, diarrhea; irritability, sleep disturbance; allergic reactions

Contraindications: allergic reactions, glucose-galactose malabsorption

DRUGS THAT SUPPRESS ERYTHROPOIESIS

Sodium phosphate P 32 solution ($\text{Na}_2\text{H}^{32}\text{PO}_4$)

Therapeutic radiopharmaceutical. For intravenous administration.

Mechanism of action: Radioactive ^{32}P from $\text{Na}_2\text{H}^{32}\text{PO}_4$ accumulates in the bone marrow tissue and disrupts erythropoiesis, which eventually decreases the number of erythrocytes and platelets.

Therapeutic indications: treatment of polycythemia vera, thrombocythemia, leukemia and other neoplastic diseases of the blood

Side effects: leukemia in 2–15% of patients within 10 years

Contraindications: anemia, leukopenia, thrombocytopenia, decompensated heart failure, hepatic and renal impairment, pregnancy, breastfeeding

LEUKOPOIESIS STIMULATING AGENTS

Classification

1. Pyrimidine derivatives: dioxomethyltetrahydropyrimidine (Methyluracil*), Pentoxyl*
2. Thiazolidine derivatives: phenylcarbetoximethylthiazolidinecarboxylic acid (Leucogen*)
3. Recombinant colony-stimulating factor preparations
 - A. Granulocyte-macrophage: molgramostim (Neustim*), sargramostim[®] (Leukin[®])
 - B. Granulocyte: filgrastim (Zarzio*)
4. Nucleic acid products: sodium nucleinate*.

Therapeutic indications: myelodysplastic syndrome; leukopenia (caused by infectious diseases, including HIV; chemotherapy of malignant neoplasms; radiotherapy); agranulocytic angina, alimentary toxic aleukia, aplastic anemia; thrombocytopenia, radiation sickness, convalescence (after severe infections), gastric and duodenal ulcers (in combination therapy), chronic wounds, burns, bone fractures, hepatitis, pancreatitis

Side effects: fever, chills, dyspnea, musculoskeletal pain, asthenia; nausea, vomiting, anorexia, diarrhea, headache, dizziness; rash, pruritus, tenderness at the injection site

Contraindications: bone marrow malignancies, lymphogranulomatosis, autoimmune diseases, pregnancy, breastfeeding, allergic reactions

Specifics of individual products

Dioxomethyltetrahydropyrimidine (Methyluracil*)

It has hematopoietic, leukopoietic, immunostimulatory and anti-inflammatory effects. By regulating nucleic acid metabolism, it accelerates wound regeneration processes,

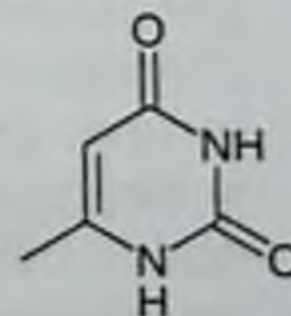


Fig. 13.6. 2,4-Dihydroxy-6-methylpyrimidine

tissue growth, granulation tissue maturation and epithelialization; it also stimulates erythropoiesis and leukopoiesis, cellular and humoral immunity factors. It has anabolic activity. It enhances the growth and expansion of cells, accelerating regeneration of damaged tissues; it accelerates the healing of wounds, ulcers, burns, and increases the body's resistance to infections. When applied topically, it has photoprotective properties. For oral, topical and rectal administration.

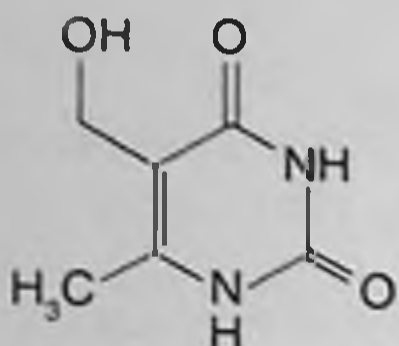


Fig. 13.7. 4-Methyl-5-hydroxymethyluracil

Pentoxyl*

- ▶ Pyrimidine derivative. It converts in the body into dioxomethyl tetrahydropyrimidine, releasing formaldehyde, which has toxic properties. For oral administration.
- ▶ It has an anti-inflammatory effect, stimulates regenerative processes in tissues, promoting the rapid healing of wounds. It slows dephosphorylation of uridine monophosphate, accelerates the production of thymidine monophosphate, which, in turn, is involved in DNA synthesis. It enhances leukopoiesis, the production of phagocytes and macrophages, nucleic acids, and antibodies (immunoglobulins).

Phenylcarbetoximethylthiazolidinecarboxylic acid (Leucogen*)

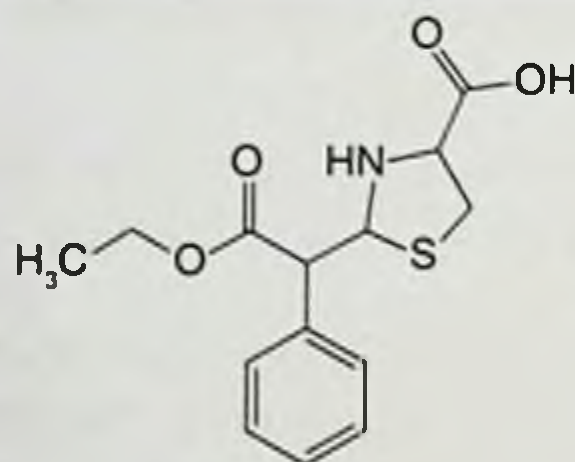


Fig. 13.8. 4-Carboxy-α-phenyl-2-thiazolidine acetic acid 2-ethyl ester

It is effective in treating diseases accompanied by leukopenia. For oral administration.

Molgramostim (Neustim*)

- ▶ Recombinant human granulocyte-macrophage colony-stimulating factor. It is formed by a strain of *Escherichia coli* that carries a genetically engineered plasmid containing the human granulocyte-macrophage colony-stimulating factor gene.
- ▶ It stimulates the growth of granulocytes, monocytes and T cells, without affecting the growth of B cells. It increases the content of mature cells and their functional activity — enhances phagocytosis, increases cytotoxicity against malignant cells. It induces the production of colony-forming units of granulocytes and macrophages. It can enhance the expression of HLA class II antigens (major histocompatibility complex) on monocytes and increase antibody production. In myelodysplastic syndromes, it effectively regulates myelopoiesis. It reduces the recovery time of myeloid hematopoiesis after bone marrow transplantation in patients with acute leukemia. After a single injection, the effect occurs in 2–4 hours, peaking in 8–16 hours. $T_{1/2}$ after intravenous

administration: 1–2 hours, $T_{1/2}$ after subcutaneous administration: 2–3 hours.
For intravenous and subcutaneous administration.

Therapeutic indications: neutropenia; reduced duration of neutropenia in patients preparing for bone marrow transplantation; mobilization of peripheral stem cells (including after myelosuppressive therapy); severe or recurrent infections in the past 12 months

Additional side effects: splenomegaly, hepatomegaly, arthralgia, myalgia, osteoporosis; elevated levels of lactate dehydrogenase, alkaline phosphatase, gamma-glutamyl transferase

Additional contraindications: severe congenital neutropenia with abnormal cytogenetics (Kostmann syndrome); doses of cytotoxic chemotherapeutic agents above recommended ones; hepatic and/or renal impairment

Filgrastim (Zarzio[®])

- ▶ Recombinant preparation of human granulocyte colony-stimulating factor produced by recombinant DNA technology. It interacts with receptors on the surface of hematopoietic cells, stimulates cell proliferation, differentiation and functional activation. It increases the blood count of neutrophils with normal functional activity. After the end of therapy, white blood cell count returns to baseline within 4 days. $T_{1/2}$: about 3.5 hours. For intravenous and subcutaneous administration.
- ▶ For therapeutic indications, side effects and contraindications, see Molgramostim.

Sodium nucleinate[®]

Nucleic acid sodium salt produced by yeast hydrolysis followed by purification. It has the activity of a polyclonal immune stimulator. By regulating the migration of T cells and the cooperation between T and B cells, it enhances the phagocytic activity of macrophages and the production of nonspecific protection factors, accelerates tissue regeneration processes, stimulates leukopoiesis. For oral administration.

Therapeutic indications: immunodeficiency states; prevention of postoperative bacterial complications and improvement of wound healing; leukopenia and agranulocytosis, lymphocytopenia; phosphoric metabolism disorder (phosphaturia, rickets, etc.); dystrophy and ulcerative processes

Side effects: allergic reactions

Contraindications: pregnancy, breastfeeding

DRUGS THAT SUPPRESS LEUKOPOIESIS (ANTI-NEOPLASTIC AGENTS)

Classification

I. Alkylating agents and drug products with similar action

1. Chlorethylamines: cyclophosphamide (Cyclophosphan[®], Endoxan[®])

2. Nitrosourea derivatives: nitrosomethylurea

3. Platinum compounds: cisplatin (Cisplatin-Teva[®], Kemoplat[®], Displanor[®]), oxaliplatin (Oxaliplatin-Ebewe[®])

II. Antimetabolites

1. Folate antagonists: methotrexate (Metoject[®])
2. Purine synthesis inhibitors: mercaptopurine (Puri-Nethol[®])
3. Pyrimidine antagonists: fluorouracil (5-Fluorouracil-Ebewe[®]), tegafur (Ftorafur[®])

III. Herbal products

1. Vinca alkaloids: vinblastine, vincristine (Vincristine sulfate[®], Vincristine-Teva[®])
2. Meadow saffron alkaloids: Colchamine[®] (Demecolcine[®], Omain[®], Colcemid[®], Demekolsin[®])

IV. Enzyme products: asparaginase (L-asparaginase[®])

1. Selective estrogen receptor modulators: tamoxifen (Tamoxifen Hexal[®])

Therapeutic indications: chemotherapy for cancer (solid tumors, leukemia, lymphoma and other malignant tumors)

Side effects:

- ▶ anorexia, stomatitis, dry mouth, nausea, vomiting, diarrhea, stomach pain, hemorrhagic colitis
- ▶ asthenia, peripheral neuropathy, arrhythmias
- ▶ leukopenia, agranulocytosis, lymphopenia, neutropenia, aplastic anemia, thrombocytopenia, myelosuppression
- ▶ bleeding and hemorrhage
- ▶ hemorrhagic cystitis, urethritis, bladder fibrosis, atypia of bladder cells; frequent, painful, or difficult urination; hyperuricemia, nephropathy, lower extremity edema, renal tubular necrosis, amenorrhea, ovarian depression, azoospermia
- ▶ toxic hepatitis, jaundice, elevated levels of hepatic transaminases, hyperbilirubinemia, etc.

Contraindications: severe renal or hepatic impairment, bone marrow hypoplasia, leukopenia, thrombocytopenia, severe anemia, pregnancy, breastfeeding

Specifics of individual products

Cyclophosphamide (Cyclophosphan[®], Endoxan[®])

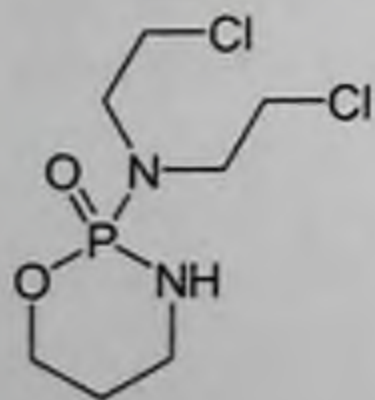


Fig. 13.9. (RS)-N,N-bis(2-Chloroethyl)-1,3,2-oxazaphosphorinane-2-amine-2-oxide

- ▶ It has a wide spectrum of antitumor activity. It inhibits the proliferation of lymphocytic clones (mainly B cells) involved in the immune response.
- ▶ Bioavailability: 75%. Crosses the placental barrier and is excreted into breast milk. Metabolized in the liver to form active metabolites with an alkylating effect. $T_{1/2}$: 3–12 hours. Excreted mainly in the urine as metabolites and as unchanged drug. For oral, intravenous, intramuscular administration.

Mechanism of action: Alkylating metabolites bind to the nucleophilic centers of protein molecules, form cross-links between DNA strands, and block the mitosis of tumor cells.

Nitrosomethylurea

- ▶ A nitrosourea derivative that has alkylating, immunosuppressive, antitumor, cytostatic effects.
- ▶ It is rapidly distributed in tissues, crosses the BBB. Metabolized in the liver (denitrogenation, hydroxylation). $T_{1/2}$: 24–72 hours. Excreted in the urine within 24 hours. For intravenous administration.

Mechanism of action: By interacting with the nucleophilic centers of protein molecules, it disrupts DNA synthesis and blocks mitosis. It causes reversible inhibition of hematopoiesis (leukopenia and thrombocytopenia).

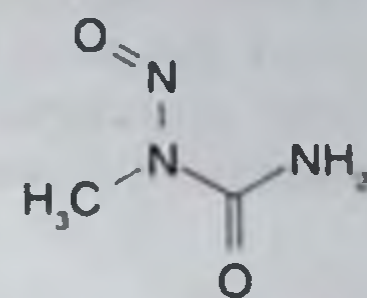


Fig. 13.10. 1-Methyl-1-nitrosourea

Cisplatin (Cisplatin-Teva⁺, Kemoplat⁺, Displanor⁺)

- ▶ Complex ammonium chloride of bivalent platinum. It has immunosuppressive and radiosensitizing properties. The highest concentrations are reached in the kidneys, liver and prostate.
- ▶ It accumulates with repeated courses of therapy (platinum is still found in tissues 6 months after treatment). It is biotransformed by rapid non-enzymatic conversion to form inactive metabolites. Excreted in the urine. For intravenous administration.

Mechanism of action: It has properties similar to those of bifunctional alkylating agents that form inter- and intra-strand cross-links in DNA, thereby disrupting its functions, which causes cell death; the product does not have cyclic and phase specificity.

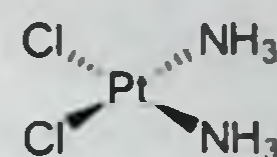


Fig. 13.11. (SP-4-2)-Diamminedichloro-platinum

Oxaliplatin (Oxaliplatin-Ebewe⁺)

It is rapidly distributed in tissues. Excreted mainly in the urine (33% within 48 hours; about half of the total dose — within 3 days), a small amount is excreted in bile. For intravenous administration.

Mechanism of action: It undergoes biotransformation to form active metabolites (dichloroplatinum, monochloromonoaquaplatinum and glutathione platinum). These metabolites interact with DNA strands and inhibit DNA replication and transcription phases, producing cytotoxic and antitumor effects.

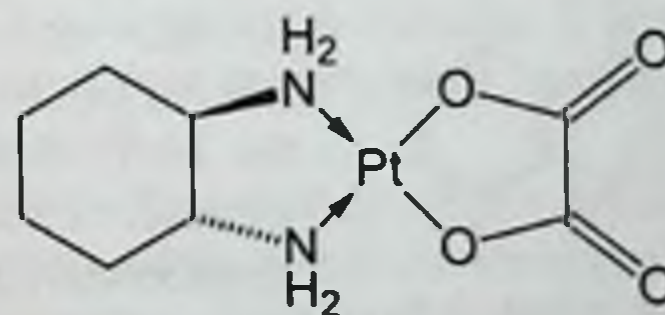


Fig. 13.12. [(1R,2R)-1,2-Cyclohexanediamine-N,N'] [oxalato(2)-O,O'] platinum

Methotrexate (Metoject⁺)

Antimetabolite that is a structural analogue of folic acid. Actively dividing cells in tumors, bone marrow, embryo, mucous membranes of the mouth, intestines, bladder are the most sensitive to it. Bioavailability: 60%. Does not cross the BBB.

Excreted into breast milk, crosses the placental barrier (has teratogenic effects on the fetus). $T_{1/2}$: 3–15 hours. About 80–90% of the administered dose is excreted in the urine as unchanged substance and 10% is excreted in bile. For oral, intramuscular, intravenous, intraarterial and intrathecal administration.

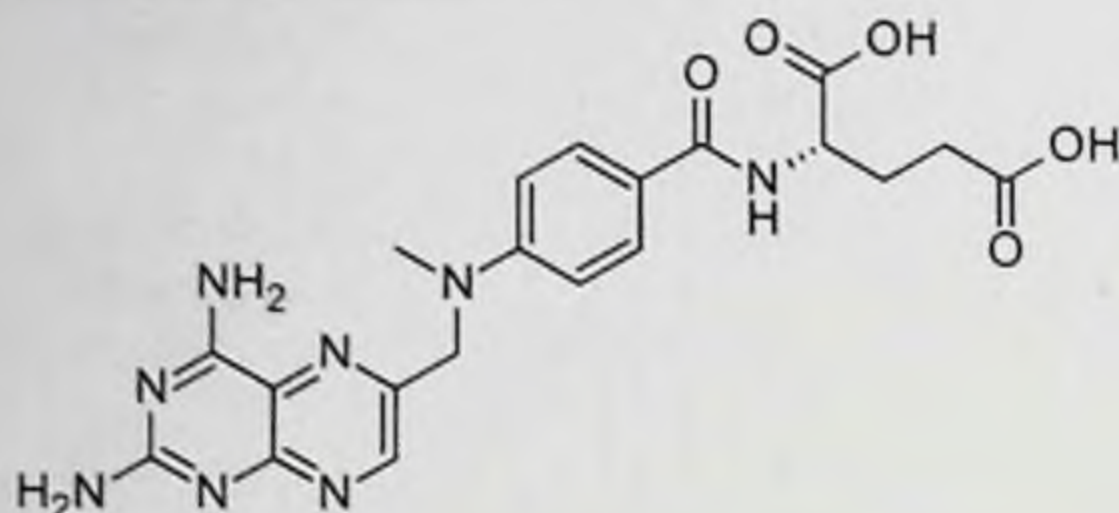


Fig. 13.13. N-[4-[(2,4-Diamino-6-pteridiny)methyl]methylamino]benzoyl-L-glutamic acid (and as disodium salt)

Mechanism of action: In the cell, the product undergoes polyglutamation to form metabolites that have an inhibitory effect on folate-dependent enzymes such as dihydrofolate reductase, thymidylate synthetase. It inhibits DNA synthesis and repair, cell mitosis, and to a lesser extent, affects RNA and protein synthesis. It has S-phase specificity, is active in tissues with high cell proliferative activity and inhibits the growth of malignant neoplasms.

Mercaptopurine (Puri-Nethol⁺)

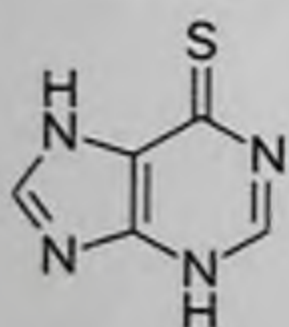


Fig. 13.14. 3,7-Dihydropurine-6-thione

- ▶ Competitive purine base antagonist; S-phase specific drug.
- ▶ It has carcinogenic, mutagenic and embryotoxic effects. Bioavailability: 50%. Poorly crosses the BBB. Metabolized in the liver; decomposed mainly with the involvement of xanthine oxidase. Excreted in the urine unchanged (7–39%) and as metabolites (thiouric acid resulting from direct oxidation involving xanthine oxidase, methylated thiopurines). $T_{1/2}$: 90–130 min. For oral administration.

Mechanism of action: It competes with hypoxanthine and guanine for hypoxanthine-guanine phosphoribosyltransferase, which converts the product into thioinosinic acid. Thioinosinic acid inhibits a number of reactions involving inosinic acid, including the conversion of inosinic acid to xanthic acid and adenylic acid through adenylosuccinate. 6-methylthioinosinate is formed by the methylation of thioinosinic acid. Along with thioinosinic acid itself, it inhibits glutamine-5-phosphoribosylpyrophosphate amidotransferase, the first enzyme in purine ribonucleotide synthesis. This disrupts the mitotic cycle (S phase), especially in proliferating cells of the bone marrow and tumors, inhibits the growth of malignant neoplasms and has a cytotoxic effect.

Fluorouracil (5-Fluorouracil-Ebewe[®])

- ▶ Uracil antimetabolite. Bioavailability: 80%. It is biotransformed and distributed in rapidly proliferating tissues (bone marrow, gastrointestinal mucosa, tumor tissues), where the highest efficacy is observed. Easily crosses the BBB. $T_{1/2}$: 8–22 min.
- ▶ Metabolized in the liver to form the active metabolite dihydro-5-fluorouracil, whose $T_{1/2}$ is much higher than fluorouracil, and inactive metabolites. Excreted mainly by the lungs as carbon dioxide (60–80%). About 7–20% is excreted in the urine as unchanged drug. For intravenous administration.

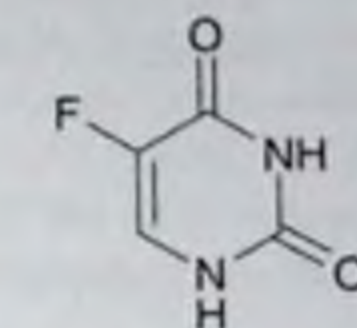


Fig. 13.15. 5-Fluoro-2,4(1H,3H)-pyrimidinedione

Mechanism of action: It is metabolized to 5-fluoro-deoxyuridine-monophosphate and 5-fluorouridine-triphosphate. 5-Fluoro-deoxyuridine-monophosphate is a competitive inhibitor of the enzyme thymidine synthetase, which inhibits DNA synthesis. It blocks the methylation reaction of deoxyuridic acid and its conversion to thymidylic acid, causing thymidine deficiency. It inhibits RNA synthesis by including 5-fluorouridine-triphosphate in its structure instead of uridine triphosphate. This disrupts the synthesis of RNA and protein, inhibits cell division.

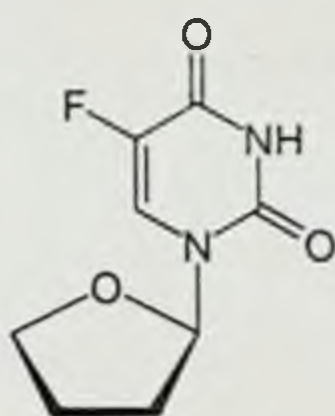


Fig. 13.16. 5-Fluoro-1-(tetrahydro-2-furanyl)-2,4(1H,3H)-pyrimidinedione (and as sodium salt)

Tegafur (Ftorafur[®])

- ▶ It is less toxic and better tolerated by patients than fluorouracil. After oral administration, it is rapidly absorbed from the GI tract and is detectable in the blood within 24 hours after a single injection. The maximum blood concentration is reached within 4–6 hours after dosing. Bioavailability is absolute. It has high lipophilicity (200-fold higher than fluorouracil), crosses biological barriers, including the BBB.
- ▶ Metabolized in the liver to form mainly fluorouracil (5-Fluorouracil-Ebewe[®]). Bioactivated locally in tumor tissue, characterized by an increased content of cytosolic hydrolytic enzymes. Less than 15% of an intravenously administered dose is excreted in the urine as unchanged substance. For oral and intravenous administration.

Mechanism of action: In the body, under the influence of thymidine and uridine phosphorylase, it is hydrolyzed to form fluorouracil. The latter is converted to 5-fluorodeoxyuridine monophosphate, a potential inhibitor of thymidylate synthetase. It blocks thymidylate synthetase and DNA synthesis, intrudes into the structure of RNA, making it defective, and inhibits cell proliferation.

Vincristine (Vincristine sulfate[®], Vincristine-Teva[®])

- ▶ Vinca (*Catharanthus roseus*) alkaloid. It is rapidly distributed in body tissues. Poorly penetrates the blood-brain barrier (BBB).
- ▶ Metabolized in the liver. The initial, mean and terminal $T_{1/2}$ are 5 minutes, 23 hours and 85 hours, respectively. The terminal $T_{1/2}$ can vary from 19 to 155 hours.

It is excreted mainly in bile (70–80% unchanged) and 10–20% is excreted in the urine. For intravenous, intrapleural administration.

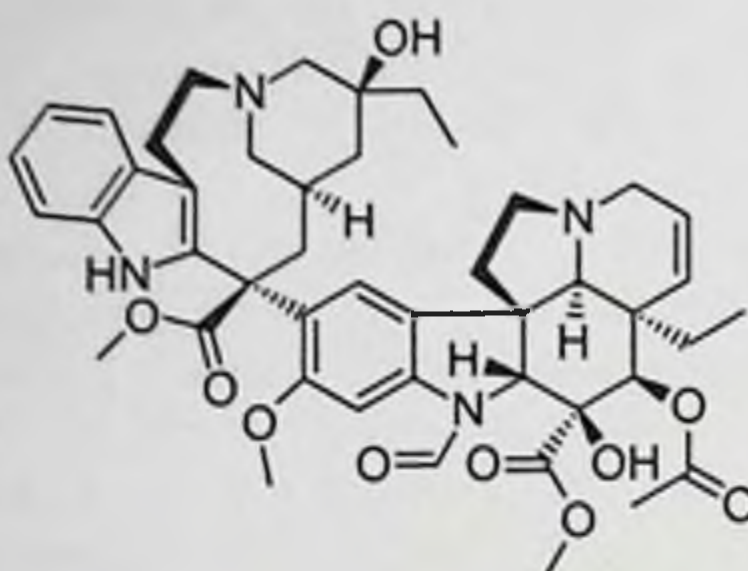


Fig. 13.17. Methyl-(3aR,4R,5S,5aR,10bR,13aR)-4-acetoxy-3a-ethyl-9-((5S,7R,9S)-5-ethyl-5-hydroxy-9-(methoxycarbonyl)-1,4,5,6,7,8,9,10-octahydro-2H-3,7-methanoazacycloundecino(5,4-b)indol-9-yl)-5-hydroxy-8-methoxy-6-oxo-3a,4,5,5a,6,11,12,13a-octahydro-1H-indolizino(8,1-cd)carbazole-5-carboxylate sulfate

Mechanism of action: Binding to tubulin protein molecules disrupts the microtubular apparatus of cells and ruptures the mitotic spindle. Mitosis stops at the metaphase stage. The metabolism of amino acids, cAMP, glutathione, the activity of calmodulin-dependent Ca^{2+} transport ATPase, cellular respiration, and the biosynthesis of nucleic acids and lipids are altered. It has an immunosuppressive effect.

Colchamine[®] (Demecolcine[®], Omain[®], Colcemid[®], Demekolsin[®])

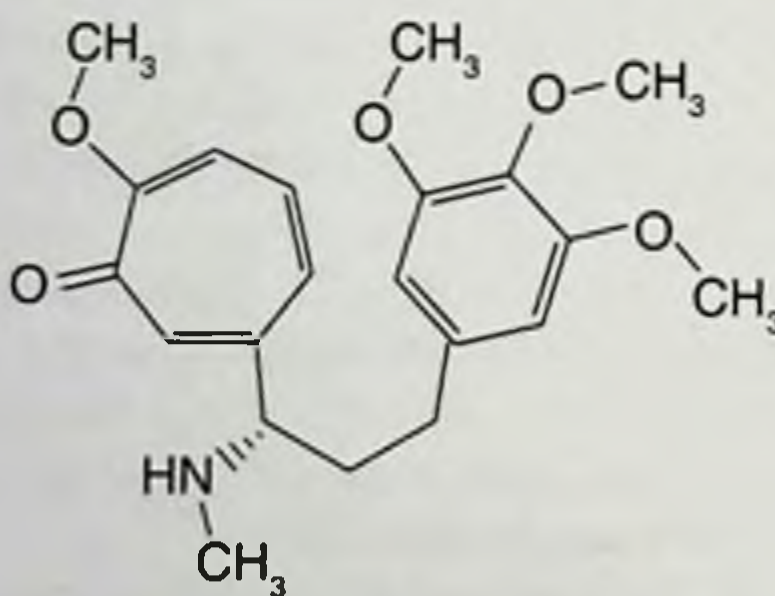


Fig. 13.18. (S)-6,7-Dihydro-1,2,3,10-tetramethoxy-7-(methylamino)benzo/a/heptalen-9-(5H)-one

It is one of the alkaloids isolated from *Colchicum Speciosum* Stev. corms. It has antimitotic activity and inhibits leukopoiesis and lymphopoiesis. For oral, topical administration.

Asparaginase (L-asparaginase[®])

- ▶ An enzyme that catalyzes the breakdown of the amino acid asparagine necessary for the vital activity of cells. The maximum inhibition of proliferation occurs during the postmitotic G_1 phase of the cell cycle.

- ▶ The maximum plasma concentration is reached in the first minutes with intravenous administration and in 14–24 hours with intramuscular administration. It enters the reticuloendothelial system and slowly breaks down to inactive substances. $T_{1/2}$ for intravenous administration: 8–30 hours, $T_{1/2}$ for intramuscular administration: 39–49 hours. Less than 1% of the administered dose is detectable in the cerebrospinal fluid. Only traces of the product are found in the urine. For intravenous, intramuscular administration.

Mechanism of action: It reduces the level of asparagine in leukemia cells, which, unlike normal cells, are unable to synthesize their own asparagine. This disrupts the synthesis of proteins, DNA and RNA.

Tamoxifen (Tamoxifen Hexal*)

- ▶ A non-steroidal drug from the group of triphenylethylenes, a selective estrogen receptor modulator. It is well absorbed and accumulates in the liver, lungs, brain, pancreas, skin and bones.
- ▶ Metabolized in the liver to active metabolites: N-desmethyl tamoxifen and endoxifen. Excretion from the body is biphasic with an initial half-life of 7–14 hours followed by a slow terminal half-life within 7 days. Excreted predominantly in bile, mainly as metabolites. For oral administration.

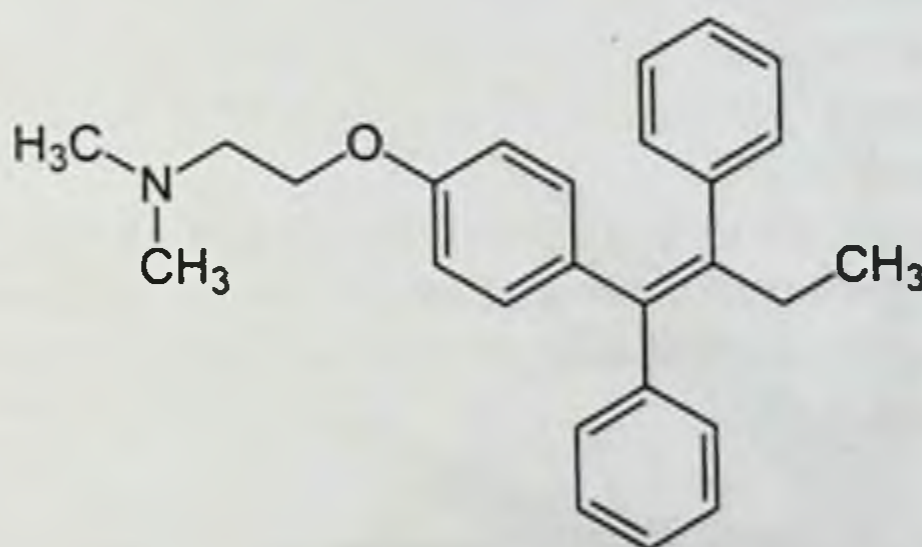


Fig. 13.19. (Z)-2-[4-(1,2-Diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine (as citrate)

Mechanism of action: It competes with estradiol for binding at cytoplasmic estrogen receptors in breast, uterine, vaginal, anterior pituitary tissues and ER-rich tumors. The tamoxifen receptor complex does not stimulate DNA synthesis in the nucleus but inhibits cell division, which promotes regression of tumor cells and their death.

14. ANTIARRHYTHMIC DRUGS

Antiarrhythmic drugs are a group of DPs used to treat or prevent heart rhythm disorders of various causes.

The antiarrhythmic effect of quinine was discovered accidentally in 1912 by one of K. Wenckebach's patients. In 1918, quinidine was found to be the most effective of the four quinine isomers. The Russian physiologist Gleb von Anrep, while working in Cairo, first noticed the cardioactive properties of the amiodarone precursor molecule, khellin, which was used to synthesize amiodarone in 1961. In the same year, verapamil, the first calcium channel blocker was synthesized. J. Black developed the first beta-blocker, propranolol, that rolled off the production line in 1968. For his discovery and development, Black was awarded the Nobel Prize in Physiology or Medicine in 1988. Flecainide was first synthesized in 1972 as a new representative of class IC antiarrhythmic drugs.

In 1987, L. V. Rozenstraukh, A. S. Smetnev, E. P. Anyukhovsky and V. M. Chikhirev were awarded the [Russian State Prize for the development of drug products to prevent and treat arrhythmias [Ethmozine[®] and diethylaminopropionylethoxycarbonylaminophenothiazine (Ethacizine[®])]. The ivabradine molecule was discovered by a Servier research group in 1992.

Arrhythmia (from the Greek *a* — a prefix that generally means “not” or “without”, *rhythmos* — “rhythm”) is a typical form of cardiac disease characterized by disturbed frequency and periodicity of excitation impulse generation and/or sequence of atrial and ventricular excitation.

Forms of cardiac rhythm disturbances

Extrasystole (premature contractions of the atrial and ventricular myocardium)

Tachyarrhythmia (supraventricular and ventricular tachycardias, atrial and ventricular fibrillation/flutter, paroxysmal arrhythmia)

Bradyarrhythmia (sinus bradycardia and atrioventricular block)

Causes of arrhythmias

- ▶ Cardiac: CAD, including myocardial infarction and unstable angina, heart failure, cardiomyopathy, acquired and congenital heart defects, myocarditis, mitral valve prolapse
- ▶ Drug-induced: cardiac glycosides, antiarrhythmic drugs (proarrhythmic action), diuretics, sympathomimetics
- ▶ Electrolyte disorders: hypokalemia, hyperkalemia, hypomagnesemia, hypercalcemia, etc.
- ▶ Toxic effects: smoking, narcotic substances (including alcohol), thyrotoxicosis, atropine poisoning, OPs, etc.

► Idiopathic arrhythmias

Anatomy and physiology of the cardiac conduction system

The cardiac conduction system consists of nodes, bundles and fibers formed by atypical (specialized) muscle cells (P, T, Purkinje) (Fig. 14.1). Cardiac conduction system cells generate excitation and transmit it to the atrial and ventricular contractile elements. P-cells are able to generate electrical impulses (have automaticity) and are almost devoid of contractile elements. T-cells are transitional, located between conductive and contractile cardiomyocytes and help different types of cells interact (have conductivity). Purkinje cells (fibers) have automaticity to a lesser extent than P-cells and conduct excitation very quickly, ensuring its distribution throughout the myocardium.

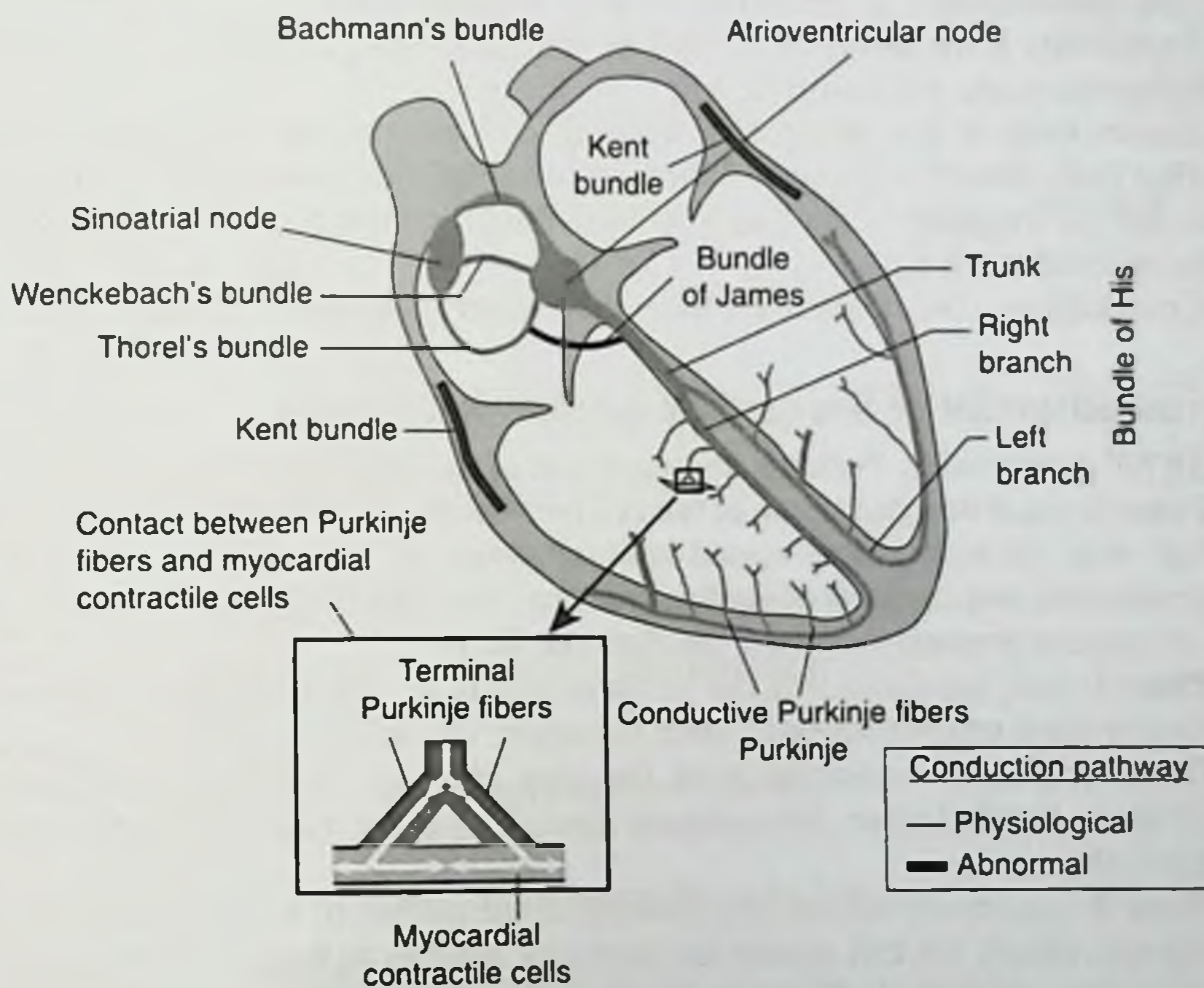


Fig. 14.1. Cardiac conduction system

Structure of the cardiac conduction system

- The sinoatrial node (Keith–Flack, sinus node) is located at the confluence of the venae cavae into the right atrium and is formed by P-cells, which are connected by T-cells to each other and contractile atrial cardiomyocytes.

- ▶ Internodal pathways in Bachmann's bundle, Wenckebach's bundle, and Thorel's bundle. The degree of histological differentiation of these structures from surrounding myocardial tissues varies greatly from person to person.
- ▶ The atrioventricular node (AV, Aschoff–Tawara node) is located in the cardiac septum, on the border of the atria and ventricles; it is formed by P-cells, Purkinje cells (fibers), and T-cells.
- ▶ The bundle of His originates from the atrioventricular node and forms two branches, ending in thin Purkinje fibers, which are in direct contact with the myocardial contractile cells. This bundle is mainly formed by Purkinje cells connected to contractile cardiomyocytes via T cells.

Cardiac functions

Automaticity is the ability of the heart to generate excitatory impulses (normally, APs are spontaneously generated by SA node P-cells).

Excitability is the ability of highly differentiated tissues to respond to a stimulus with excitation and generation of AP.

Conductivity is the ability of a tissue to conduct excitation from one site to another [APs from P-cells spread through the atrial conduction system to the AV node and the intraventricular system of His–Purkinje fibers (from the endocardium to the epicardium)].

Contractility is the ability of the heart to contract under the influence of impulses.

Action potential of the cardiac conduction system

An AP generated by Purkinje fibers consists of the following phases.

Phase 0: rapid depolarization of the cell membrane caused by the inward current of Na^+ ions through voltage-gated sodium channels. The duration of phase 0 determines the conductivity of cardiomyocytes. The shorter phase 0, the higher the rate of impulse propagation along the Purkinje fibers.

Phase 1: early repolarization due to the release of K^+ ions from the cell along the electrochemical gradient through open potassium channels.

Phase 2: plateau associated with the slow entry of Ca^{2+} ions into the cell, which slows repolarization for a certain time. This phase ends when the calcium channels close.

Phase 3: late repolarization associated with the release of K^+ ions from the cell. During this phase, the cell membrane potential reaches its baseline level, which is also its resting potential (-90 mV in Purkinje fibers).

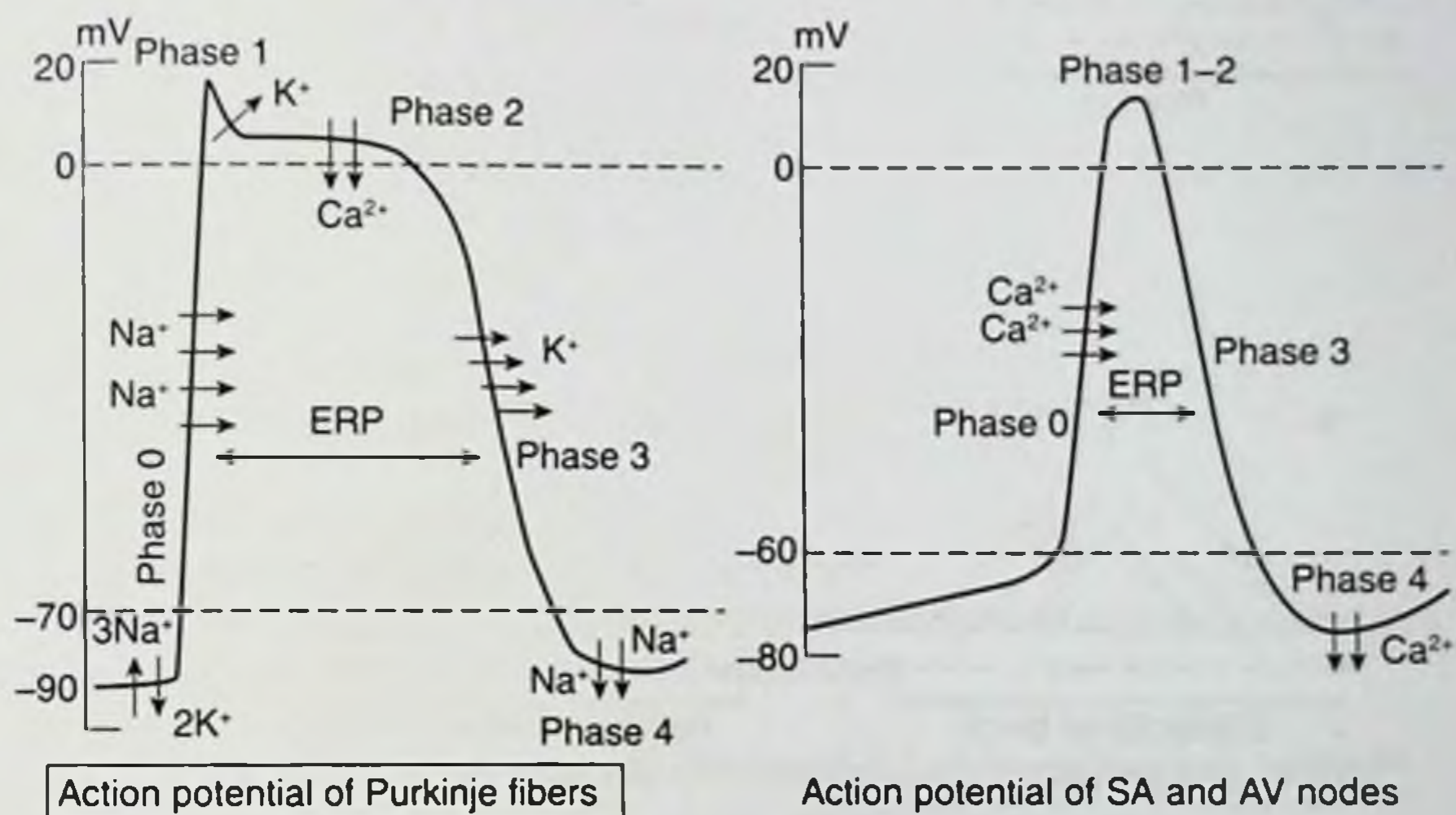
From phase 0 until the end of phase 2 and during the initial portion of phase 3, cells do not respond to excitatory stimuli. During this time, even a strong stimulus does not trigger spread of excitation. The period during which the cell cannot start a new AP is defined as the effective refractory period (ERP). The ERP magnitude depends on the AP duration and is therefore determined by the duration of phase 3 (rate of repolarization).

Phase 4: slow diastolic depolarization. For pacemaker cells, this phase is characterized by slow spontaneous depolarization associated with a slowly increasing

inward sodium current (and only to a small extent by inward calcium current) and a gradual decrease in outward potassium current. As a result, the membrane potential gradually reaches the threshold level. Automaticity depends on the rate of slow diastolic (spontaneous) depolarization (the higher the rate of depolarization, the higher the automaticity).

There are certain differences between APs generated in Purkinje fibers, SA and AV nodes.

In the SA node, membrane depolarization in phase 0 and phase 4 is associated with the entry of Ca^{2+} ions into cardiomyocytes. In the AV node, membrane depolarization in phase 0 and phase 4 of the AP is associated with the entry of both Ca^{2+} and Na^{+} ions into the cell (Fig. 14.2).



- Phase 0 — Rapid depolarization (conduction and excitability)
- Phase 1 — Early repolarization
- Phase 2 — Plateau
- Phase 3 — Late repolarization (action potential duration)
- Phase 4 — Slow diastolic depolarization (automaticity)

Fig. 14.2. Action potential mechanism

Mechanisms of arrhythmias:

1. Changes in the functional state of the myocardium and conduction system. *Abnormal automaticity* manifests as impaired impulse generation in the SA node or the appearance of ectopic pacemakers. From an electrophysiological perspective, the appearance of ectopic pacemakers and increased discharge frequency can be associated with an increased rate of diastolic depolarization (phase 4), a decreased resting membrane potential (maximum diastolic potential; the potential becomes less electronegative) and a lower AP threshold (the threshold becomes more electronegative). *Conduction disturbances* manifest as varying degrees of conduction block in the cardiac conduction system. Conductivity is assessed by the rate of increase

in the AP's amplitude (phase 0). With a decrease in conductivity, the rate of systolic depolarization (phase 0) decreases (the maximum AP value is reached more slowly). The functional block can be unidirectional. In this case, arrhythmias occur by the reentry mechanism (or reentrant excitation) (Fig. 14.3). Such arrhythmias can occur both in the atria and the ventricles.

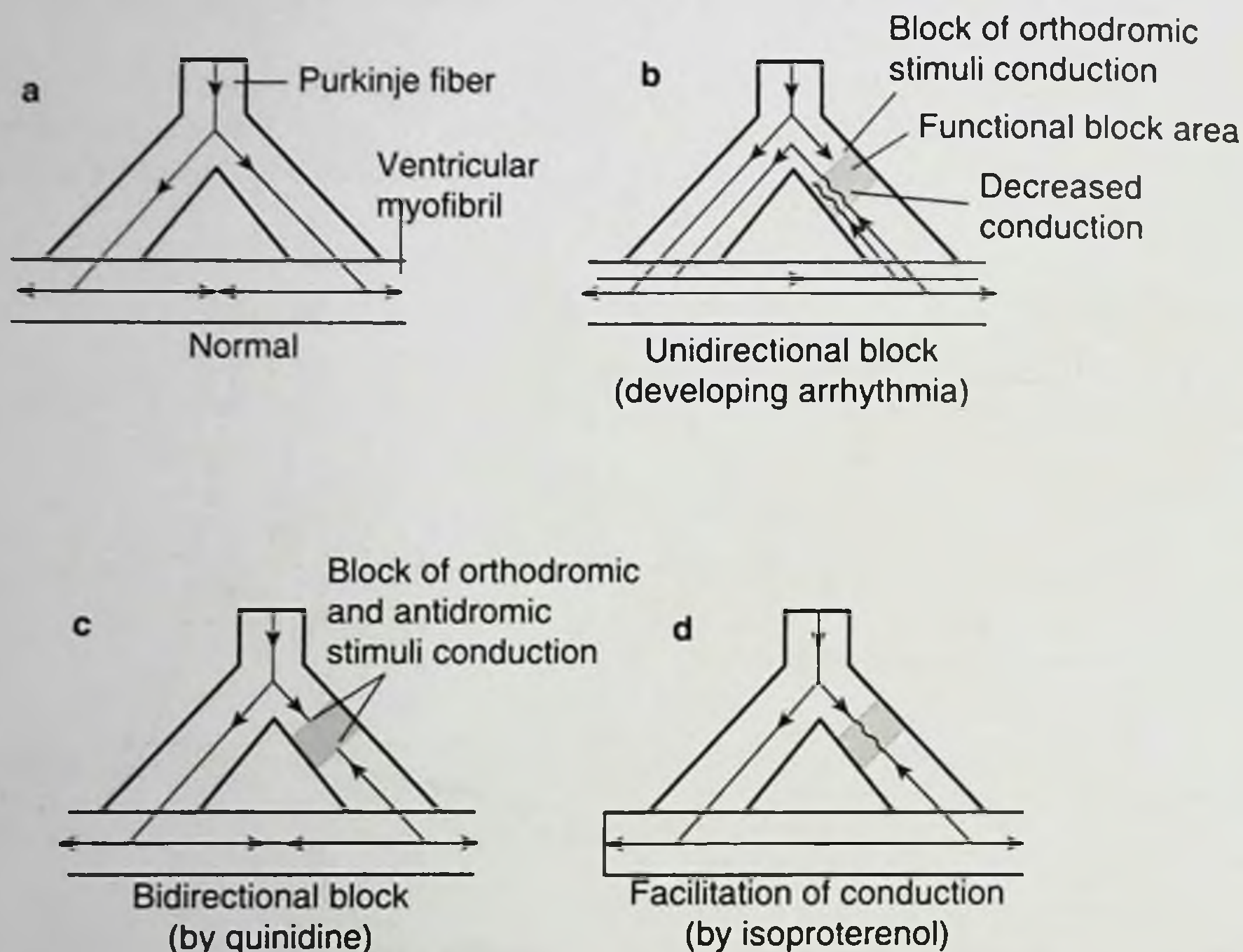


Fig. 14.3. Development of arrhythmia by the reentry mechanism (Kharkevich D.A., 2021)

The ERP magnitude is important for the development of arrhythmias (Fig. 14.2). When it is smaller, the possibility of extrasystoles and more frequent stimuli increases. This is often accompanied by a shorter repolarization phase (phases 2 and 3) and, accordingly, AP duration.

2. Triggered activity involves an abnormal tone in cardiac adrenergic and cholinergic innervation. Stimulation of the cardiac β_1 -ARs accelerates diastolic depolarization (phase 4), which increases the rhythm (Fig. 14.2). SA and AV nodal conduction improves. Repolarization and AP duration become shorter. All this contributes to the development of arrhythmias. The catecholamines circulating in the blood are important. In excessive concentrations, they can cause arrhythmias. Rhythm disturbances also occur when cardiac ARs are sensitized to catecholamines (e.g., in hyperthyroidism). Cholinergic innervation (ACh) has the opposite effect on many parameters. Thus, the automaticity of the SA and AV nodes decreases, and the heart rate slows. AV nodal conduction worsens, its ERP extends, and AV block may develop.

Groups of drug products by use**I. Agents used for tachyarrhythmia and extrasystoles**

- Sodium channel blockers
- Calcium channel blockers
- Potassium channel blockers
- Bradycardia causing agents
- Beta-blockers
- Other agents

II. Agents used for bradyarrhythmias and conduction disorders

- Muscarinic receptor antagonists (MRA)
- Beta-adrenergic agonists (β -AAs)

Vaughan-Williams classification

- ▶ **Class I — sodium channel blockers**
 - **Class IA (quinidine and quinidine-like agents)**
 - Quinidine (Quinidine sulfate[®])
 - Procainamide (Novocainamide[®])
 - Disopyramide (Rytmilene[®])
 - Ajmaline (Gilurymal[®])
 - **Class IB**
 - Lidocaine (Xycaine[®])
 - Phenytoin (Diphenin[®])
 - **Class IC**
 - Flecainide acetate[®] (Tambocor[®])
 - Propafenone (Rytmonorm[®], Propanorm[®])
 - Diethylaminopropionylethoxycarbonylaminophenothiazine (Ethacizine[®])
 - Lappaconitine hydrobromide (Allapinine[®])
- ▶ **Class II — beta-blockers**
 - A. Non-selective beta-blockers: propranolol (Anaprilin[®], Obsidan[®], Inderal[®])
 - B. Cardioselective beta-blockers
 - Atenolol (Atenova[®])
 - Metoprolol (Betaloc[®])
 - Betaxolol (Lokren[®])
 - Bisoprolol (Concor[®])
- ▶ **Class III — membrane-stabilizing drugs**
 - Amiodarone (Cordarone[®])
 - Sotalol (Sotahexal[®])
- ▶ **Class IV — calcium channel blockers**
 - Verapamil (Isoptin SR 240[®], Finoptin[®])
 - Diltiazem (Cardil[®], Dilzem[®])
- ▶ **Class V — selective heart rate-lowering drugs: ivabradine (Coraxan[®])**
- ▶ **Class VI — other agents:**
 - Digoxin
 - Potassium & magnesium products
 - Adenosine

Classification based on mechanism of action

I. Agents that mainly block cardiac ion channels

1. Sodium channel blockers (class I)

– Class IA (quinidine and quinidine-like agents)

- Quinidine (Quinidine sulfate^o)
- Procainamide (Novocainamide⁺)
- Disopyramide (Rytmilene^o)
- Ajmaline (Gilurytmal^o)

– Class IB

- Lidocaine (Xycaine^o)
- Phenytoin (Diphenin⁺)

– Class IC

- Flecainide acetate^o (Tambocor^o)
- Propafenone (Rytmonorm⁺, Propanorm⁺)
- Diethylaminopropionylethoxycarbonylaminophenothiazine (Ethacizine⁺)
- Lappaconitine hydrobromide (Allapinine⁺)

2. L-type calcium channel blockers (class IV)

– Verapamil (Isoptin SR 240⁺, Finoptin^o)

– Diltiazem (Cardil⁺, Dilzem^o)

3. Potassium channel blockers (agents that delay repolarization and, consequently the AP; class III)

– Amiodarone (Cordarone⁺)

– Sotalol (Sotahexal⁺)

4. Agents that selectively block the mixed Na⁺/K⁺ inward (I_f) current (selective heart rate-lowering drugs, class V)

– Ivabradine (Coraxan⁺)

II. Agents that mainly affect cardiac innervation

1. Agents that block sympathetic activity (class II)

A. Non-selective beta-blockers

- Propranolol (Anaprilin⁺, Obsidan⁺, Inderal⁺)

B. Cardiospecific beta-blockers (bind to β₁ receptors)

- Atenolol (Atenova⁺)
- Metoprolol (Betaloc⁺)
- Betaxolol (Lokren⁺)
- Bisoprolol (Concor⁺)

2. Agents that enhance sympathetic activity (β-AAAs)

– Isoprenaline (Isadrine^o)

3. Muscarinic receptor antagonists (MRAs)

– Atropine (Atropine sulfate⁺)

III. Other agents with antiarrhythmic activity

A. Potassium & magnesium products

– Potassium chloride

– Potassium-magnesium aspartate (Panangin⁺, Asparcam⁺)

B. Cardiac glycosides

– Digoxin

C. Adenosine (Adenocor⁺)

AGENTS THAT MAINLY BLOCK CARDIAC ION CHANNELS

Sodium channel blockers (class I)

Class IA

Mechanism of action (Fig. 14.4, 14.5)

- ▶ Delays spontaneous depolarization in phase 4 (block open sodium channels).
- ▶ Suppresses the AP rise in phase 0.
- ▶ Extends the ERP by blocking potassium channels in phases 2 and 3 of repolarization.
- ▶ Increases the early after depolarization threshold.

Main changes in electrophysiological parameters

- ▶ Reduces automaticity (Purkinje fibers).
- ▶ Slows conduction.
- ▶ Prolongs repolarization and extend the ERP.

Therapeutic indications: supraventricular and ventricular extrasystoles, atrial tachycardia, AV tachycardia, paroxysmal atrial fibrillation and atrial flutter

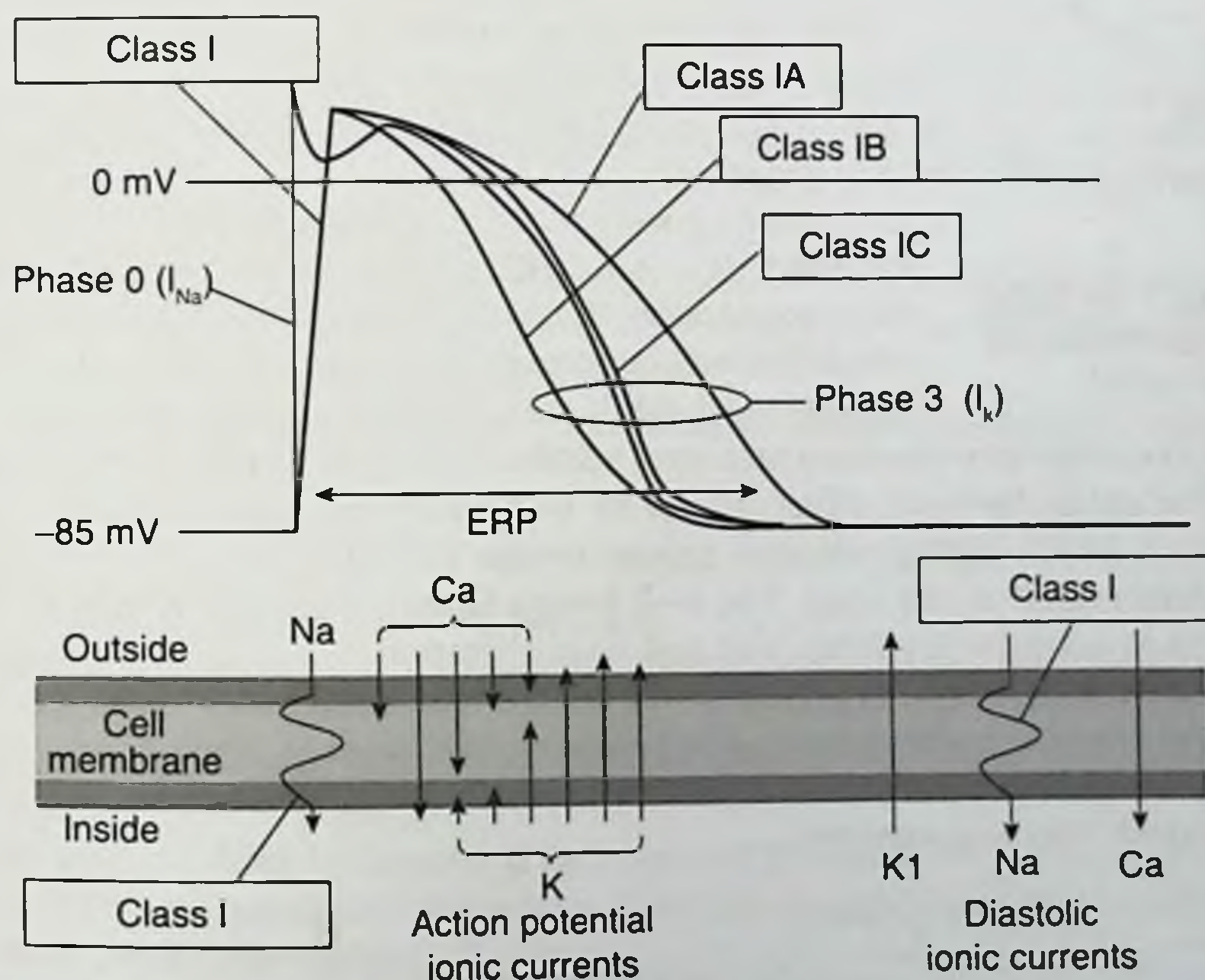


Fig. 14.4. Mechanism of action of class I antiarrhythmic drugs

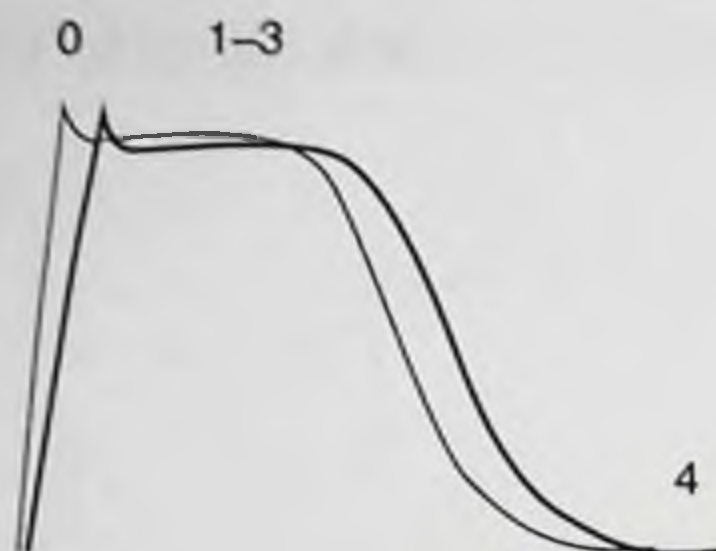


Fig. 14.5. Mechanism of action of class IA drugs. Thin line — normal action potential. Thick line — AP under the influence of class IA antiarrhythmic drugs

Side effects: decreased AV conduction (development of AV block), decreased myocardial contractility, hypotension, atropine-like effects, arrhythmogenic effects (often manifested as pirouette-type arrhythmias), allergic reactions

Contraindications: SA, AV, intraventricular blocks; *QT* prolongation, pirouette-type ventricular tachycardia, myocardial infarction (acute stage), hypotension, severe forms of congestive heart failure, angle-closure glaucoma, prostatic hyperplasia

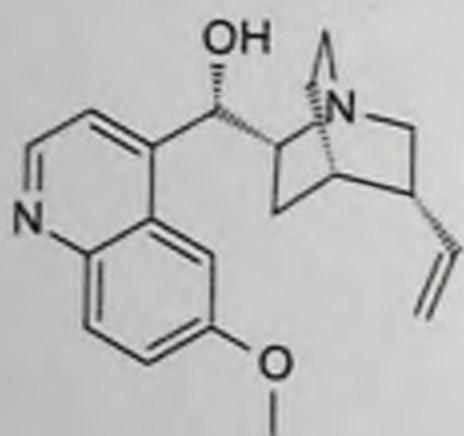


Fig. 14.6. (8R,9S)-6-Methoxycinchonan-9-ol (as sulfate)

Specifics of individual products

Quinidine (Quinidine sulfate^u) — Excluded from the Russian List of Vital and Essential Drugs in 2012; authorization in Russia was revoked in 2013. It is only used as a reference drug for this group.

► Cinchona bark alkaloid (dextrorotatory isomer of quinine). It acts on all chambers of the heart. It inhibits the transmission of excitation from the vagus nerve to the heart (inhibits muscarinic receptors). It reduces peripheral resistance (α -AR block). It has a negative inotropic effect.

It is completely absorbed after oral administration. Bioavailability: 70–80%. The antiarrhythmic effect occurs in 1–3 hours and lasts 6–8 hours or 12 hours (when taking extended-release dosage forms).

► Metabolized in the liver. $T_{1/2}$: 6–7 hours. Excreted in the urine unchanged and as active metabolites. For oral administration.

Additional side effects: quinidine shock (severe ventricular arrhythmias, asystole), lupus-like syndrome, thrombocytopenic purpura, idiosyncrasy, tinnitus, headache

Procainamide (Novocainamide*)

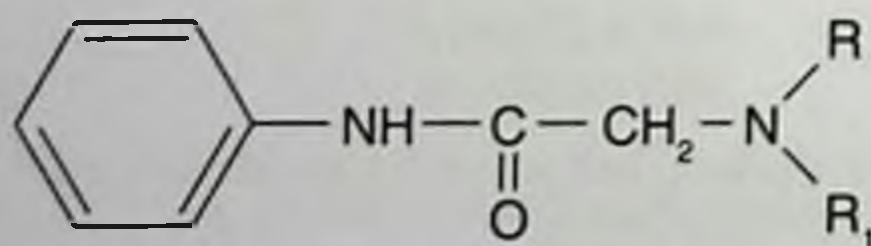


Fig. 14.7. 4-Amino-N-[2-(diethylamino)ethyl]benzamide (as hydrochloride)

- ▶ Its chemical structure is similar to that of procaine (it contains an amide group instead of an ether group). To a lesser extent than quinidine, it reduces myocardial contractility and has vagolytic activity. It has no effect on α -ARs. It reduces arterial and venous pressure, thus can cause orthostatic collapse (moderate ganglion blocking effect). It is rapidly and completely absorbed. Bioavailability: 85%. It crosses the BBB, placental barrier, and is excreted into breast milk.
- ▶ Metabolized in the liver to form an active metabolite, N-acetylprocainamide; first-pass effect. $T_{1/2}$: 3–5 hours, excreted in the urine (50–60% unchanged) and bile. For oral administration every 3–6 hours, for intramuscular, intravenous administration (reduction of paroxysmal tachycardia).

Additional therapeutic indications: recurrent ventricular tachycardia.

Additional side effects: lupus-like syndrome (in 30% of patients)

Disopyramide (Rytmilen[®])

- ▶ Its efficacy is similar to that of quinidine. After oral administration, it is rapidly and almost completely absorbed. Bioavailability: 80%. Crosses the placental barrier, excreted into breast milk. It has negative inotropic effects and significantly inhibits muscarinic receptors, increases the coronary vascular tone.
- ▶ Metabolized in the liver with the involvement of cytochrome P450 isoenzyme CYP3A4. The major metabolite is mono-N-dealkylated disopyramide, which has some antiarrhythmic and anticholinergic activity. $T_{1/2}$: 4–10 hours.

Excreted in the urine (about 50% unchanged, 20% as N-dealkylated metabolite and 10% as other metabolites) and in bile (about 20%). For oral administration 4 times daily, for intravenous administration.

Additional therapeutic indications: paroxysmal ventricular tachycardia, ventricular fibrillation

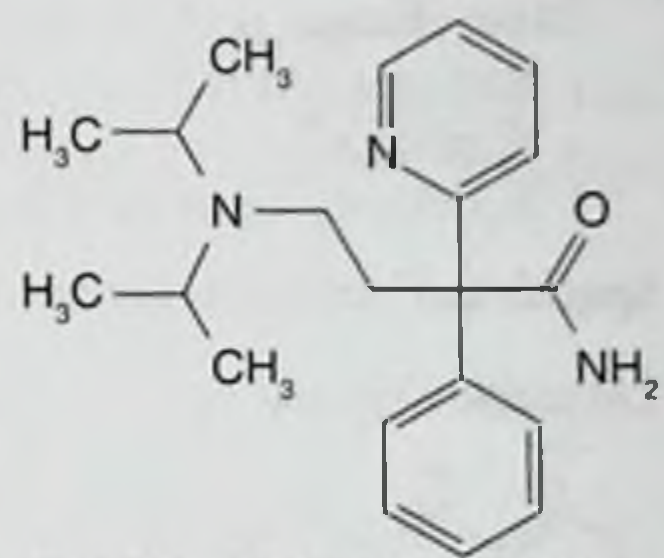


Fig. 14.8. α -[2-[bis(1-Methylethyl) amino]ethyl]- α -phenyl-2-pyridineacetamide (as phosphate)

Class IB

Mechanism of action (Fig. 14.4, Fig. 14.9)

- ▶ Delays spontaneous depolarization in phase 4 (block inactivated open sodium channels).
- ▶ Does not change (lidocaine) or accelerate (phenytoin) the increase in depolarization in phase 0.
- ▶ Shortens the ERP by increasing the release of K^+ ions in phases 2 and 3.
- ▶ Stops circus movements since they eliminate the functional block zone in the main conduction pathway.
- ▶ Has the biggest effect on the ventricles, since the AP is longer, repolarization is slow, therefore sodium channels are open and inactivated for a long time.

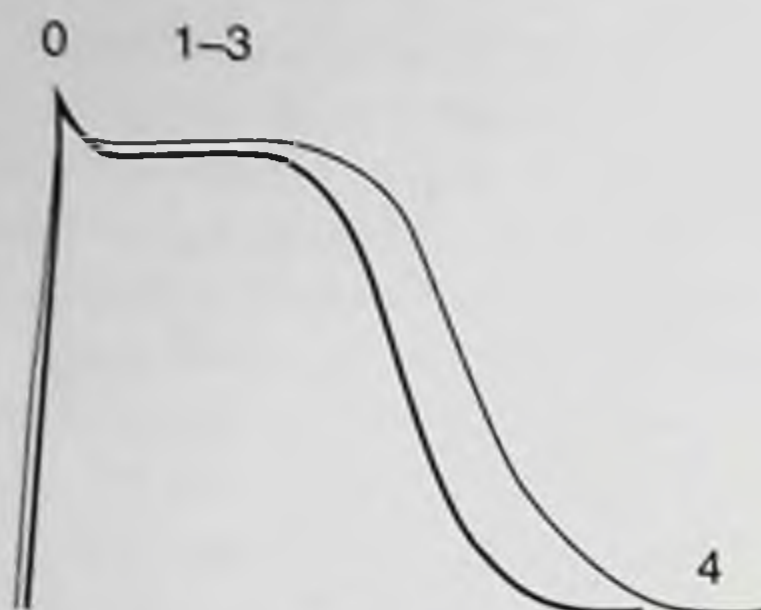


Fig. 14.9. Mechanism of action of class IB drugs. Thin line — normal action potential. Thick line — AP under the influence of class IB antiarrhythmic drugs

Main changes in electrophysiological parameters

- ▶ Reduces automaticity (Purkinje fibers)
- ▶ Slightly affects conductivity
- ▶ Accelerate repolarization and shortens the ERP.

Specifics of individual products

Lidocaine (Xycaine®)

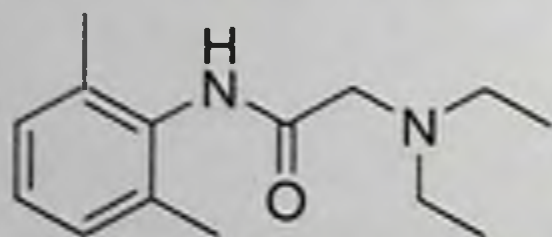


Fig. 14.10. 2-(Diethylamino)-N-(2,6-dimethylphenyl)acetamide

- ▶ Has antiarrhythmic and local anesthetic effects. Has no cardiodepressant action (does not affect contractility), vagolytic effect. Easily crosses the blood-tissue barriers. Excreted into breast milk. Has rapid and short-term action (time of action with a single injection: 10–20 minutes).

- ▶ Metabolized in the liver, about 90% of the administered dose undergoes N-dealkylation to form monoethylglycinexylidide and glycinexylide. $T_{1/2}$ after intravenous bolus injection: 1.5–2.0 hours, $T_{1/2}$ with continuous intravenous infusions: 3 hours or more. Metabolites are excreted in the urine, with the content of unchanged lidocaine in the urine not exceeding 10%. For parenteral administration (intravenous administration — emergency treatment of ventricular tachycardia and extrasystole, intramuscular administration — prevention of ventricular fibrillation in myocardial infarction and glycoside intoxication).

Therapeutic indications: ventricular extrasystole and tachycardia (including due to glycoside intoxication), ventricular fibrillation in acute myocardial infarction, all types of local anesthesia

Side effects: somnolence, confusion, convulsive reactions, hypotension, decreased AV conduction

Contraindications: sick sinus syndrome, AV block, bradycardia, cardiogenic shock, myasthenia, a history of drug-induced seizures

Phenytoin (Diphenin®)

- ▶ Its action is similar to that of lidocaine. It has antiarrhythmic and anticonvulsant activity. It has no obvious effect on myocardial contractility and blood pressure.

Bioavailability: less than 50%. Crosses the blood-tissue barriers. It has centralized action — it reduces adrenergic effects on the heart, which enhances the therapeutic effect in tachyarrhythmias. It is long-acting and can accumulate.

- ▶ Metabolized in the liver by glucuronidation to inactive metabolites (the major metabolite is 5-(p-hydroxyphenyl)-5-phenylhydantoin). $T_{1/2}$ after intravenous administration: 9–14 hours, $T_{1/2}$ after oral administration: 22–28 hours; 35–60% excreted in the urine, 40–65% in bile. For oral administration 2–3 times daily, for intravenous administration.

Therapeutic indications: ventricular arrhythmias, epilepsy with partial seizures

Side effects: hypotension (with intravenous administration); ataxia, nystagmus, diplopia, hyperplastic gingivitis (gingival hyperplasia)

Contraindications: heart failure, Morgagni–Adams–Stokes syndrome, 2nd–3rd degree AV block, sinoatrial block, renal and hepatic disorders, pregnancy and breastfeeding

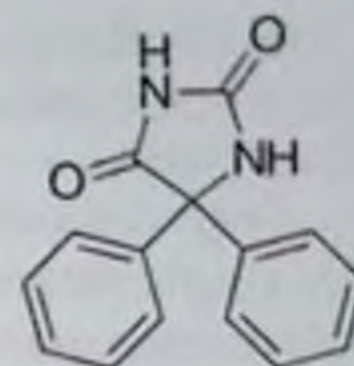


Fig. 14.11.
5,5-Diphenyl-2,4-imidazolidinedione
(as sodium salt)

Class IC

Mechanism of action (Fig. 14.4, Fig. 14.12)

- ▶ Blocks sodium channels.
- ▶ Delays depolarization (phase 0).
- ▶ Does not change repolarization (phases 1–3).
- ▶ Significantly slows conduction in the atrial, ventricular myocardium and conduction system.

Main changes in electrophysiological parameters

- ▶ Reduces automaticity (Purkinje fibers)
- ▶ Significantly inhibits conduction.
- ▶ Has little effect on repolarization and ERP.

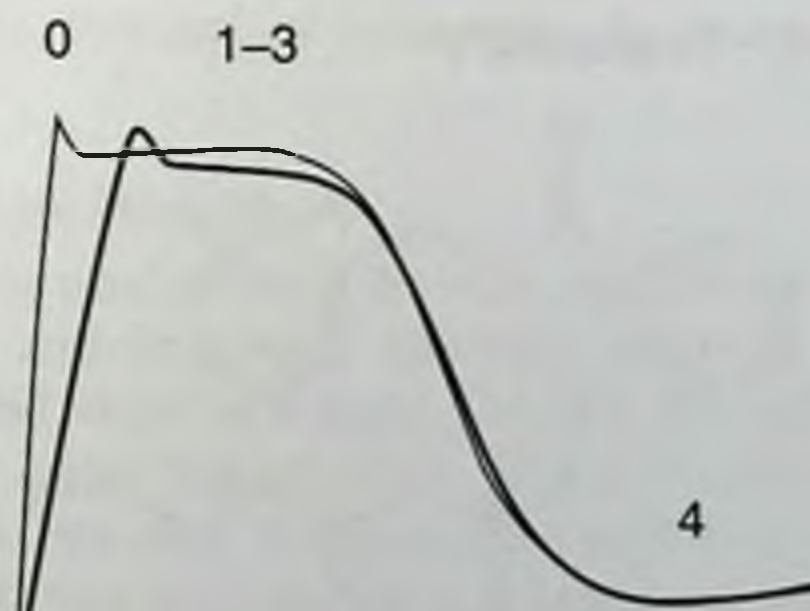


Fig. 14.12. Mechanism of action of class IC drugs. Thin line — normal action potential. Thick line — AP under the influence of class IC antiarrhythmic drugs

Therapeutic indications: supraventricular and ventricular extrasystoles, tachyarrhythmias refractory to the action of other antiarrhythmic drugs

Side effects: arrhythmogenic effect, sinus node arrest, AV block, impaired intraventricular conduction, decompensation of congestive heart failure (cardiac depression)

Contraindications: sick sinus syndrome, 2nd degree SA block, 2nd–3rd degree AV block, intraventricular conduction system block, *QT* prolongation syndrome, severe heart failure, hypotension, postinfarction cardiosclerosis, hepatic and renal impairment

Specifics of individual products

Flecainide acetat[®] (Tambocor[®])

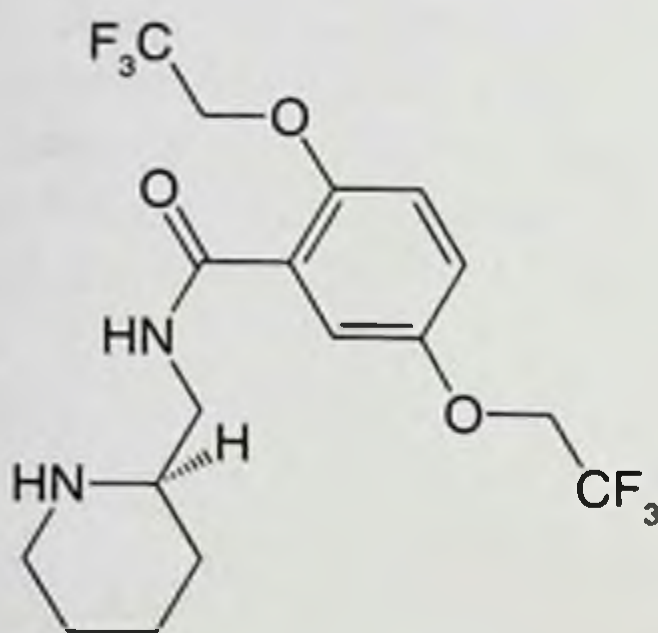


Fig. 14.13. (RS)-N-(Piperidin-2-ylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide

- ▶ Its structure is similar to procainamide. It has antiarrhythmic and local anesthetic effects. Well absorbed in the GI tract. Bioavailability: about 85%. Crosses the placental barrier and is excreted into breast milk. Significantly reduces myocardial contractility.
- ▶ Metabolized in the liver to form metabolites, $T_{1/2}$: 7–23 hours, excreted mainly in the urine. For oral administration 2 times daily, for intravenous administration.

Propafenone (Rytmonorm[®], Propanorm[®])

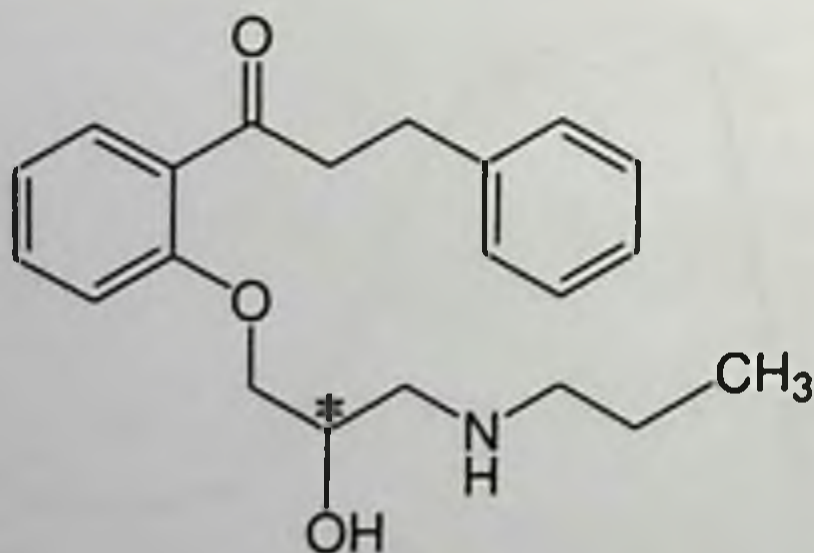


Fig. 14.14. 1-[2-[2-Hydroxy-3-(propylamino)propoxy]phenyl]-3-phenylpropan-1-one

- ▶ Also blocks β -ARs and trivially blocks calcium channels. Bioavailability varies from 3% to 40% due to first-pass metabolism. The onset of action occurs in 30 min after oral administration, reaching a maximum in 2–3 hours, and lasts 8 hours.

- ▶ Metabolized in the liver to form 11 metabolites, including metabolically active 5-hydroxypropafenone and N-depropylpropafenone, which have antiarrhythmic activity comparable to propafenone. There are groups of patients with fast (90%) and slow (10%) metabolism. $T_{1/2}$ for the first group is 5.5 hours and 17.2 hours for the second group. Differences in metabolic rate are genetic. 38% excreted in the urine as metabolites, 1% unchanged; 53% in bile as metabolites. For oral administration at the initiation of therapy every 8 hours with up-titration every 3–4 days and further switching to 2–3 times intravenous administration.

Additional side effects: bronchospasm, nausea, vomiting, constipation, lupus-like syndrome

Additional contraindications: chronic obstructive pulmonary disease

Diethylaminopropionylethoxycarbonylaminophenothiazine (Ethacizine*)

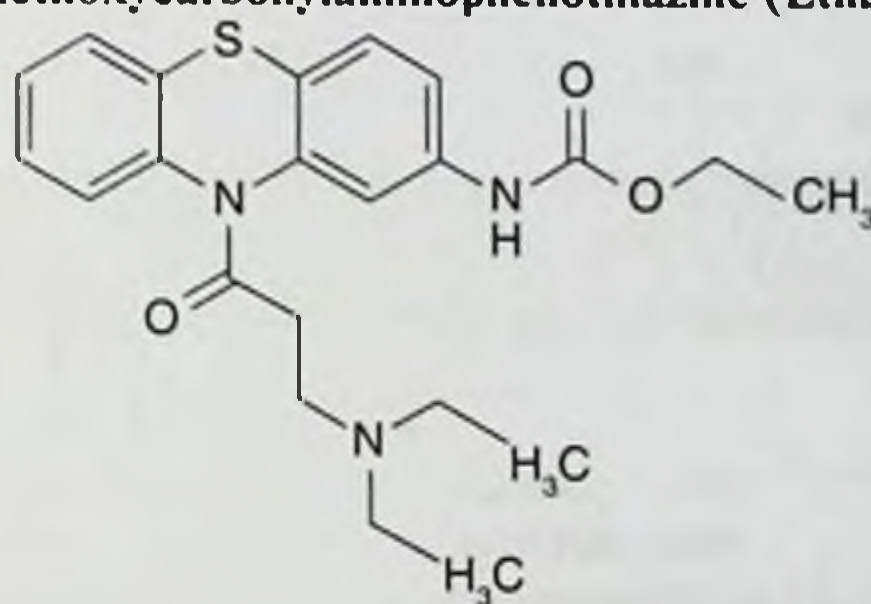


Fig. 14.15. 10-(3-diethylaminopropionyl)-2-(ethoxycarbonylamino)phenothiazine (as hydrochloride)

- ▶ This product blocks sodium and calcium channels. It has a negative inotropic effect. It has local anesthetic and antispasmodic activity. Moderate atropine-like effect. Rapidly absorbed in the GI tract after oral administration. Bioavailability: 40%. The antiarrhythmic effect occurs within 1–2 days.
- ▶ Metabolized in the liver to form active metabolites, $T_{1/2}$: 2 hours, excreted in the urine as metabolites. For oral administration 2–3 times daily, for intravenous administration.

Lappaconitine hydrobromide (Allapinine*)

- ▶ Hydrobromide of the alkaloid from the herb, *Aconitum leucostomum* Worosch. It has moderate antispasmodic, coronary dilating, muscarinic blocking, local anesthetic and sedative effects. Crosses the BBB. Essentially has no negative inotropic or antihypertensive effects. Bioavailability is 40% as the product undergoes intensive first-pass biotransformation. The effect occurs in 40–60 min, reaching a maximum in 4–5 hours and lasts 8 hours or more. With intravenous administration, the antiarrhythmic effect occurs in 15–20 minutes and lasts 6–8 hours (the maximum effect is reached in 2 hours). It has a narrow therapeutic index.
- ▶ Metabolized in the liver, $T_{1/2}$: 1.0–1.2 hours, excreted in the urine. For oral administration every 6–8 hours.

L-type calcium channel blockers (class IV)

Mechanism of antiarrhythmic action

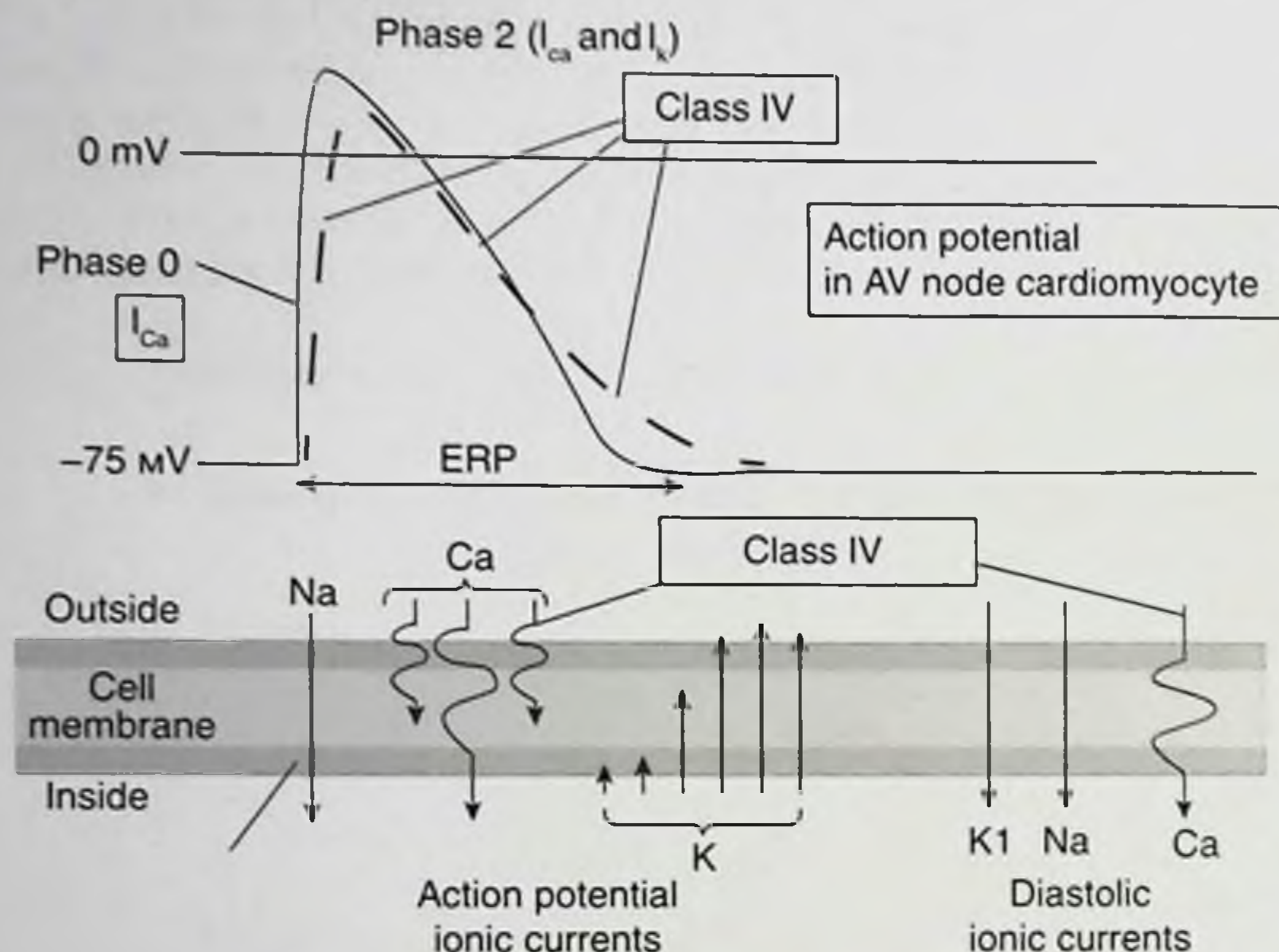


Fig. 14.16. Mechanism of action of class IV drugs (Petrov V.I., 2011). Solid line — normal action potential. Dashed line — AP under the influence of class IV antiarrhythmic drugs

These drugs block L-type voltage-gated calcium channels in the cardiomyocyte membrane (Fig. 14.16).

- ▶ Delays AP development in the sinus and AV nodes (phase 0).
- ▶ Extends the ERP by disrupting the entry of Ca^{2+} ions in phase 2 of repolarization.
- ▶ Increases the late after depolarization threshold.
- ▶ Prevents circus movements in the AV node.

Main changes in electrophysiological parameters

- ▶ Decreased SA nodal automaticity
- ▶ Significantly reduced conductivity
- ▶ Increased ERP (in the AV node).

Group specifics

- ▶ They differ in their primary action on the heart and blood vessels:
 - **Phenylalkylamines** (verapamil, etc.) mainly block the calcium channels of cardiomyocytes.
 - **Dihydropyridines** (nifedipine, amlodipine, etc.) mainly block the calcium channels of vascular smooth muscle cells.
 - **Benzothiazepines** (diltiazem) affect the heart and blood vessels equally.

Phenylalkylamines, mainly verapamil, and, less often, benzothiazepines (diltiazem), are used as antiarrhythmic drugs. They have antiarrhythmic, antianginal, antihypertensive effects. Not administered concomitantly with beta-blockers (due to

possible summation of effects on cardiac conductivity and contractility) or cardiac glycosides (increases their blood concentration).

Therapeutic indications: treatment and prevention of supraventricular arrhythmias (paroxysmal supraventricular tachycardia, atrial fibrillation and flutter, extrasystole), exertional angina and Prinzmetal angina, hypertension

Side effects: bradycardia, SA and AV blocks, facial hyperemia, increased fatigue, peripheral edema (local arterial vasodilation without sufficient venous outflow), atonic constipation, hypotension, heart failure

Contraindications: Wolff–Parkinson–White (WPW) syndrome with antidromic ventricular tachycardia, bradycardia, sick sinus syndrome, 2nd–3rd degree AV block, acute myocardial infarction, cardiogenic shock, severe impairment of the left ventricular contractility

Specifics of individual products

Verapamil (Finoptin[®], Isoptin SR 240[®])

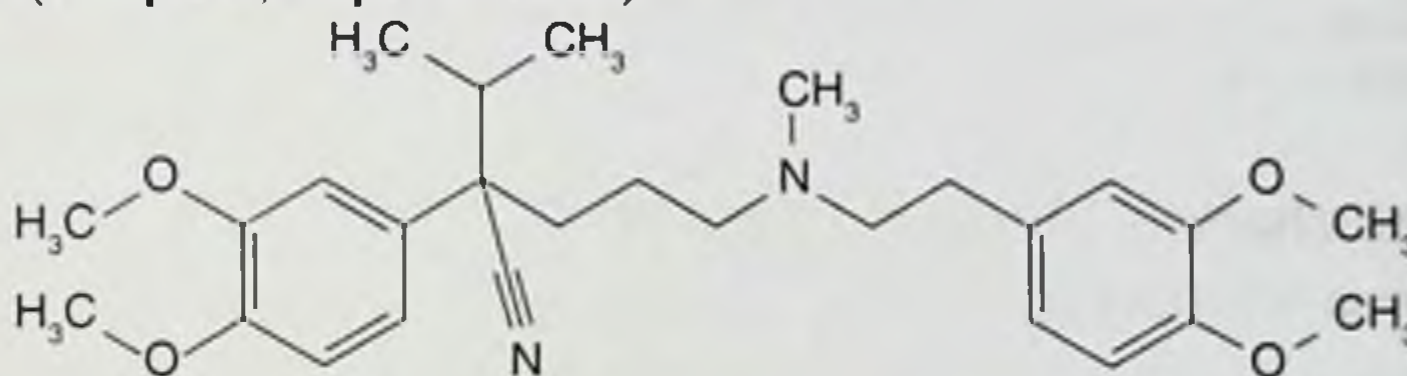


Fig. 14.17. α -[3-[[2-(3,4-Dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy- α -(1-methylethyl) benzeneacetonitrile (as hydrochloride)

- ▶ Reduces myocardial oxygen demand, has vasodilating, negative inotropic and chronotropic effects. Well absorbed after oral administration. Excreted into breast milk, crosses the placental barrier. Bioavailability: 20–35% due to significant first-pass effect. With repeated use, it increases approximately 2-fold. After intravenous administration, the antiarrhythmic effect occurs in 1–5 minutes, time of action: 2 hours.
- ▶ Metabolized in the liver by N-dealkylation and O-demethylation to form several metabolites; the major metabolite is norverapamil, which has less pronounced antihypertensive activity than unchanged verapamil. After a single oral dose, $T_{1/2}$ is 3–7 hours, after repeated doses it is 4.5–12 hours; after intravenous administration, the initial $T_{1/2}$ is about 4 minutes, the terminal one is 2–5 hours. Excreted mainly in the urine and about 16% in bile. For oral administration 3 times daily, for intravenous administration.

Diltiazem (Cardil[®], Dilzem[®])

- ▶ It has a stronger effect on the vascular smooth muscles and the cardiac conduction system, inhibits the inotropic function of the heart less than verapamil. Produces less significant peripheral vasodilation than nifedipine (see “Antihypertensive drugs” section). Bioavailability: 40% (significant first-pass effect). The onset of action occurs within 3 minutes after bolus intravenous administration, in 2–3 hours (extended-release capsules) or 30–60 minutes

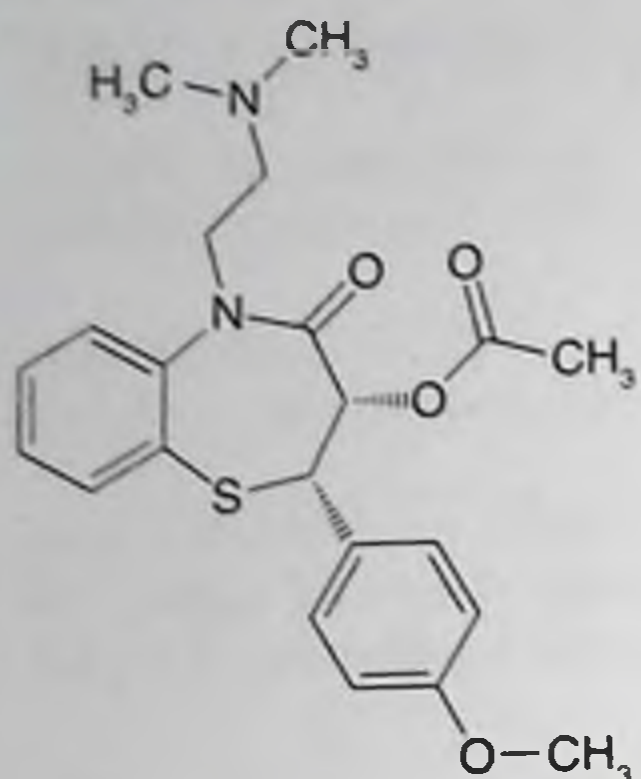


Fig. 14.18. (2S-cis)-3-(Acetoxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (as hydrochloride)

(tablets) after oral administration. Time of action after oral administration: 4–8 hours (tablets) and 12–24 hours (extended-release capsules).

► Metabolized in the liver by deacetylation, demethylation with cytochrome P450 involvement (in addition to conjugation). Two major metabolites are deacetyldiltiazem and desmethyldiltiazem. The deacetylated metabolite acts as a coronary vasodilator and can accumulate. $T_{1/2}$ after intravenous administration: 1–3 hours, $T_{1/2}$ after oral administration: 3–4.5 hours. Excreted in the urine and bile as metabolites, approximately 2–4% is excreted in the urine unchanged. For oral administration 2–3 times daily, 1–2 times daily with extended-release dosage forms, for intravenous administration.

Potassium channel blockers (class III)

Mechanism of action (Fig. 14.19)

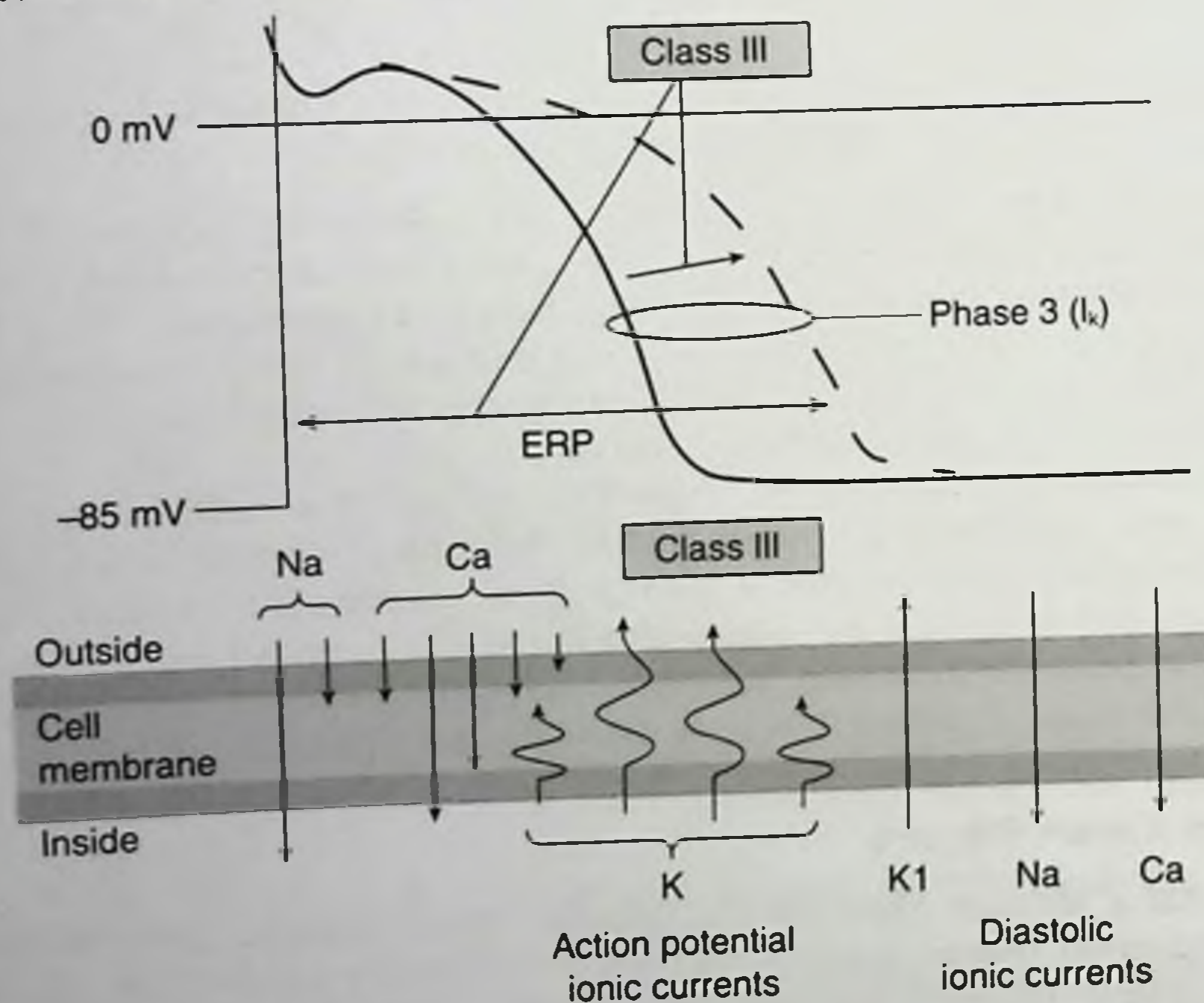


Fig. 14.19. Mechanism of action of class III drugs (Petrov V.I., 2011). Solid line — normal action potential. Dashed line — AP under the influence of class III antiarrhythmic drugs

- ▶ Delays spontaneous depolarization in phase 4 (blocks calcium and inactivated sodium channels).
- ▶ Extends the ERP (suppresses the potassium current in phase 2 and block potassium channels in phase 3) of the atria, ventricles, AV node, bundle of His and Purkinje fibers, as well as additional excitation pathways.
- ▶ Disrupts the AP in conduction system cells.

Main changes in electrophysiological parameters

- ▶ Decreases automaticity (in the SA node, Purkinje fibers)
- ▶ Slows conduction.
- ▶ Prolongs repolarization and extend the ERP.

Therapeutic indications: ventricular and supraventricular tachyarrhythmias and extrasystoles

Side effects: sinus bradycardia and intracardiac conduction disorders, hypotension, arrhythmogenic effect (less common for amiodarone than other antiarrhythmic drugs)

Contraindications: 2nd–3rd degree SA and AV block, sick sinus syndrome, sinus bradycardia, QT prolongation syndrome, hypotension

Amiodarone (Cordarone®)

- ▶ Contains 37% iodine, structurally similar to thyroid hormones but does not have their properties. It blocks potassium, sodium, calcium channels, and also has α -, β -blocking action (reduces blood pressure, improves coronary circulation). It acts on all chambers of the heart. It can be used as an antiarrhythmic agent in myocardial infarction and heart failure. It circulates in the blood for a long time, the maximum effect occurs in 1 week. When taken orally, it is absorbed with a bioavailability of 35–65%. With intravenous administration, the effect occurs in 15 minutes. Arrhythmogenic effects are rare. No withdrawal syndrome after treatment discontinuation. It accumulates in well-perfused organs (liver, lungs, spleen) and is deposited in adipose tissue.
- ▶ Metabolized in the liver with the involvement of cytochrome P450 isoenzymes CYP3A4 and CYP2C8. Its major metabolite — desethylamiodarone — is pharmacologically active and may enhance the antiarrhythmic effect of the parent compound. It has a long half-life but also great individual variability (therefore, when increasing or decreasing it, one should remember that at least 1 month is needed to stabilize the new plasma concentration of amiodarone). After oral administration, it is eliminated in two phases: initial $T_{1/2}$ (phase 1) is 4–21 hours, $T_{1/2}$ in phase 2 is 25–110 days. For oral and intravenous administration.

Additional side effects: interstitial pneumonia, alveolitis or pulmonary fibrosis, development of hypo- or hyperthyroidism, reversible corneal deposition of lipofuscin pigment, sometimes leading to blurred vision, rainbow vision; photosensitivity, gray-blue skin discoloration in the face, neck and hands; ataxia, tremor, nausea,

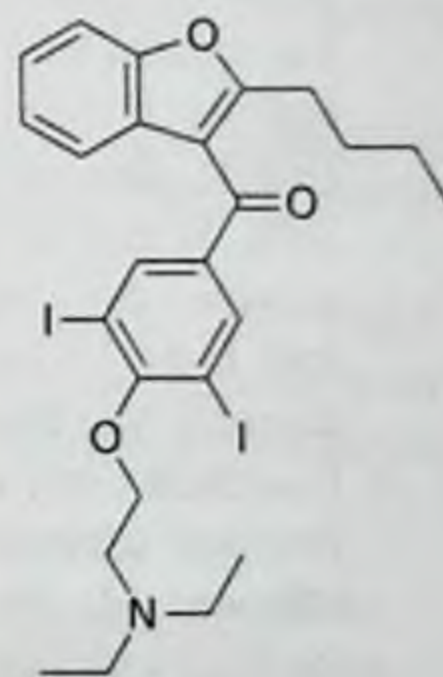


Fig. 14.20. (2-Butyl-3-benzofuranyl) [4-[(2-diethylamino)ethoxy]-3,5-diiodophenyl]methanone (and as hydrochloride)

constipation, hepatic impairment, hemolytic and aplastic anemia, thrombocytopenia, bronchospasm

Additional contraindications: thyroid dysfunction, allergic reaction to iodine, hypokalemia, chronic obstructive pulmonary disease

Sotalol (Sotahexal[®])

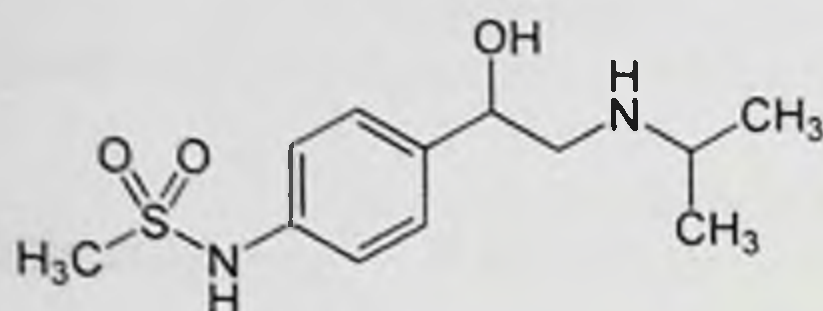


Fig. 14.21. N-[4-[1-Hydroxy-2-[(1-methylethyl)amino]ethyl]phenyl]methanesulfonamide (as hydrochloride)

- ▶ An optically inactive mixture of isomers where the L-isomer blocks β -ARs (non-selectively) more strongly than the D-isomer. Both isomers block potassium channels. It has negative chrono-, dromo-, bathmo- and inotropic effects. It also has antianginal, antiarrhythmic, and antihypertensive effects. Its antiarrhythmic activity is inferior to amiodarone. Poorly penetrates the blood-brain barrier (BBB). Bioavailability: 86–100%. Food intake reduces bioavailability by 18–20%. It can accumulate (especially in the elderly). The antiarrhythmic effect occurs 1 hour after oral administration, reaching a maximum in 2.5–4.0 hours and lasts 24 hours. After intravenous administration, the effect occurs in 5 minutes and lasts 90–120 minutes.
- ▶ Essentially not metabolized in the liver. $T_{1/2}$: 7–18 hours. Excreted in the urine. For oral administration twice daily, for intravenous administration.

Additional side effects: decreased myocardial contractility, bronchospasm

Additional contraindications: heart failure, Prinzmetal angina, chronic obstructive pulmonary disease

Drugs that selectively block the mixed Na^+ - K^+ inward (I_f) current (class V)

Ivabradine (Coraxan[®])

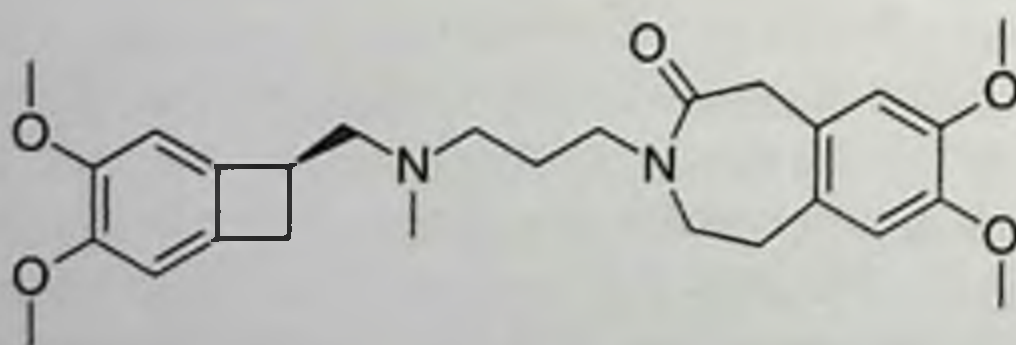


Fig. 14.22. (S)-3-(3-(((3,4-Dimethoxybicyclo(4.2.0)octa-1,3,5-trien-7-yl)methyl)methylamino)propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one

Mechanism of action: selective and specific inhibition of If ion channels, which control spontaneous diastolic depolarization in the sinus node and regulate heart rate (phase 4 of AP extends while automaticity decreases).

- ▶ Includes two cyclic structures, benzodiazepine and benzocyclobutene, connected by an azapentane chain. It does not affect the conduction of impulses along the intra-atrial, AV and intraventricular pathways. Specific, dose-dependent slowing of the heart rate. It has an antianginal effect, improves myocardial contractility and has no antihypertensive effect. It reduces left ventricular remodeling. Chronic use of this product does not lead to tolerance. No withdrawal syndrome after discontinuation. Bioavailability after oral administration is 40% due to the first-pass effect. It is logical to use it in combination with cardioselective beta-blockers.
- ▶ Metabolized in the liver and intestines by oxidation with the cytochrome P450 isoenzyme CYP3A4. The major active metabolite is an N-desmethyl derivative, accounting for 40% of the parent compound dose. The active metabolite of ivabradine is also metabolized by the cytochrome P450 isoenzyme CYP3A4. $T_{1/2}$: 2 hours. Excreted in the urine and bile. For oral administration twice daily.

Therapeutic indications: sinus tachycardia, stable exertional angina, congestive heart failure

Side effects: bradycardia, AV block, sick sinus syndrome, ventricular premature beats, atrial fibrillation, changes in light perception (photopsia), blurred vision, diplopia

Contraindication: bradycardia, sick sinus syndrome, SA block, AV block, artificial pacemaker, unstable and acute heart failure, unstable angina pectoris, acute cerebrovascular disease, cardiogenic shock, acute myocardial infarction, hypotension, severe hepatic impairment

AGENTS THAT MAINLY AFFECT CARDIAC INNERVATION

Agents that block sympathetic activity (class II)

These drugs eliminate the influence of adrenergic innervation, the arrhythmogenic effect of catecholamines on all parts of the cardiac conduction system and the myocardial contractile cells in the ventricles.

Classification

A. Non-selective beta-blockers

- Propranolol (Anaprilin⁺, Obsidan⁺, Inderal⁺)

B. Cardioselective beta-blockers (bind to β_1 receptors)

- Atenolol (Atenova⁺)
- Metoprolol (Betaloc⁺)
- Betaxolol (Lokren⁺)
- Bisoprolol (Concor⁺)

Mechanism of antiarrhythmic action (Fig. 14.23).

- ▶ Delays spontaneous depolarization in phase 4 (blocks β_1 -ARs of the cardiac conduction system).
- ▶ Slows the AP rise in phase 0.

- ▶ Inhibits early and late after-depolarization.
- ▶ Decreases the automaticity of pacemakers, suppresses the activity of ectopic foci, reduces conductivity in the AV junction and inside the ventricles.

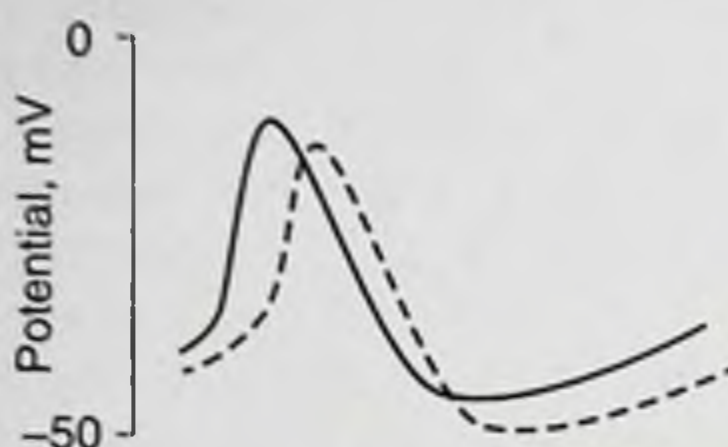


Fig. 14.23. Mechanism of action of class II drugs. Solid line — normal action potential. Dashed line — AP under the influence of class II antiarrhythmic drugs

Main changes in electrophysiological parameters

- ▶ Reduced conductivity, automaticity, excitability (in all chambers of the heart).
- ▶ Increased ERP.

Specific properties

- ▶ Reduce myocardial contractility
- ▶ Antianginal and antihypertensive effects
- ▶ Intravenous administration of metoprolol reduces mortality in the acute phase of myocardial infarction.

Therapeutic indications: supraventricular tachyarrhythmias and extrasystoles, ventricular extrasystoles, CAD, hypertension

Side effects and contraindications: see section “Direct- and indirect-acting adrenergic blockers”

Agents that enhance sympathetic activity (β -adrenergic agonists)

Isoprenaline (Isadrine[®])

Mechanism of antiarrhythmic action: Stimulates β_1 -ARs, accelerates diastolic depolarization (phase 4) and increases the frequency and strength of heart contractions. Improves SA and AV nodal conduction.

Therapeutic indications: 2nd and 3rd degree AV block, Adams–Stokes syndrome

Side effects and contraindications: see section “Direct- and indirect-acting adrenergic agonists”

Muscarinic receptor antagonists (MRA)

Atropine (Atropine sulfate[®])

Mechanism of antiarrhythmic action: By blocking M_2 muscarinic receptors, the product eliminates the parasympathetic nervous system’s influence on the SA and AV nodes, enhances automaticity in these nodes (increases heart rate) and improves AV nodal conduction.

Therapeutic indications: AV block, bradycardia

Side effects and contraindications: see section “Cholinergic blockers”.

VARIOUS AGENTS WITH ANTIARRHYTHMIC ACTIVITY

Potassium & magnesium products

- ▶ Potassium chloride
- ▶ Combination drugs: potassium and magnesium aspartate [Panangin[®], Asparcam[®] (a Russian drug similar to potassium and magnesium aspartate (Panangin[®])]

Mechanism of antiarrhythmic action: K⁺ ions are actively transported into cells, including cardiomyocytes, by Na⁺/K⁺-ATPase, a magnesium-dependent enzyme. These products increase the membrane potential and reduce myocardial excitability and automaticity.

Main changes in electrophysiological parameters

- ▶ Decreased automaticity (slows the heart rate)
- ▶ Prevents myocardial conduction and excitability
- ▶ Reduced cardiac contractility

Therapeutic indications: tachyarrhythmias due to electrolyte disorders (primarily hypokalemia, hypomagnesemia caused by saluretics, intractable vomiting, profuse diarrhea) and associated with an overdose of cardiac glycosides. For oral and intravenous administration.

Side effects: paresthesia, hypotension, hyperkalemia, hypermagnesemia, dyspepsia, bradyarrhythmia

Contraindications: hyperkalemia, hypermagnesemia, bradyarrhythmia, impaired renal excretory function, acute metabolic acidosis, pregnancy and breastfeeding

Specific properties of combination drugs: The formulation includes potassium aspartate and magnesium aspartate. Asparaginate transports K⁺ and Mg²⁺ ions, helping them to penetrate into the intracellular space. Respiratory depression is possible (since magnesium is the product constituent). For oral and intravenous administration.

Potassium and magnesium products are administered intravenously as part of a polarizing solution (consisting of insulin, glucose, potassium chloride and magnesium sulfate). Insulin promotes the transfer of glucose from plasma to the cell along with K⁺ ions. This solution got its name since it restores the membrane potential, i.e., increase in cardiomyocyte polarization.

Magnesium products (magnesium sulfate, magnesium chloride, magnesium orotate, magnesium aspartate) also have antiarrhythmic activity. They are especially effective in hypomagnesemia.

Magnesium sulfate (Cormagnesin[®])

Mechanism of antiarrhythmic action: It reduces the excitability of cardiomyocytes, restores ion balance, stabilizes cell membranes, disrupts Na⁺ current, slows the inward Ca²⁺ current and unidirectional K⁺ current.

It is used to treat polymorphic ventricular tachycardia (pirouette-type), administered intravenously. The systemic effects occur quickly; the time of action is 30 minutes. Intravenous administration can cause respiratory depression and shock due to hypermagnesemia (calcium chloride is an antidote).

Contraindications: SA and AV blocks

Side effects and contraindications: see section "Antihypertensive drugs"

Cardiac glycosides

Digoxin*

Mechanism of antiarrhythmic action: Due to a positive inotropic effect, blood is ejected into the aorta with greater force during the systole, which activates the aortic arch and carotid sinus baroreceptors (carotid sinus reflex). This increases the vagal tone and delays the generation of action potentials in the sinoatrial node. The vagal tone also increases due to the cardiovascular reflex (a reaction that occurs when the cardiac mechanoreceptors are stretched). A direct vagotonic effect cannot be ruled out. This reduces the heart rate, the velocity of excitation conduction through atypical cells, including in the AV node, and increases the AV nodal and atrial ERP.

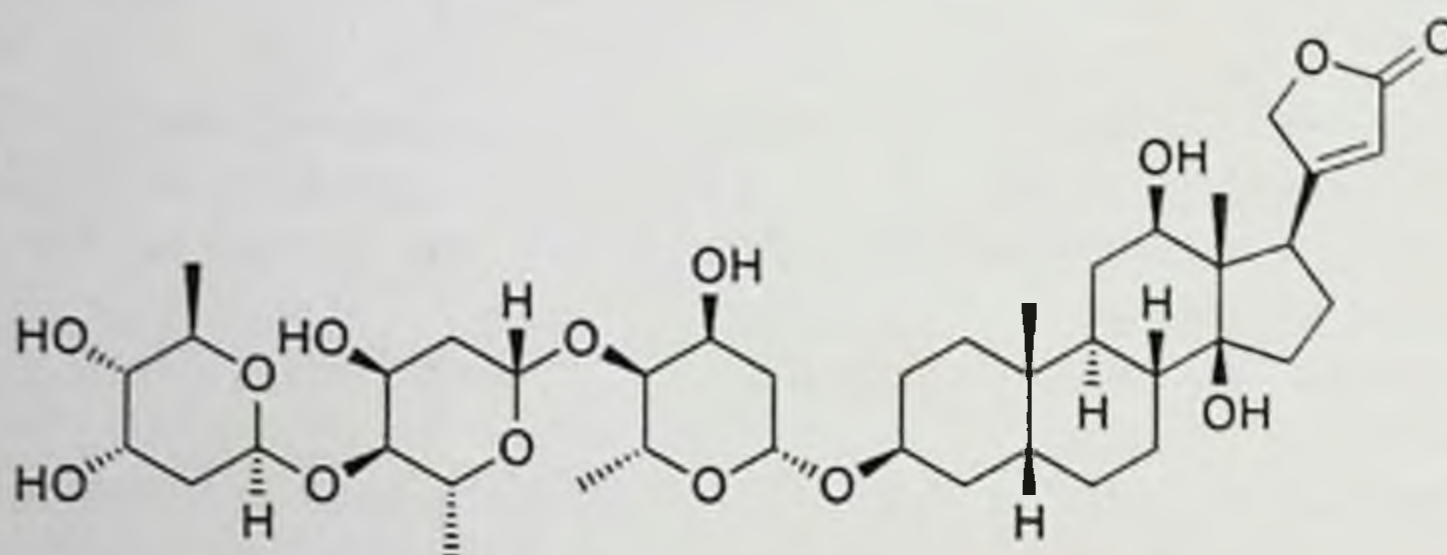


Fig. 14.24. (3 β ,5 β ,12 β)-3-[(O-2,6-Dideoxy- β -D-ribo-hexopyranosyl-(1 $\rightarrow$ 4)-O-2,6-dideoxy- β -D-ribo-hexopyranosyl-(1 $\rightarrow$ 4)-2,6-dideoxy- β -D-ribo-hexopyranosyl)oxy]-12,14-dihydroxycard-20(22)-enolide

- ▶ **Bioavailability:** 65–80%. It accumulates. After oral administration, the cardiotonic effect occurs in 1–2 hours, reaching a maximum within 8 hours, after intravenous administration it occurs in 20–30 minutes.
- ▶ **Metabolized in the liver.** $T_{1/2}$: 36–48 hours. Excreted mainly in the urine. In patients with congestive heart failure, it causes flow-mediated dilation, moderately increases diuresis (mainly due to improved hemodynamics). For oral and intravenous administration.

Therapeutic indications: paroxysmal supraventricular arrhythmias (atrial fibrillation, atrial and AV nodal tachycardia), acute and congestive heart failure

Side effects: arrhythmogenic effect (ventricular extrasystoles, AV block); vision with a yellow-green tint, decreased visual acuity, macropsia and micropsia; headache, dizziness, disorientation, sleep disturbance; nausea, vomiting, diarrhea, abdominal pain; allergic reactions; thrombocytopenic purpura

Contraindications: severe forms of ventricular arrhythmia, Wolff–Parkinson–White syndrome with atrial fibrillation, 2nd and 3rd degree AV block, hypertrophic obstructive cardiomyopathy, breastfeeding

Adenosine*

Mechanism of antiarrhythmic action: By activating A₁ adenosine receptors in atrial, sinus and AV nodal cardiomyocytes, adenylate cyclase is blocked, causing the cAMP concentration and calcium current to decrease. This delays the generation of impulses in the sinoatrial node, decreases the conduction time, and interrupts the pathways for excitation re-entry through the AV node.

Main changes in electrophysiological parameters

- ▶ Inhibits sinus node automaticity
- ▶ Slows AV conduction
- ▶ Extends the AV nodal ERP

An endogenous purine nucleoside that modulates many physiological processes. It has a vasodilatory effect (except for renal afferent arterioles and hepatic veins where it causes vasoconstriction).

After intravenous administration, it very rapidly undergoes biotransformation due to circulating enzymes in erythrocytes and vascular endothelial cells, primarily by deamination, to inactive inosine, and also by phosphorylation with adenosine kinase to adenosine monophosphate. $T_{1/2}$ from blood: less than 10 seconds. Excreted in the urine as metabolites (the predominant final metabolite is uric acid). For intravenous administration.

Therapeutic indications

- ▶ For intravenous bolus injection: paroxysmal supraventricular tachycardia (including Wolff–Parkinson–White syndrome)
- ▶ For intravenous infusion: differential diagnosis of supraventricular tachyarrhythmias (tachycardia with wide *QRS* complexes), diagnostic electrophysiological testing (localization of AV block)

Side effects: facial redness, cardialgia, dyspnea, headache, dizziness

Contraindications: 2nd and 3rd degree AV block, sick sinus syndrome, asthma

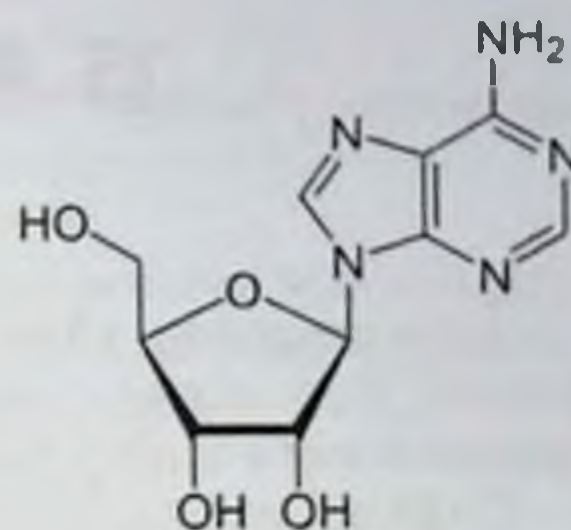


Fig. 14.25. (2R,3R,4R,5R)-2-(6-Aminopurin-9-yl)-5-(hydroxymethyl)oxolane-3,4-diol

15. ANTIANGINAL DRUGS

Antianginal drugs (from the Greek *anti*, meaning "against"; from the Latin *angina pectoris*, from *angere*, meaning "to choke") are drugs used for the treatment and prophylaxis of coronary artery disease (CAD).

CAD is a pathological condition in which the blood supply to the myocardium is inadequate. Myocardial ischemia occurs when its oxygen demand exceeds the body's ability to deliver oxygen through the coronary arteries. In most cases, the main causes of CAD are atherosclerotic plaques and functional stenosis of the coronary microvasculature. Other causes of CAD (less than 5 % of cases) include congenital anomalies of coronary arteries, coronary vasculitis in systemic diseases and collagen vascular diseases, Kawasaki disease, bacterial endocarditis, overdose with vasoconstrictors and certain narcotics, diffuse coronary artery stenosis in a transplanted heart, etc.

Principles of pharmacotherapy in CAD.

- ▶ Decrease cardiac work and, consequently, decrease cardiac oxygen demand (by lowering heart rate, reducing cardiac preload and afterload, lowering myocardial metabolism)
- ▶ Increase coronary blood flow and increase myocardial oxygenation (by dilating coronary blood vessels)

Classification

I. Drugs reducing myocardial oxygen demand

A. β and α , β adrenergic blockers

- β_1 , β_2 ABs: propranolol (Anaprilin[®])
- β_1 ABs: metoprolol (Egilok[®]), bisoprolol (Concor[®]), betaxolol (Lokren[®]), nebivolol (Nebilet[®]), atenolol (Betacard[®])
- α , β ABs: carvedilol (α_1 , β_1 , β_2) (Dilatrend[®]), labetalol (α_1 , β_1 , β_2) (Trandate[®]) (excluded from Russian State Register of Medicinal Products)

B. If channel inhibitors: ivabradine (Coraxan[®])

II. Drugs increasing oxygen delivery to the myocardium

A. Myotropic coronary dilators: dipyridamole (Curantyl[®])

B. Reflex inhibitors of coronary spasm: menthol solution in isovaleric acid methyl ester (Validol[®])

III. Drugs reducing myocardial oxygen demand and improving myocardial blood supply

A. Organic nitrates

- Nitroglycerin[®]
- Long-acting pharmaceutical forms of nitroglycerin: nitroglycerin (Trinitrolong[®], Sustac[®], Nitrong[®])
- Long-acting nitrates: isosorbide dinitrate (Nitrosorbide[®], Isoket[®]), isosorbide mononitrate (Monocinque[®])

B. L-type calcium channel blockers

- Phenylalkylamine derivatives: verapamil (Isoptin SR 240[®])

- Benzothiazepine derivatives: diltiazem (Cardil[®])
- Dihydropyridine derivatives: nifedipine (Adalat[®], Corinfar[®]), amlodipine (Normodipine[®]), felodipine (Plendil[®])

C. Potassium channel activators: nicorandil (Cordinic[®])

D. Other: molsidomine (Sydnopharm[®], Corvaton[®]), amiodarone (Cordarone[®])

The following products are used in combination therapy for CAD: cardioprotective drugs, antiplatelet drugs, lipid-lowering drugs, psychotropic drugs.

Specific properties by drug group

Drugs reducing myocardial oxygen demand

β and α , β adrenergic blockers

Pharmacological effects: antianginal, antihypertensive, antiarrhythmic.

The mechanism of antianginal action is associated with blockade of β 1ARs and elimination of adrenergic effects on the myocardium, resulting in decreased heart rate and cardiac contractile force. Cardiac work decreases, and subsequently, myocardial oxygen demand decreases. This eliminates imbalance between oxygen demand and oxygen delivery that occurs in angina. Central adrenergic effects are inhibited (for lipophilic drugs).

Therapeutic indications: CAD, hypertension, supraventricular tachyarrhythmias and extrasystoles, ventricular extrasystoles

Side effects: marked bradycardia, AV block, hypotension, aggravation of heart failure; increase in triglycerides, very-low-density lipoproteins and decrease in high-density lipoproteins; hypoglycemia; bronchospasm; increased peripheral vascular tone; fatigue, weakness, decreased performance, depression (for lipophilic drugs); increased peristalsis; erectile dysfunction, low sex drive; withdrawal syndrome

Contraindications: bradycardia (< 50 bpm), sick sinus syndrome, impaired AV conduction, hypotension, (systolic BP < 100 mmHg), obstructive respiratory failure, history of asthma, decompensated diabetes, peripheral circulation disorders, decompensated heart failure, pregnancy, breastfeeding

Specifics of individual products

β and α , β adrenergic blockers: see "Direct-acting and indirect-acting adrenergic blockers".

If channel inhibitors

Mechanism of antianginal action: If channel inhibitors selectively block only open sinus node If channels, interacting with protein on the inner side of the membrane. It is more effective in tachycardia because If channels open more frequently. As a result of impaired conduction in If channels, the ion current is attenuated, while spontaneous diastolic depolarization slows and heart rate decreases (Fig. 15.1). Cardiac oxygen demand is reduced, with cardiac contractility and blood supply simultaneously improving, especially in the deep subendocardial layers of the heart.

Specific properties: If channel inhibitors do not affect repolarization and AP, do not prolong *PQ*, *ST* intervals or the *QRS* complex, do not narrow coronary arteries, do not exert antihypertensive action.

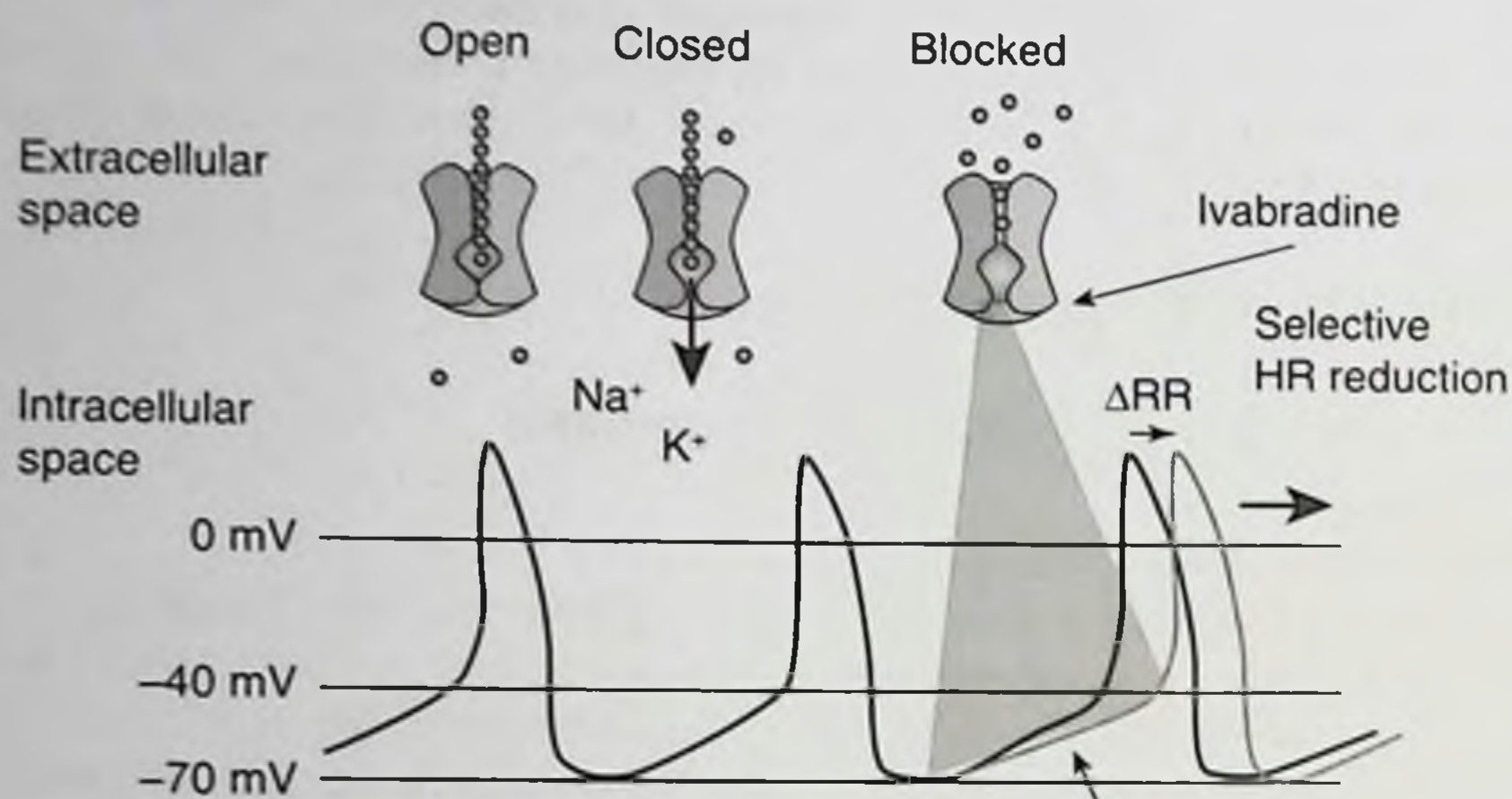


Fig. 15.1. Mechanism of action of ivabradine

Therapeutic indications: exertional angina pectoris, CHF, sinus tachycardia

Side effects: bradycardia, AV block, ventricular or supraventricular extrasystoles, photopsia (caused by blockade of I_f channels in the retinal photoreceptors), headache, dizziness, dyspepsia

Contraindication: bradycardia, sick sinus syndrome, sinoatrial block, AV block, presence of an artificial cardiac pacemaker, cardiogenic shock, acute myocardial infarction, hypotension, unstable angina, severe hepatic impairment, acute stroke, pregnancy, breastfeeding period, less than 18 years of age

Ivabradine (Coraxan[®])

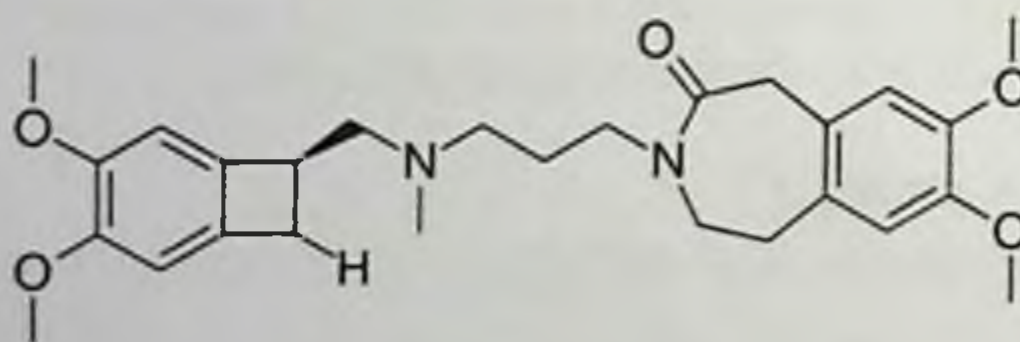


Fig. 15.2. (S)-3-(3-(((3,4-Dimethoxybicyclo(4.2.0)octa-1,3,5-trien-7-yl)methyl)methylamino)propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one

- ▶ Includes two cyclic structures, benzodiazepine and benzocyclobutene, connected by an azapentane chain. Exhibits antianginal and antiarrhythmic activity. No tolerance develops with chronic use. No withdrawal syndrome after discontinuation.
- ▶ ▶ Bioavailability: 40 %, $T_{1/2}$: 2 hours. Metabolized in the liver and intestine by oxidation. The main active metabolite is a N-desmethyl derivative, accounting

for 40 % of ivabradine dose. Excreted in the urine and bile. For oral administration twice daily.

Drugs increasing oxygen delivery to the myocardium

Myotropic coronary dilators

Dipyridamole (Curantyl®)

- ▶ Pyrimidine derivative. Has vasodilating action. Has inhibitory effect on platelet aggregation, improves microcirculation.
- ▶ Bioavailability: 37–66 %. $T_{1/2}$: 20–30 min. Metabolized predominantly in the liver by glucuronidation, 20 % of the drug is included in the enterohepatic circulation. Excreted predominantly in the bile. For oral administration 3–4 times daily, for intravenous administration.

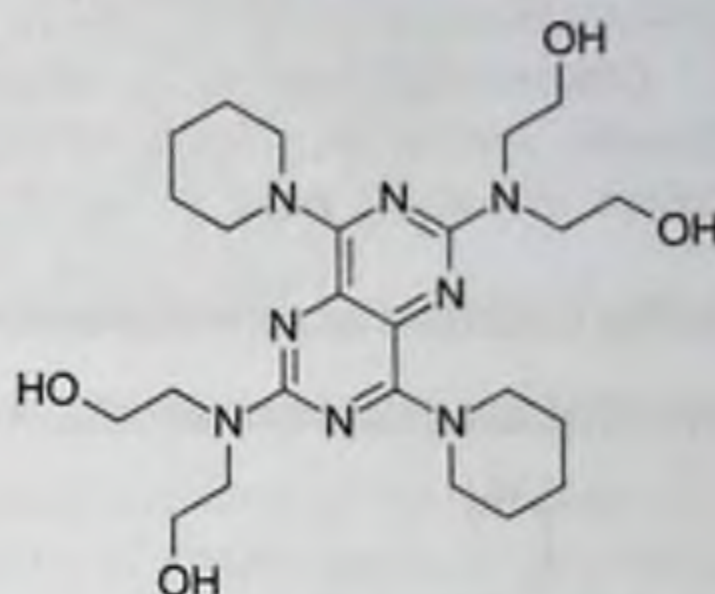


Fig. 15.3. 2,2',2,2'-[(4,8-Di-1-piperidinylpyrimido[5,4-d]pyrimidine-2,6-diyl)dinitrilo]tetrakis[ethanol]

Mechanism of antianginal action: Dipyridamole inhibits adenosine deaminase and inhibits reuptake of adenosine by red blood cells, thereby increasing its blood concentration. Adenosine accumulates in the myocardium causing coronary dilation (relaxation of arteriolar smooth muscles) (Fig. 15.4).

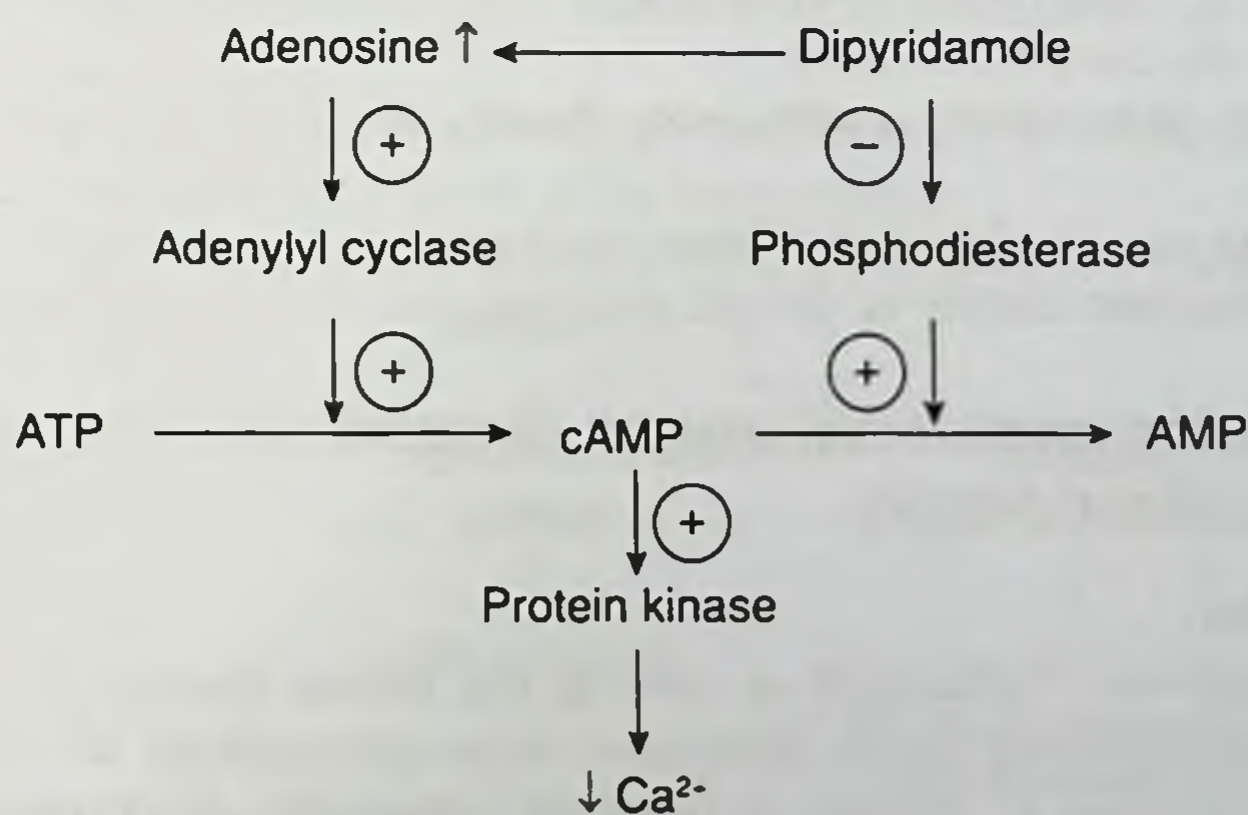


Fig. 15.4. Mechanism of action of dipyridamole

Therapeutic indications: angina pectoris without coronary atherosclerotic events; prophylaxis of arterial and venous thrombosis, occlusion of stents and aortocoronary shunts

Side effects: nausea, vomiting, diarrhea; headache, dizziness; myalgia; hypotension, facial redness, heart palpitations; thrombocytopenia, bleeding; allergic reactions; coronary steal syndrome

When a coronary branch is occluded by atheromatous plaque, dipyridamole does not improve oxygen delivery to the ischemic area — it might actually worsen its blood supply. This is due to the small coronary vessels already being maximally dilated in the ischemic myocardium (compensatory reaction to hypoxia). Dipyridamole dilates the arterioles and collaterals in the unchanged part of the myocardium, and this further reduces blood and oxygen flow to the ischemic area (coronary steal syndrome).

Contraindications: unstable angina, acute myocardial infarction, generalized stenotic coronary atherosclerosis, aortic stenosis, decompensated chronic heart failure; chronic hepatic and/or renal impairment

Reflex inhibitors of coronary spasm

Menthol solution in isovaleric acid methyl ester (Validol[®])

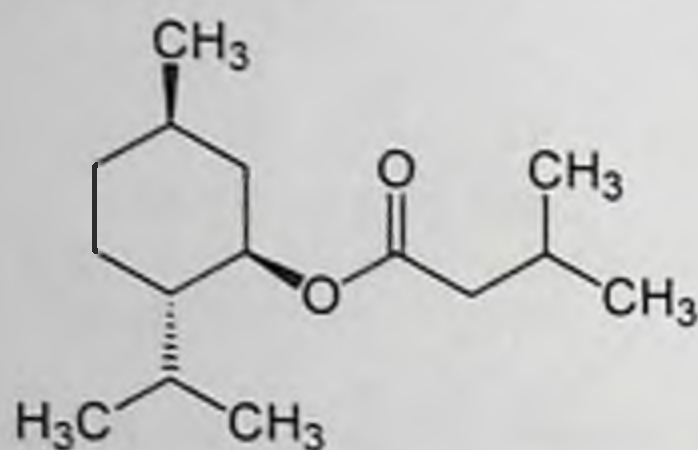


Fig. 15.5. (1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl-3-methylbutanoate

- ▶ 25–30 % menthol solution in isovaleric acid methyl ester. Has moderate reflex vasodilating and sedative action. The therapeutic effect occurs in 5 min following sublingual administration.
- ▶ Metabolized in the liver, excreted in the urine as glucuronides.

Mechanism of action: The reflex vasodilating action is caused by irritation of sensitive nerve endings in the oral mucosa. It stimulates the production and release of enkephalins, endorphins and a number of other peptides, histamine, kinins, which are actively involved in the regulation of vascular permeability.

Therapeutic indications: combination therapy for neurosis, cardialgia, angina pectoris

Side effects: nausea, dizziness, allergic reactions

Contraindications: history of allergic reactions, less than 18 years of age

Drugs reducing myocardial oxygen demand and improving myocardial blood supply

Organic nitrates

Nitroglycerin was synthesized in 1846 by the Italian chemist A. Sobrero, who noticed that nitroglycerin causes headaches when administered sublingually at low doses. One year later, C. Hering, a German homeopath, determined therapeutic doses for retrosternal chest pain and obtained nitroglycerin tablets. In 1857, T. L. Brunton, a Scottish physician, discovered that amyl nitrite could relieve retrosternal chest pain in angina pectoris 30–60 seconds after inhalation. In 1879, W. Murrell, an English physician, pharmacologist and toxicologist published a series of articles in the English journal *Lancet*, where he described the hemodynamic effects of nitroglycerin and justified its sublingual administration for the relief of angina attacks.

One of the first patients to take nitroglycerin was the inventor of dynamite, A. Nobel (Fig. 15.6).

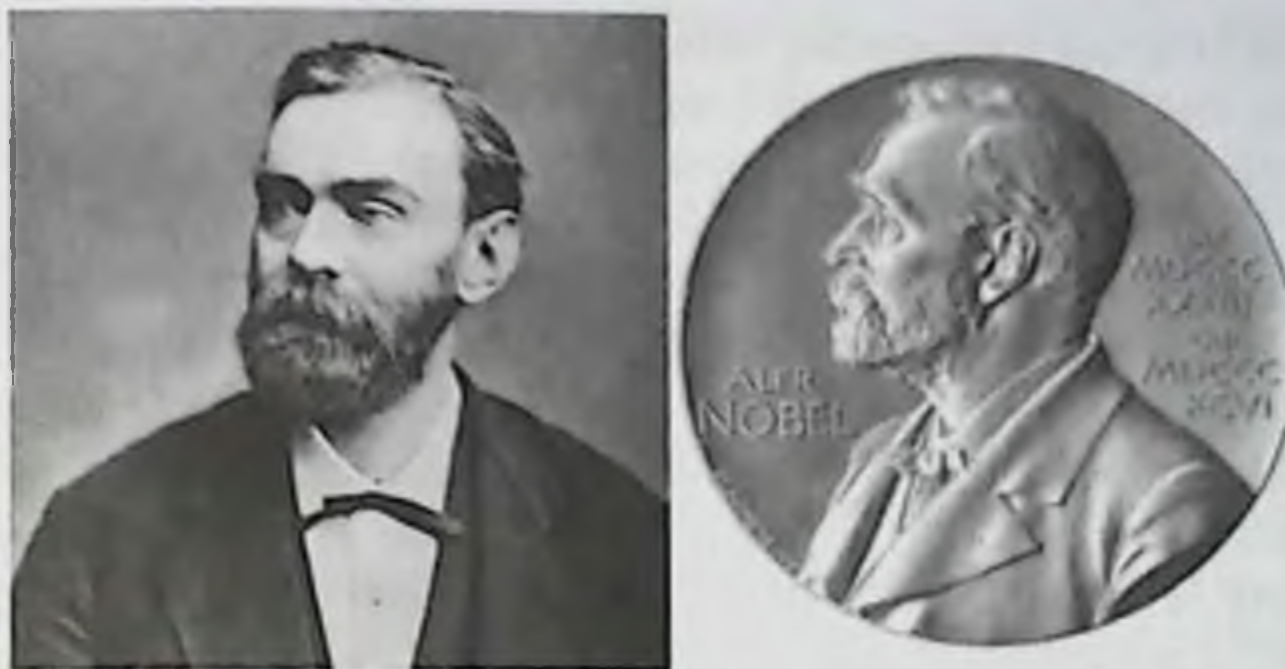


Fig. 15.6. Alfred Bernhard Nobel was a Swedish chemist, engineer, inventor, businessman, and philanthropist.

In 1895, Nobel described having retrosternal squeezing pain at a consultation with specialists in Paris. He was informed of the possibility of angina pectoris associated with inadequate supply of oxygen to the heart muscle. According to the standards of clinical medicine at the time, the specialists recommended brief strict bed rest, nitroglycerin, and treatment at a health resort. Nobel refused to take nitroglycerin: he, who made his fortune from the invention that resulted from the substance discovered by A. Sobrero, was instructed to use it to relieve angina attacks! In a letter to a close friend, Nobel wrote, "Isn't it the irony of fate that I have been prescribed nitroglycerin to be taken internally!"

Pharmacological effects of organic nitrates (Fig. 15.7):

- ▶ decrease cardiac oxygen demand, reduce preload (vein dilation) and afterload (artery dilation)
- ▶ dilate the epicardial sections of coronary arteries and increase oxygen delivery to ischemic areas in the deep layers of the myocardium
- ▶ inhibit platelet aggregation and formation of blood clots in coronary vessels.

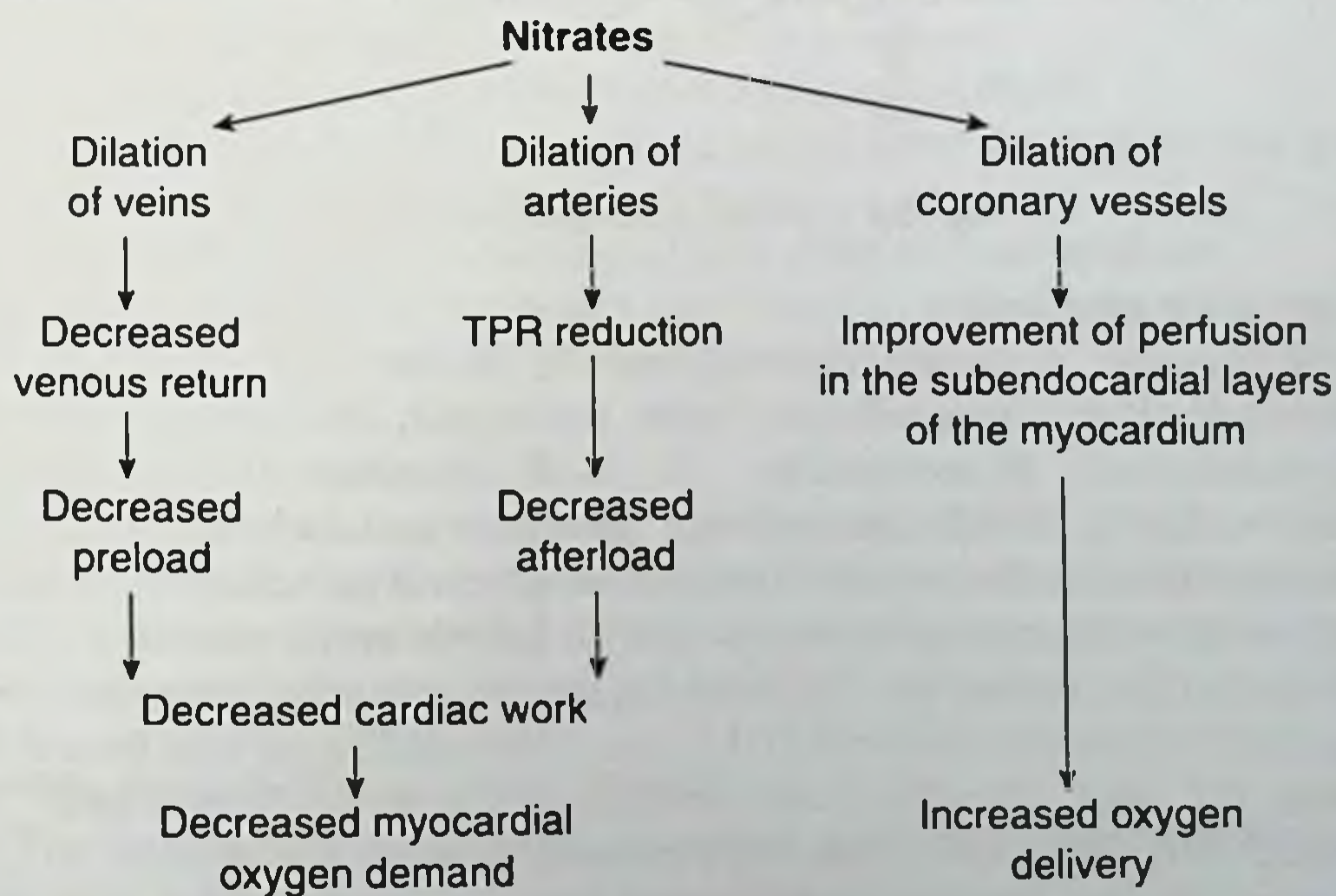


Fig. 15.7. Pharmacological effects of organic nitrates

Mechanism of action: After being reduced by the sulfhydryl groups of glutathione in the vascular endothelium, nitrates form the NO group. Nitrates dilate veins, and venous deposition of blood reduces preload: right and left ventricular distension, end-diastolic pressure, and myocardial tension are reduced. Cardiac oxygen demand is reduced, collateral vessels open, blood circulation in the subendocardial areas of the myocardium is restored, and the size of the ischemic area decreases. Nitrates dilate peripheral arteries, reduce TPR, and cardiac afterload. Nitrates prevent reflex vasoconstriction, acting on the vasomotor center, reducing the release of catecholamines into the blood, dilating the major coronary vessels in the epicardium, improving blood perfusion in the ischemic areas of the myocardium. Nitrates stimulate the production of prostacyclin, which has vasodilating and antiplatelet properties.

The hemodynamic effects of nitrates are similar to the action of the endothelium-derived vasodilating factor NO. NO is formed in the endothelium of arteries and veins during arginine metabolism, and quickly penetrates into smooth muscle since it is lipophilic. It activates soluble guanylate cyclase which increases cGMP concentrations. This cyclic nucleotide, which causes dephosphorylation of myosin light chain kinase through the protein kinase system, prevents the formation of actomyosin. $T_{1/2}$: 6–30 s. Nitric oxide is produced in higher amounts in arteries than in veins, but soluble guanylate cyclase in venous smooth muscle is most sensitive to it.

Specifics of individual products

Nitroglycerin*

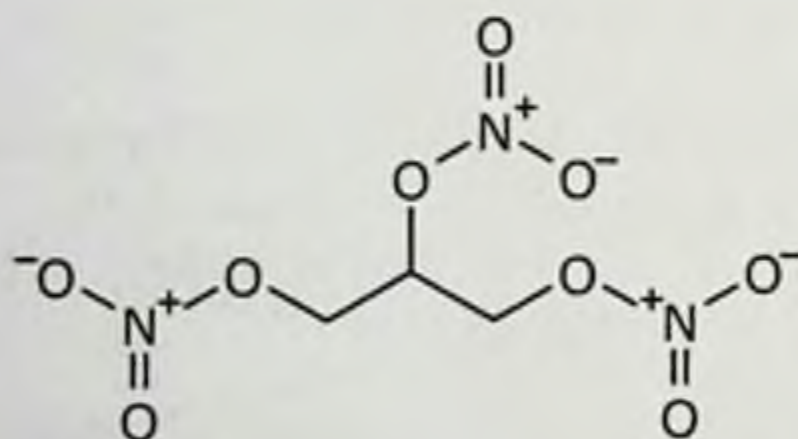


Fig. 15.8. 1,3-Dinitrooxypropan-2-yl-nitrate

- ▶ Lipophilic substance
- ▶ Nitroglycerin is extensively metabolized in the liver (first-pass effect); therefore, it is most effective with sublingual, transbuccal, intravenous administration. Bioavailability: 10–15 %. Sublingual, transbuccal, and intravenous administration prevent first-pass metabolism. Dinitrates and mononitrates are the primary metabolites; glycerol is the final metabolite. $T_{1/2}$ following sublingual administration: 1.0–4.4 min and 7 min for metabolites. Bioavailability is absolute. $T_{1/2}$ following intravenous administration: 1–3 min. An angina attack is relieved in 1.5 min when sublingual and buccal dosage forms are used; the effects are maintained for up to 30 min and 5 hours, respectively. Metabolites are excreted in the urine.

Nitroglycerin drug products by time of action:

- ▶ short-acting nitroglycerin — up to 30 min

- ▶ intermediate-acting nitroglycerin (Trinitrolong[®], Sustac[®]) — up to 4–5 hours
- ▶ long-acting nitroglycerin (Nitrong[®]) — up to 7–8 hours.

By pharmaceutical form:

- ▶ for intravenous administration: nitroglycerin (Perlinganit[®], Nitro[®])
- ▶ for sublingual administration: nitroglycerin tablets, spray
- ▶ for transbuccal administration: nitroglycerin (Trinitrolong[®])
- ▶ for oral administration: nitroglycerin (Sustac[®], Nitrong[®])

Therapeutic indications: relief of angina attacks [nitroglycerin (Trinitrolong[®])], prophylaxis of angina attacks [nitroglycerin (Trinitrolong[®], Sustac[®], Nitrong[®])], prophylaxis of coronary artery spasm during coronary angiography, acute coronary syndrome, acute myocardial infarction, acute left ventricular failure (intravenous administration)

Side effects: headache, dizziness (due to dilation of cerebral vessels and increased IOP), hypotension leading to orthostatic collapse, reflex tachycardia, flushing of the face and neck, dyspepsia, rebound syndrome, tolerance

Regular treatment results in nitrate tolerance in 50–60 % of patients. Long-acting nitrates cause the greatest tolerance. Continuous intravenous nitroglycerin infusion is accompanied by tolerance in 65 % of patients.

Mechanisms of tolerance

- ▶ Nitrate reduction becomes impaired due to depletion of reduced glutathione resources in the vascular endothelium (sulfhydryl groups of glutathione are oxidized to disulfide groups during the conversion of -NO₂ group to -NO group).
- ▶ NO is rapidly oxidized to the peroxynitrite radical.
- ▶ The sensitivity of guanylate cyclase to the action of NO decreases, the inactivation of cGMP accelerates.
- ▶ The vasoconstrictor endothelin-1 is released from endothelium.
- ▶ Reflex activation of the sympathetic nervous system occurs [the concentration of vasoconstrictors (catecholamines, renin, angiotensin (AT) II) increases].

The following measures are taken to prevent tolerance:

- ▶ the nitrate dose is increased to ensure a temporary effect
- ▶ intermediate-acting nitrates are administered immediately prior to any expected physical exertion at intervals of 6–8 hours
- ▶ Nitrate administration is alternated with other antianginal drugs.

Rebound syndrome: BP increases significantly, with frequent angina attacks, episodes of painless myocardial ischemia and infarction (vasoconstrictors are rapidly activated). This syndrome occurs less frequently when nitroglycerin is used in long-acting dosage forms.

Contraindications: hypotension, cardiogenic shock, cardiac tamponade, marked aortic and mitral stenosis, cerebral hemorrhage, head injury, increased intracranial pressure, cerebral ischemia, closed-angle glaucoma, pregnancy, breastfeeding

Isosorbide dinitrate (Nitrosorbide[®], Isoket[®])

- ▶ The antianginal effect develops slowly and lasts longer; its hemodynamic action is 10 times less potent than nitroglycerin.

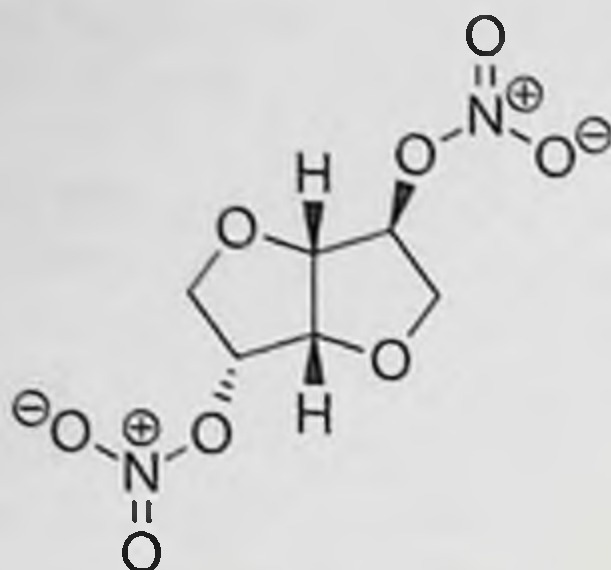


Fig. 15.9. 1,4:3,6-Dianhydro-2,5-di-O-nitro-D-glutitol

- ▶ Metabolized in the liver to two active metabolites: isosorbide-5-mononitrate (75–85 %) with $T_{1/2}$ of 5 hours and isosorbide-2-mononitrate (15–25 %) with $T_{1/2}$ of 2.5 hours.
- ▶ When sprayed on the oral mucosa, the effect occurs within 1–3 min and lasts 90–120 min. Bioavailability: 60 %. $T_{1/2}$: 30–60 min. For oral administration, bioavailability is 22 % (first-pass effect), $T_{1/2}$ is 4 hours, onset of action is 15–30 min. Time of action is 4–6 hours, 8–12 hours for long-acting tablets; no first-pass effect for intravenous infusion; $T_{1/2}$: 10 min. Excreted in the urine and bile. Daily, preferably overnight, nitrate-free intervals of 8–12 hours are recommended to prevent tolerance.

Therapeutic indications: prophylaxis of angina attacks (tablets, capsules), relief of angina attacks (sublingual tablets, spray), myocardial infarction, acute heart failure [isosorbide dinitrate (Isoket[®]) in ampoules for intravenous administration]

Isosorbide mononitrate (Monocinque[®])

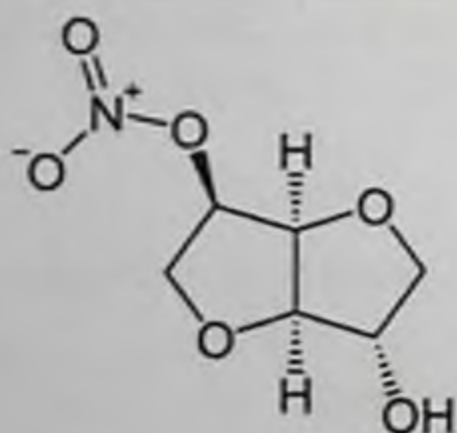


Fig. 15.10. 1,4:3,6-Dianhydro-D-glucitol 5-nitrate

- ▶ Major metabolite of isosorbide dinitrate. The effect occurs in 30–45 min and lasts 12 hours. Tolerance develops less frequently and more slowly than dinitrate. Does not cause rebound syndrome.
- ▶ Bioavailability is absolute. $T_{1/2}$: 4–6 hours. Metabolized to form two pharmacologically inactive glucuronides. Excreted in the urine mainly as metabolites (98 %). For oral administration 1–2 times daily.

Therapeutic indications: prophylaxis of angina attacks.

L-type calcium channel blockers

Mechanism of antianginal action:

- ▶ Phenylalkylamines decrease the influx of Ca^{2+} into cardiomyocytes, sinus node cells and cardiac conduction system cells (decreased heart rate and cardiac contractile force, cardiac work, and myocardial oxygen demand), into smooth muscle cells of coronary vessels, increase coronary blood flow.
- ▶ Dihydropyridines decrease the influx of Ca^{2+} into smooth muscle cells of both coronary and peripheral vessels, which causes dilation, improves coronary blood flow, and reduces cardiac preload and afterload.

- ▶ Benzothiazepines decrease the influx of Ca^{2+} into cardiomyocytes and smooth muscle cells during the depolarization phase, which results in decreased myocardial contractility, slower AV conduction, decreased HR, lower myocardial oxygen demand (decreased energy consumption by myocardial cells, activity of the stimulus formation and excitation conduction system, decreased tone of peripheral arteries and arterioles, with simultaneous TPR, BP reduction), dilated coronary arteries, increased coronary blood flow, thereby preventing or eliminating coronary spasm.

Verapamil (Isoptin SR 240*)

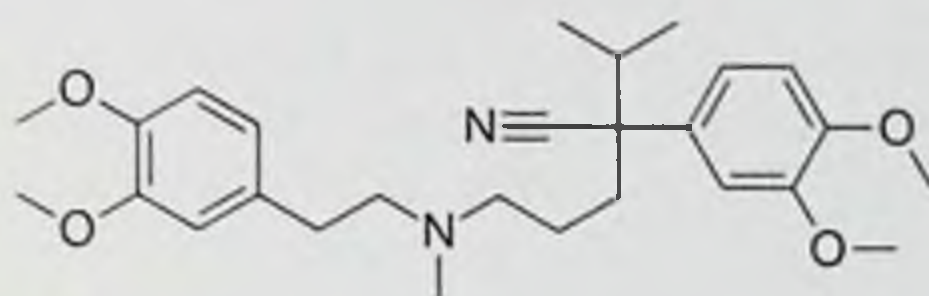


Fig. 15.11. 5-[(3,4-Dimethoxyphenethyl)-methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile hydrochloride

- ▶ Phenylalkylamine derivative. Exhibits antianginal, antiarrhythmic, and antihypertensive activity. Crosses the BBB and placental barrier.
- ▶ Bioavailability: 20–35 %, undergoes metabolism during the first pass through the liver. Metabolized in the liver to form norverapamil and 11 other metabolites. $T_{1/2}$ is 2.8–7.4 hours following a single oral dose, 4.5–12.0 hours following repeated dosing. $T_{1/2}$ is 2–5 hours following intravenous administration. Onset of action is 1–2 hours following oral administration, 3–5 min following intravenous administration. Time of action is 8–10 hours for oral administration (tablets), 10–20 min for intravenous administration. Excreted in the urine and bile (about 16 %).

Therapeutic indications: treatment of Prinzmetal angina (drug of choice), exertional angina, supraventricular tachyarrhythmias, hypertension

Side effects: bradycardia, AV block, BP reduction, decompensated heart failure; peripheral edema; nausea, vomiting, constipation; dizziness, headache, syncope, anxiety, asthenia, somnolence; allergic reactions

Contraindications: bradycardia, conduction disorders, chronic and acute heart failure, hypotension, cardiogenic shock, acute myocardial infarction, pregnancy, breastfeeding period, pediatric age (below 18 years); concomitant use of β ABs

Diltiazem (Cardil*)

- ▶ Benzothiazepine derivative. Exhibits antianginal, antiarrhythmic, antihypertensive activity. Excreted into breast milk.
- ▶ Bioavailability: 40 %, undergoes extensive metabolism during the first pass through the liver. $T_{1/2}$: 1–3 hours (for intravenous administration), 3.0–4.5 hours (for oral administration). Time of action: 4–8 hours (for oral administration). Metabolized in the liver by deacetylation, demethylation with cytochrome P450 involvement. Two metabolites are formed: deacetyldiltiazem and

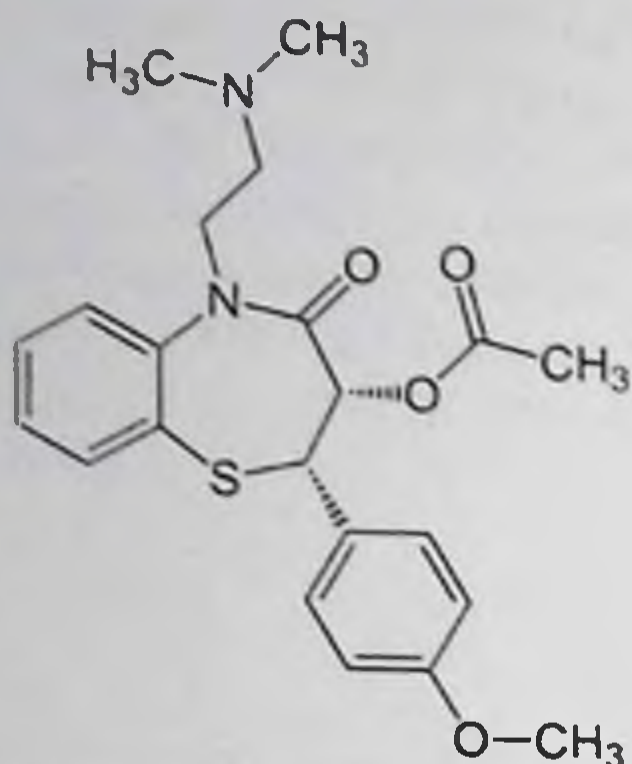


Fig. 15.12. (2S-cys)-3-(Acetoxy)-5-[2-(dimethylamino) ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (as a hydrochloride)

desmethyldiltiazem. The deacetylated metabolite has the properties of a coronary vasodilator. Excreted as metabolites in the bile and urine.

Therapeutic indications: angina pectoris (stable angina,

Prinzmetal angina), prophylaxis of coronary artery spasm during coronary angiography or coronary artery bypass surgery, hypertension, paroxysmal supraventricular tachycardia

Side effects and contraindications: see "Verapamil"

Nifedipine (Adalat[†], Corinfar[†])

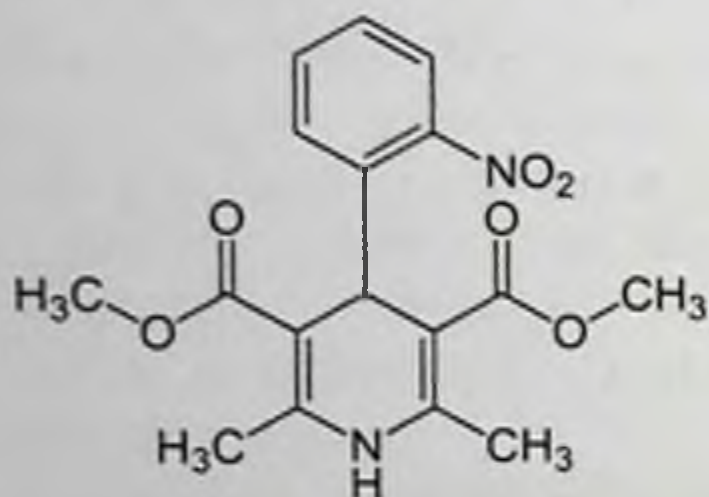


Fig. 15.13. 2,6-Dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester

► Dihydropyridine derivative. Exhibits antianginal and antihypertensive activity. Excreted into breast milk.

► Bioavailability: 40–60 %. Undergoes metabolism during the first pass through the liver. $T_{1/2}$: 3.6 hours following intravenous administration, 2–4 hours following oral administration. For oral administration, the action occurs in 30–60 min and lasts 4–6 hours; for sublingual administration, the action occurs in 5–10 min and reaches its maximum within 15–45 min. For tablets with two-phase release, the effect develops

in 10–15 min and lasts 21 hours. Metabolized in the liver to form inactive metabolites. Excreted in the urine and bile.

Therapeutic indications: prophylaxis of angina attacks (including Prinzmetal angina), hypertension, relief of hypertensive crisis, hypertrophic cardiomyopathy, pulmonary hypertension

Side effects: facial hyperemia with hot flashes, tachycardia, hypotension, dizziness, headache, constipation, nausea, peripheral edema, allergic reactions

Contraindications: acute myocardial infarction (first 8 days), cardiogenic shock, aortic stenosis, decompensated heart failure, hypotension, pregnancy, breastfeeding, less than 18 years of age

Amlodipine (Normodipine[®])

► Dihydropyridine derivative. Exhibits antianginal and antihypertensive activity. Long-acting (up to 24 hours)

- ▶ Bioavailability: 64–80 %. $T_{1/2}$: 35–50 hours. Metabolites do not exhibit any significant pharmacological activity. Excreted in the urine and bile and into breast milk. For oral administration once daily.

Therapeutic indications: prophylaxis of angina attacks (including Prinzmetal angina), hypertension

Side effects: peripheral edema (ankles and feet), flushing of the face, BP reduction, headache, dizziness, increased fatigue, somnolence, nausea, constipation, allergic reactions

Contraindications: hypotension, left ventricular outflow tract obstruction, shock (including cardiogenic shock), acute myocardial infarction, decompensated heart failure, pregnancy, breastfeeding period, less than 18 years of age

Felodipine (Plendil*)

- ▶ Dihydropyridine derivative, racemic mixture. The effect develops in 2 hours and lasts 24 hours
- ▶ Bioavailability: 15 %, does not depend on the timing of food intake. $T_{1/2}$: 25 hours, the plateau phase is reached within about 5 days. Metabolized in the liver by CYP3A4 isoenzyme. About 70 % of the administered dose is excreted in urine as metabolites, the rest is excreted in bile. For oral administration once daily.

Therapeutic indications: stable angina, hypertension

Side effects: hypotension; facial flushing with hot flashes; swollen ankles; headache, paresthesia, dizziness, syncope; nausea, dyspepsia; allergic reactions

Contraindications: decompensated heart failure, acute myocardial infarction, unstable angina, hypertrophic obstructive cardiomyopathy, pregnancy, breastfeeding, less than 18 years of age

Potassium channel activators

Nicorandil (Cordinic*)

- ▶ Exhibits nitrate-like properties and the ability to open potassium channels.
- ▶ Bioavailability: 75 %. Does not undergo extensive metabolism in the liver. $T_{1/2}$: 50 min. Excreted mainly in the urine. For oral administration 1–3 times daily.

Mechanism of action: Through activation of ATP-sensitive potassium channels, nicorandil causes hyperpolarization of the

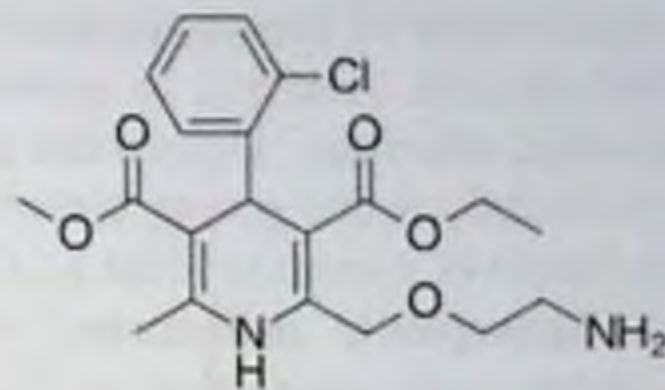


Fig. 15.14. (±)-2-[(2-Aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinecarboxylic acid 3-ethyl 5-methyl ester

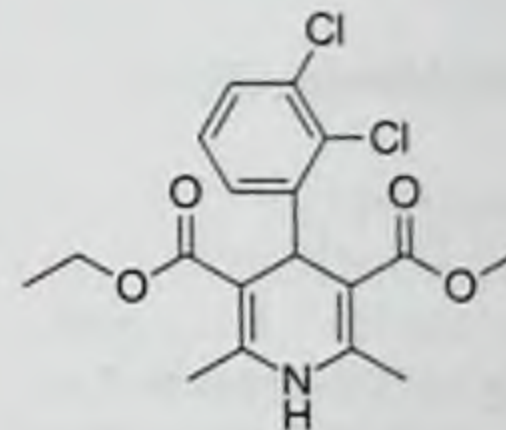


Fig. 15.15. (RS)-3-Ethyl-5-methyl-4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

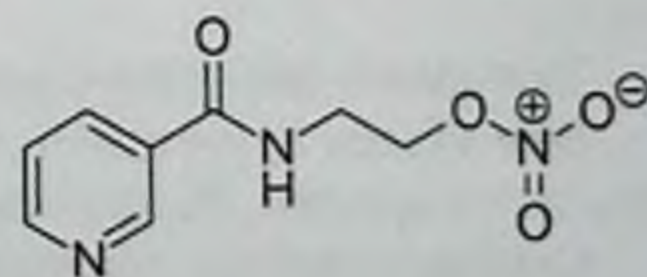


Fig. 15.16. 2-(Pyridine-3-carbonylamino)ethylnitrate

membranes of vascular smooth muscle cells, decreases the influx of Ca^{2+} ions into the cytosol, resulting in smooth muscle relaxation, artery dilation, and decreased cardiac afterload. Due to the presence of a nitrate group, it relaxes smooth muscles (especially in the venous system) by increasing intracellular cGMP, which leads to an increase in venous volume and a decrease in preload.

Therapeutic indications: treatment of angina pectoris in patients who are inadequately controlled or have contraindications or intolerance to β ABs and/or calcium channel blockers

Side effects: headache, dizziness, hypotension, tachycardia, hot flashes, nausea, vomiting, weakness

Contraindications: hypotension, decompensated heart failure, hypovolemia, pulmonary edema, pregnancy and breastfeeding, less than 18 years of age

Other drugs

Molsidomine (Sydnopharm⁺, Corvaton⁺)

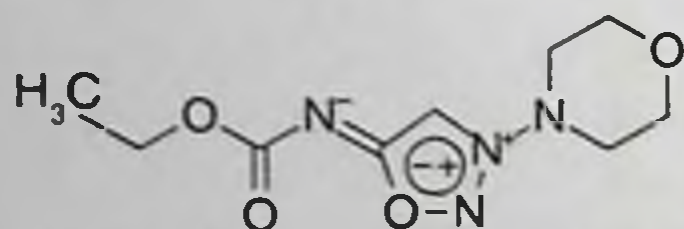


Fig. 15.17. 1-Ethoxy-N-(3-morpholino-5-oxadiazol-3-iumyl) methanimide

► Sydnonimine derivative. The onset of action is 2–10 min for sublingual administration and 1 hour for oral administration. Molsidomine crosses the placental barrier (10–50 %) and is excreted into breast milk. Can have a marked cumulative effect.

► **Bioavailability:** 60–70 %. Food intake slows absorption. Converted in the liver to pharmacologically active derivatives SIN-1 (linsidomine or 3-morpholinosydnonimine) and its non-enzymatic unstable metabolite SIN-1A (N-morpholino-N-aminosyntonitrile), eventually releasing NO to form pharmacologically inactive SIN-1C. Time of action: 5–7 hours, $T_{1/2}$: 3.5 hours. Excreted in the urine as metabolites (about 85–90 %). For oral, sublingual administration.

The mechanism of action is due to NO being formed during its metabolism, which stimulates guanylate cyclase. This results in cGMP accumulation, which relaxes vascular smooth muscles. Molsidomine decreases venous pressure, left ventricular end-diastolic pressure, and pulmonary artery pressure. It reduces myocardial oxygen demand. It dilates major coronary arteries and improves collateral circulation (Fig. 15.18).

Therapeutic indications: prophylaxis of angina attacks

Side effects: hypotension, facial flushing, headache, dizziness, nausea, diarrhea, decreased appetite, allergic reactions

Contraindications: cardiogenic shock, hypotension, pregnancy (first trimester), breastfeeding

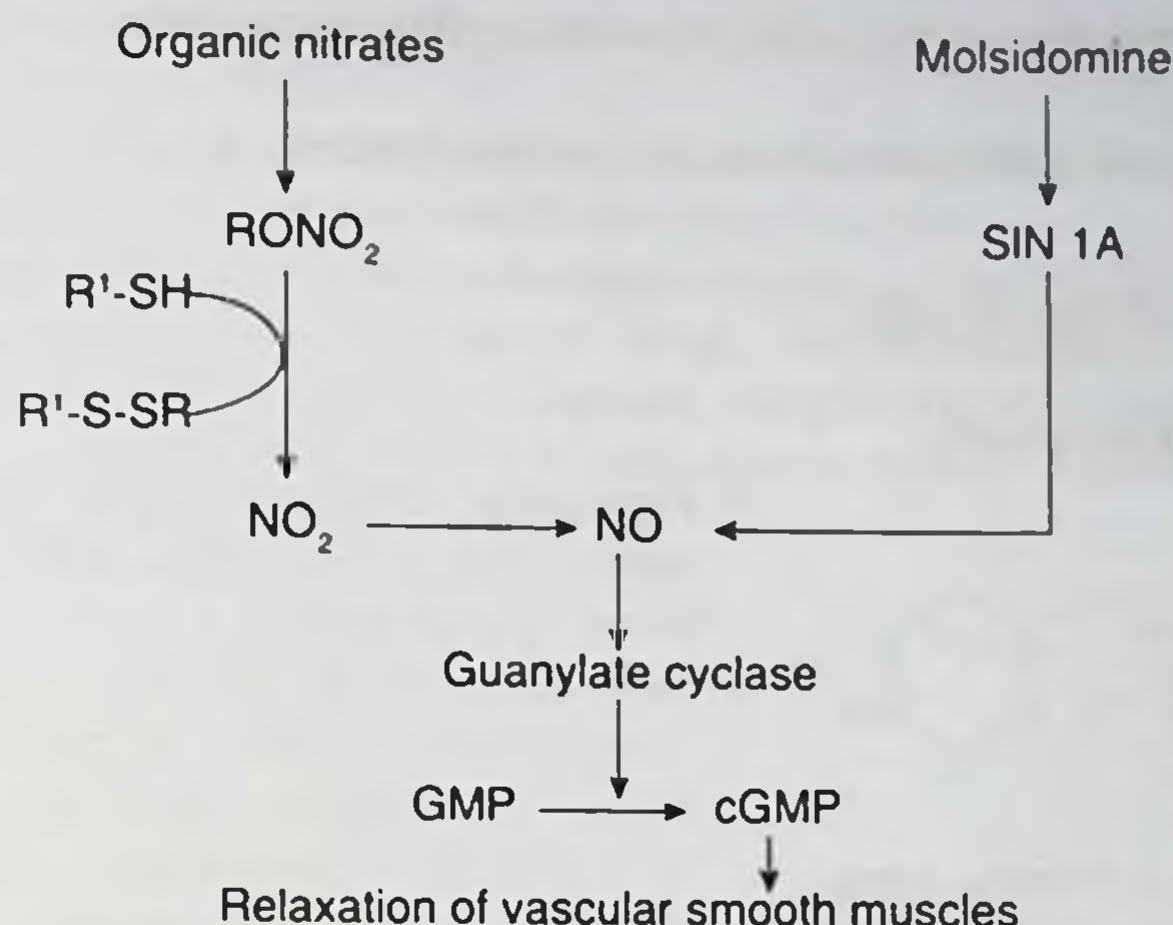


Fig. 15.18. Mechanism of antianginal action of molsidomine

Amiodarone (Cordarone®)

- ▶ Exhibits antianginal and antiarrhythmic activity. Crosses the BBB and placental barrier, excreted in the breast milk. For oral administration. The onset of action is 2–3 days to 2–3 months; the time of action varies from several weeks to several months. For intravenous administration, the maximum effect is reached in 15 min and lasts 1–3 hours.
- ▶ Bioavailability: 50 %. Metabolized in the liver to form the active metabolite desethylamiodarone by deiodination. Long-term treatment may result in iodine concentrations reaching up to 60–80 % of amiodarone concentrations. Amiodarone is an inhibitor of the hepatic cytochrome P450 isoenzymes CYP2C9, CYP2D6 and CYP3A4, CYP3A5, CYP3A7. Following oral administration, $T_{1/2}$ is 4–21 hours for phase 1 and 25–110 days for phase 2. Following intravenous administration, $T_{1/2}$ is 4–10 days. Excreted in the bile and urine. For oral and intravenous administration.

Mechanism of antianginal action: Amiodarone blocks cardiac transmembrane ion channels (mainly potassium channels, to a lesser extent calcium and sodium channels), inhibits excitation of α ARs and β ARs. The adrenergic blocking activity and blockade of potassium and calcium channels result in negative dromotropic and chronotropic effects, decreasing myocardial oxygen demand. It reduces coronary vascular resistance since it also acts as a vasodilator.

Therapeutic indications: exertional angina and angina at rest, atrial and ventricular extrasystoles, Wolff-Parkinson-White syndrome, atrial flutter and

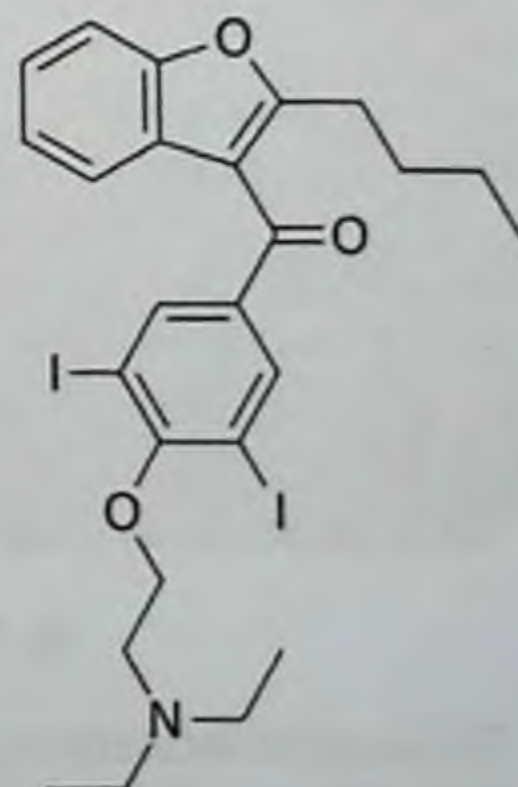


Fig. 15.19. (2-Butyl-3-benzofuranyl) [4-[(2-diethylamino)-ethoxy]-3,5-diiodophenyl] methanone

fibrillation, ventricular tachycardia, ventricular fibrillation; arrhythmias secondary to heart failure

Side effects and contraindications: see "Antiarrhythmic drugs"

Cardioprotective drugs

Trimetazidine (Preductal[®])

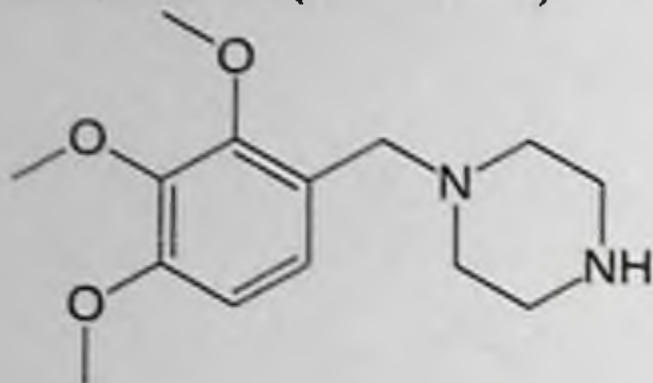


Fig. 15.20. 1-[(2,3,4-Trimethoxyphenyl)methyl]piperazine (as a dihydrochloride)

- ▶ Piperazine derivative. Exerts cardioprotective, antianginal, antihypoxic action. Crosses the blood-tissue barriers.
- ▶ Bioavailability: 84 %, $T_{1/2}$: 7.0 hours. Blood concentrations are maintained for 24 hours. Excreted in the urine (with about 60 % excreted as unchanged drug). For oral administration 2–3 times daily.

Mechanism of action:

- ▶ Trimetazidine inhibits the enzyme needed for mitochondrial β -oxidation of fatty acids — acetyl coenzyme A acetyltransferase (thiolase) — which helps to switch energy production from β -oxidation of fatty acids to glucose oxidation. This result in a significant decrease in cardiac oxygen demand, better use of residual oxygen and increased production of ATP and phosphocreatine (Fig. 15.21).
- ▶ Trimetazidine delays the activation of anaerobic glycolysis and eliminates intracellular acidosis.
- ▶ Trimetazidine increases the activity of glutathione peroxidase in plasma that prevents lipid peroxidation in lipoproteins.

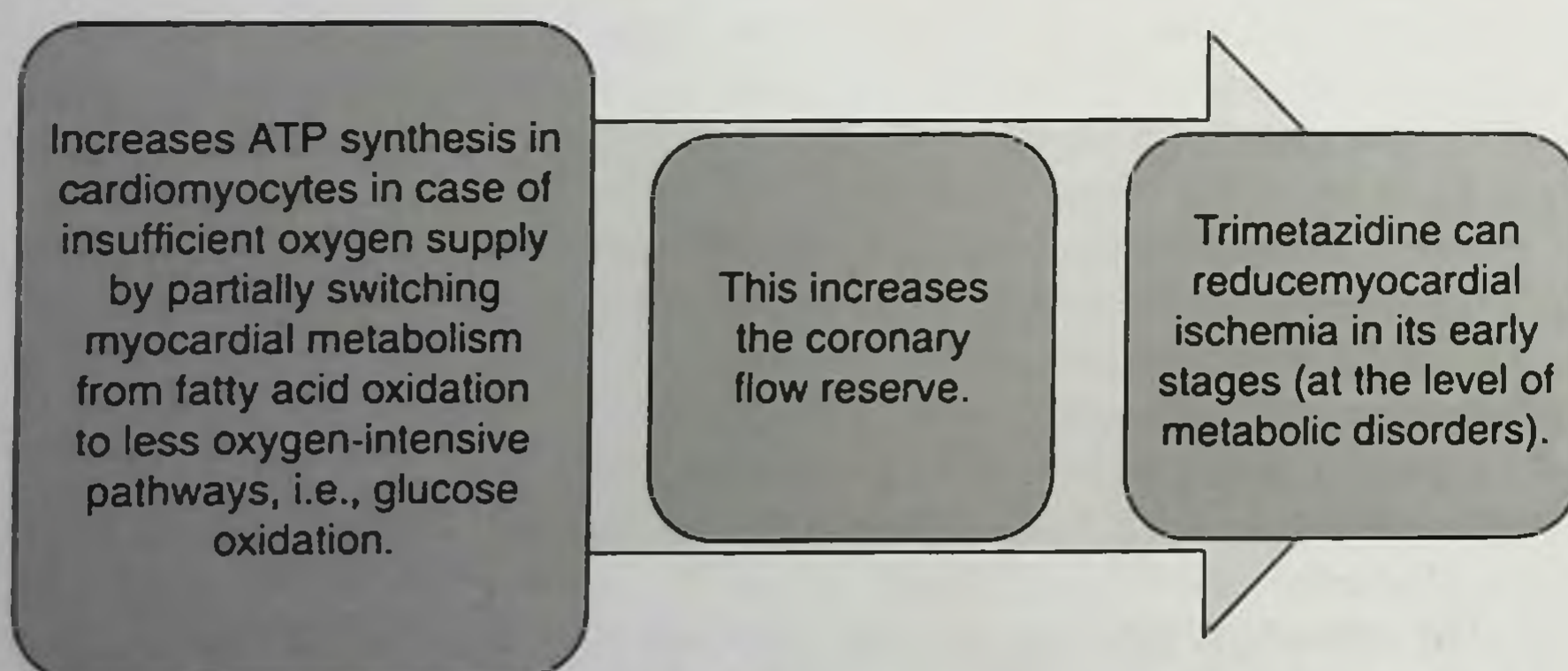


Fig. 15.21. Mechanism of action of trimetazidine

Therapeutic indications: prophylaxis of angina attacks (in combination therapy)

Side effects: abdominal pain, diarrhea, dyspepsia, nausea, vomiting, asthenia, dizziness, headache

Contraindications: Parkinson's disease, renal impairment, less than 18 years of age, pregnancy, breastfeeding

Myocardial infarction is one of the clinical forms of CAD that involves ischemic necrosis of myocardial tissue due to insufficient blood supply

Treatment options for myocardial infarction: narcotic analgesics, sedative therapy, antiplatelets, anticoagulants, fibrinolytic drugs, antiarrhythmic drugs, plasma substitutes, correction of acid-base imbalances, oxygen therapy: breathing oxygen through nasal catheters at 2–8 L/min is indicated in arterial hypoxemia (arterial oxygen saturation < 95 %), supportive care

16. ANTIHYPERTENSIVE DRUGS

Antihypertensive drugs are drugs used to treat hypertension.

Hypertension is a condition where BP is higher than the threshold values determined by tests that have demonstrated a relationship with higher cardiovascular risk. It benefits from treatment to reduce BP below these threshold levels.

Normal BP values are < 120 mmHg for systolic BP and/or < 80 mmHg for diastolic BP.

Elevated BP values are within the range of 120–129 mmHg for systolic BP and 80–84 mmHg for diastolic BP.

Target levels differ for various patient populations with hypertension. Achieving these levels during treatment results in the most favorable risk-benefit ratio (side effects vs. cardiovascular risk reduction).

Essential hypertension is a chronic disease that mainly manifests as high blood pressure not associated with any evident causes leading to secondary forms of hypertension (symptomatic hypertension).

Secondary (symptomatic) hypertension is hypertension with a known cause that can be eliminated by an appropriate intervention.

A hypertensive crisis occurs when a significant increase in BP is associated with acute damage to target organs, often life-threatening, and requires urgent medical care to lower blood pressure, usually with intravenous therapy.

The important pathogenetic elements of hypertension development and progression are:

- ▶ activation of the sympathoadrenal system (predominantly through α ARs and β ARs)
- ▶ activation of the renin–angiotensin–aldosterone system (RAAS), including increased production of mineralocorticoids (e.g., aldosterone) due to hyperactivation of the RAAS
- ▶ disruption of the membrane transport of cations (Na^+ , Ca^{2+} , K^+)
- ▶ increased renal reabsorption of Na^+
- ▶ endothelial dysfunction with predominant production of vasoconstrictors [tissue AT (angiotensin) II, endothelin] and decreased production of vasodepressors (bradykinin, NO, prostacyclin, etc.)
- ▶ structural changes in the vascular wall of muscular (resistance) and elastic arteries, including due to low-grade inflammation
- ▶ impaired microcirculation (decreased capillary density)
- ▶ disruption of the baroreceptors that sense arterial BP
- ▶ increased stiffness of large blood vessels.

In patients with hypertension, regardless of their age and CV risk, it is recommended to lower their BP to values below 140/90 mmHg as the initial target level and, if the drugs are well-tolerated, to a target level of 130/80 mmHg or lower due to the proven benefits in reduction of CV risk.

Five groups of antihypertensive drugs serve as the basis for hypertension treatment to lower BP and reduce the number of cardiovascular events (Clinical Guidelines, 2020): angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics.

DRUGS AFFECTING THE NERVOUS SYSTEM

Classification

- I. Centrally acting (decreases vasomotor center activity)
 1. α_2 AAs: clonidine (Clophelin⁺, Haemiton⁺, Catapresan⁺), methyldopa (Methyldopa⁺, Aldomet⁺, Dopegyt⁺), guanfacine (Estulic⁺)
 2. Imidazoline receptor agonists: moxonidine (Physiotens⁺, Moxarel⁺)
- II. Peripherally acting
 1. Ganglionic blockers: azamethonium bromide (Pentamine⁺), trepirium iodide (Hygronium⁺)
 2. Sympatholytics: reserpine in combination drugs
 - Adelphane-Esidrex⁺ (hydrochlorothiazide, dihydralazine, reserpine), Normatens⁺ (dihydroergocristine, clopamide, reserpine)
 3. α ABs
 - $\alpha_1\alpha_2$ ABs: phentolamine (Regitine⁺), dihydroergotoxine (Redergin⁺)
 - α_1 ABs: prazosin (Minipress⁺), doxazosin (Cardura⁺)
 4. β ABs
 - $\beta_1\beta_2$ ABs: propranolol (Anaprilin⁺, Inderal⁺, Obsidan⁺)
 - β_1 ABs: metoprolol (Egilok⁺, Betaloc⁺), atenolol (Betacard⁺) bisoprolol (Concor⁺), nebivolol (Nebilet⁺)
 5. $\alpha\beta$ ABs: labetalol (Trandate⁺) (excluded from Russian State Register of Medicinal Products), carvedilol (Dilatrend⁺)

Centrally acting antihypertensive drugs

α_2 AAs: clonidine, methyldopa, guanfacine — see “Direct- and indirect-acting adrenergic agonists”

Moxonidine (Physiotens⁺, Moxarel⁺)

- ▶ Imidazoline derivative, imidazoline receptor agonist. Bioavailability: 88 %, food intake does not affect absorption. Maximum blood concentrations are reached in 1 hour. Time of action after a single dose: up to 24 hours.
- ▶ About 10–20 % of the drug undergoes biotransformation in the liver, dehydrated moxonidine being its main metabolite with a pharmacodynamic activity accounting for 10 % of that of moxonidine. $T_{1/2}$ of moxonidine and its metabolite is 2.5 hours and 5 hours, respectively. Excreted predominantly in urine, with less than 1 % excreted in bile. For oral administration 1–2 times daily.

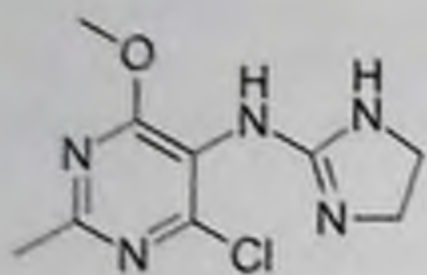


Fig. 16.1. 4-Chloro-5-(2-imidazolin-2-ylamino)-6-methoxy-2-methylpyrimidine

Mechanism of action: Moxonidine is a highly selective agonist of I₁ receptors located in the rostral ventrolateral medulla. By stimulating these receptors on the solitary tract, moxonidine inhibits vasomotor center activity through a system of inhibitory interneurons and, thus, reduces the descending sympathetic effects on the cardiovascular system: decreased cardiac output, TPR, BP. Moxonidine lowers plasma renin, AT II, and aldosterone levels, has a low affinity for α 2ARs. It produces both short-term (mainly due to its action on the sympathetic centers of the brain) and long-term (by inhibiting renin release and

improving kidney function) antihypertensive effect. Moxonidine reduces myocardial hypertrophy, helps to reduce fat hydrolysis, lower free fatty acids, increase glucose metabolism and insulin sensitivity, decrease triglyceride levels, increase high-density lipoproteins.

Therapeutic indications: treatment of essential hypertension, including in patients with metabolic syndrome or diabetes

Side effects: dry mouth, somnolence (at the start of treatment), lower limb edema

Contraindications: sick sinus syndrome, AV blocks, marked bradycardia, acute and chronic heart failure, hepatic impairment, pregnancy, breastfeeding, less than 18 years of age

Peripherally acting antihypertensive drugs: see "Cholinergic blockers", "Direct- and indirect-acting adrenergic blockers".

DRUGS ACTING ON MUSCLES

Sodium nitroprusside^o was first used in 1928; by 1955 it was widely used in clinical practice. The first calcium channel blocker, verapamil, was obtained in 1961, nifedipine was synthesized in 1966, and diltiazem was synthesized in 1971. Amlodipine was patented in 1982 and approved for medical use in 1990. Minoxidil was synthesized in the late 1950s and registered for the treatment of hypertension in 1979. Diazoxide was approved for medical use in 1973.

Classification

I. L-type calcium channel blockers

1. Phenylalkylamines: verapamil (Isoptin SR 240^o, Finoptin^o, Falicard^o)
2. Dihydropyridines: nifedipine (Corinfar^o, Adalat^o, Fenihidine^o, Cordafen^o), amlodipine (Normodipine^o, Norvasc^o)
3. Benzothiazepines: diltiazem (Dilzem^o, Cardil^o).

II. Potassium channel activators: diazoxide (Hyperstat^o, Eudemine^o), Minoxidil^o.

III. Direct-acting vasolidators: hydralazine (Apressin^o), sodium nitroprusside dihydrate (Naniprus^o), magnesium sulfate (Cormagnesin^o), bendazol (Dibazol^o), drotaverine (No-Spa^o).

Specifics of individual products by group

L-type calcium channel blockers

Transmembrane transport of Ca^{2+} ions occurs through special voltage-gated calcium channels. L-type channels are located in cardiomyocytes, in cells of the cardiac conduction system (sinoatrial and AV nodes) and vascular smooth muscle cells. They open when the membrane is depolarized, causing slow entry of Ca^{2+} ions into the cell and the formation of a slow calcium-mediated action potential. Entry of Ca^{2+} ions into cells is a trigger for the release of these ions from intracellular depots. Voltage-gated calcium channels are structured as protein complexes. The α_1 subunits blocked by the drug serve as voltage-gated sensors.

Mechanism of antihypertensive action: Voltage-gated L-type calcium channels serve as pharmacological targets for calcium channel blockers such as phenylalkylamine, benzothiazepine, dihydropyridine derivatives.

Blockade of L-type channels by phenylalkylamine and benzothiazepine derivatives disrupts the entry of Ca^{2+} ions in response to depolarization. Since the Ca^{2+} concentrations do not increase under the cytoplasmic membrane, Ca^{2+} is not released from the sarcoplasmic reticulum. Consequently, the Ca^{2+} content in the cytosol is insufficient to combine with troponin C and trigger contraction. Phenylalkylamines and benzothiazepines reduce myocardial contractility, decrease HR, cardiac output, TPR and lower BP. Phenylalkylamines affect vascular calcium channels to a lesser extent than benzothiazepines.

Dihydropyridine derivatives have essentially no effect on the cytoplasmic voltage-gated calcium channels of the myocardium and cardiac conduction system. They have a greater effect on vascular smooth muscle cells. They block the cytoplasmic L-type calcium channels on vascular smooth muscles, disrupting the entry of Ca^{2+} ions through these channels in response to depolarization. Since the Ca^{2+} concentrations do not increase inside the cytoplasmic membrane, Ca^{2+} is not released from the sarcoplasmic reticulum, no calcium–calmodulin complex is formed, myosin light-chain kinase is not activated, myosin light chains are not phosphorylated, no contraction occurs, thus the blood vessels dilate.

Verapamil (Isoptin SR 240⁺, Finoptin[®], Falicard[®])

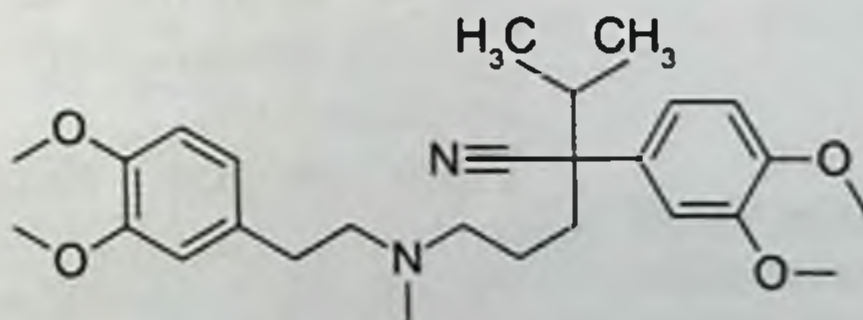


Fig. 16.2. α -[3-[[2-(3,4-Dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy- -(1-methylethyl) benzeneacetonitrile (and as a hydrochloride)

- ▶ Phenylalkylamine derivative. Bioavailability: 20–35 % (first-pass effect), maximum blood concentrations are reached in 1–2 hours. Crosses the BBB and placental barrier.
- ▶ Metabolized in the liver to form norverapamil (20 % of hypotensive activity of verapamil) and N-dealkylnorverapamil. $T_{1/2}$: 2–7 hours after a single dose and 4–12 hours after repeated dosing. Excreted in small amounts as unchanged drug (3–4 %), with the rest excreted as metabolites (70 %) in the urine and about 25 % excreted in bile. For oral administration 2–3 times daily, for intravenous administration.

Pharmacological effects: antihypertensive, antiarrhythmic, antianginal, hypolipidemic (decreases low-density lipoprotein levels, increases high-density lipoprotein levels), increases glucose tolerance (increases glucose uptake by hepatocytes, inhibits glucagon secretion), nephroprotective (increases renal blood flow, decreases proteinuria)

Therapeutic indications: treatment of essential hypertension (oral administration 2–3 times daily), relief of hypertensive crisis (intravenous administration); paroxysmal supraventricular tachycardia, sinus tachycardia, atrial extrasystoles, atrial flutter and fibrillation, prophylaxis of angina attacks (including Prinzmetal angina)

Side effects: sinus bradycardia, AV block, symptoms of heart failure, increased fatigue, nausea, vomiting, atonic colon, peripheral edema, facial hyperemia

Contraindications: cardiogenic shock, bradycardia, sick sinus syndrome, second- or third-degree AV block, acute myocardial infarction, heart failure, pregnancy, breastfeeding

Diltiazem (Dilzem[®], Cardil[®])

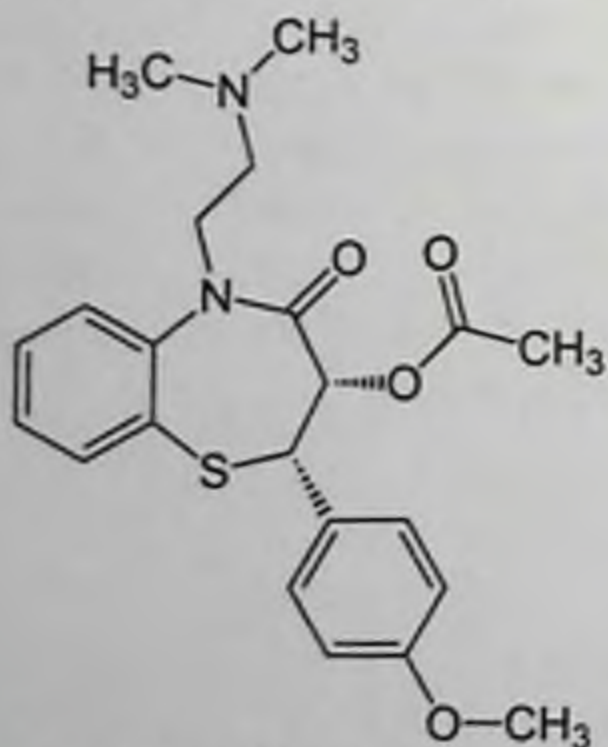


Fig. 16.3. (2S-cis)-3-(Acetoxy)-5-[2-(dimethylamino) ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (as a hydrochloride)

- ▶ Benzothiazepine derivative. Bioavailability: 40 % (first-pass effect), maximum plasma concentrations are reached in 4–6 hours.
- ▶ Metabolized in the liver by deacetylation, demethylation with cytochrome P450 involvement. Excreted in bile (65 %) and to a lesser extent in the urine (35 %). $T_{1/2}$: 1–3 hours (intravenous administration), 3.0–4.5 hours (oral administration). For oral administration 3–4 times daily, for intravenous administration.

Pharmacological effects: antihypertensive, antiarrhythmic, antianginal effects

Therapeutic indications, side effects, contraindications: see "Verapamil"

Nifedipine (Corinfar[®], Adalat[®], Fenihiidine[®], Cordafen[®])

- ▶ 1,4-dihydropyridine derivative.
Bioavailability: 40–60 % (first-pass effect).
Onset of action: 20 min for oral administration, 5 min for sublingual administration; time of action: 4–6 hours (12–24 hours for long-acting pharmaceutical forms). Crosses the BBB and placental barrier, excreted into breast milk.
- ▶ Fully metabolized in the liver by cytochrome P450 isoenzymes CYP3A4, CYP3A5 and CYP3A7. Excreted as inactive metabolites mainly in urine (80 %) and in bile (20 %). $T_{1/2}$: 2–4 hours, 3.8–16.9 hours for long-acting pharmaceutical forms. For oral administration 3 times daily, for sublingual, intravenous administration.

Pharmacological effects: antihypertensive, antianginal, antiplatelet, antiteratogenic

Therapeutic indications: treatment of essential hypertension, relief of hypertensive crisis (intravenous, sublingual administration), relief and prophylaxis of angina attacks (including Prinzmetal angina), pulmonary hypertension

Side effects: tachycardia, peripheral edema (ankles, feet, shins), facial hyperemia, atonic constipation, headache, inhibition of hematopoiesis

Contraindications: decompensated chronic heart failure, sick sinus syndrome, acute myocardial infarction, cardiogenic shock, unstable angina, pregnancy, breastfeeding, less than 18 years of age

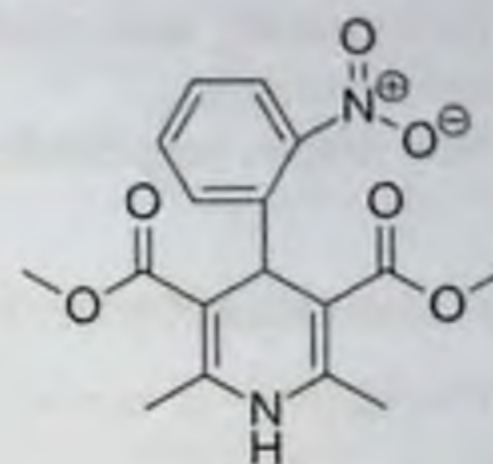


Fig. 16.4. 2,6-Dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester

Amlodipine (Normodipine[®], Norvasc[®])

- ▶ 1,4-dihydropyridine derivative, mixture of stereoisomers, with pharmacologically active S-amlodipine. Bioavailability: 64–80 %. Crosses the BBB. Maximum blood concentrations are reached in 6–12 hours.
- ▶ Biotransformation occurs in the liver to form inactive metabolites. $T_{1/2}$: 35–48 hours, excreted in the urine predominantly as metabolites (60 %), with 10 % excreted as unchanged drug and 20–25 % excreted in the bile. For oral administration once daily.

Pharmacological effects: antihypertensive, antianginal, antiplatelet effects

Specific properties: improved pharmacokinetic profile, more vasoselective, longer action, smoother increase in plasma concentrations. Does not affect myocardial contractility and conduction, does not cause reflex increase in heart rate. The absence of clinically relevant cardiodepressant action distinguishes it from verapamil and diltiazem, which are not recommended for use in patients with left ventricular ejection fraction of < 40 %. The absence of reflex tachycardia distinguishes it from nifedipine and other dihydropyridines.

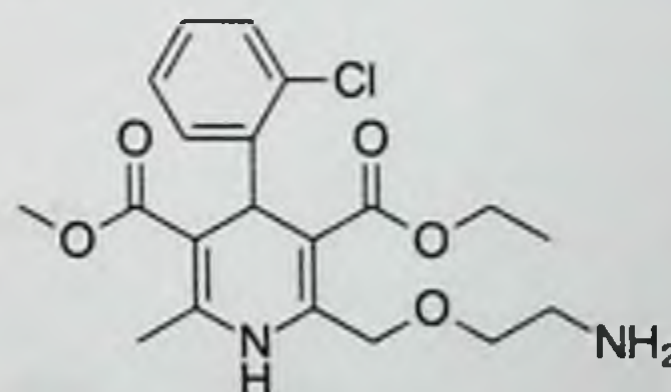


Fig. 16.5. (±)-2-[(2-Aminoethoxy) methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinecarboxylic acid 3-ethyl 5-methyl ester

Therapeutic indications: treatment of essential hypertension, stable or vasospastic angina

Side effects, contraindications: see "Nifedipine"

Potassium channel activators

Mechanism of action: Potassium channel activators activate (open) ATP-sensitive potassium channels, increasing the release of K^+ ions from vascular smooth muscles, and causing membrane hyperpolarization. Voltage-gated calcium channels close, causing the intracellular content of Ca^{2+} ions to decrease. Muscle relaxation, vasodilation, and BP reduction occur. Potassium channel activators predominantly dilate resistance vessels (arterioles) and to a lesser extent change the tone of capacitance vessels (veins) and venous return to the heart (Fig. 16.6).

Diazoxide (Hyperstat[®], Eudemine[®])

- ▶ Benzothiadiazine derivative (thiazide). The antihypertensive action occurs 1 min after intravenous administration, reaches its maximum in 2–5 min, and lasts up to 2–12 hours.
- ▶ Metabolized in the liver. Excreted in the urine: 50 % is excreted as unchanged drug, the rest is excreted as metabolites. $T_{1/2}$: 2–28 hours. For intravenous administration.

Therapeutic indications: hypertensive crisis; second-line agent

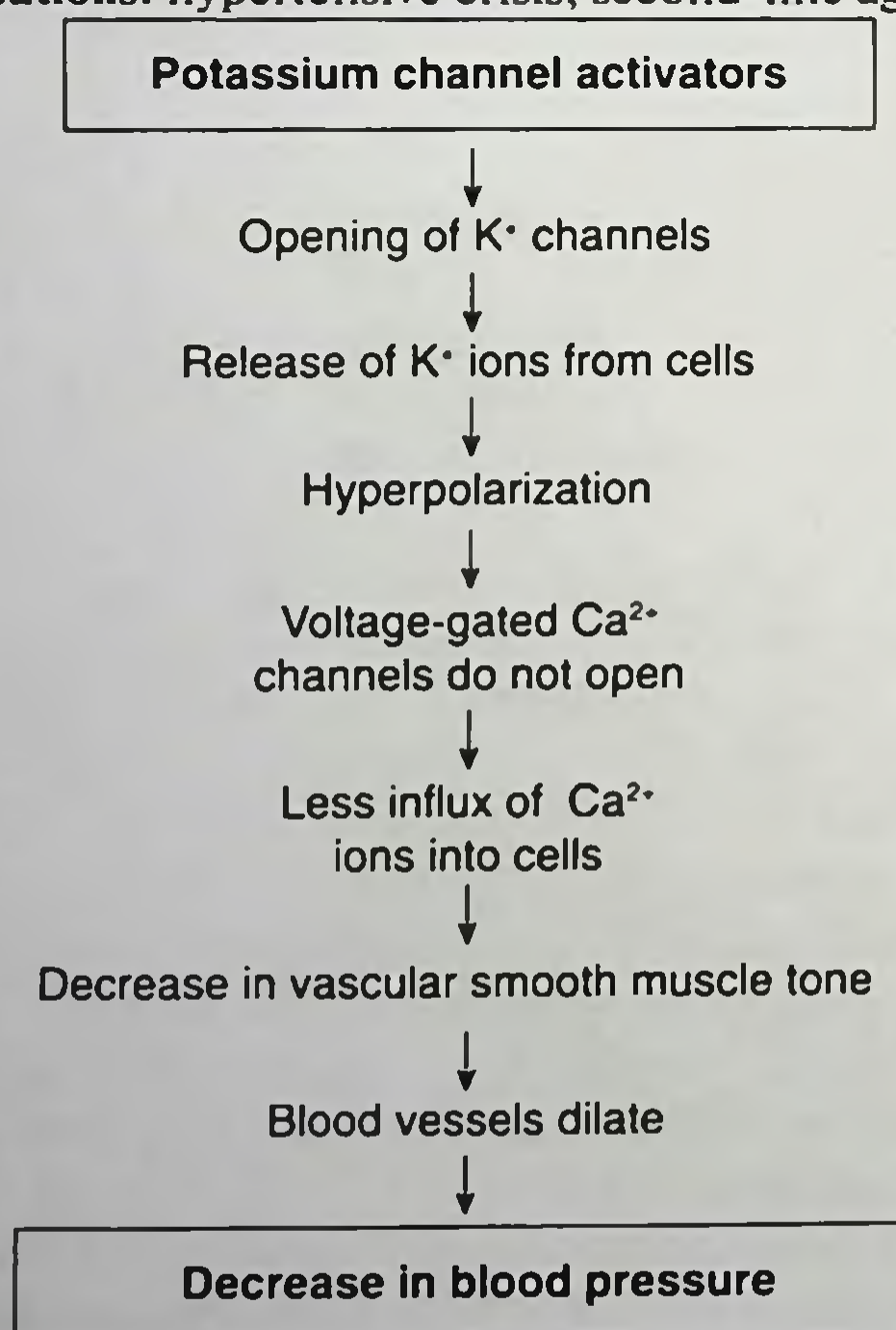


Fig. 16.6. Mechanism of action of potassium channel activators (Kharkevich D. A., 2021)

Side effects: tachycardia, increased cardiac output, increased myocardial oxygen demand, orthostatic collapse, Na^+ and water retention (swollen feet and ankles, rapid weight gain), hypertrichosis (in 20 % of patients), hyperglycemia, hyperuricemia, skin redness

Contraindications: acute stroke, acute myocardial infarction, childbirth, breastfeeding

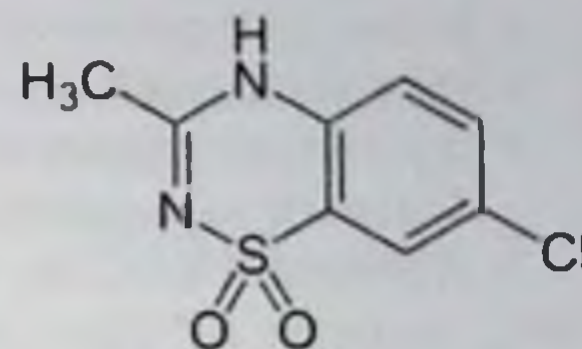


Fig. 16.7. 7-Chloro-3-methyl-2H-1,2,4-benzothiadiazine-1,1-dioxide (as a sodium salt)

Minoxidil*

- ▶ Pyrimidine derivative, nitric oxide (NO) agonist, activates the guanylate cyclase enzyme involved in vasodilation. Bioavailability: 90 %. Pharmacologically active after metabolic conversion in the liver to minoxidil NO sulfate; the antihypertensive effect develops in 2–4 hours, time of action is 24 hours due to metabolite accumulation in the vascular wall.
- ▶ Undergoes biotransformation in the liver to form weakly active metabolites. About 10–20 % of the dose is excreted in the urine as unchanged drug, the rest is excreted as glucuronides. $T_{1/2}$: 3–4 hours. For oral administration 1–2 times daily.

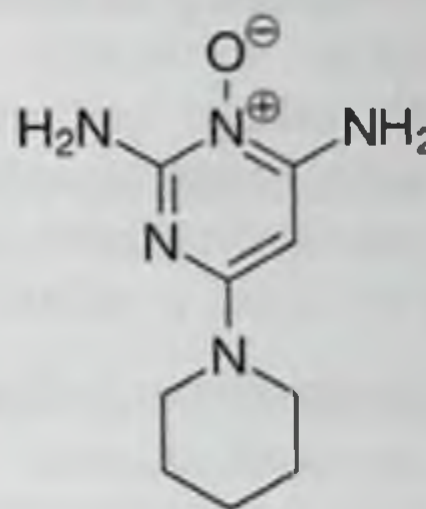


Fig. 16.8. 6-(1-Piperidiny)-2,4-pyrimidinediamine-3-oxide

Therapeutic indications: severe forms of hypertension resistant to other antihypertensive drugs; second-line agent

Side effects, contraindications: see “Diazoxide”

Direct-acting vasodilators

Hydralazine (Apressin®)

- ▶ Phthalazine derivative with hydrazine group (hydrazinophthalazine). Subject to first-pass effect, bioavailability is about 50 % for moderate acetylators and 30 % for fast acetylators. Onset of action: 5–30 min, maximum plasma concentrations are reached in 1–2 hours, time of action: 3–8 hours.
- ▶ Biotransformation occurs in the liver to form active metabolites. $T_{1/2}$: 2–8 hours. 52–90 % is excreted in the urine (with 2–4 % excreted as unchanged drug after oral administration and 11–14 % after intravenous administration), 10 % is excreted in the bile. For oral administration 3–4 times daily, for intravenous administration.

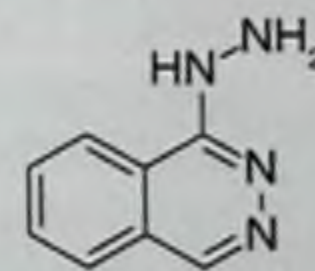


Fig. 16.9. 1-Hydrazinylphthalazine

Mechanism of action:

- ▶ Hydralazine inhibits the inactivation of endogenous vasodilating factors, including nitric oxide, due to the presence of a hydrazine group in the drug molecule.

- ▶ It disrupts the entry of Ca^{2+} into smooth muscle cells, inhibits the release of Ca^{2+} from intracellular depots, and prevents phosphorylation of myosin light chains.
- ▶ Hydralazine reduces the activity of dopamine beta-hydroxylase, which converts dopamine to noradrenaline.

It dilates predominantly resistance vessels (arterioles and small arteries), decreases TPR, decreases BP (diastolic to a greater extent than systolic BP). Hydralazine has little effect on postcapillary capacitance vessels. It improves cerebral and peripheral circulation and increases renal blood flow by increasing the stroke output and heart rate. Hydralazine reduces TXA₂ synthesis, reducing platelet aggregation.

Therapeutic indications: hypertension, hypertensive crisis, congestive heart failure, eclampsia

Side effects: tachycardia, cardialgia, edema in various locations, lupus-like syndrome, lymphadenopathy, peripheral neuritis, facial hyperemia, nausea, vomiting

Contraindications: systemic lupus erythematosus, peripheral neuropathy, marked atherosclerosis, pregnancy, breastfeeding

Sodium nitroprusside dihydrate (Naniprus[®])

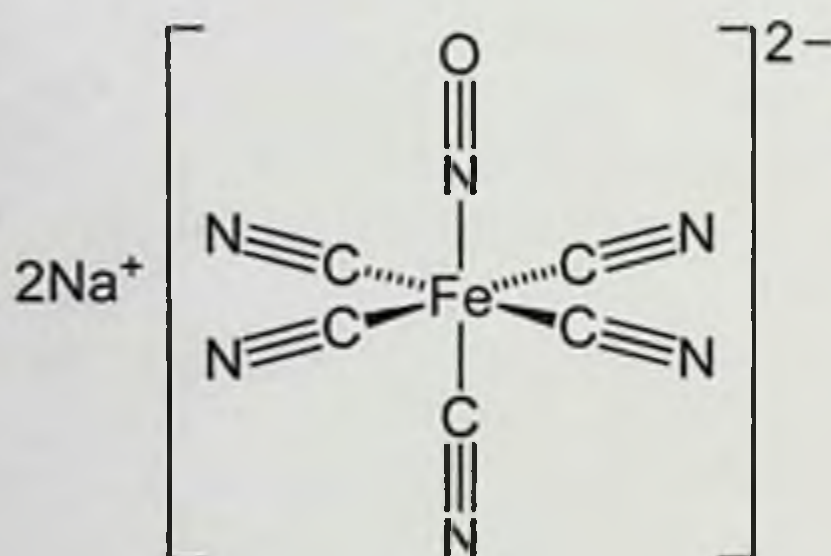


Fig. 16.10. Disodium pentakis(cyano-C)nitrosylferrate (2-) (and as a dihydrate)

- ▶ Complex compound containing an iron atom, a nitro group, and five cyano groups. Crosses the BBB and placental barrier, excreted into breast milk. The antihypertensive action occurs within 1–2 min after the start of infusion and lasts another 1–10 min.
- ▶ Metabolized by red blood cell enzymes to methemoglobin and cyanides, which are transformed into thiocyanate in the liver by thiosulfate sulfurtransferase (rhodanase). $T_{1/2}$: 4 hours. 80 % is excreted in the urine as thiocyanate (with 20 % excreted as unchanged drug) and in bile. For intravenous administration.

Mechanism of action: Following intravenous administration, a sodium nitroprusside molecule enters a red blood cell, where it receives an electron from an iron atom in the oxyhemoglobin. This non-enzymatic electron transfer leads to the formation of the unstable nitroprusside radical and methemoglobin. The nitroprusside molecule spontaneously decomposes into five cyanide ions and the active nitroso group, NO. NO interacts with glutathione to form S-nitrosothiols. These compounds activate soluble guanylate cyclase which triggers cGMP synthesis. Increased cGMP production

decreases the content of cytosolic free Ca^{2+} ions, which causes relaxation of vascular smooth muscle cells (Fig. 16.11).

Sodium nitroprusside has an effect on resistance (arterioles, small arteries) and capacitance (venules, small veins) vessels. By dilating peripheral arteries, it reduces cardiac afterload, decreases left ventricular tension, and lowers BP. By dilating peripheral veins, it reduces cardiac preload, which results in improved systemic and intracardiac hemodynamics, decreased pressure in the pulmonary circuit; reflex tachycardia occurs. Sodium nitroprusside increases renin secretion and reduces platelet aggregation.

Therapeutic indications: hypertensive crisis, acute left ventricular failure, controlled hypotension

Side effects: tachycardia, orthostatic collapse, restlessness, muscle spasms, hyperreflexia, nausea, vomiting

Contraindications: increased intracranial pressure, acute stroke, aortic stenosis, severe hepatic and/or renal impairment, optic atrophy, glaucoma, pregnancy, breastfeeding

Magnesium sulfate (Cormagnesin®)

Exerts an antihypertensive effect following parenteral (intramuscular, intravenous) administration. Crosses the BBB, placental barrier, excreted into breast milk.

Time of action: 30 min for intravenous administration. Excreted in the urine.

Mg^{2+} is a “physiological” calcium antagonist and calcium channel blocker that can displace calcium from binding sites.

The mechanism of antihypertensive action consists of a direct muscle action, inhibition of the vasomotor center, negative chronotropic and inotropic effects, as well as inhibition of excitation transmission in autonomic ganglia

Pharmacological effects: antihypertensive, antispasmodic, tocolytic, antiarrhythmic, anticonvulsant; hypnotic, narcotic at high doses

Therapeutic indications (parenteral administration): hypertensive crisis, polymorphic ventricular tachycardia (Torsade de pointes), encephalopathy, eclampsia, threatened preterm labor, epilepsy syndromes, heavy metal poisoning

Side effects (parenteral administration): symptoms of hypermagnesemia: bradycardia, inhibition of AV conduction, diplopia, marked hypotension, CNS depression, decreased deep tendon reflexes, respiratory depression, nausea, vomiting, polyuria, paresthesia

Contraindications (parenteral administration): hypermagnesemia, respiratory depression, bradycardia, AV block, marked renal impairment, administration within 2 hours of delivery, pregnancy, breastfeeding

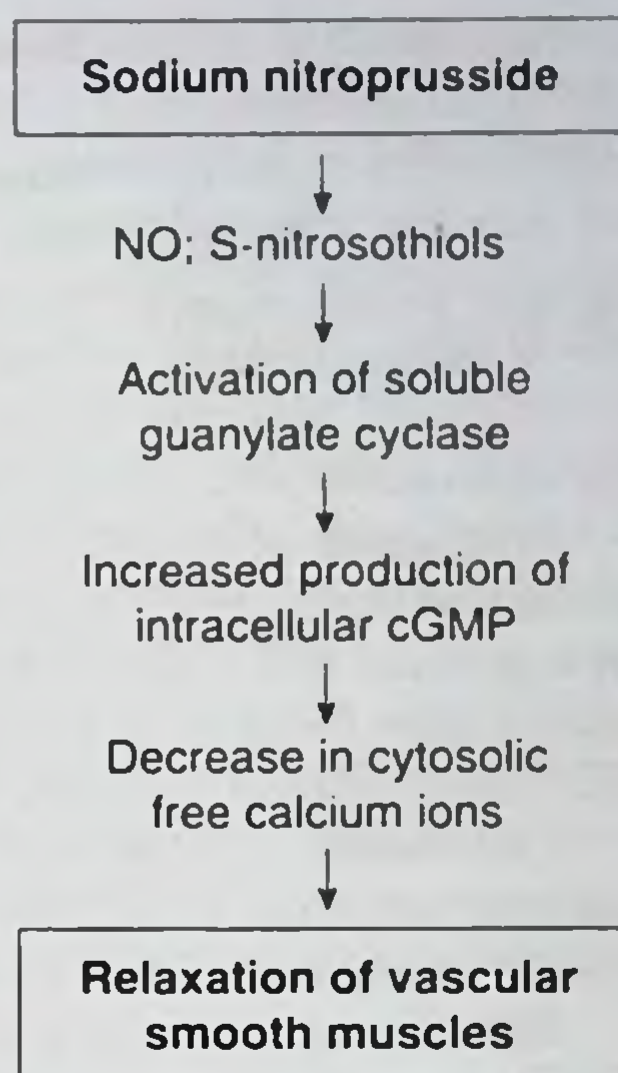


Fig. 16.11. Mechanism of action of sodium nitroprusside (Kharkevich D. A., 2021)

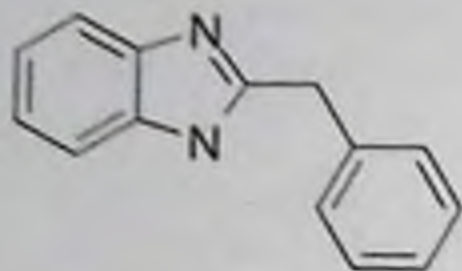


Fig. 16.12. 2-(Phenylmethyl)-1H-benzimidazole

Bendazol (Dibazol*)

Benzimidazole derivative, myotropic antispasmodic, exerts a stimulating effect on synaptic transmission in the spinal cord. The antihypertensive action occurs within 30–60 min for intramuscular administration, within 15–20 min for intravenous administration. Time of action: 2–3 hours. For oral administration 2–3 times daily, for intravenous, intramuscular administration.

Mechanism of antihypertensive action: Bendazol blocks PDE and promotes the accumulation of cAMP in the cytoplasm of myofibrils, which, in turn, is accompanied by a decrease in Ca^{2+} levels and muscle relaxation. Relaxation of the vascular smooth muscle cells in the peripheral arteries is accompanied by a decrease in TPR and BP. The antihypertensive activity is moderate and the effect duration is short.

Therapeutic indications: hypertensive crisis (intravenous, intramuscular administration), hypertension, smooth muscle spasm of internal organs (gastric ulcer, pylorospasm, colon spasm, etc.), sequelae of poliomyelitis and facial nerve palsy

Side effects: dizziness, headache, hot flashes, excessive sweating, nausea

Contraindications: conditions accompanied by increased muscle tone and seizure syndrome, pregnancy, breastfeeding, less than 18 years of age

Drotaverine (No-Spa*)

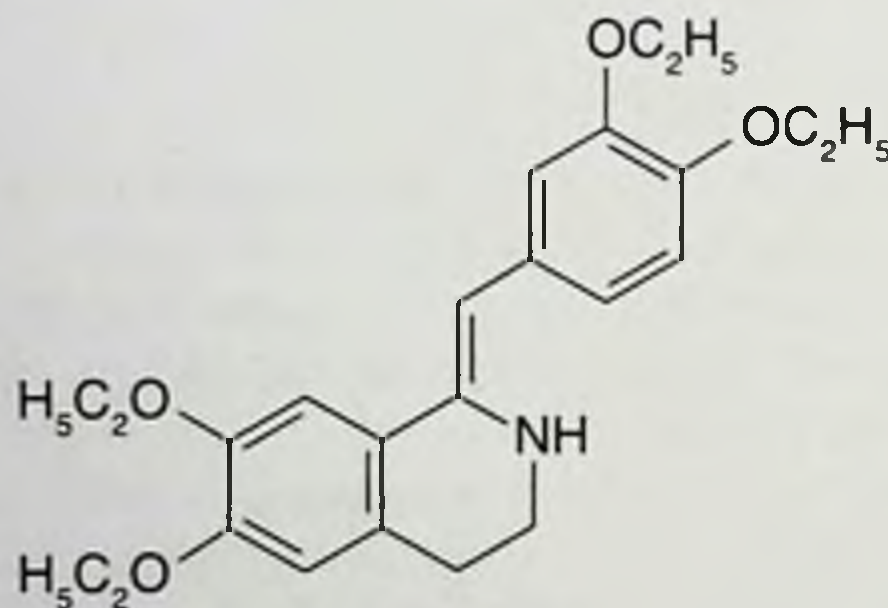


Fig. 16.13. 1-[3,4-Diethoxyphenyl)methylene]-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline (as a hydrochloride)

- ▶ Isoquinoline derivative, myotropic antispasmodic. Bioavailability: 65 % (first-pass effect). Time to reach maximum blood concentrations: 45–60 min. Does not cross the BBB.
- ▶ Metabolized in the liver by O-desethylation, metabolites are conjugated with glucuronic acid. The main metabolite is 4'-desethyldrotaverine, the other metabolites are 6-desethyldrotaverine and 4'-desethyldrotaveraldine. $T_{1/2}$: 8–10 hours, > 50 % is excreted in the urine (predominantly as metabolites), about 30 % is excreted in the bile. For oral administration 2–3 times daily, for intramuscular, subcutaneous administration.

Mechanism of antihypertensive action: Drotaverine reduces the influx of ionized active Ca^{2+} into smooth muscle cells by inhibiting PDE and intracellular cAMP accumulation, which activates cAMP-dependent phosphorylation of myosin light chain kinases. The phosphorylation of myosin light chain kinases reduces the affinity for Ca^{2+} ions, the calmodulin complex, which results in the inactivated form of myosin light chain kinases supporting muscle relaxation. Moreover, cAMP affects the cytosolic concentration of Ca^{2+} ions by stimulating the transport of these ions into the extracellular space and the sarcoplasmic reticulum. Dilation of blood vessels, BP reduction, increase in cardiac output, and decrease in smooth muscle tone of internal organs occur. Drotaverine can be used as an antispasmodic in cases when muscarinic receptor antagonists are contraindicated.

Therapeutic indications: hypertensive crisis (combination therapy); peripheral vasospasm (obliterating endarteritis, Raynaud syndrome), cerebral vasospasm, coronary vasospasm; smooth muscle spasm of the gastrointestinal tract, bile ducts, and urinary tract; threatened miscarriage

Side effects: tachycardia, dizziness, hot flashes, excessive sweating, nausea, constipation

Contraindications: cardiogenic shock, prostate adenoma, severe hepatic and/or renal impairment, pregnancy, breastfeeding period

DRUGS ACTING ON THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Renin inhibitors have been researched since the 1970s. The direct renin inhibitor aliskiren was registered in 2007. In 1975, American researchers D. Cushman, M. Ondetti, and B. Rubin synthesized the first non-peptide representative of ACE inhibitors, which was named captopril. This drug was patented in 1976 and approved for medical use in 1980. In 1986, the first AT_I receptor blocker, losartan, was synthesized.

The RAAS plays an important part in BP regulation. Renin is secreted by the kidneys in response to decreased circulating blood volume and BP. It cleaves angiotensinogen to the inactive decapeptide AT I. AT I is converted to the active octapeptide AT II under the influence of ACE. AT II binds cellular receptors and causes vasoconstriction, release of catecholamines from the adrenal medulla and presynaptic nerve terminals. It also stimulates the secretion of aldosterone and reabsorption of Na^+ . In addition, AT II inhibits renin release, thus providing the system with a negative feedback mechanism. AT II acts at various levels (vascular bed, sympathetic nervous system, adrenal medulla), increasing TPR and BP (Fig. 16.14).

Renin is the first stage of the RAAS cascade. It is a proteolytic enzyme generated from the prorenin precursor and secreted in the juxtaglomerular apparatus by myoepithelial cells of the efferent glomerular arteriole.

The following factors regulate renin release:

- ▶ baroreceptors in afferent arterioles, which are activated by a decrease, and inhibited by an increase, in perfusion pressure at the kidneys

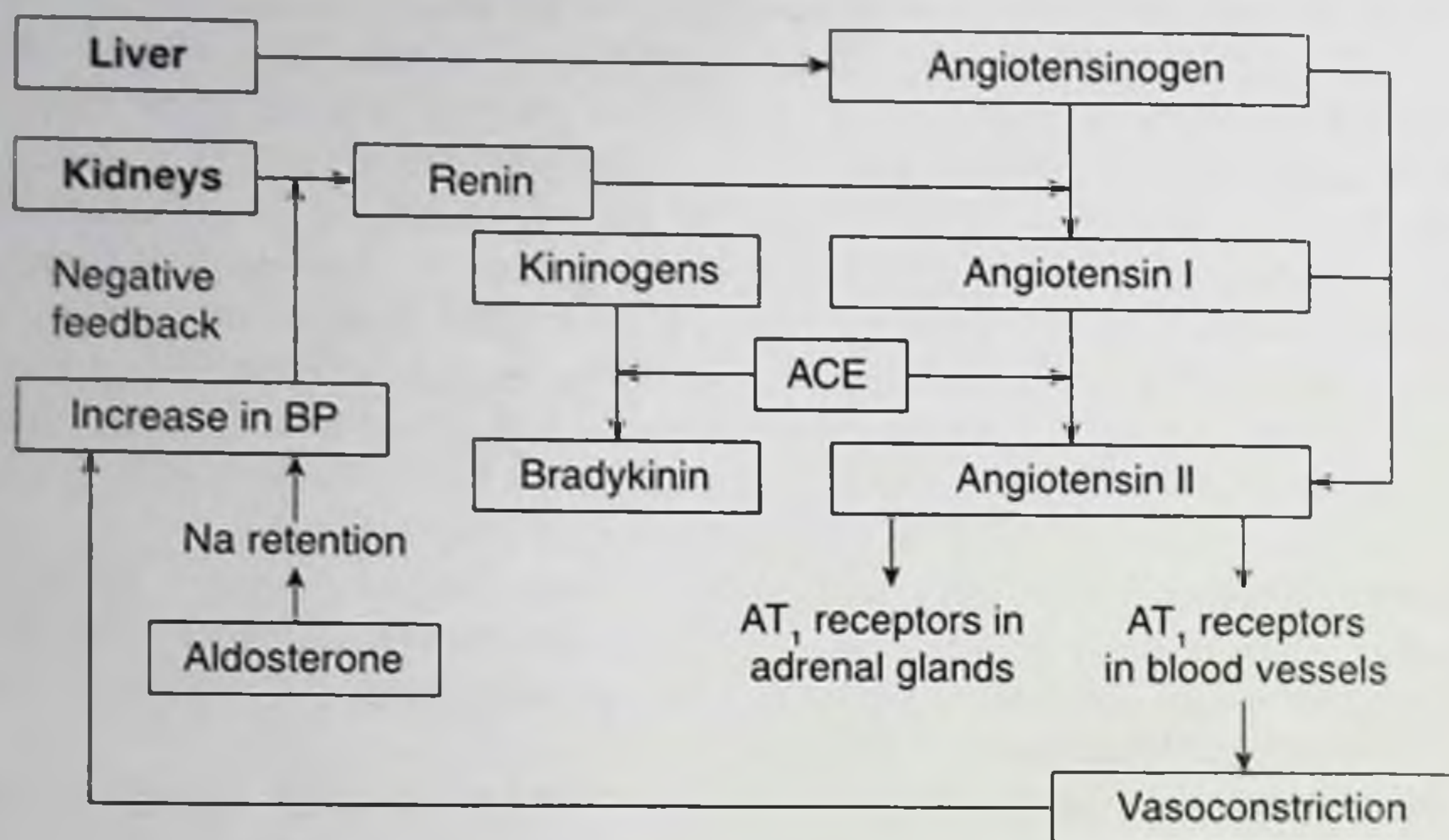


Fig. 16.14. Renin-angiotensin-aldosterone system

- ▶ changes in Na^+ concentrations which are detected by *macula densa cells*: more Na^+ in the distal convoluted tubule leads to higher renin secretion
- ▶ activation of the sympathetic nervous system, which is carried out through β_1 and β_2 ARs
- ▶ direct inhibitory action of AT II and aldosterone through negative feedback.

Renin secretion is a key factor in RAAS activation. In addition to the kidneys, renin formation occurs in the vascular endothelium of numerous tissues, myocardium, brain, salivary glands, zona glomerulosa of the adrenal cortex. Angiotensinogen is a substrate for renin. Angiotensinogen is an α_2 globulin containing more than 400 amino acid residues. Angiotensinogen formation occurs mainly in the liver as well as in perivascular adipose tissue and fibroblast-like cells. It is stimulated by glucocorticoids, estrogens, thyroid hormones and proinflammatory cytokines (interleukin-1, tumor necrosis factor α). Renin hydrolyzes the peptide bond in the angiotensinogen molecule and splits off the N-terminal decapeptide (AT I), which has no biological activity. Under the influence of ACE (a carboxydipeptidyl peptidase) found in endothelial cells, lungs and plasma, two amino acids are removed from the C-terminal of AT I, resulting in the formation of an octapeptide, AT II.

AT II is converted by aminopeptidases to AT III, a heptapeptide that exhibits AT II activity. However, the plasma concentrations of heptapeptide are 4 times lower than those of octapeptide, and therefore most of the effects occur due to AT II.

Specific proteases (angiotensinases) cleave AT II and AT III further. AT II stimulates aldosterone secretion by zona glomerulosa cells in the adrenal cortex, which, in turn, causes Na^+ ions and water retention, increases circulating blood volume and BP. AT II, when present in the blood in high concentrations, has a potent vasoconstrictor effect and other numerous negative effects: increased oxidative stress and lower nitric oxide bioavailability with activation of endothelial apoptosis, vascular remodeling, increased arterial stiffness, accelerated development of atherosclerosis.

AT II is a key mediator of damage to various organs in hypertension. It causes myocardial hypertrophy, coronary artery constriction and *QT* prolongation; in the brain: increased activity of the sympathetic division of the autonomic nervous system, deterioration of the cerebral circulation; in the kidneys: increased renin production, nephropathy, albuminuria, and fibrosis. Damage to these organs can cause myocardial infarction, stroke, heart failure, renal impairment.

Aldosterone, the third component, acts on distal convoluted tubules and facilitates the release of K^+ , Mg^{2+} and reabsorption of Na^+ , Cl^- , water. This results in larger circulating blood volume, higher BP and increased renal blood flow. Aldosterone receptors are present not only in the kidneys but also in the heart and blood vessels.

In the body, the RAAS helps maintain normal BP values; ensures water and salt balance; maintains blood acid-base balance; contributes to tissue growth and differentiation processes, modulation of inflammation and apoptosis; potentiates the synthesis and secretion of certain neurohumoral substances.

The RAAS plays a role in the development and progression of hypertension, chronic heart failure, chronic kidney disease and systemic atherosclerosis.

Classification

1. Renin inhibitors

- Aliskiren (Rasilez[®]).

2. ACE inhibitors (AT II synthesis inhibitors)

- First generation (short-acting, administered 3–4 times daily)
 - Captopril (Capoten[®]).
- Second generation (intermediate-acting, administered 2 times daily)
 - Enalapril (Renitec[®], Ednit[®], Enap[®])
- Third generation (long-acting, administered once daily)
 - Fosinopril (Monopril[®])
 - Lisinopril (Diroton[®]).

3. Angiotensin receptor blockers (ARBs).

- Losartan (Cozaar[®], Lozap[®])
- Valsartan (Diovan[®])
- Telmisartan (Micardis[®]).

4. Vasopeptidase inhibitors

- Omapatrilat[®] (Vanlev[®]).

Specifics of individual products by group

Renin inhibitors

Substances that inhibit renin production are most effective when renin release is increased. This occurs when:

- ▶ blood pressure and volume in the afferent arterioles of renal glomeruli decreases
- ▶ $NaCl$ in distal convoluted tubules decreases [the signal is transmitted from epithelial *macula densa* cells to juxtaglomerular cells they come into contact with]
- ▶ the tone of adrenergic innervation increases
- ▶ prostacyclin and PGE_2 production increases.

Consequently, renin production can be reduced by suppressing adrenergic innervation. This can be accomplished by reducing central sympathetic tone

(clonidine, methyldopa), blocking impulse transmission at the level of presynaptic terminals (reserpine) and β_1 ARs [propranolol (Anaprilin[®]), etc]. Reduced renin release has a known, but small, contribution to the antihypertensive action of the listed drugs.

Aliskiren (Rasilez[®])

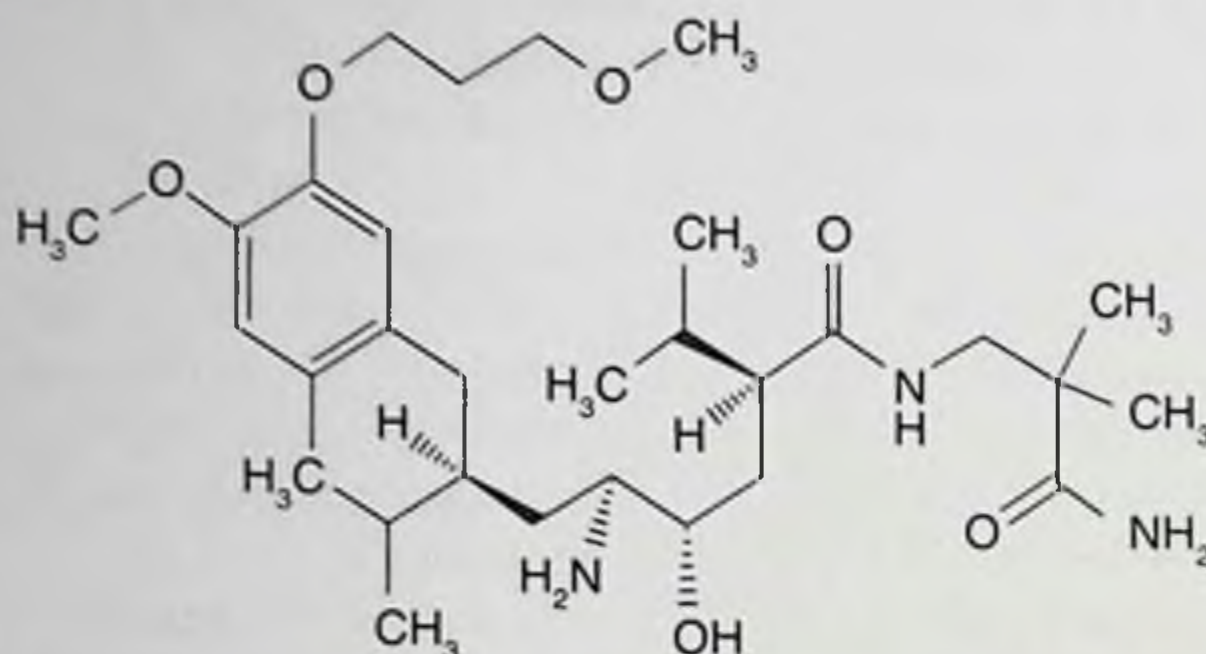


Fig. 16.15. (2S, 4S, 5S, 7S)-5-Amino-N-(2-carbamoyl-2,2-dimethylethyl)-4-hydroxy-7-[[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl]-8-methyl-2-(propan-2-yl) nonanamide

- ▶ Direct selective non-peptide renin inhibitor. Maximum plasma concentrations are reached in 1–3 hours.
- ▶ About 1.4 % of the dose undergoes biotransformation in the liver with the involvement of the cytochrome P450 isoenzyme CYP3A4. Excreted as unchanged drug in bile (91 %), in the urine (less than 1 %). $T_{1/2}$: 40 hours. For oral administration once daily.

Mechanism of action: Aliskiren binds to the active site of the renin molecule, preventing renin from binding to angiotensinogen and thereby blocking the formation of AT I, the precursor of AT II.

Aliskiren inhibits the RAAS at the rate-limiting reaction stage, unlike ACE inhibitors and ARBs, which block the system at later stages. It has selective affinity for plasma renin: it binds the catalytic center of renin activity and does not decrease its plasma concentrations. Aliskiren neutralizes the inhibition of negative feedback, which results in decreased renin activity (by 50–80 % in patients with hypertension) and AT I and AT II concentrations. Direct blockade of renin with aliskiren is one of the most practical strategies to improve the long-term prognosis (Fig. 16.16).

Pharmacological effects

- ▶ Antihypertensive
- ▶ Regression of left ventricular hypertrophy in patients with hypertension
- ▶ Nephroprotective: decrease in renin and prorenin receptors in kidneys, reduction of profibrotic processes and podocyte apoptosis

Therapeutic indications: Hypertension

Side effects: dry cough, peripheral edema, hyperkalemia, dyspepsia

Contraindications: history of angioedema during administration of aliskiren, severe chronic renal and/or hepatic impairment, pregnancy, breastfeeding, less than 18 years of age

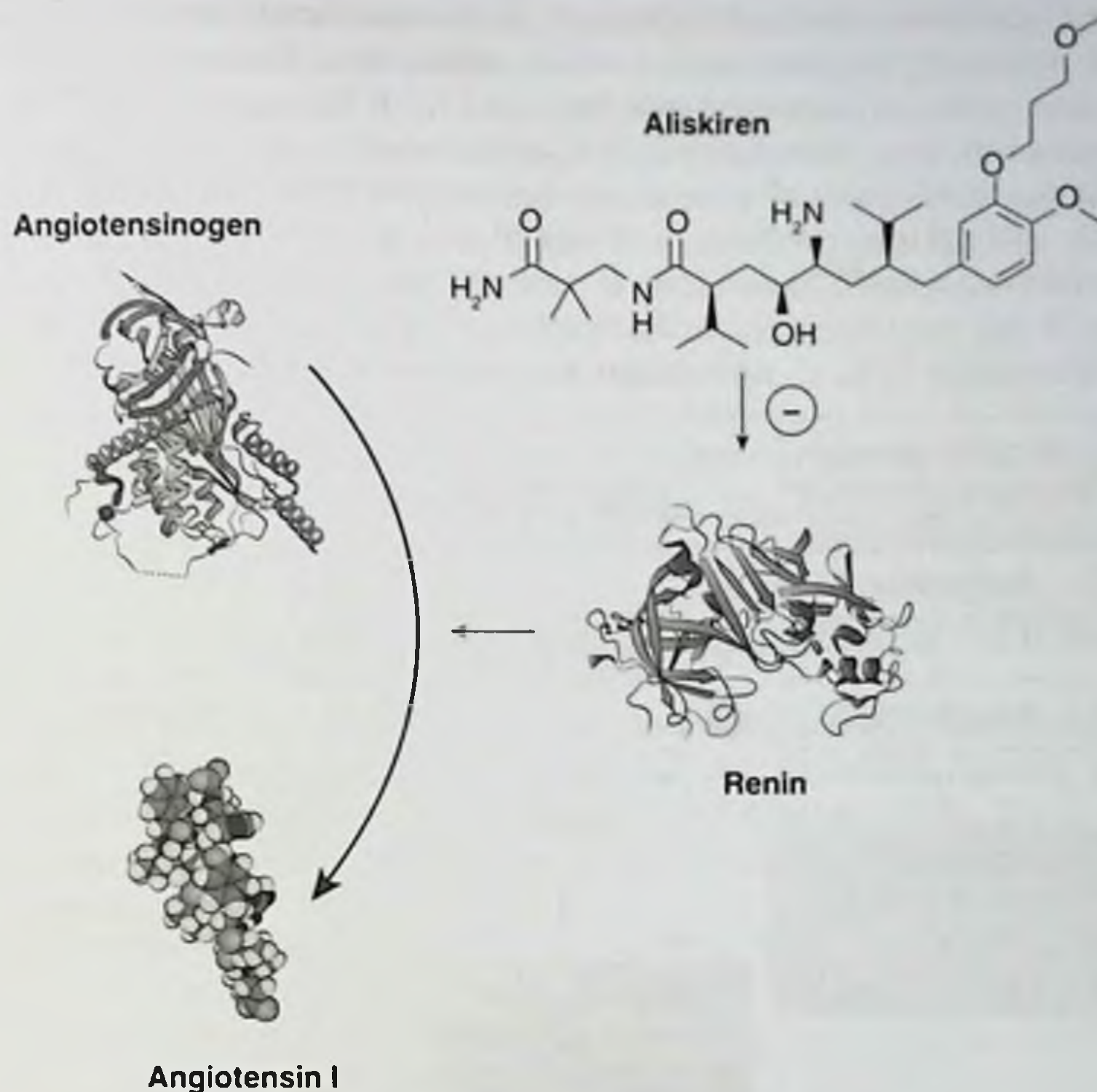


Fig. 16.16. Mechanism of action of aliskiren

ACE inhibitors

ACE (kininase II) is formed in the vascular endothelium, lungs, kidneys, and other peripheral tissues and promotes the conversion of AT I to highly active AT II. ACE has two primary physiological effects. First, it converts AT I to AT II, which is one of the most potent vasoconstrictors. Second, being kininase II, it destroys kinins, which produce local vasodilation.

Thus, pharmacological inhibition of this enzyme blocks the systemic and organ synthesis of AT II and lets kinins accumulate in the blood and tissues. These effects manifest clinically as marked antihypertensive action, due to a reduction of total peripheral and local renal resistance.

Mechanism of action: Inhibition of AT II formation by ACE inhibitors improves endothelial function, decreases inflammation and thrombosis markers, and slows atherogenesis (Fig. 16.17).

An important feature is that ACE inhibitors block the breakdown of bradykinin, causing levels of this protein to rise. This promotes the release of NO and arterial dilatation, reduces BP and has a cardioprotective effect by preventing apoptosis. Bradykinin also stimulates the synthesis of PGE₂ and PGI₂ (prostacyclin), which

$\mu\text{mol/L}$), hematological disorders (porphyria, leukopenia, severe anemia), pregnancy, breastfeeding, less than 18 years of age.

Specifics of individual products

Captopril (Capoten[®])

- ▶ The chemical structure contains a sulfhydryl group, which has lipophilic properties, and behaves like an active drug. Bioavailability: 35–40 % (first-pass effect). Maximum blood concentrations are reached 1 hour after oral administration, time of action: 8 hours. The effect occurs 15–20 min after sublingual administration. Captopril does not cross the BBB, but it crosses the placental barrier, and is excreted into breast milk.
- ▶ Undergoes biotransformation in the liver to form captopril disulfide dimer and captopril-cysteine disulfide; its metabolites are pharmacologically inactive. Excreted in urine as metabolites and as unchanged drug (40–50 %). $T_{1/2}$: 2–3 hours. For oral administration 3–4 times daily, for sublingual administration.

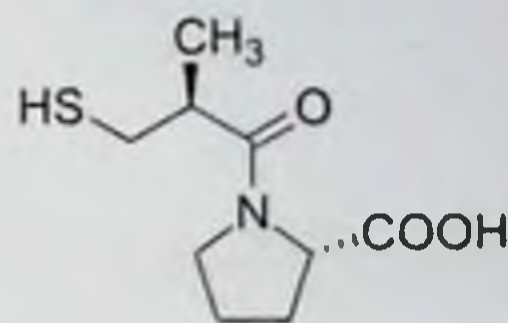


Fig. 16.18. (2S)-1-[(2S)-2-Methyl-3-sulfanylpentanoyl]pyrrolidine-2-carboxylic acid

Enalapril (Renitec[®], Ednit[®])

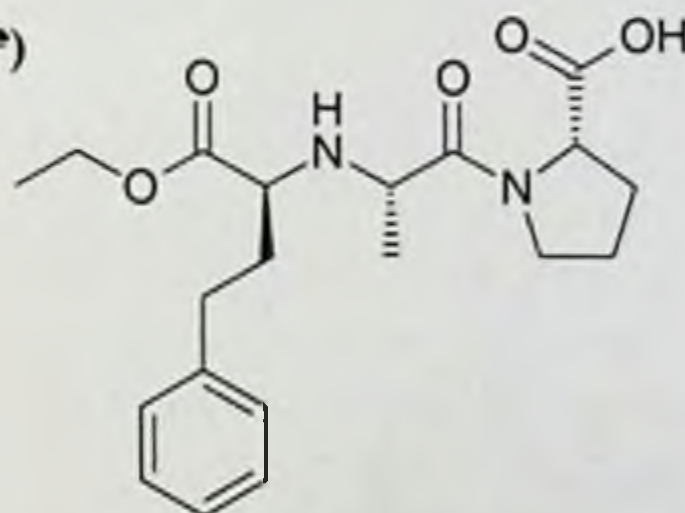


Fig. 16.19. (S)-1-[N-[1-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline maleate

- ▶ Carboxyalkyl dipeptide, lipophilic substance, pharmacologically active after metabolic conversion to enalaprilat. Bioavailability: 40%, maximum plasma concentrations are reached in 1 hour for enalapril and in 3–4 hours for enalaprilat.
- ▶ About 60 % is excreted in the urine (20 % as enalapril and 40 % as enalaprilat), and 33 % is excreted in the bile (6 % and 27 %, respectively). $T_{1/2}$: 11 hours. For oral administration twice daily, for intravenous administration (enalaprilat).

Lisinopril (Diroton[®])

- ▶ Carboxyalkyl dipeptide, its structure and action are similar to those of enalapril, regarded as its lysine analogue, hydrophilic. Bioavailability: 25 %, food intake does not affect absorption. Poorly crosses the BBB and placental barrier. Maximum blood concentrations are reached in 7 hours. Long-acting.
- ▶ Lisinopril does not undergo biotransformation and is excreted in the urine as unchanged drug. $T_{1/2}$: 12 hours. For oral administration once daily.

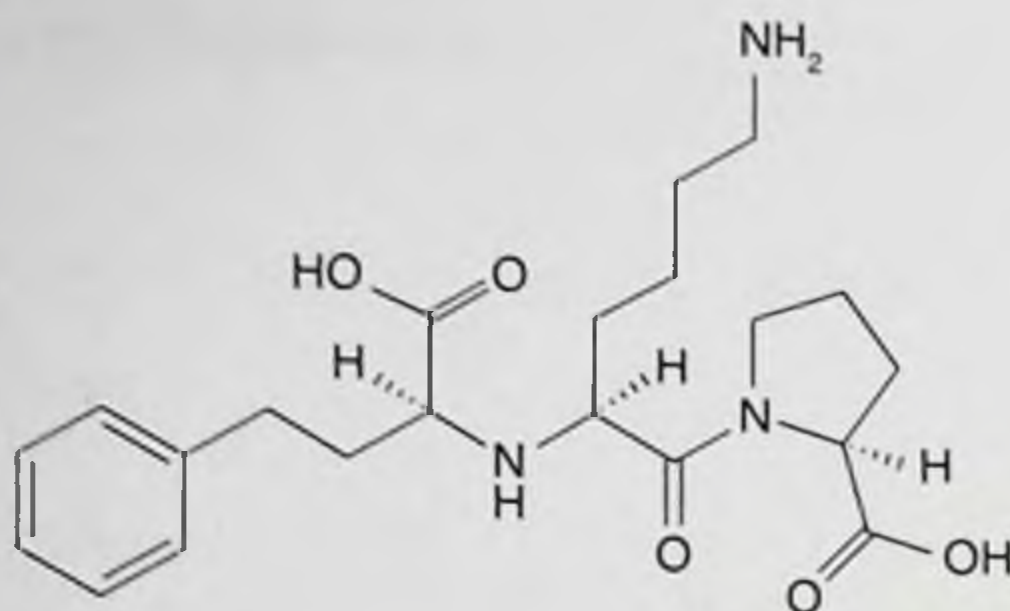


Fig. 16.20. (2S)-1-[(2S)-Amino-2-[[[(1S)-1-carboxy-3-phenylpropyl]amino]hexanoyl]pyrrolidine-2-carboxylic acid

Fosinopril (Monopril®)

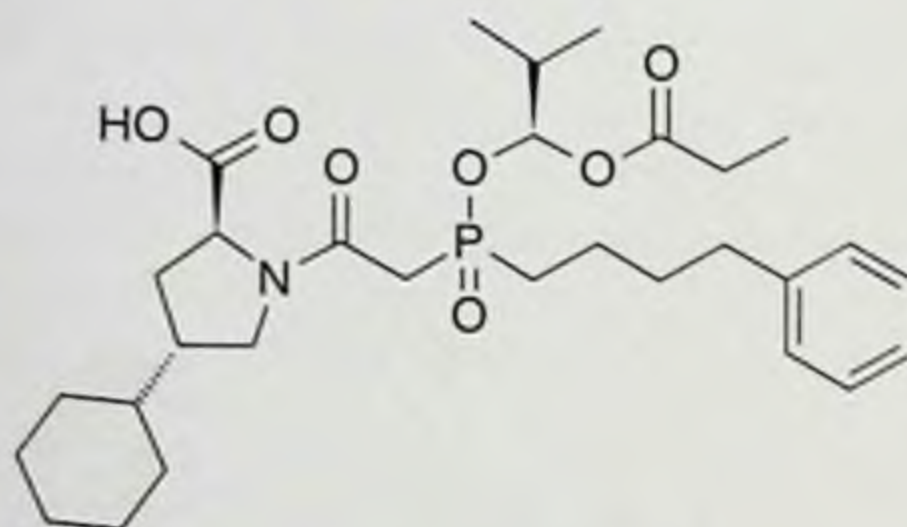


Fig. 16.21. (4S)-4-Cyclohexyl-1-[1R-[-(S)-1-oxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl]-L-proline propionate (as a sodium salt)

- ▶ Has a L-proline residue in the molecule (similar to lisinopril) and a phosphinyl group. Bioavailability: 40 %. Maximum blood concentrations are reached in 3 hours. Decreases the blood levels of endothelin, which is a potent vasoconstrictor and vascular remodeling factor. Long-acting.
- ▶ Pharmacologically active after metabolic conversion by hydrolysis in the liver and in the gastrointestinal mucosa to fosinoprilat. Excreted in the urine and bile. $T_{1/2}$: 11.5 hours. In patients with renal impairment, completely excreted in bile, which removes restrictions for use in these patients. For oral administration once daily.

Angiotensin receptor blockers (ARBs)

Angiotensin receptors are G-protein-coupled receptors, with AT II and its derivatives serving as their ligands.

ACE inhibitors do not block AT II biosynthesis completely. This is due to the fact that AT II formation in tissues is also regulated by other enzymes. Thus, the transition of AT I to AT II is associated with the enzyme chymase (serine protease), etc. For this reason, a more complete shutdown of the RAAS can only be achieved with ARBs..

The effects of AT II occur through specific, angiotensin receptors (Table 16.1). Two major subtypes of AT II receptors are AT_1 and AT_2 . AT_1 receptors are located predominantly in the vascular smooth muscles, heart, liver, adrenal cortex, kidneys, lungs, and in some areas of the brain. The highest number of AT_2 receptors is found in fetal tissue;

their number decreases in the postpartum period. In adults, they are mainly expressed in the cells of the heart, blood vessels, adrenal glands, kidneys, reproductive organs.

Classification

- ▶ Biphenyl tetrazole derivatives: losartan (Cozaar®)
- ▶ Biphenyl non-tetrazole compounds: telmisartan (Micardis®)
- ▶ Non-biphenyl non-tetrazole compounds: eprosartan (Teveten®)
- ▶ Non-heterocyclic compounds: valsartan (Diovan®)

Table 16.1. Effects of angiotensin receptor stimulation

AT ₁ receptors	AT ₂ receptors
Vasoconstriction	Vasodilation
Stimulation of synthesis, secretion of aldosterone, vasopressin, noradrenaline release	Natriuretic action
Tubular Na ⁺ reabsorption	Nitric oxide and prostacyclin release
Decreased renal blood flow	Antiproliferative action
Proliferation of vascular smooth muscle cells, myocardial hypertrophy	Stimulation of apoptosis
Inhibition of renin production	Differentiation and development of embryonic tissues

Mechanism of action: Affects the RAAS and sympathoadrenal system, which are the main neurohumoral regulators of vascular tone. These drugs block the AT II effects mediated through AT₁ receptors in blood vessels and adrenal glands, such as arterial vasoconstriction, Na⁺ and water retention, vascular and myocardial remodeling. In addition, they interact with presynaptic adrenergic receptors, which results in a significant decrease in the release of noradrenaline into the synaptic cleft and prevents sympathetic vasoconstriction.

ARBs are highly selective for AT₁ receptors (Fig. 16.22).

They inhibit the action of AT II on AT₁ receptors in blood vessels (dilates blood vessels) and the adrenal cortex (decrease aldosterone secretion) and eliminate other AT II effects. Blockade of AT₁ receptors is accompanied by activation of AT₂ receptors. The drugs contribute to the protective effects of AT II by enhancing its action on AT₂ receptors. They cause systemic vasodilation and TPR reduction without increasing HR; diuretic effect, antiproliferative action, primarily in the cardiovascular system, inhibitory action on abnormal remodeling of target organs. In addition, the mechanism of action contributes to this drug group’s good safety profile: the possibility of bradykinin accumulation and cough associated with it, which is often encountered when taking ACE inhibitors, is eliminated.

Pharmacological effects

- ▶ Antihypertensive
- ▶ Reduced platelet aggregation, decreased blood levels of triglycerides, total cholesterol, low-density lipoproteins, increased high-density lipoproteins
- ▶ Nephroprotective: decreased proteinuria, serum creatinine levels, hyperuricemia as a result of blockade in nephrocytes of transport systems involved in urate reabsorption
- ▶ Prevention of cerebral vascular remodeling, cerebral arterial dilatation and neuronal regeneration in the post-ischemic period.

Therapeutic indications: hypertension; renovascular hypertension; CHF caused by systolic and diastolic left ventricular dysfunction, including in patients after myocardial infarction; reduce the risk of stroke in patients with hypertension and left ventricular

hypertrophy; diabetic nephropathy (treatment and prophylaxis); microalbuminuria and proteinuria of non-diabetic etiology

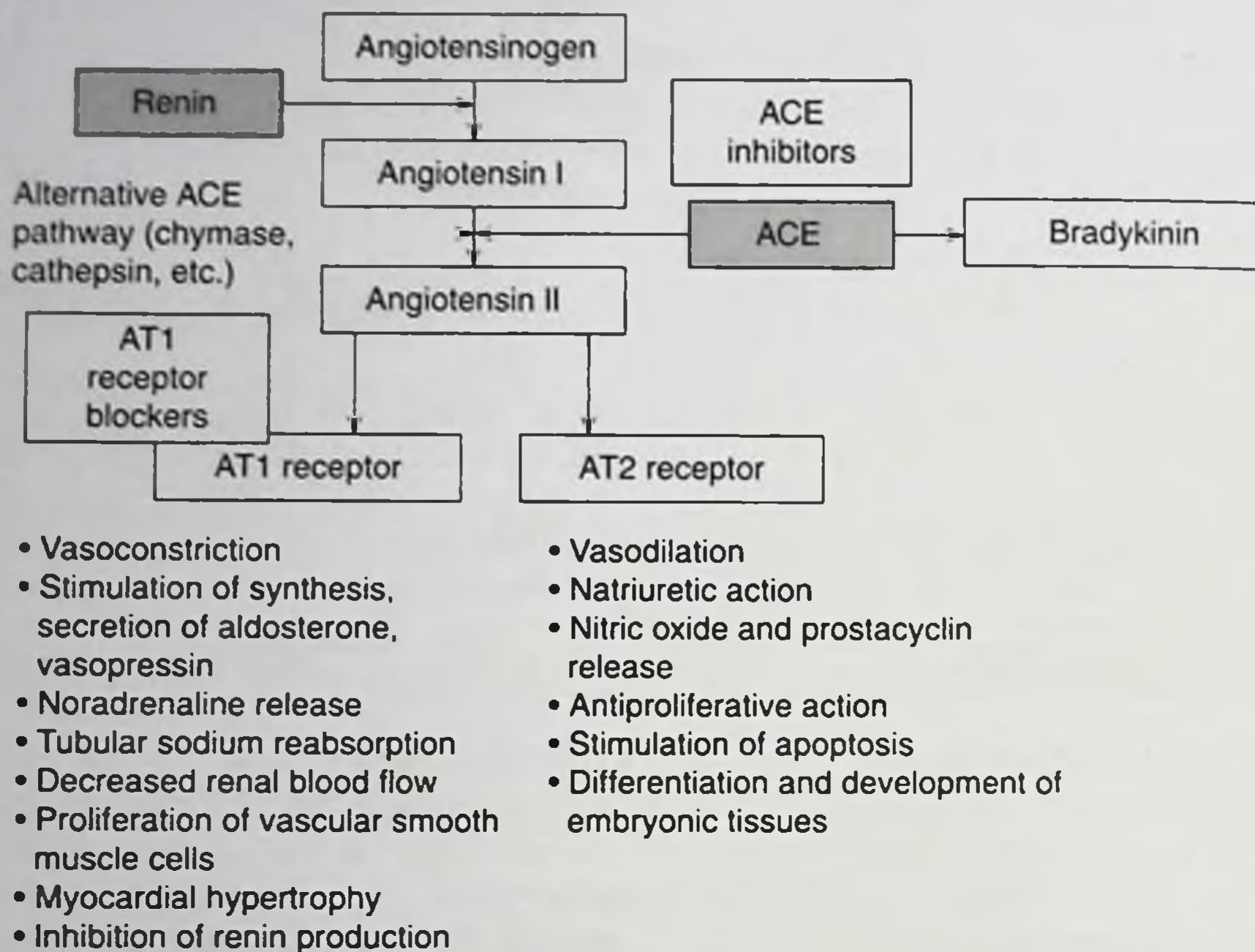


Fig. 16.22. Mechanism of action for angiotensin receptor blockers

Side effects (rare): hyperkalemia, arrhythmias, asthenia, diarrhea, taste disturbance, sleep disorders, peripheral neuropathy

Contraindications: hyperkalemia, bilateral renal artery stenosis, hypotension, pregnancy, breastfeeding, less than 18 years of age

Specifics of individual products

Losartan (Cozaar[®], Vasotens[®])

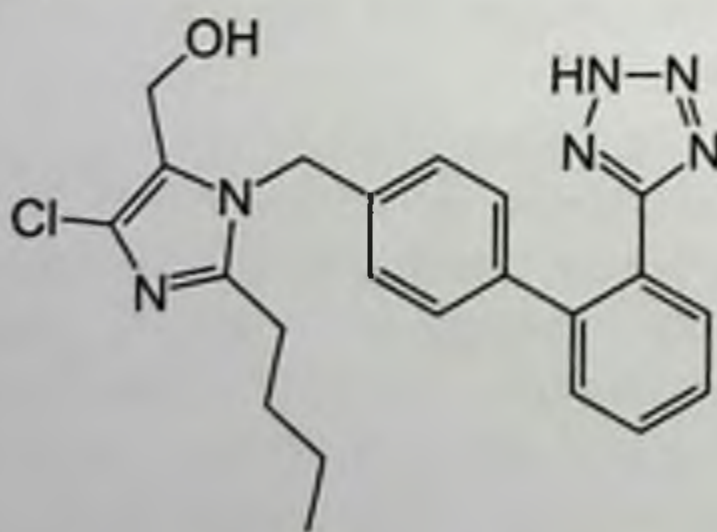


Fig. 16.23. 2-Butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-imidazol-5-methanol (as a potassium salt)

- ▶ Biphenyl tetrazole derivative, competitive AT II antagonist. Bioavailability: 33 % (first-pass effect). Maximum concentrations of losartan and its active metabolite are reached in 1 hour and 3–4 hours, respectively. Following a single dose, the antihypertensive action is maximal in 6 hours and then gradually decreases over 24 hours. A stable decrease in BP is observed by weeks 3–6 of treatment. Has an uricosuric action. Poorly crosses the BBB.
- ▶ Undergoes biotransformation by carboxylation due to the cytochrome P450 isoenzyme CYP2C9 to form the main metabolite (EXP3174), which is 10–40 times more active than the parent substance, as well as inactive metabolites. Excreted in the urine (35 %) and bile (60 %).
- ▶ $T_{1/2}$ of losartan: 1.5–2.0 hours, $T_{1/2}$ of the metabolite: 6–9 hours. For oral administration once daily.

Valsartan (Diovan®)

- ▶ Non-heterocyclic compound, its chemical structure is similar to losartan (tetrazolylphenyl-benzyl fragment) but contains an L-valine amino acid residue in the molecule; competitive AT II antagonist. Maximum blood concentrations are reached in 2 h, bioavailability: 25 %. Time of action: up to 24 hours.
- ▶ About 20 % undergoes biotransformation by hydrolysis to form an inactive metabolite (valeryl-4-hydroxyvalsartan). Excreted in bile (70 %) and in urine (30 %). $T_{1/2}$: 9 hours. For oral administration once daily.

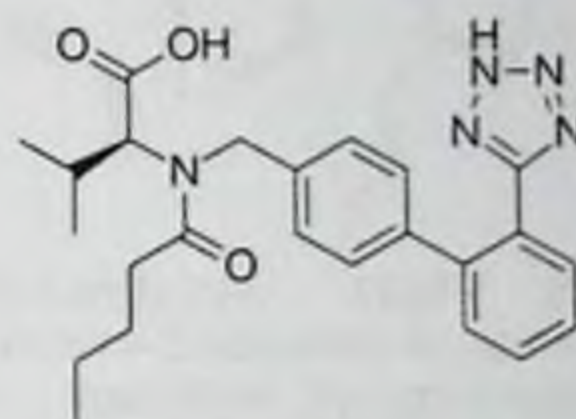


Fig. 16.24. (S)-N-(1-Carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl] amine

Telmisartan (Micardis®)

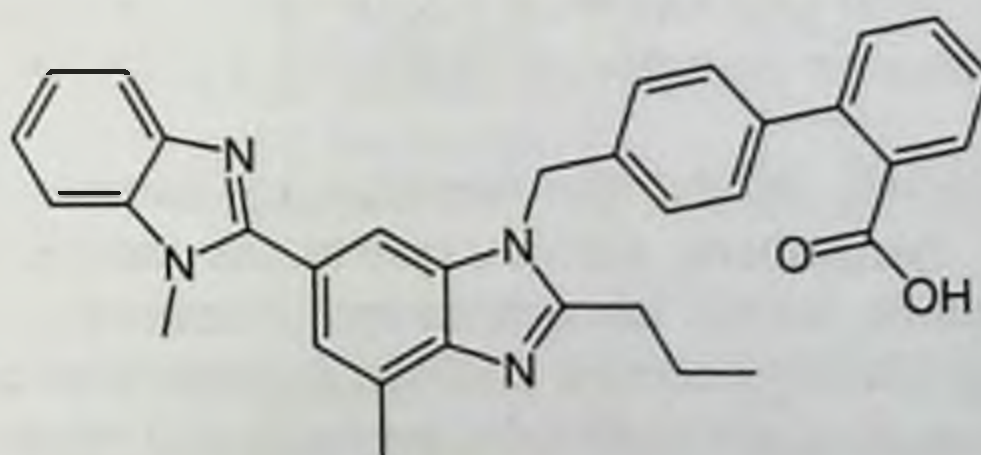


Fig. 16.25. 2-(4-([4-Methyl-6-(1-methyl-1H-1,3-benzodiazol-2-yl)-2-propyl-1H-1,3-benzodiazol-1-yl]methyl)phenyl)benzoic acid

- ▶ Highly selective (non-competitive) AT I receptor blocker; in addition to blocking the RAAS, it is an agonist of PPAR- γ receptors (peroxisome proliferator-activated receptors gamma), whose activation plays an important role in regulating glucose and insulin metabolism (increases tissue sensitivity to insulin and enhances glucose utilization in muscles and tissues), and produces anti-inflammatory, antioxidant, and antiproliferative effects.
- ▶ Biphenyl non-tetrazole compound, insurmountable (non-competitive) AT II antagonist. Bioavailability: 40–60 % (first-pass effect). The antihypertensive

effect occurs in 3 hours, lasts > 24 hours, and stabilizes 4–8 weeks into the treatment course.

- ▶ Metabolized in the liver by conjugation with glucuronic acid to form inactive acyl glucuronide. Excreted predominantly in bile (85 % unchanged telmisartan and 11 % glucuronide), renal excretion does not exceed 2 %. $T_{1/2}$: 20–30 hours. For oral administration once daily.

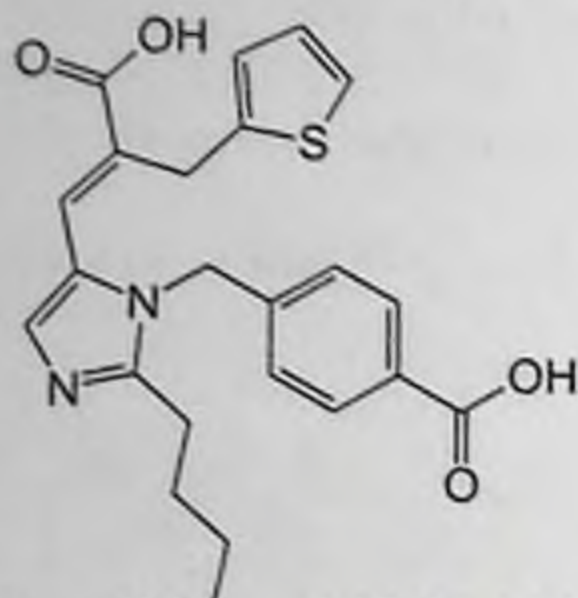


Fig. 16.26. 4-((2-Butyl-5-[2-carboxy-2-(thiophen-2-ylmethyl)ethyl-1-en-1-yl]-1H-imidazol-1-yl)methyl) benzoic acid

Eprosartan (Teveten[®])

- ▶ Non-biphenyl non-tetrazole compound, competitive AT II antagonist. Blocks norepinephrine release from sympathetic nerve terminals due to its action on presynaptic AT₁ receptors. Bioavailability: 13 %, maximum blood concentrations are reached in 1–2 hours.
- ▶ Undergoes minimal biotransformation in the liver. Excreted mainly as unchanged drug: 90 % in the bile, 7 % in the urine; less than 2 % is excreted in the urine as glucuronides. $T_{1/2}$: 5–9 hours. For oral administration once daily.

Vasopeptidase inhibitors

An alternative for blocking the RAAS is inhibiting neutral endopeptidase, which is responsible for the breakdown of natriuretic peptides. Natriuretic peptides inhibit RAAS activity, exhibit antiproliferative properties, and prevent hypertrophy, reduce plasma renin levels. The natriuretic peptide system is represented by three different isoforms: atrial natriuretic peptide, brain natriuretic peptide (which are mainly synthesized in cardiomyocytes) and type C endothelial natriuretic peptide (which is synthesized in endothelial cells and renal tubular cells). In terms of their biological functions, these natriuretic peptides are endogenous inhibitors of the RAAS and endothelin-1.

These neurohormones inhibit the secretion of aldosterone, renin and AT II and activate the sympathetic nervous system. As natural antagonists of the sympathoadrenal system, RAAS, vasopressin and aldosterone, natriuretic peptides cause peripheral vasodilation, increase diuresis, decrease arterial pressure, cardiac preload and afterload, decrease endothelin synthesis and release, slow the growth of smooth muscle, cardiac, endothelial cells and cardiomyocyte fibroblasts. The natriuretic peptide system is involved in metabolic regulation: lipid oxidation, adipocyte formation and differentiation, adiponectin activation, insulin secretion, and carbohydrate tolerance, which may help protect against metabolic syndrome.

Peptide degradation occurs under the influence of neutral endopeptidase (neprilysin), an enzyme that is detected in largest amounts in the epithelial cells of proximal tubules. Inhibition of neutral endopeptidase increases the concentrations of circulating natriuretic peptides in hypertension and heart failure, which are characterized by relative deficiency of these biologically active substances. Inhibition of neprilysin leads to potentiation of the natriuretic, diuretic, and vasodilating effects of endogenous natriuretic peptide and, as a result, to a decrease in BP. However,

neprilysin also contributes to the degradation of other vasoactive peptides: AT I, AT II, and endothelin-1.

The combination of the effects of ACE inhibitors and neprilysin inhibitors significantly potentiates hemodynamic and antiproliferative effects as a result of complementary actions, which resulted in the creation of drugs with a dual mechanism of action, i.e., vasopeptidase inhibitors. As a result, vasopeptidase inhibitors have a much greater potential for achieving the desired antihypertensive effect regardless of RAAS activity and Na^+ retention level, while providing some organ protection (regression of hypertrophy, albuminuria, vascular stiffness).

Omapatrilat[®] (Vanlev[®])

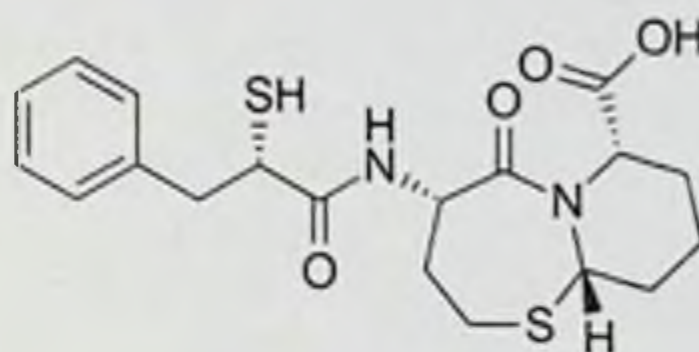


Fig. 16.27. (4S,7S,10aS)-Octahydro-4-[(S)- α -mercaptohydrocinnamamido]-5-oxo-7H-pyrido [2,1-b] [1,3] thiazepine-7-carboxylic acid

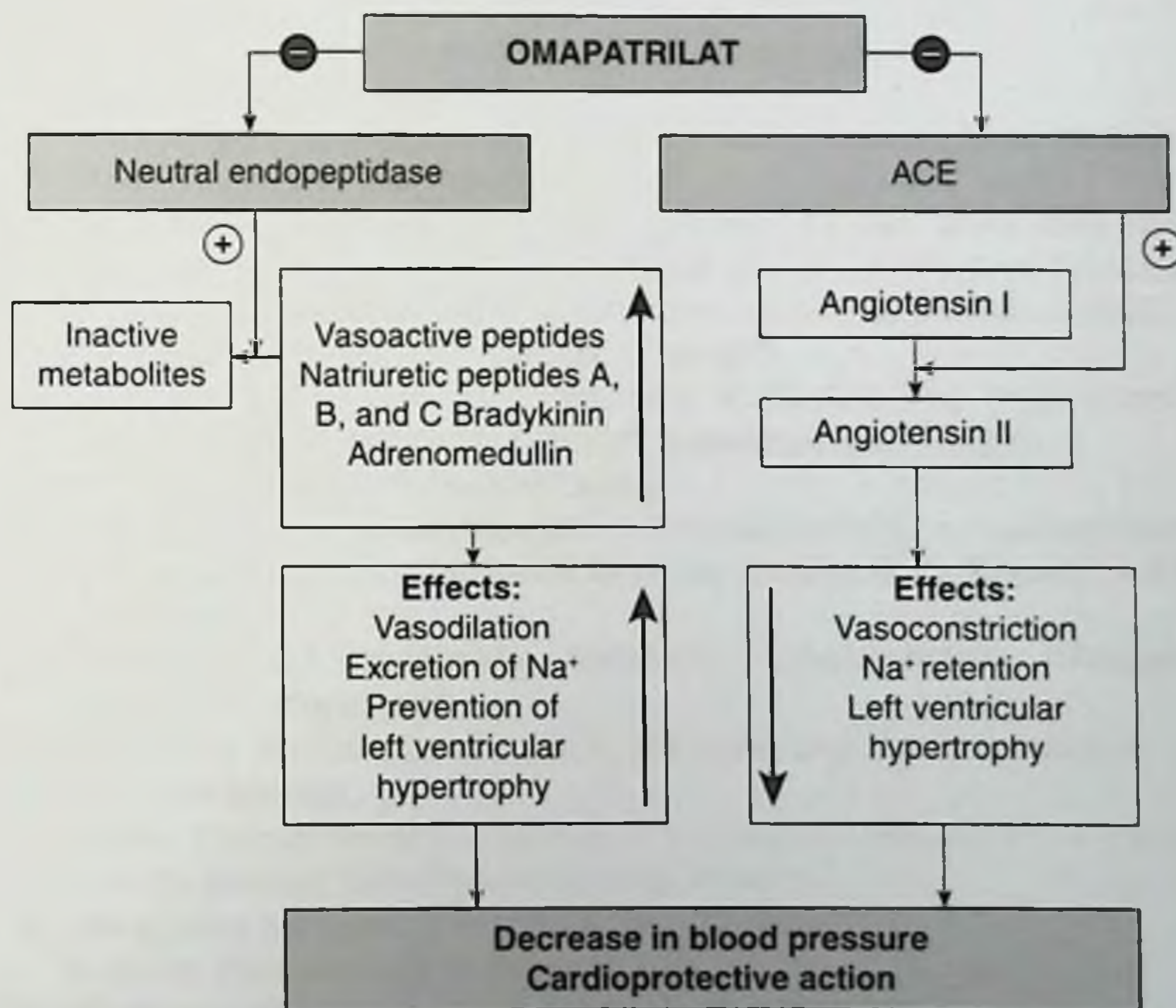


Fig. 16.28. Mechanism of action for omapatrilat[®]

Omapatrilat was discovered and developed by the pharmaceutical company Bristol Myers Squibb but clinical trials were unsuccessful due to safety concerns: increased effects on kinin levels with synergistic inhibition of ACE and neprilysin and potential angioedema, which became an obstacle for implementation in medical practice.

Mechanism of action: Omapatrilat selectively inhibits ACE and neprilysin (an enzyme produced by the vascular endothelium and involved in the degradation of natriuretic peptide as well as bradykinin), activates a large number of endogenous vasodilator peptides (including atrial natriuretic peptide, bradykinin, and adrenomedullin) and inhibits AT II formation (Fig. 16.28).

17. DIURETICS

Diuretics (derived from Greek *diures* — “urinate”) are drugs of different chemical structures that inhibit renal tubular reabsorption of water and salts and enhance their excretion in urine, increasing the urine production rate and consequently, reducing the fluid content in bodily tissues and cavities.

W. Withering, a British physician, first described using foxglove products to treat edema in 1785. Increased diuresis caused by mercury compounds was the basis for using calomel as a diuretic in the 19th century. In the early 20th century, xanthine derivatives (theophylline, caffeine) and urea were used. The discovery of the first antibacterial drugs (sulfonamides) triggered the development of modern diuretics. When acidosis was reported during the use of sulfonamides, research on this effect resulted in purposeful creation of the first diuretic — acetazolamide. Chemical modifications of benzyl sulfonamide resulted in the production of thiazide and then loop diuretics. Aldosterone antagonists were created in the 1960–70s..

Classification by predominant site of action (Fig. 17.1)

1. Drugs that increase the glomerular filtration rate or drugs with a concomitant diuretic effect
 - A. Xanthines: Aminophylline (Euphylline[•]), Theophylline[•]
 - B. Cardiac glycosides: Digoxin[•]
 - C. Herbal products: juniper fruits, bearberry leaves, horsetail herb, clusterberry leaves, birch buds, Laspenephryl[•]
2. Drugs acting on the entire renal tubule (proximal tubules, descending limb of Henle's loop, collecting duct) — osmotic: mannitol (Mannit[•]), urea (Uroderm[•])
3. Drugs acting on proximal convoluted tubules — carbonic anhydrase inhibitors: acetazolamide (Diacarb[•]), dorzolamide (Trusopt[•])
4. Drugs acting on the thick ascending limb of Henle's loop (loop diuretics): furosemide (Lasix[•]), torasemide (Diuver[•]), ethacrynic acid (Uregit[•])
5. Drugs acting mainly on early distal tubules
 - A. Thiazide: hydrochlorothiazide (Hypothiazide[•]), cyclopenthiazide (cyclomethiazide[•]) — excluded from the Russian State Register of Drug Products
 - B. Thiazide-like: indapamide (Arifon[•]), chlorthalidone (Oxodoline[•], Hygroton[•]), clopamide[•]
6. Drugs acting on late distal tubules and collecting ducts (potassium- and magnesium-sparing)
 - A. Sodium channel blockers: triamterene[•], amiloride (amiprazid[•]) — excluded from the Russian State Register of Drug Products
 - B. Aldosterone antagonists: spironolactone (verospiron[•])
Selective aldosterone receptor antagonist: eplerenone (Inspra[•])

Classification by chemical structure and mechanism of action

- I. Drugs that have a direct effect on renal tubular epithelial cells
 1. Substances containing a sulfonamide group:

- A. Thiazides: hydrochlorothiazide (Hypothiazide[®]), cyclopenthiiazide (cyclomethiazide[®]) — excluded from the Russian State Register of Drug Products
- B. Compounds of various structures: furosemide (Lasix[®]), torasemide (Diuver[®]), clopamide[®], chlorthalidone (Oxodoline[®], Hygroton[®])
- 2. Xanthines: Aminophylline (Euphylline[®]), Theophylline[®]
- 4. Pteridine derivatives: triamterene[®]
- 5. Pyrazinoylguanidine derivatives: amiloride (amiprazid[®]) — excluded from the Russian State Register of Drug Products
- II. Aldosterone antagonists: spironolactone (verospiron[®])
Selective aldosterone receptor antagonist: eplerenone (Inspra[®])
- III. Osmotically active diuretics: mannitol (Mannit[®]), urea (Uroderm[®])

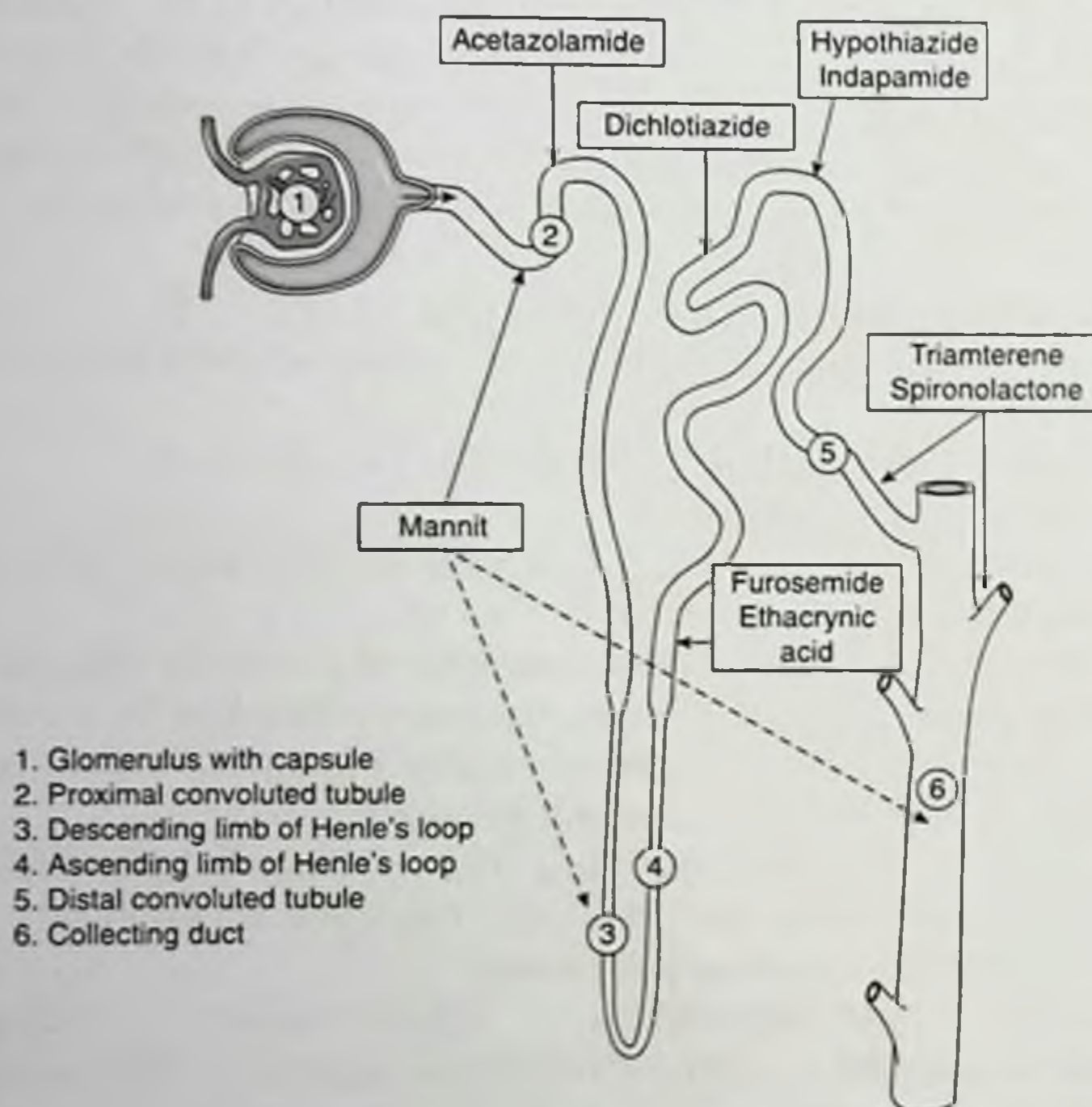


Fig. 17.1. Site of action of diuretics (D. A. Kharkevich, 2021)

Classification by strength of diuretic action (Na^+ excretion fraction given in parentheses):

- ▶ Highly active (15–25%) — loop diuretics
- ▶ Moderately active — osmotics (5–8%), thiazides, thiazide-like diuretics (5–10%)
- ▶ Weak — dimethylxanthines, carbonic anhydrase inhibitors, potassium- and magnesium-sparing (3–5%)

By nature of diuretic effect: diuretics are divided into saluretics, potassium- and magnesium-sparing, and hydrouretics (osmotic).

By the rate of onset and duration of diuretic action:

- ▶ Rapid and short-term diuretic effect: osmotic [mannitol (Mannit®)] and highly active (furosemide)
- ▶ Moderate onset and duration of action: dimethylxanthines, carbonic anhydrase inhibitors, thiazides, potassium- and magnesium-sparing (triamterene, amiloride)
- ▶ Delayed and prolonged diuretic effect — thiazide-like, potassium- and magnesium-sparing (spironolactone)

Therapeutic indications: edema in cardiac, liver and kidney failure; cerebral, pulmonary, laryngeal edema; hypertension; decontamination of infectious, toxic conditions (forced diuresis); glaucoma; epilepsy; diabetes insipidus

Basic anatomy and physiology of the urinary system

The structural and functional unit of the kidneys — nephron — is the point of action of diuretics. The nephron is a unit, various parts of which differ not only functionally, but also morphologically. Its structure includes a proximal section, which includes proximal convoluted and straight tubules; a distal section, which is divided into the ascending limb of Henle's loop and convoluted tubules; and collecting ducts (Fig. 17.2). Three main processes of urine production occur in the nephron: filtration, tubular reabsorption, and secretion (Fig. 17.3).

Water and low molecular weight plasma components cross the glomerular filter because of the difference between the blood hydrostatic pressure within the glomerular capillaries (70 mm Hg), oncotic pressure exerted by plasma proteins (30 mm Hg) and capsular hydrostatic pressure (20 mm Hg). Filtration occurs only if the blood pressure within the glomerular capillaries exceeds the sum of the oncotic pressure exerted by plasma proteins and the capsular hydrostatic pressure. The glomerular filter is less permeable for high-molecular-weight substances (proteins with a high relative molecular weight and lipids). Consequently, filtration produces about 170 liters of glomerular filtrate.

Reabsorption and secretion occur all along the nephron: in the proximal tubules, Henle's loop, distal tubules, and the collecting ducts. Glomeruli filter blood plasma through capillary membranes and nephron capsules at a rate of 120 mL/min. In the proximal convoluted tubules, 65% of ultrafiltrate is reabsorbed; Na^+ , K^+ , Ca^{2+} (70%), Mg^{2+} (20–25%), HCO_3^- , phosphates (80%), amino acids, glucose, vitamins are reabsorbed into blood, water is absorbed along the osmotic gradient. The tubular fluid in the late proximal tubule resembles a simple NaCl solution. Organic acid (uric acid, n-aminohippuric acid) and diuretic secretory systems are located in the middle of proximal tubules. Organic bases (creatinine, choline) are secreted in the upper and middle segments. Organic anion transport proteins are involved in the secretion mechanism.

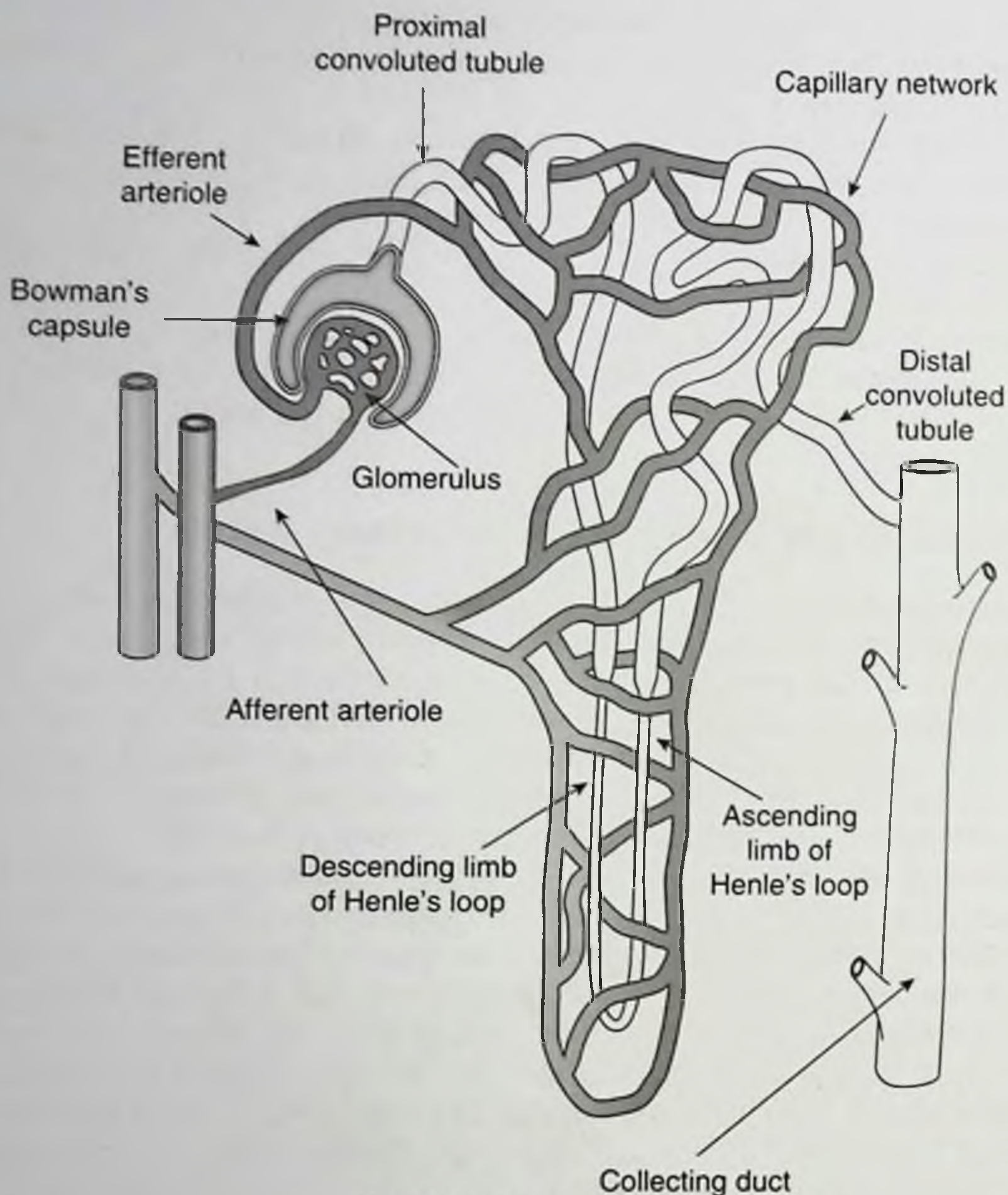


Fig. 17.2. Nephron structure

In the descending limb of the Henle's loop, water is reabsorbed along the osmotic gradient into the hyperosmotic renal medulla. The tubular fluid becomes hyperosmotic. Na^+ and urea are reabsorbed in the thin ascending limb. Na^+ , K^+ , Ca^{2+} (20%), and Mg^{2+} (70–75%) are reabsorbed in the thick ascending limb of the loop. About 25% of the tubular fluid is reabsorbed in Henle's loop.

In the distal convoluted tubules, Na^+ , Ca^{2+} are reabsorbed without water entering the blood, while K^+ and H^+ are secreted. Tubular fluid retains the hypoosmoticity that originated in the ascending limb. The following hormones are involved in reabsorption of ions in distal convoluted tubules: the mineralocorticoid aldosterone increases Na^+ reabsorption and stimulates K^+ and H^+ secretion; parathyroid hormone increases Ca^{2+} reabsorption through apical membrane channels and $\text{Na}^+/\text{Ca}^{2+}$ exchange in the basolateral membrane.

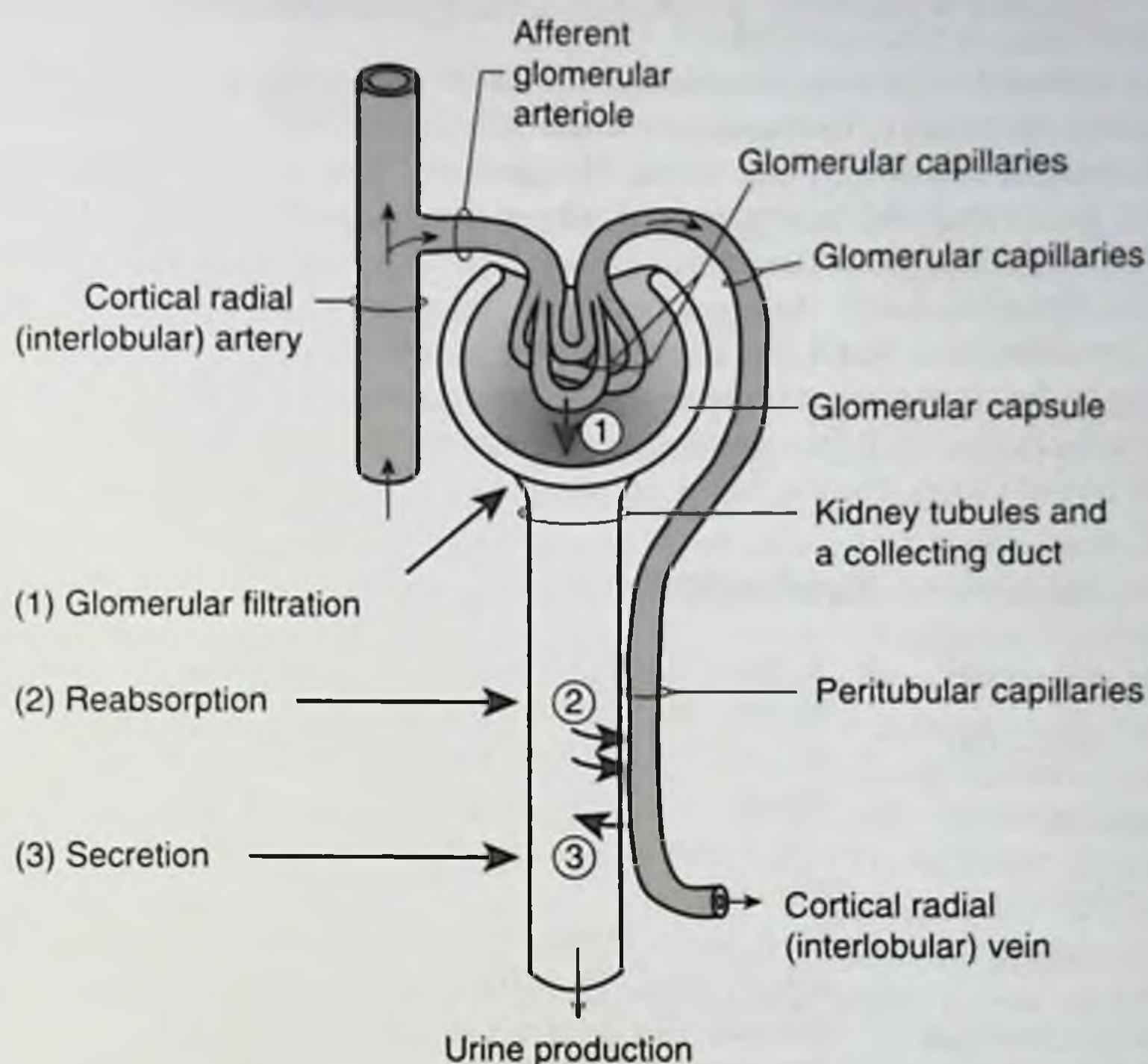


Fig. 17.3. Process of urine formation (Smith L.A., Marieb E., 2018)

In the collecting ducts under the influence of vasopressin (antidiuretic hormone), water is reabsorbed into the hyperosmotic environment of the renal medulla, aldosterone-mediated Na^+ reabsorption, K^+ and H^+ secretion continue, Mg^{2+} (5%) is absorbed. The urine becomes hyperosmotic. The tubuloglomerular feedback mechanism regulates urine production. When the concentration of NaCl in the tubular fluid increases, this excites macula densa receptors (a region of densely packed columnar epithelial cells in the distal convoluted tubule of the nephron adjacent to the renal corpuscle) which causes adenosine secretion, which consequently limits filtration by narrowing the afferent glomerular arteriole.

Specifics of individual products by group

Drugs acting on the entire renal tubule

Osmotic diuretics are drugs that have the osmotic activity of aqueous solutions. The diuretic effect is determined by two properties:

- ▶ as osmotically active compounds, they are capable of attaching numerous water molecules to their molecules;
- ▶ as hydrated molecules, osmotic diuretics are filtered in the renal glomeruli, passing along the length of the nephron without being reabsorbed.

Mechanism of action: Once in the bloodstream, they are combined with water, filtered, pass along the nephron, and take a certain amount of water with them. By removing water from the cells, they increase the volume of extracellular fluid, reducing blood viscosity. As a consequence, renal blood flow increases, including in the medulla, and NaCl is washed with the blood. Medulla osmolality decreases resulting in decreased water reabsorption in the thin descending limb of Henle's loop, which reduces the NaCl concentration in the tubular fluid entering the thin ascending limb of Henle's loop. Passive NaCl reabsorption is consequently inhibited.

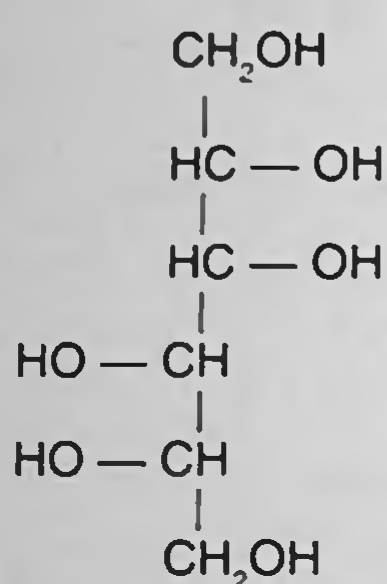


Fig. 17.4. (2R,3R,4R,5R)-Hexan-1,2,3,4,5,6-hexol

Mannitol (Mannit[®])

- ▶ A hexahydric sugar alcohol that does not pass through blood-tissue barriers (except for the glomerular).
- ▶ It significantly increases blood osmotic pressure; circulating blood volume increases at first, but then, as the diuretic effect develops, it decreases. It does not affect glomerular filtration.
- ▶ Diuresis increases after 15–20 min, the duration of action is 4–5 hours. T_{1/2} is 100 min. It is excreted unchanged by the kidneys. For intravenous administration.

Therapeutic indications: cerebral edema, status epilepticus, acute glaucoma attack, surgery with extracorporeal circulation, acute liver failure, post-transfusion complications caused by incompatible blood transfusion, acute poisoning with barbiturates and other substances (forced diuresis)

Side effects: dehydration (dry skin and mucous membranes, dyspepsia, myasthenia, seizures, thirst, hallucinations, BP decrease), electrolyte imbalance, tachycardia, chest pain, thrombophlebitis, allergic reactions

Contraindications: organic kidney injury, congestive heart failure, hemorrhagic stroke, subarachnoid hemorrhage, severe forms of dehydration, hyponatremia, hypochloremia, hypokalemia, acute tubular necrosis, history of allergic reactions

Urea

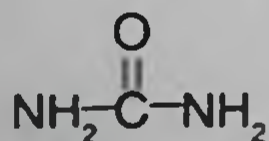


Fig. 17.5. Carbonic acid diamide (urea)

Currently used only topically in dermatology; available as an ointment: rea (Uroderm[®]), as part of combination products: Comfoderm M2[®] (methylprednisolone aceponate, urea); Fungoterbin Neo[®] (terbinafine, urea).

Drugs acting predominantly on proximal convoluted tubules

Carbonic anhydrase inhibitors

Acetazolamide (Diacarb[®])

- ▶ Systemic carbonic anhydrase inhibitor with weak diuretic activity. Diuretic effect occurs after 2 hours, reaches a maximum after 6 hours and lasts 12 hours.
- ▶ Acetazolamide is not biotransformed ($T_{1/2}$ is 6–9 hours); it is excreted in urine as unchanged drug. For oral administration 1–2 times daily.

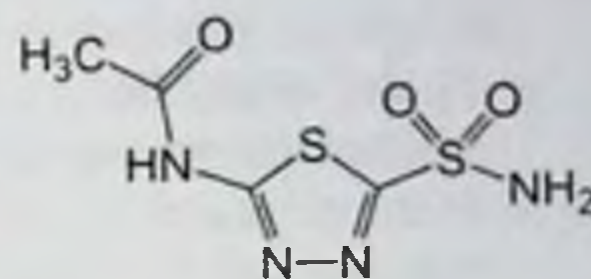


Fig. 17.6. N-[5-(Amino sulfonyl)-1,3,4-thiadiazol-2-yl] acetamide

Carbonic anhydrase accelerates hydration and carbonic acid dehydration reactions by a factor of 1000. Carbonic anhydrase reabsorption of Na^+ has several stages: antiport occurs in the nephrocyte apical membrane bringing Na^+ in the cells and pushing H^+ out into the tubular fluid; carbonic acid is formed in the urine: $\text{H}^+ + \text{HCO}_3^- \rightarrow \text{H}_2\text{CO}_3$; brush border carbonic anhydrase catalyzes the dehydration of carbonic acid to release carbon dioxide: $\text{H}_2\text{CO}_3 \rightarrow \text{H}_2\text{O} + \text{CO}_2$; as a lipophilic substance, carbon dioxide is reabsorbed into nephrocytes and combines with water in their cytoplasm thanks to cytoplasmic isozyme carbonic anhydrase: $\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3$; carbonic acid in cells dissociates into ions: $\text{H}_2\text{CO}_3 \rightarrow \text{H}^+ + \text{HCO}_3^-$; exchanged with Na^+ , H^+ cations exit into tubular fluid; HCO_3^- anions are excreted into blood through the basal membrane by Na^+ symporter. Urine becomes acidic and an alkaline buffer enters the blood to maintain the acid-base balance.

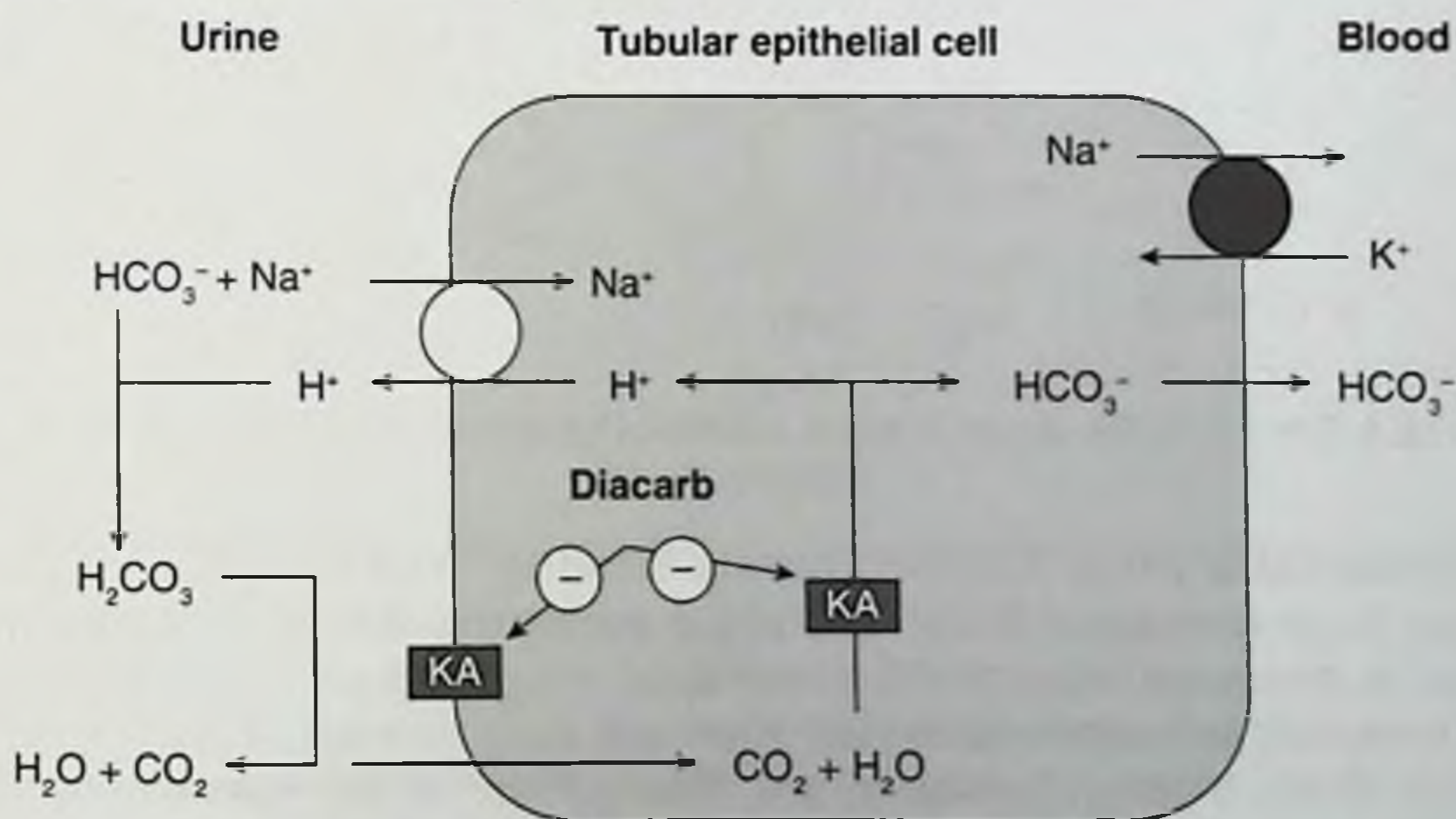


Fig. 17.7. Mechanism of action of Diacarb. CA — carbonic anhydrase

Mechanism of diuretic effect: It inhibits the carbonic anhydrase enzyme, reducing the production of carbonic acid and decreasing HCO_3^- and Na^+ tubular reabsorption; urinary excretion of Na^+ , HCO_3^- increases, elevating urine pH (Fig. 17.7). It increases

Na^+ excretion up to 3–5%, K^+ by up to 70%, HCO_3^- by up to 35%; it significantly increases the excretion of phosphates (poorly reabsorbed hydrogen phosphates are formed in alkaline urine), slightly stimulates excretion of Cl^- and has no effect on Ca^{2+} or Mg^{2+} excretion. Uric acid secretion is impaired during long-term use.

Diacarb inhibits carbonic anhydrase in other tissues:

- ▶ In the ciliary body of the eye, it inhibits the production of aqueous humor (intraocular pressure decreases by 40–60% on average)
- ▶ In the pia mater, it inhibits cerebrospinal fluid production (decreases intracranial pressure and neuronal excitability).

Therapeutic indications: edema (mild to moderate severity, in combination with alkalosis); epilepsy (in combination therapy), disruptions in cerebrospinal fluid flow, intracranial hypertension (in combination therapy); glaucoma (in combination therapy)

Side effects: metabolic acidosis, hypokalemia, kidney stones, allergic reactions

Contraindications: acidosis, sulfonamide intolerance, hypokalemia, Addison's disease, severe liver and kidney failure, uremia, pregnancy, breastfeeding period

Dorzolamide (Trusopt®)

- ▶ Carbonic anhydrase inhibitor for topical administration. It inhibits intraocular fluid production by 50% after 2 hours of use as eye drops. Duration of effect is 12 hours.
- ▶ Metabolized to form N-desethyl dorzolamide. After completion of the treatment course, $T_{1/2}$ is about 4 months. Dorzolamide and its metabolite are excreted in urine. Administered 2–3 times daily.

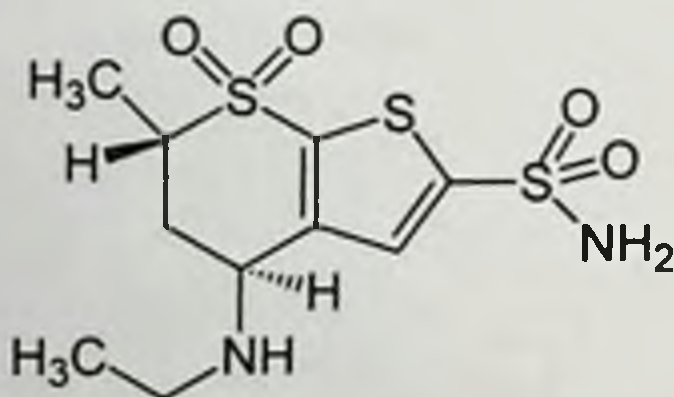


Fig. 17.8. 4-(Ethylamino)-5,6-dihydro-6-methyl-4-N-thieno[2,3-b]-thiopyran-2-sulfonamide-7,7-dioxide (as hydrochloride)

Mechanism of action: It inhibits carbonic anhydrase in the ciliary body and helps reduce the production of HCO_3^- ions with a consequent slowing of Na^+ and fluid transport, decreasing intraocular fluid secretion.

Therapeutic indications: open-angle glaucoma

Side effects: transient burning in eyes, allergic conjunctivitis, superficial punctate keratitis

Contraindications: sulfonamide intolerance, severe kidney failure, pregnancy, breastfeeding

Drugs acting predominantly on the thick ascending limb of Henle's loop (loop diuretics)

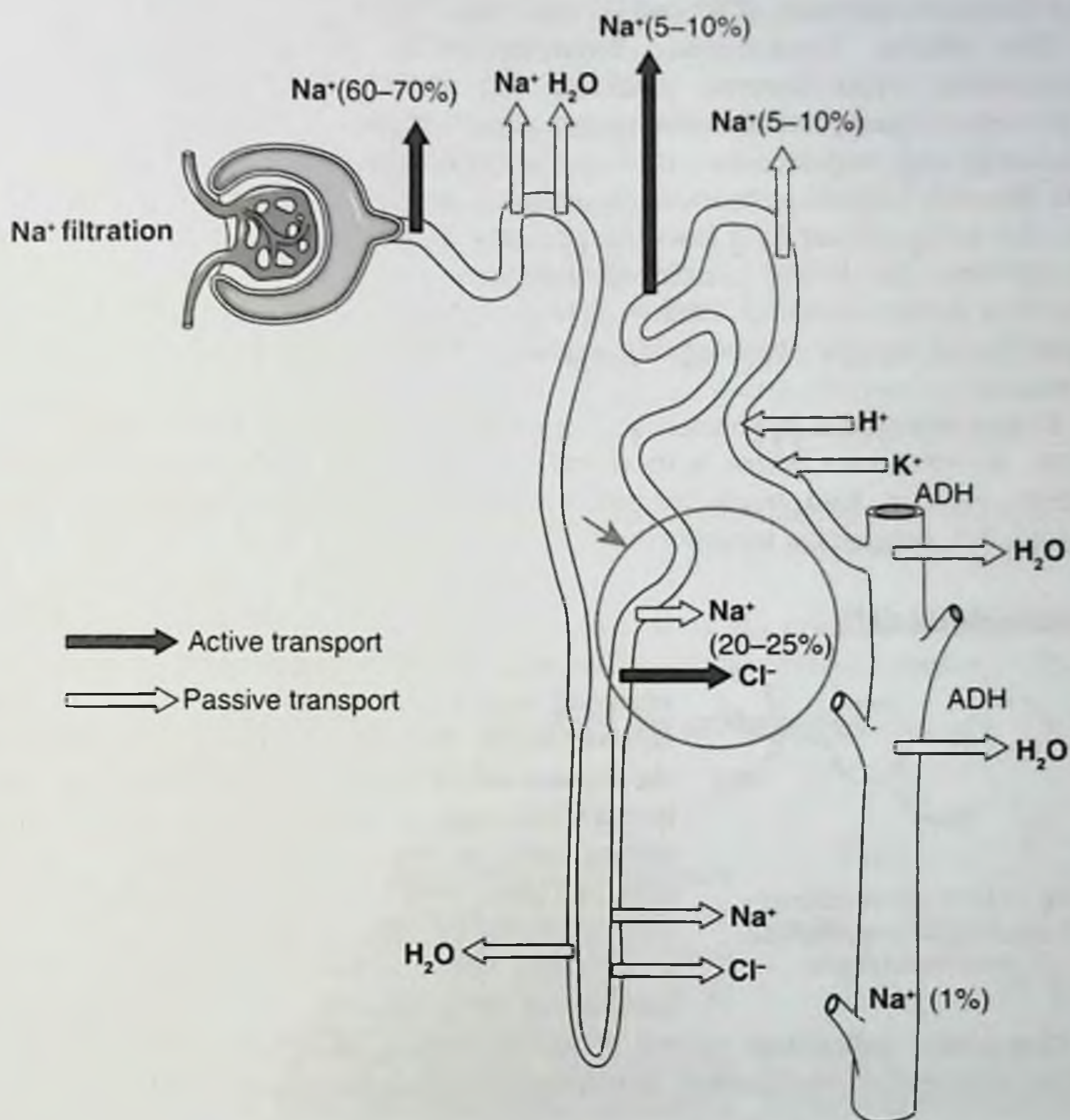


Fig. 17.9. Mechanism of action of loop diuretics. The arrows indicate where the drugs act.

Mechanism of action: As organic acids, they are secreted from the proximal convoluted tubules via the organic anion transporter 3, enter the tubular fluid and because of its flow, reach the thick ascending limb of Henle's loop. In the nephrocyte apical membrane, they inhibit Na^+ , K^+ , 2Cl^- symport (coupled transport of two different organic molecules or ions across the cell membrane due to active transport by specific proteins located inside the membrane) by blocking the Cl^- binding site on the symporter protein. Under the influence of loop diuretics, the synthesis of PGE and prostacyclin from arachidonic acid increases, renal arteries are dilated and blood supply to the kidneys improves. In nephrocytes, diuretics inactivate $\text{Na}^+/\text{K}^+ \text{--ATPase}$ in the basal membrane, microsomal Ca^{2+} -dependent ATPase, adenylate cyclase, PDEase, PGDH, and also impair tissue respiration. The excretion of Na^+ (15–25%),

K^+ , H^+ , Ca^{2+} , Mg^{2+} , Cl^- increases (Fig. 17.9). In the lumen of the ascending limb, under the influence of loop diuretics, the positive potential caused by the normal cyclic transport of K^+ ions decreases, which stimulates the excretion of Mg^{2+} and Ca^{2+} ions. Excessive secretion of K^+ and H^+ ions

Side effects: hypokalemia, hypomagnesemia, hypocalcemia (except for torasemide); hypochloremic alkalosis; dehydration, hypovolemia; orthostatic hypotension; tachycardia; ototoxicity; hyperuricemia with gout exacerbation (decreased uric acid secretion in proximal convoluted tubules due to competition with diuretics for binding to transport proteins, increased reabsorption of uric acid in response to significant fluid loss) (furosemide); hyperglycemia (transport of glucose through liver and skeletal muscle cell membranes and its intracellular utilization are impaired, insulin secretion is reduced) [except ethacrynic acid (Uregit[®])]; interstitial nephritis (furosemide, torasemide); muscle weakness; allergic reactions; dyspeptic disorders

Contraindications: hypokalemia, dehydration, alkalosis, hepatic precoma and coma, severe kidney failure with anuria, mechanical obstruction of urinary tract, diabetes mellitus, gout, treatment with antibiotics — aminoglycosides etc. (increased ototoxicity), pregnancy, breastfeeding

Furosemide (Lasix[®])

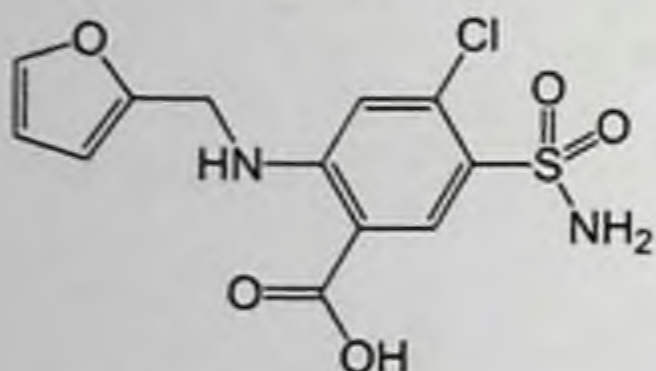


Fig. 17.10. 5-(Aminosulfonyl)-4-chloro-2[(2-furanylmethyl)] aminobenzoic acid

Contains a sulfonamide group, crosses the placental barrier and is excreted into breast milk. Bioavailability: 60–70%. After oral administration, the diuretic effect occurs in 15–30 minutes, reaches its maximum in 1–2 hours and lasts 6–8 hours. After intravenous injection, it occurs in 5 min, peaks in 30 min, and lasts 2 hours. $T_{1/2}$ is 0.5–1.0 hours. Excreted mainly (88%) by the kidneys unchanged and as metabolites; 12% — in bile. For oral, intramuscular, intravenous administration.

Therapeutic indications: edema of various origins, pulmonary edema, cerebral edema, eclampsia, hypertension, hypertensive crisis, hypercalcemia, forced diuresis

Torasemide (Diuver[®])

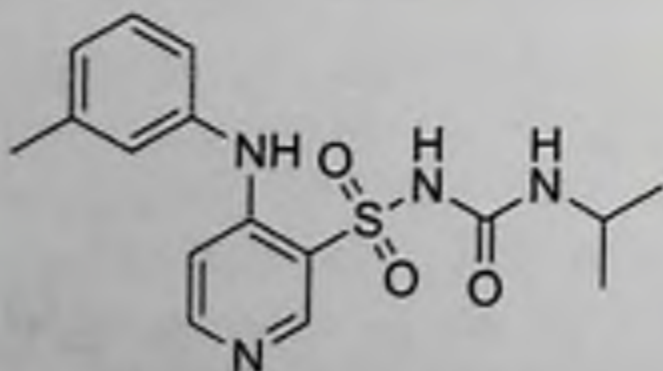


Fig. 17.11. N-[(Isopropylamino) carbonyl]-4-[(3-methylphenyl) amino]pyridine-3-sulfonamide

- Contains a sulfonamide group and exerts a longer action than furosemide. It also interferes with the effects of aldosterone — it inhibits secretion of this hormone by the adrenal cortex and disrupts its binding to receptors in the distal tubule's nephrocytes. Hypokalemia develops to a lesser extent.
- Bioavailability: 80–90%. The maximum effect develops 2–3 hours post-dose and lasts 8–10 hours. $T_{1/2}$ is 3.5 hours. It is metabolized in the liver,

excreted in bile (about 80%) and urine (about 20%). For oral administration once daily.

Therapeutic indications: edema of various origins (in congestive heart failure, liver, kidney, and lung diseases), hypertension

Ethacrynic acid (Uregit*)

- ▶ A prodrug, dichlorophenoxyacetic acid derivative. The active compound is formed after the methylene group of ethacrynic acid binds to the sulfhydryl group of cysteine. Its diuretic activity is inferior to furosemide. Diuretic effect starts 30–60 min post-dose, reaching a maximum in 2 hours and lasts 6–9 hours. The effect is more pronounced when not taken daily, but with a 1 or 2 day break between doses. Does not cross the BBB.
- ▶ Bioavailability is absolute. $T_{1/2}$: 1–4 hours. Excreted mainly in urine as unchanged drug (60–80 %) and as conjugates (20–30 %); 20–30 % is excreted in bile. For oral and intravenous administration.

Therapeutic indications: edema of various origins (in congestive heart failure, hepatic cirrhosis, nephrotic syndrome), hypertension (as combined therapy)

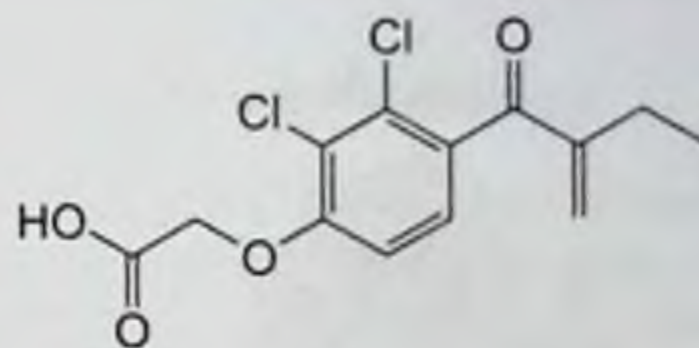


Fig. 17.12. 2,3-Dichloro-4-(2-methylene-1-oxobutyl)-phenoxyacetic acid

Drugs acting predominantly on early distal tubules (thiazide and thiazide-like)

Hydrochlorothiazide (Hypothiazide*)

- ▶ A thiazide diuretic, benzothiadiazine derivative with a sulfonamide group. It is a weak acid and, like loop diuretics, it is secreted from the proximal convoluted tubules (via the organic anion transporter 1); its diuretic effect is moderately pronounced.
- ▶ Bioavailability: 60–80%. Crosses the placental barrier and is excreted into breast milk. The diuretic effect develops in 30–60 min, reaches its maximum in 4–6 hours, and lasts 6–12 hours. $T_{1/2}$ for patients with normal renal function is 6.4 hours, $T_{1/2}$ for patients with moderate kidney failure is 11.5 hours. Excreted in urine as unchanged drug. For oral administration once daily.

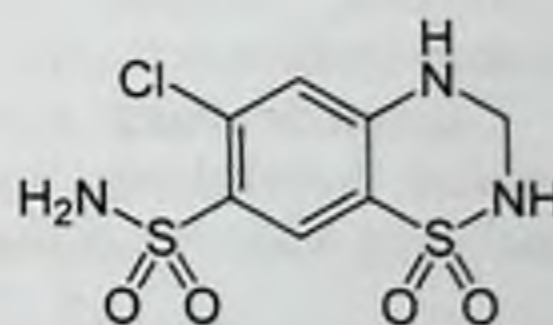


Fig. 17.13. 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide

Mechanism of action: Because of the tubular fluid flow, it reaches the early distal convoluted tubules. It suppresses Na^+ , Cl^- symport in the apical membrane by binding to the Cl^- binding site on the symporter protein. Moderately inhibits carbonic anhydrase in the proximal convoluted tubules. Under its influence, the excretion of Na^+ (5–10%), K^+ , H^+ , Mg^{2+} , Cl^- increases, the excretion of HCO_3^- and phosphates increases slightly, and Ca^{2+} is retained in blood. Ca^{2+} reabsorption is enhanced in the proximal convoluted tubules and Henle's loop through the $\text{Na}^+/\text{Ca}^{2+}$ exchanger. Hypercalcemia suppresses parathyroid hormone secretion by the parathyroid

glands, which impairs Mg^{2+} absorption in the thick ascending limb. It reduces BP in hypertension because it decreases the circulating blood volume (Fig. 17.14).

Therapeutic indications: hypertension (both as monotherapy and in combination therapy), edema of various origins, reduction of symptomatic polyuria in nephrogenic diabetes insipidus, prevention of calcium-phosphate stones in the urinary tract in hypercalciuria, glaucoma (in combination therapy)

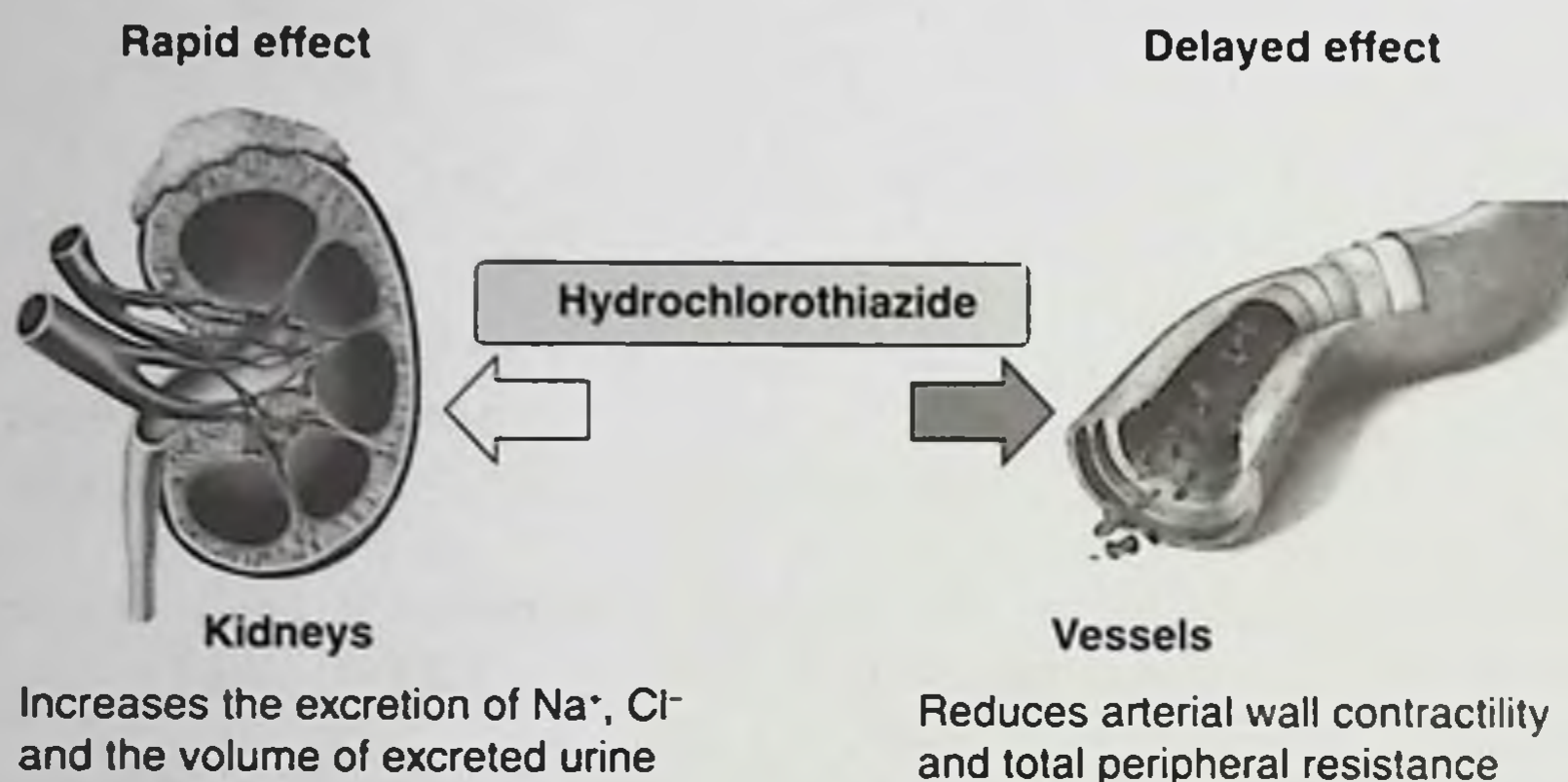
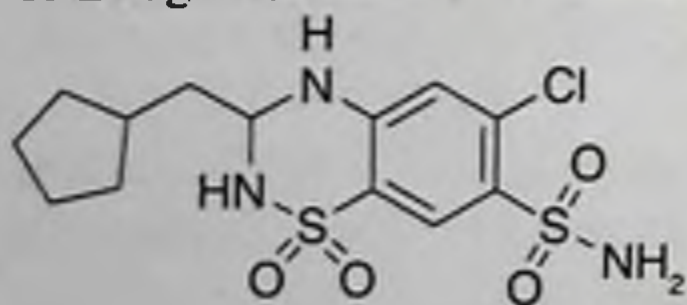


Fig. 17.14. Mechanism of action of hydrochlorothiazide

Side effects: hypokalemia, hypomagnesemia, hypercalcemia, hypochloremic alkalosis, hyperuricemia, hypotension, hyperglycemia, dizziness, headache, xanthopsia, fatigue, dyspeptic disorders, skin rash, photosensitization, thrombocytopenia. Serum lipid levels may increase when high doses are administered.

Contraindications: anuria, severe kidney failure, severe liver failure, diabetes mellitus, hypokalemia, hyponatremia, hypercalcemia, gout, adrenal insufficiency (including Addison's disease), pregnancy (1st trimester), breastfeeding

Cyclopenthiazide (cyclomethiazide[®]) — excluded from the Russian State Register of Drug Products. It is available abroad under the trade names Navidrex[®], Salimid[®].



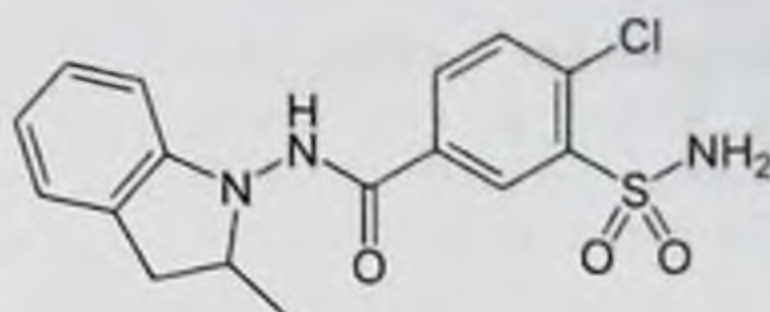
Indapamide (Arifon⁺)

Fig. 17.16. 3-(Aminosulfonyl)-4-chloro-N-(2,3-dihydro-2-methyl-1H-indol-1-yl)benzamide

- ▶ A thiazide-like diuretic, it contains a sulfonamide group and crosses blood-tissue barriers, including the placental one. Its pharmacological properties are similar to those of thiazides. Does not affect plasma lipid content, carbohydrate metabolism (including in diabetic patients). Hypotensive effect develops by the end of the first week of use, lasts for 24 hours after a single dose.
- ▶ Bioavailability: 93%. Metabolized in the liver. $T_{1/2}$: 18 hours. 60–80% is excreted by the kidneys as metabolites (about 7% is excreted unchanged), 20% is excreted in bile. For oral administration once daily.

Mechanism of action: It inhibits reabsorption of Na^+ ions in the cortical segment of Henle's loop, increases urinary excretion of Na^+ , Cl^- , Ca^{2+} , Mg^{2+} ions and K^+ ions to a lesser extent. It reduces the vascular wall's sensitivity to norepinephrine and angiotensin II; stimulates the synthesis of PGE₂, inhibits the flow of Ca^{2+} ions into vascular smooth muscle cells and thus reduces total peripheral resistance.

Therapeutic indications: hypertension

Side effects: hypokalemia, hypochloremia, hyponatremia, hypotension, arrhythmia, nausea, vomiting, headache, dizziness, allergic reactions

Contraindications: stroke, anuria, severe kidney failure, severe liver failure, hypokalemia, pregnancy, breastfeeding, less than 18 years of age

Chlorthalidone (Oxodoline⁺, Hygroton⁺)

- ▶ Thiazide-like diuretic that contains a sulfonamide group. The diuretic effect develops 2–4 hours post-dose (2.6 hours on average); duration of effect reaches 48–72 hours. The antihypertensive effect develops gradually over 2–4 weeks after the start of therapy.

- ▶ Bioavailability: 64%. $T_{1/2}$: 40–60 hours. Excreted in urine as unchanged drug. For oral administration 1–2 times daily.

Mechanism of action: Inhibits reabsorption of Na^+ and Cl^- ions in distal and partially proximal tubules, promotes excretion of K^+ , Mg^{2+} ions and water, retains Ca^{2+} . It reduces extracellular fluid volume and blood plasma volume, thus total peripheral resistance decreases.

Therapeutic indications: hypertension; edema of various origins (in congestive heart failure, nephrotic syndrome, hepatic cirrhosis)

For side effects and contraindications: see "Indapamide".

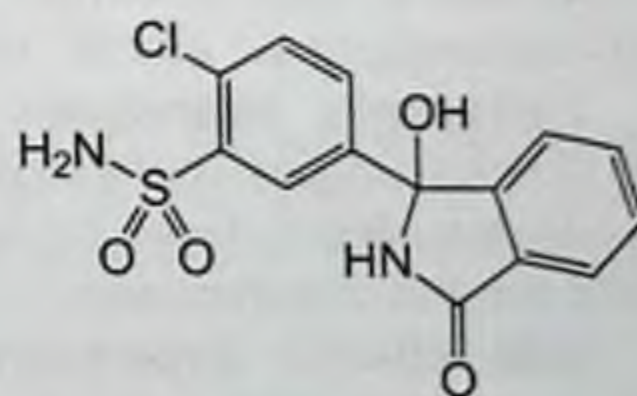


Fig. 17.17. 2-Chloro-5-(2,3-dihydro-1-hydroxy-3-oxo-1H-isoindol-1-yl)benzolsulfonamide

Clopamide*

- ▶ A long-acting thiazide-like sulfonamide diuretic. Onset of action is 1–3 hours, maximum effect occurs after 6 hours, duration of effect is up to 24 hours. It increases the volume of excreted urine, reducing the circulating blood volume and decreasing BP.
- ▶ $T_{1/2}$: 5.8–7.2 hours. Excreted by the kidneys as glucuronides (1/3) and unchanged drug (2/3). For oral administration once daily.
- ▶ Included in these combination drugs: Normatens* (dihydroergocristine, clopamide, reserpine); cristepine* (dihydroergocristine, clopamide, reserpine); Viskaldix* (clopamide, pindolol)

Mechanism of action: see “Chlorthalidone”

For therapeutic indications, side effects and contraindications, see “Indapamide”.

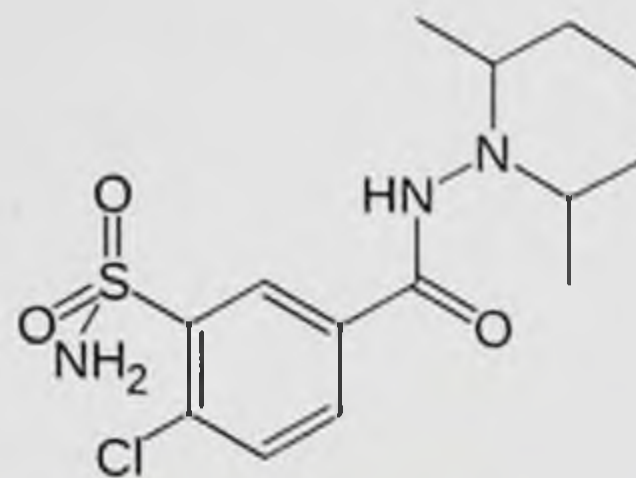


Fig. 17.18. 4-Chloro-N-(cis-2,6-di-methylpiperidyl)-3-sulfamoyl benzamide

Drugs acting predominantly on the late distal tubules and collecting ducts (potassium- and magnesium-sparing diuretics)

Direct blockers of sodium channels in the apical membrane of proximal tubular epithelial cells in distal convoluted tubules and collecting ducts

Mechanism of action: They block sodium channels in the late distal convoluted tubules and early collecting ducts, which leads to increased Na^+ excretion (excreted Na^+ fraction reaches only 1–2%, since the intensity of its reabsorption in these sections is low). Due to decreased Na^+ inflow into the cell, the apical membrane is hyperpolarized, which cause a less negative transepithelial potential and subsequent K^+ and H^+ secretion.

Therapeutic indications: hypertension (in combination therapy), edema of various origins (congestive heart failure, chronic kidney failure, nephrotic syndrome, liver failure), prevention of hypokalemia/hypomagnesemia associated with the use of saluretics

Side effects: hyperkalemia, dizziness, headache, paresthesia, fatigue, dyspepsia, allergic reactions

Contraindications: hyperkalemia, severe kidney and liver failure, pregnancy, breastfeeding, allergic reactions

Triamterene

- ▶ A pteridine derivative (an analog of xanthopterin, a butterfly wing pigment). The diuretic effect is weak; it occurs within 1 hour post-dose, reaching a maximum after 1 hour, and lasts up to 6–12 hours.
- ▶ Bioavailability: 50–70%. $T_{1/2}$: 2 hours. Extensively metabolized and excreted in urine as metabolites and as unchanged drug (variable amounts). For oral administration twice daily.

- ▶ Included in these combination drugs: Triamtel[®], Triampur Compositum[®], Apo-Triazide[®].

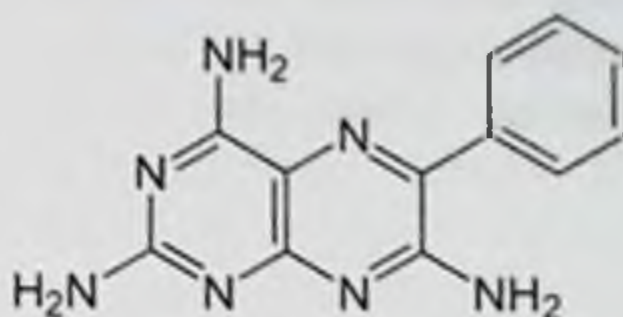


Fig. 17.19. 2,4,7-Triamino-8-phenylpteridine

Amiloride (amiprazid[®]) — excluded from Russian State Register of Medicinal Products.

- ▶ A pyrazinoylguanidine derivative. It has a less pronounced diuretic effect than thiazide diuretics. Duration of action: 12–24 hours.
- ▶ Bioavailability: 50%. $T_{1/2}$: 6–9 hours, terminal half-life: 20 hours and more. Excreted in urine as unchanged drug.
- ▶ Included in these combination drugs: Moduretic[®] (amiloride, hydrochlorothiazide), amilozide[®], hemopres[®]

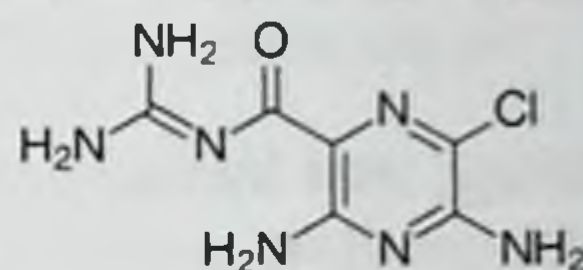


Fig. 17.20. N-Amidino-3,5-diamino-6-chloropyrazinecarboxamide hydrochloride

Aldosterone antagonists

Spironolactone (verospiron[®])

- ▶ The effect occurs on day 2–5 of administration. It has an antihypertensive effect by itself, enhances the diuretic and antihypertensive effects of thiazide and loop diuretics, and alleviates the hypokalemia that they cause. The diuretic effect of Spironolactone does not affect the acid-base balance. It is effective in acidosis and alkalosis.
- ▶ Bioavailability: 93%. $T_{1/2}$: 13–24 hours. Metabolized in the liver to several active sulfur-containing metabolites (80%), including canrenone (20%), penetrates poorly into organs and tissues, but crosses the placental barrier; canrenone is excreted into breast milk. Excreted in urine. For oral administration 1–3 times daily.

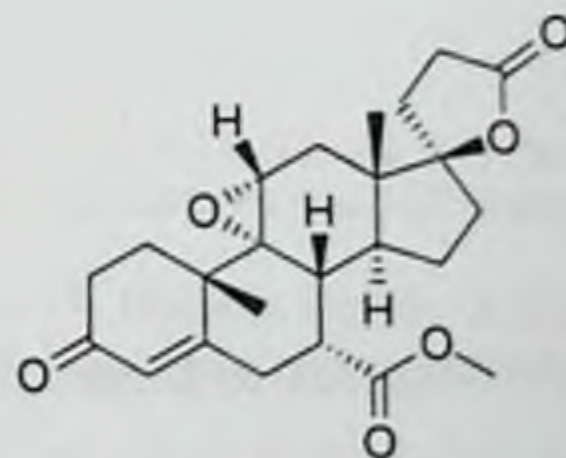


Fig. 17.21. S-[(7R,8R,9S,10R,13S,14S,17R)-10,13-Dimethyl-3,5'-dioxospiro[2,6,7,8,9,11,12,14,15,16-decahydro-1H-cyclopenta[a]phenantren-17,2'-oxolane]-7-yl]ethanethioate

Mechanism of action: As a competitive aldosterone antagonist (blocks intracellular receptors to mineralocorticoids) in late distal tubules and cortical collecting ducts, it increases the excretion of Na^+ , Cl^- and water. By inhibiting Na^+ reabsorption, it prevents depolarization of the apical membrane of nephrocytes, which causes K^+ retention in the blood, reducing H^+ secretion. The diuretic effect is weak, since little Na^+ is reabsorbed in the distal nephron; it increases the excreted Na^+ fraction only to 3–5%, moderately increases Cl^- excretion, preserves K^+ , H^+ and Mg^{2+} in the body.

Indications: edema due to congestive heart failure, hypokalemia/hypomagnesemia (as a preventative aid during treatment with diuretics), essential hypertension (combination therapy), hyperaldosteronism

Side effects: reversible gynecomastia, impotence, dysmenorrhea, hirsutism; hyperkalemia, hyponatremia, nausea, vomiting, diarrhea, dizziness, drowsiness, ataxia, allergic reactions

Contraindications: Addison's disease, hyperkalemia, hyponatremia, severe kidney failure, anuria, pregnancy, breastfeeding

Selective aldosterone receptor antagonist

Eplerenone (Inspra[®])

See the section "Steroid Hormones".

Drugs that increase the glomerular filtration rate or drugs with a concomitant diuretic effect

Xanthines

Theophylline⁺

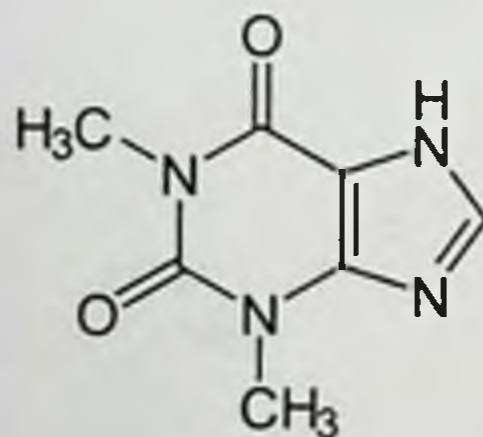


Fig. 17.22. 3,7-Dihydro-1,3-dimethyl-1H-purine-2,6-dione (1,3-Dimethylxanthine)

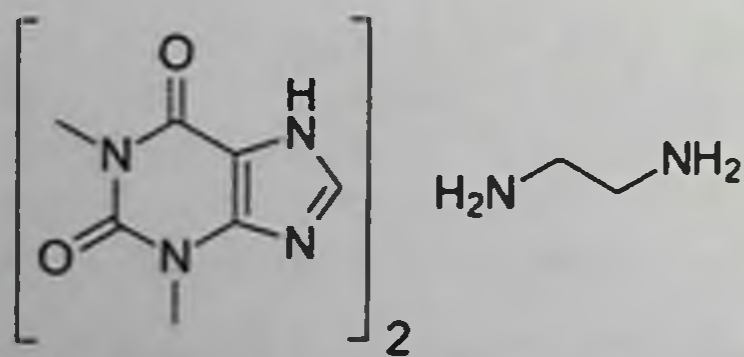


Fig. 17.23. 3,7-Dihydro-1,3-dimethyl-1H-purine-2,6-dione (theophylline) with 1,2-ethylenediamine (2:1) (Theophylline (80 %) with 1,2-ethylenediamine (20 %))

Aminophylline (Euphylline⁺)

Xanthines have a mild diuretic effect (increase Na^+ excretion to 3–5%).

Mechanism of diuretic effect: Xanthines block adenosine A1 receptors, eliminating their inhibitory effect on adenylate cyclase activity and cAMP synthesis. In high doses, they inhibit PDE III-V isozymes, delaying the inactivation of cyclic nucleotides. Thus, the cellular levels of cAMP increase. Xanthines increase blood supply to the kidneys (enhance cardiac activity

and dilate renal arteries); stimulate glomerular filtration (increase renal blood flow, dilate the afferent arteriole to a greater extent than the efferent arteriole); reduce nephrocyte contact with urine by accelerating its flow through the tubules; inhibit water reabsorption in the descending limb of the Henle's loop; inhibit Na^+

reabsorption in the proximal tubules (cAMP inhibits $\text{Na}^+/\text{HCO}_3^-$ symport in the basal membrane).

Therapeutic indications: edema of various origins (combination therapy), management of broncho-obstructive syndrome such as asthma, COPD; pulmonary hypertension

Side effects: tachycardia, hypotension, more frequent angina attacks, dizziness, headache, insomnia, agitation, tremor, nausea, vomiting, diarrhea, tenderness at the injection site, exfoliative dermatitis

Contraindications: hypotension, paroxysmal tachycardia, extrasystoles, myocardial infarction; epilepsy; stomach and duodenal ulcers, hyperacid gastritis; severe liver and kidney failure; pregnancy, breastfeeding

Cardiac glycosides

Digoxin[†]

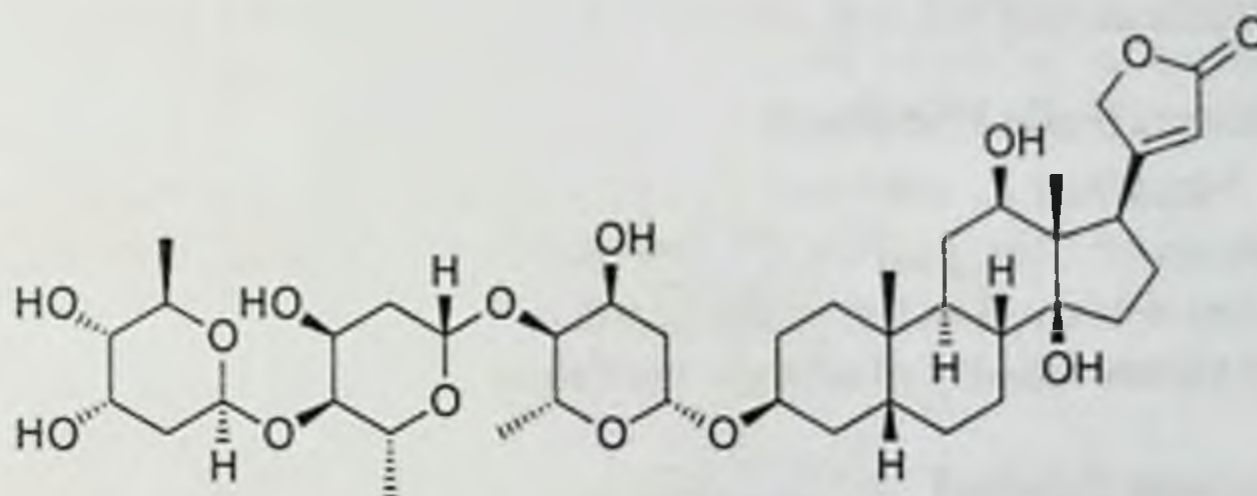


Fig. 17.24. (3 β ,5 β ,12 β)-3-[(O-2,6-Dideoxy- β -D-ribo-hexopyranosyl-(1 $\rightarrow$ 4)-O-2,6-dideoxy- β -D-ribo-hexopyranosyl)-(1 $\rightarrow$ 4)-O-2,6-dideoxy- β -D-ribo-hexopyranosyl)oxy]-12,14-dihydroxycard-20(22)-enolide

A digitalis glycoside extract from the leaves of the plant *Digitalis lanata*. It has a cardiotonic action (causes positive inotropic, negative chronotropic and dromotropic action) and has a weak diuretic effect.

Mechanism of diuretic effect: The increase in cardiac output per minute (due to inhibition of Na^+/K^+ -ATPase of cardiomyocyte membrane) has a positive effect on blood circulation in general. Venous stasis decreases. Total peripheral resistance decreases, blood supply and oxygenation are improved. Kidney function normalizes, diuresis increases. The potential for a direct effect on the kidneys, resulting in reduced Na^+ reabsorption, cannot be ruled out.

Therapeutic indications: congestive heart failure, atrial fibrillation, paroxysmal supraventricular tachycardia, atrial flutter

Herbal products

Juniper fruits (*Baccae Juniperi* [juniper berries (*Fructus Juniperi*)])

Dried mature berries of *Juniperus communis* L., *Cupressaceae* family. They contain essential oil (not less than 0.5%), sugars, organic acids, resins, and other substances. For oral administration as infusions.

Contraindications: nephritis, history of allergic reactions

Bearberry leaves (*Folia Arctostaphyli Uvae ursi*), bear's ear

Arctostaphylos Uva-Ursi (L.) Spreng. wild-harvested shrub leaves, *Ericaceae* family. The leaves contain arbutin (6%), a glycoside metabolized in the body to form hydroquinone, organic acids, tannins (30–35%), and other substances.

For oral administration as infusions or tea as a diuretic and disinfectant in bladder inflammation or urinary tract infection. Bearberry leaves are often included in diuretic teas.

Contraindications: history of allergic reactions

Horsetail herb (*Herba Equiseti Arvensis*)

Equisetum arvense L cryptogam perennial herbaceous plant shoots, *Equisetaceae* family. The shoots contain large amounts of silicic acid, astringents, saponins, malic acid, mineral salts, etc.

For oral administration as tea.

Contraindications: nephritis and nephrosonephritis, history of allergic reactions

Clusterberry leaves (*Folia Vitisidaea*)

Vaccinium Vitisidaea L. wild-harvested evergreen shrub leaves, *Ericaceae* family. The leaves contain arbutin, a glycoside, flavonols, organic acids, and other substances.

For oral administration as tea or infusions.

Contraindications: history of allergic reactions

Birch buds (*Gemmae Betulae*)

Betula pubescens Ehrh dried buds, *Betulaceae* family. The buds contain essential oil (not less than 0.2%), tannins.

For administration as infusions in edema of renal or cardiac origin.

Contraindications: history of allergic reactions

Laspenephryl[†]

Laspenephryl is derived from the *Lespedeza capitata* stems and leaves, *Fabaceae* family, and anise fruits. It increases diuresis (by increasing glomerular filtration), increases Na⁺ and, to a lesser extent, K⁺ excretion, increases urinary excretion of nitrogenous waste. For oral administration.

A generic Russian drug Lespeflan (*Lespeflanum*), an ethanol-water solution of *Lespedeza bicolor* (Turcz.) purified extract has been developed. The therapeutic indications are the same as Laspenephryl[†].

Therapeutic indications: combination therapy for chronic kidney failure

Contraindications: history of allergic reactions

18. PROTEIN AND POLYPEPTIDE HORMONES

Hormones are biologically active substances produced by endocrine glands. Once in the bloodstream, they regulate the metabolism and functions of virtually every organ and tissue. Endocrine gland malfunction causing either a decrease or increase in hormone production leads to the development of diseases requiring hormonal or antihormonal therapy.

Principles of hormonal regulation

The synthesis and release of hypothalamic and anterior pituitary hormones are controlled by feedback loops (positive or negative) (Fig. 18.1). The activity of the hypothalamus and the pituitary gland depends on circulating hormone levels. A decrease in hormone levels in blood stimulates the hypothalamic-pituitary system, while an increase is accompanied by an inhibitory effect.

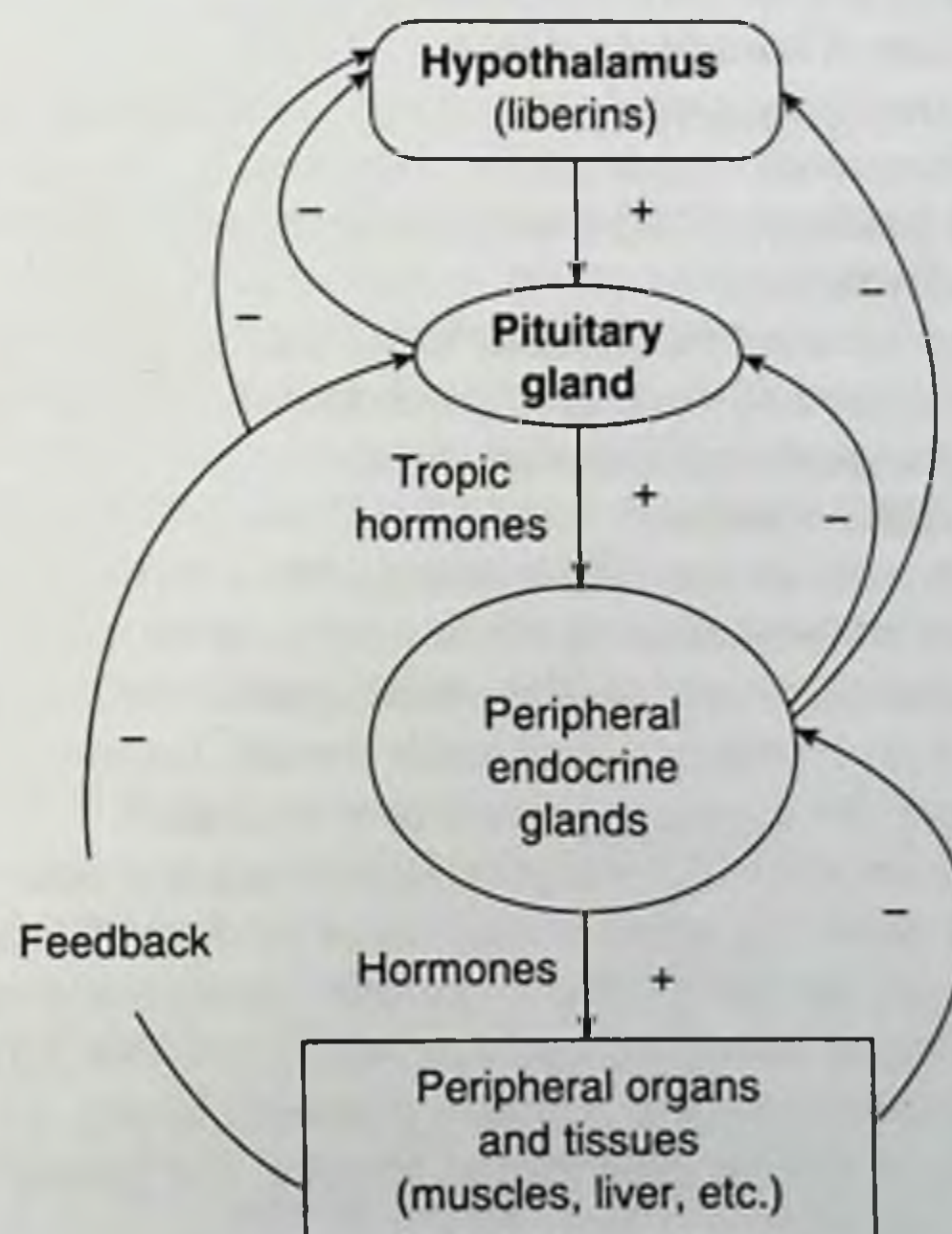


Fig. 18.1. Regulation of hormone secretion. + sign = positive feedback, - sign = negative feedback

Hormonal products — drugs containing hormones or their synthetic analogs used for hormone therapy.

Depending on the production method there are: natural hormone products produced from animal raw materials — endocrine glands of slaughtered cattle — as well as from blood and urine of some animals and humans (insulin); products in the form of gland or dried tissue extracts that contain hormones with a mixture of tissue substances [parathyroid gland (parathyroidin), adrenal (cortin), pituitary (puitrin[®]) extracts]; synthetic products that are chemically identical to natural hormones and their derivatives [adrenocortical (prednisolone, dexamethasone), gonadal (methyltestosterone, estradiol) hormones]; synthetic products with hormone-like properties that differ in their chemical structure from the relevant hormones (estrogenic products, stilbene derivatives, dihydrotachysterol); combination products that are a mixture of two or more hormonal preparations (e.g., Ambosex consists of a mixture of female and male sex hormones).

Hormonal products by chemical structure

- ▶ Protein and polypeptide substances are hypothalamic, pituitary gland, parathyroid and pancreatic hormones, calcitonin
- ▶ Amino acid derivatives are thyroid hormone products
- ▶ Steroids are adrenocortical and gonadal hormone products

When an endocrine gland is hyperactive, hormone antagonists that block the relevant receptors or inhibit hormone synthesis are used.

Mechanism of action of hormonal products.

- ▶ Membrane (extracellular) mechanism is typical of protein, peptide and amino acid-derived hormones (hydrophilic hormones), hypothalamic, pituitary, pancreatic and parathyroid hormones, thyrocalcitonin from the thyroid gland, except for iodothyronines.
- ▶ Cytosolic (intracellular) mechanism is characteristic of steroid hormones (hydrophobic hormones) such as glucocorticoids, sex hormones (androgens, estrogens, progestogens) and iodothyronines.

Membrane mechanism of action

Hydrophilic hormones cannot diffuse through the cell membrane. Receptors for this group of hormones are located on the surface of the cell membrane. Since hormones cannot enter cells, a secondary mediator between hormones and intracellular processes is required to transmit the hormonal signal inside the cell. Inositol phospholipids, Ca^{2+} ions, and cyclic nucleotides can serve as secondary mediators.

- ▶ A hormone (H) interacts with a receptor (R) to form a hormone-receptor complex (HR), at which point the receptor undergoes conformational rearrangements. This in turn leads to membrane G-protein conformational rearrangements and the activation of adenylate cyclase, which converts ATP to cAMP (Fig. 18.2). The intracellular cAMP activates a protein kinase, which catalyzes the phosphorylation of various intracellular proteins and generates the hormone's final effect.
- ▶ Interaction of the hormone (H) with the receptor (R) increases the permeability of calcium channels on the cell membrane, allowing extracellular Ca^{2+} to enter the cytosol. Inside the cell, Ca^{2+} ions interact with calmodulin, a modulating protein. The calcium-calmodulin complex activates calcium-dependent protein kinases, which stimulate the phosphorylation of various proteins and generate the final effects (Fig. 18.3).

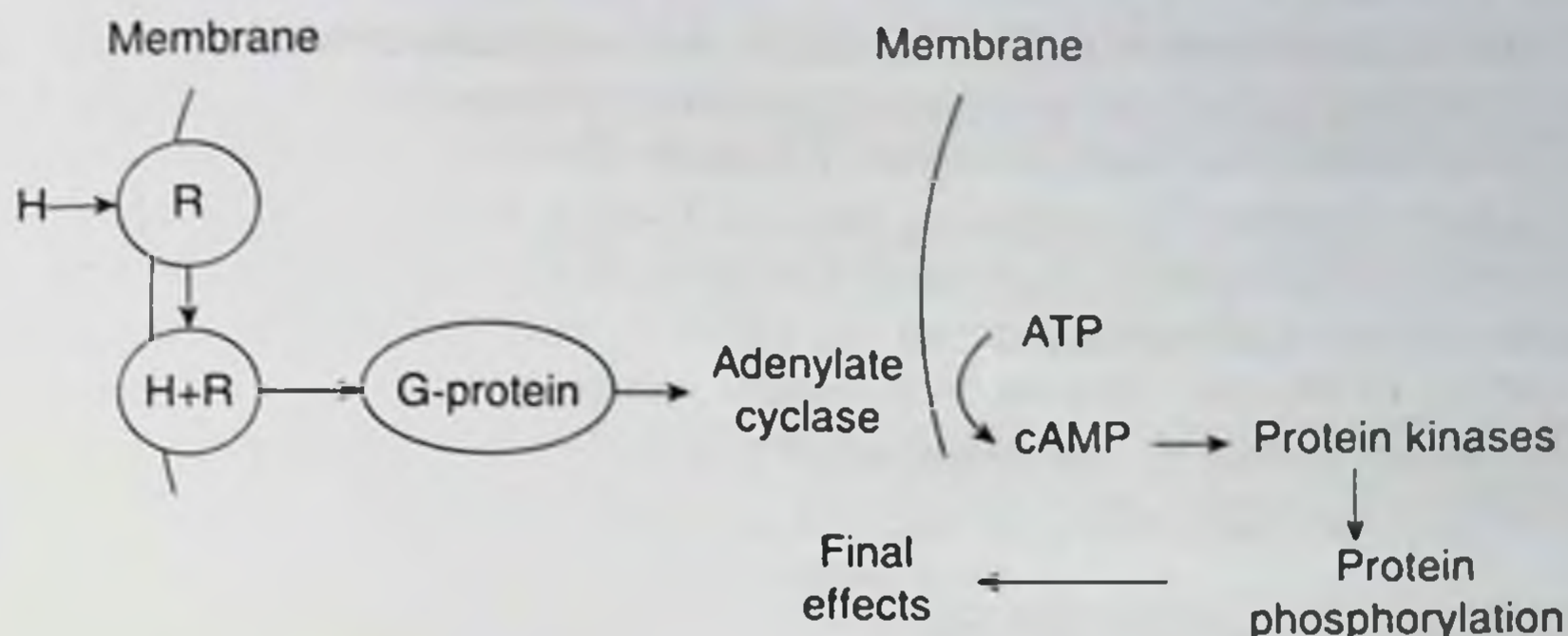
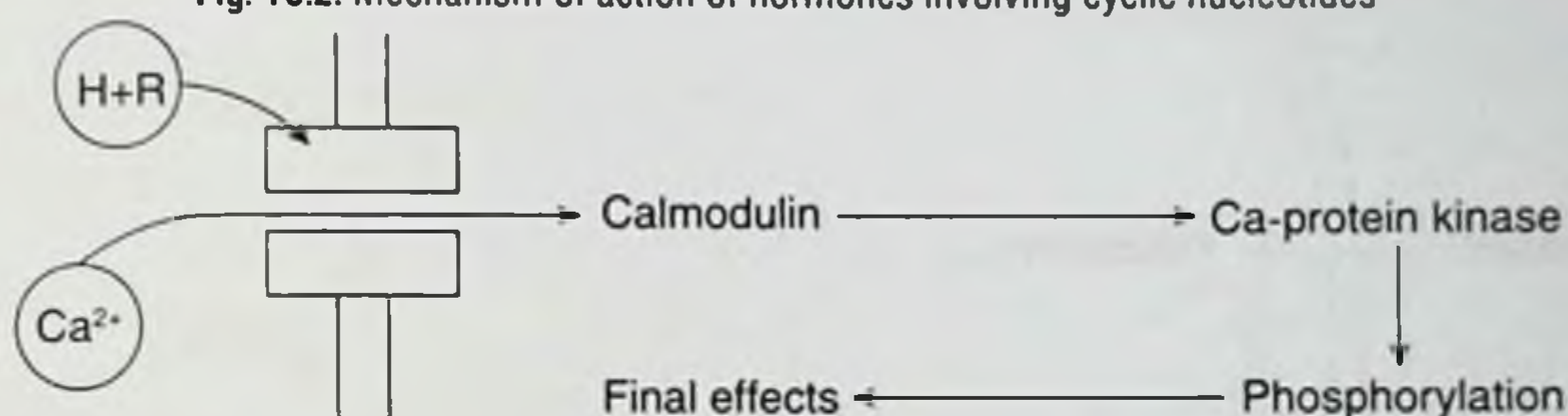
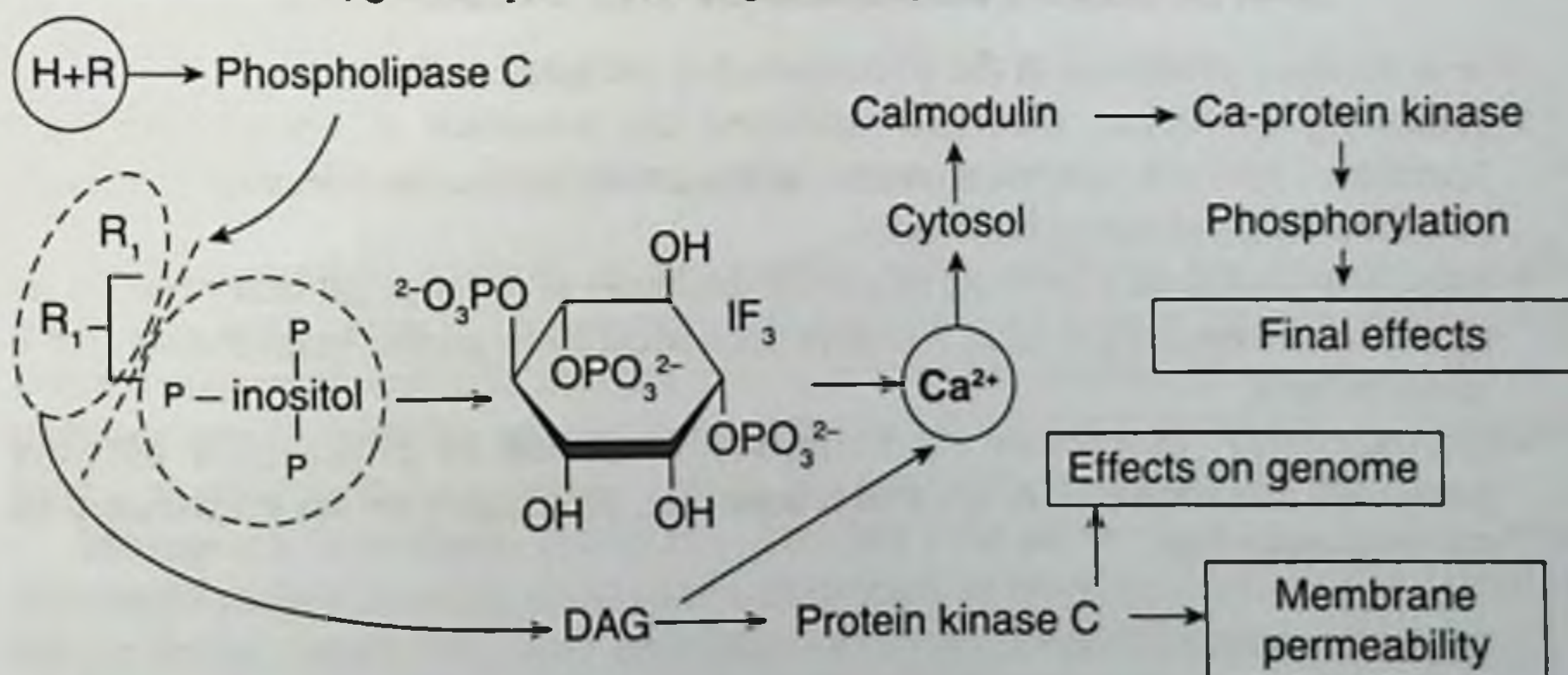


Fig. 18.2. Mechanism of action of hormones involving cyclic nucleotides

Fig. 18.3. Mechanism of action of hormones involving Ca^{2+} ions

- ▶ The formed hormone-receptor complex (HR) activates phospholipase C in the cell membrane, which cleaves phosphatidylinositol into the secondary messengers diacylglycerol and inositol-3-triphosphate (Fig. 18.4). They activate the release of Ca^{2+} ions from intracellular stores into the cytosol. Ca^{2+} ions interact with calmodulin, which activates protein kinases and subsequent protein phosphorylation accompanied by the hormone's final effects. Diacylglycerol also activates protein kinase C, which ensures phosphorylation of serine or threonine residues on specific target proteins, which can alter membrane permeability. In certain cases, gene expression is regulated by second messengers.

Fig. 18.4. Mechanism of action of hormones involving diacylglycerol (DAG) and inositol-3-triphosphate (IP₃)
P — phosphate

Cytosolic mechanism of action. Lipophilic hormones can enter the cell through the cell membrane; their receptors are located in the cytosol, on the mitochondria, and on the nuclear surface. Hormone receptors have two domains: a hormone-binding domain and a DNA-binding domain. When it interacts with the hormone, the receptor changes its structure and becomes free of chaperones. As a result, the hormone-receptor complex acquires the ability to enter the nucleus and interact with certain DNA sites. This, in turn, triggers a change in the rate of transcription (RNA synthesis) and, as a consequence, the rate of translation (protein synthesis) (Fig. 18.5).

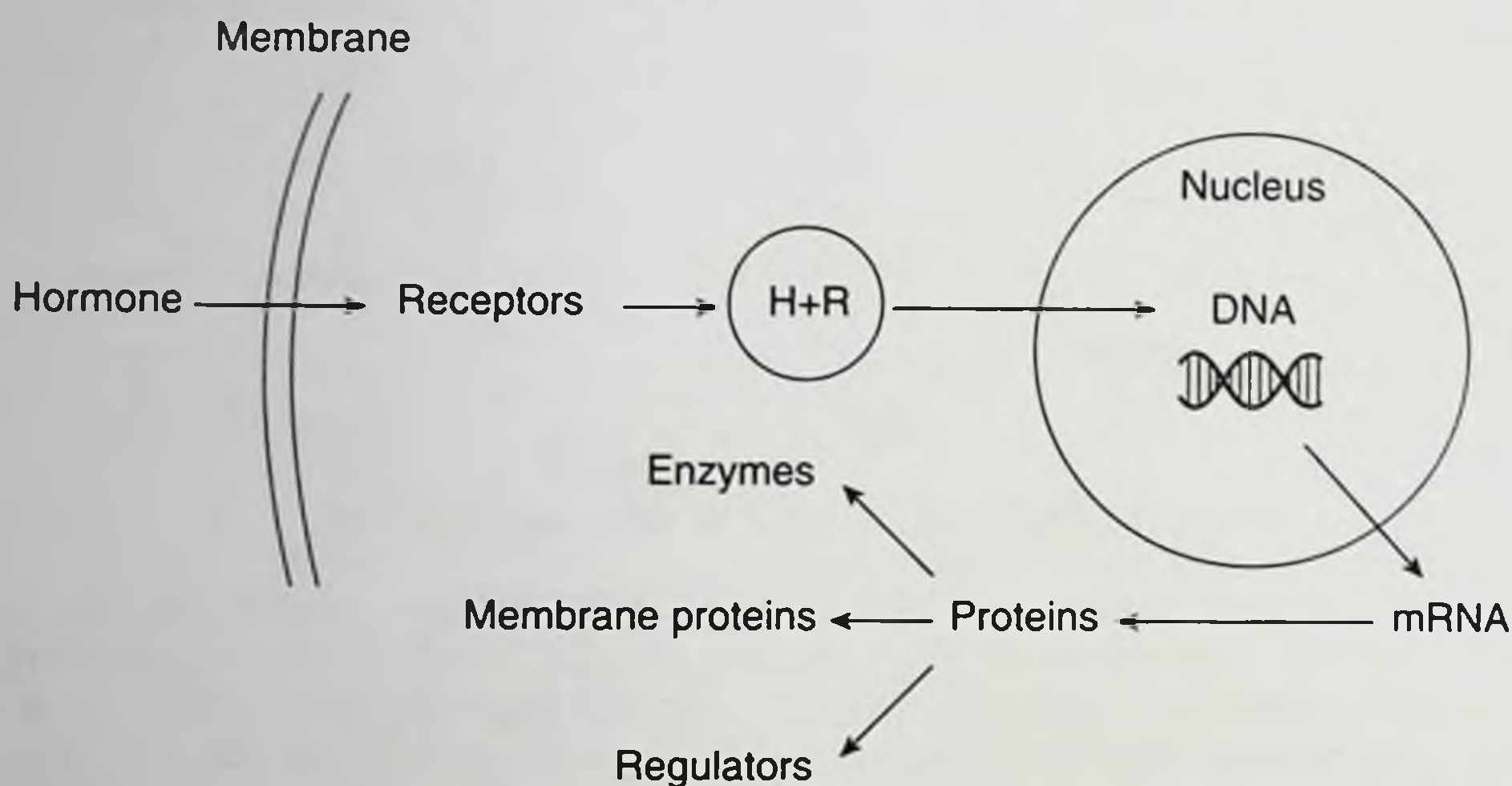


Fig. 18.5. Cytosolic mechanism of action of hormones

HORMONES PRODUCED BY HYPOTHALAMUS

The hormones produced in the hypothalamus are listed in Table 18.1.

- ▶ Releasing hormones (liberins) stimulate the secretion of anterior pituitary hormones (growth hormone-releasing hormone, prolactin-releasing hormone, gonadotropin-releasing hormone).
- ▶ Inhibitory hormones (statins) block the secretion of anterior pituitary hormones (growth hormone-inhibiting hormone [somatostatin], prolactin inhibiting factor [dopamine]).
- ▶ Oxytocin and vasopressin are traditionally referred to as posterior pituitary hormones due to their storage and release site, although they are synthesized by the hypothalamus.

Table 18.1. Hormones and hormonal products

Liberins	Statins	Products
Corticotropin-releasing hormone		
Thyrotropin-releasing hormone		Rilathyron (+)
Gonadotropin-releasing hormone		Gonadorelin, Leuprolide, Nafarelin (-/+)
Growth hormone-releasing hormone	Growth hormone-inhibiting hormone	Somatostatin (-), Octreotide (-), Sermorelin (+)
Prolactin-releasing hormone	Prolactin inhibiting factor	
Melanotropin-releasing hormone	Melanostatin	

+ stimulates, - inhibits

Specifics of individual products

Somatostatin (Stilamin*)

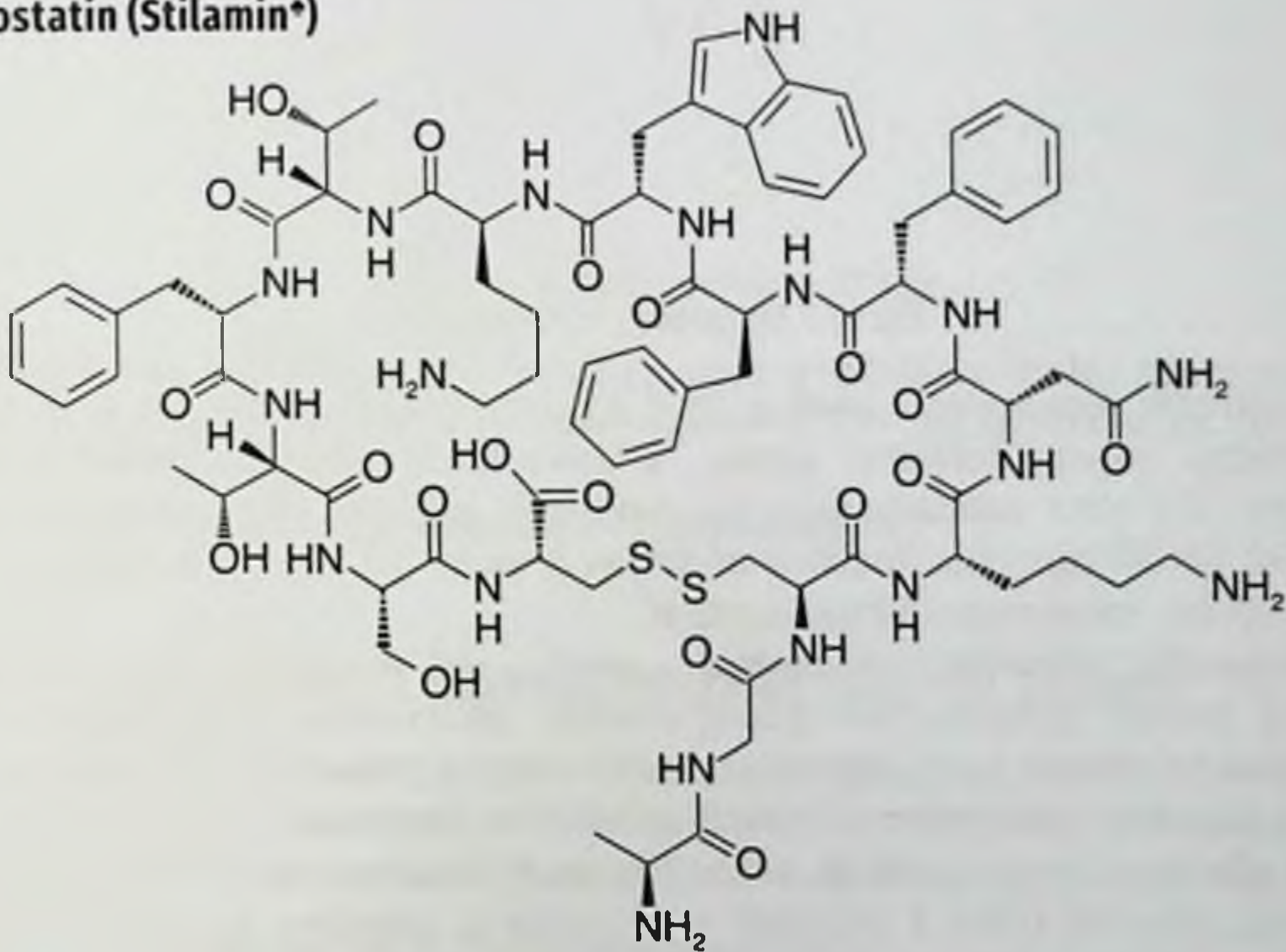


Fig. 18.6. Somatostatin structural formula

A 14-amino acid synthetic cyclic peptide, whose structure and action are similar to natural somatostatin. Somatostatin reduces the secretion of gastrin, gastric juice, pepsin, endocrine and exocrine pancreatic secretions, inhibits glucagon secretion. It prevents growth hormone release, reduces the blood flow in internal organs. Treatment is carried out only in the inpatient setting. For intravenous administration.

Therapeutic indications: acromegaly, bleeding from peptic ulcer and duodenal ulcer, esophageal variceal bleeding, erosive and hemorrhagic gastritis, pancreatic, biliary, intestinal fistulas (in combination therapy), prevention of complications after pancreatic surgery

Side effects: nausea, vomiting, abdominal pain, dizziness, bradycardia

Contraindications: pregnancy and breastfeeding

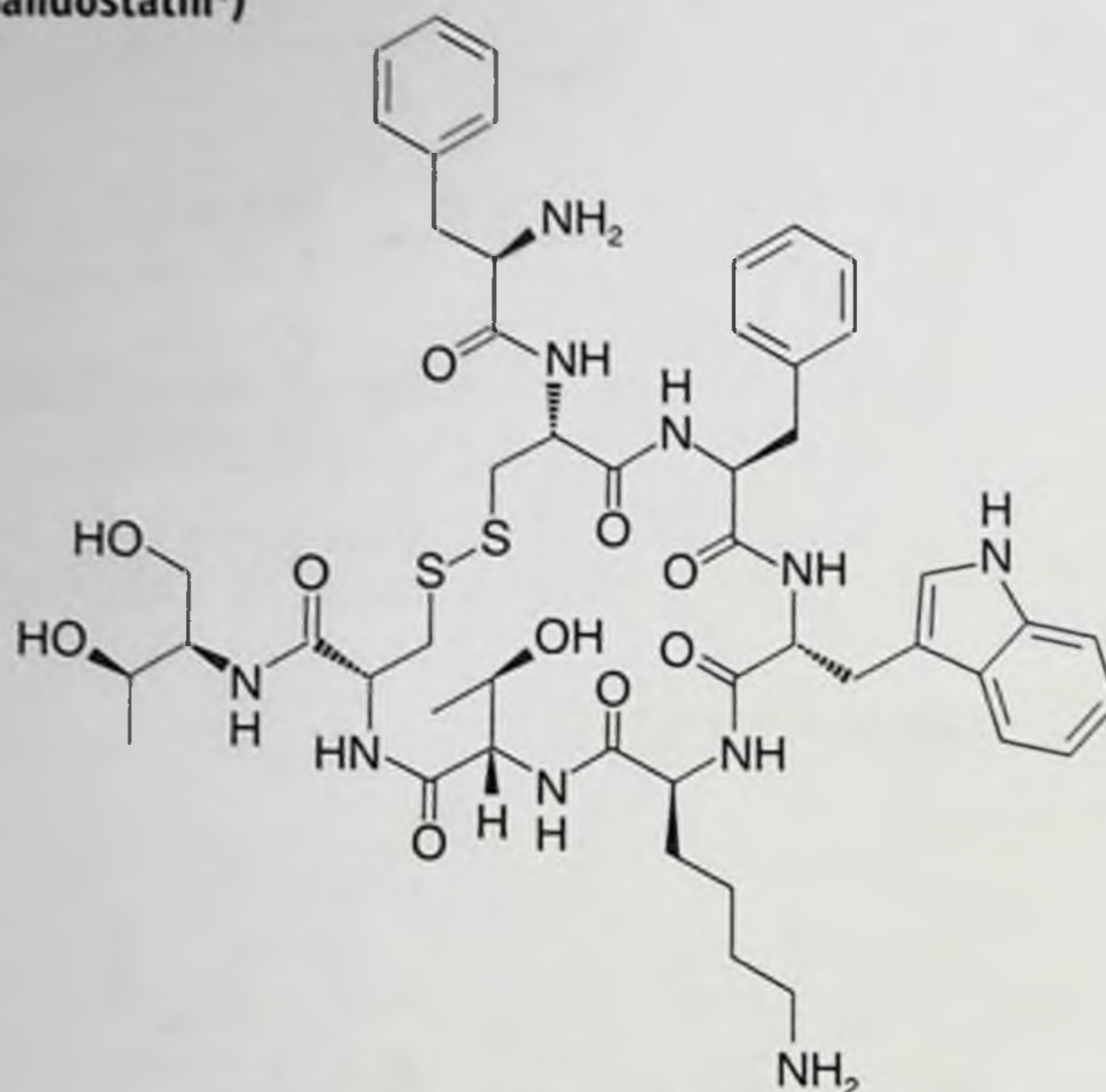
Octreotide (Sandostatin[®])

Fig. 18.7. Octreotide structural formula

A synthetic somatostatin analog. It is 45 times more active than somatostatin at inhibiting growth hormone release, 2 times more active at inhibiting insulin secretion. $T_{1/2}$ after subcutaneous injection: 80–100 min, $T_{1/2}$ after intravenous injection: 10–90 min; the duration of action is about 12 hours. For subcutaneous, intramuscular, intravenous administration.

Therapeutic indications: acromegaly, gastric and duodenal ulcers, hormone-secreting tumors (gastrinomas, glucagonomas, insulinomas, somatoliberinomas), stopping and preventing esophageal variceal bleeding in patients with hepatic cirrhosis, acute pancreatitis, prevention of complications after pancreatic surgery

Side effects: nausea, vomiting, abdominal pain, flatulence, diarrhea, liver disease; with long-term use (after 6 months) — cholestasis, gallstone formation, transient decrease in glucose tolerance, headache, bradycardia

Contraindications: pregnancy and breastfeeding

Lanreotide[®]

A synthetic somatostatin analog. It works similarly to octreotide, but for a longer period of time. Lanreotide inhibits the secretion of growth hormone and TSH (thyroid-stimulating hormone) by the anterior pituitary, inhibits secretion of many peptides and other biologically active substances, including gastrin, insulin, glucagon, digestive enzymes, hydrochloric acid, vasoactive intestinal peptide, serotonin. $T_{1/2}$ is 2.7–7.7 days. For intramuscular, subcutaneous administration.

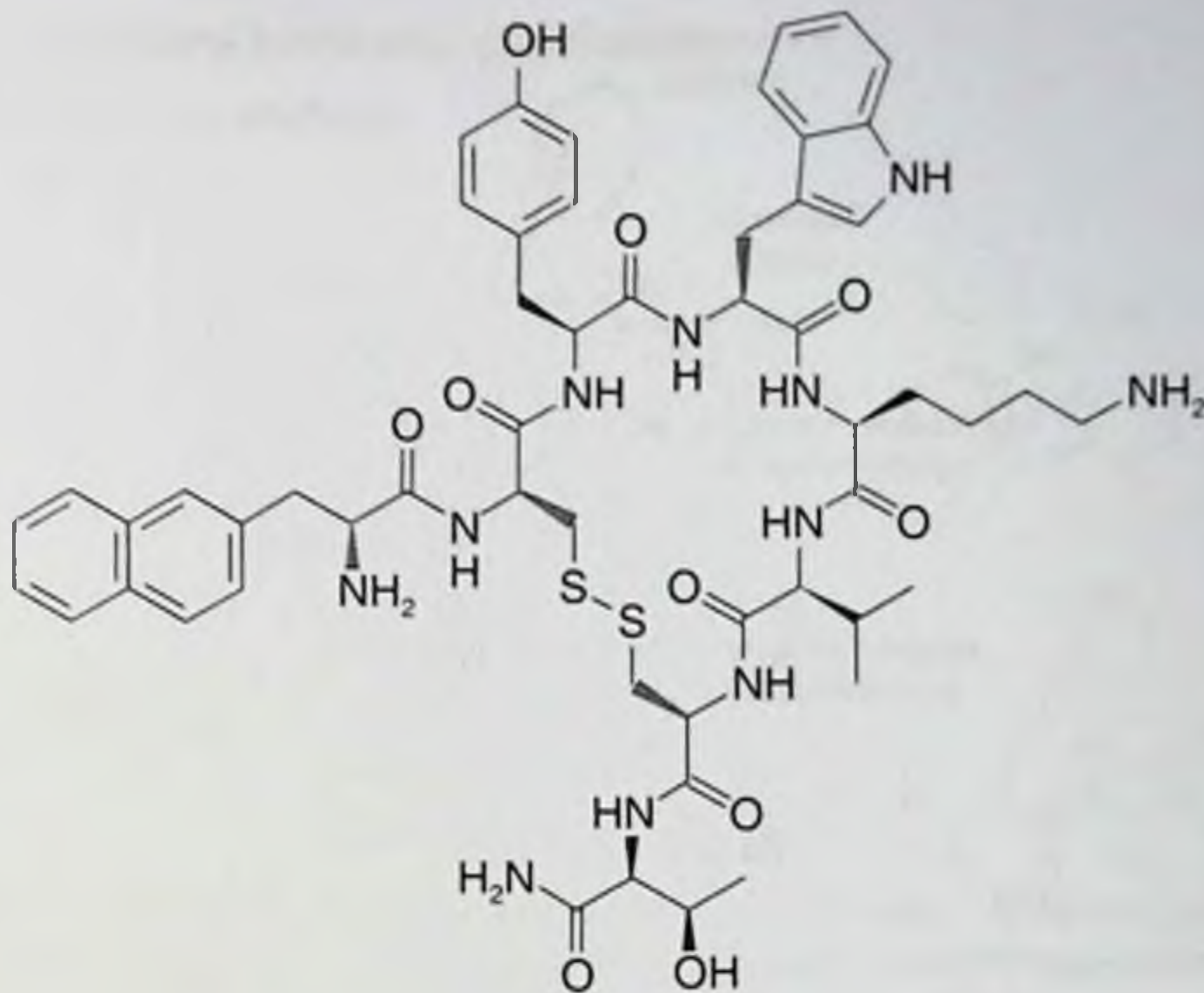


Fig. 18.8. Lanreotide structural formula

Therapeutic indications: acromegaly, gastroenteropancreatic neuroendocrine tumors (symptomatic treatment), prevention of complications after pancreatic surgery, acute pancreatitis

For side effects and contraindications: see "Octreotide".

HORMONES PRODUCED BY PITUITARY GLAND

The pituitary gland consists of three lobes: anterior, posterior, and intermediate.

The anterior and intermediate lobes contain glandular cells that make up the "anterior pituitary"; the posterior lobe is also called the neurohypophysis (Fig. 18.9).

The anterior lobe produces the following hormones:

- ▶ Adrenocorticotrophic hormone: stimulates the adrenal cortex.
- ▶ Growth hormone: stimulates protein synthesis in cells, glucose formation and fat breakdown, and generalized body growth.
- ▶ Thyroid-stimulating hormone: regulates the synthesis and secretion of thyroid hormones.
- ▶ Prolactin: regulates lactation, differentiation of various tissues, growth and metabolic processes.
- ▶ Follicle-stimulating hormone: promotes the maturation of ovarian follicles, stimulates the proliferation of the endometrium, and ensures mature spermatogenesis.
- ▶ Luteinizing hormone: causes ovulation and formation of the corpus luteum, the maturation of Leydig cells, and testosterone production.

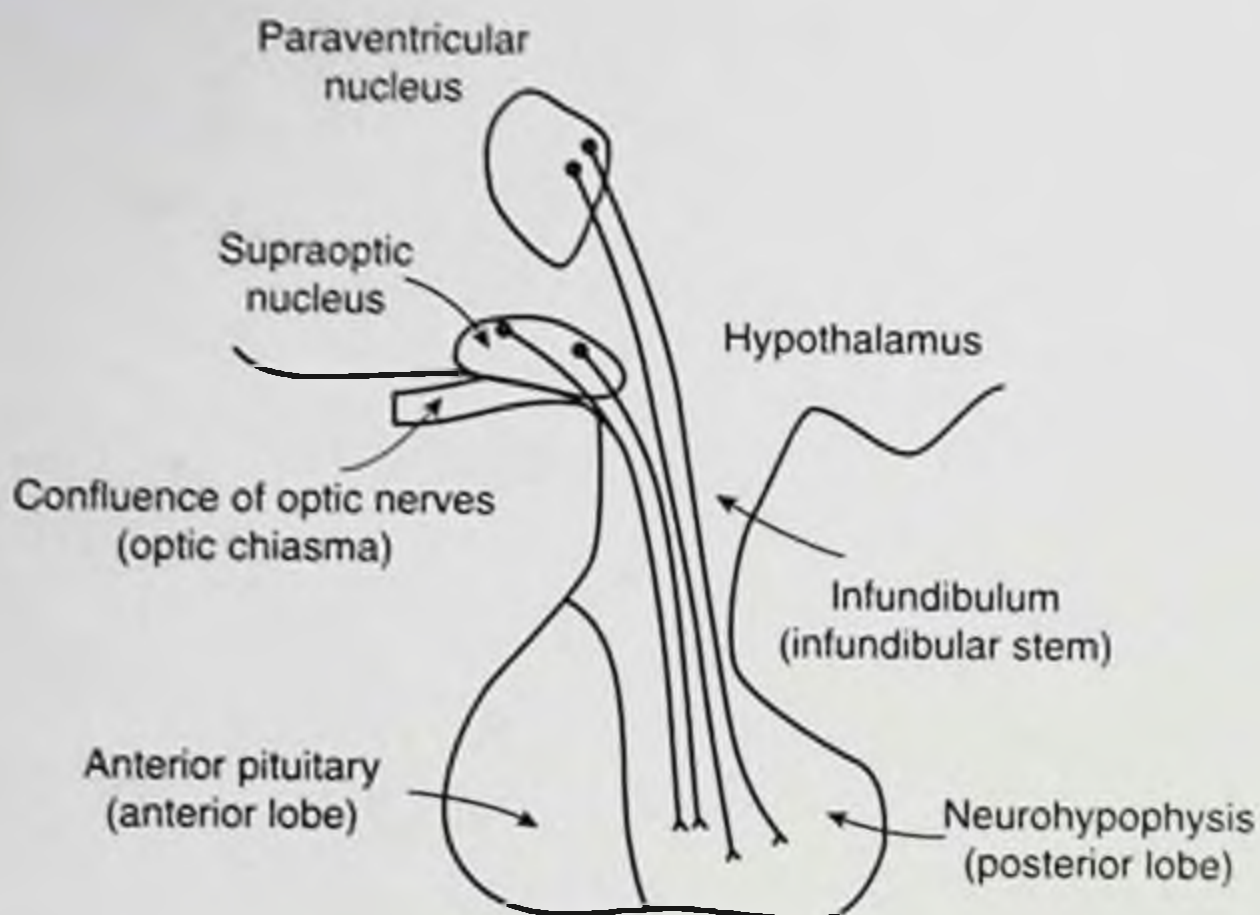


Fig. 18.9. Pituitary gland

The intermediate lobe secretes melanocyte-stimulating hormones, which regulate melanin synthesis (melanogenesis) by melanocytes of the skin, hair, and retinal pigment epithelium.

The posterior lobe consists of nerve endings and glia-like cells (pituicytes). It contains oxytocin and vasopressin (antidiuretic hormone). These hormones are formed in neurosecretory cells originating in the supraoptic and paraventricular nuclei of the hypothalamus. Their axons course along the infundibular stem to its posterior lobe. The ends of these axons come into close contact with the capillaries of the neurohypophysis, where oxytocin and vasopressin are released. Both hormones are released under the influence of nerve impulses. Vasopressin regulates urination by enhancing water reabsorption from the tubular fluid, providing water-salt homeostasis. Oxytocin stimulates the uterine smooth muscle during labor and lactation (Table 18.2).

Table 18.2. Anterior and posterior pituitary gland hormones and their products

Hormone	Pituitary hormone products and analogs
Adrenocorticotrophic hormone (ACTH, Corticotropin)	Corticotropin, Cosyntropin
Growth hormone (Somatotropin)	Growth hormone (Somatotropin), Somatrem
Thyroid-stimulating hormone (TSH, Thyrotropin)	Thyrotropin
Luteotropic hormone (LTH, Prolactin, Lactotropin, Mammotropin)	Lactin
<i>Gonadotropins</i> Follicle-stimulating hormone (FSH) (Follitropin)	Menopausal gonadotropins (Menotropins)
Luteinizing hormone (LH, Lutropin)	Chorionic gonadotropin (Prolan)
Oxytocin	Oxytocin
Vasopressin (antidiuretic hormone)	Vasopressin, Desmopressin, Lypressin
	Pituitrin, Adiurectin (contains both hormones)

Anterior pituitary hormone products

Specifics of individual products

Corticotropin*

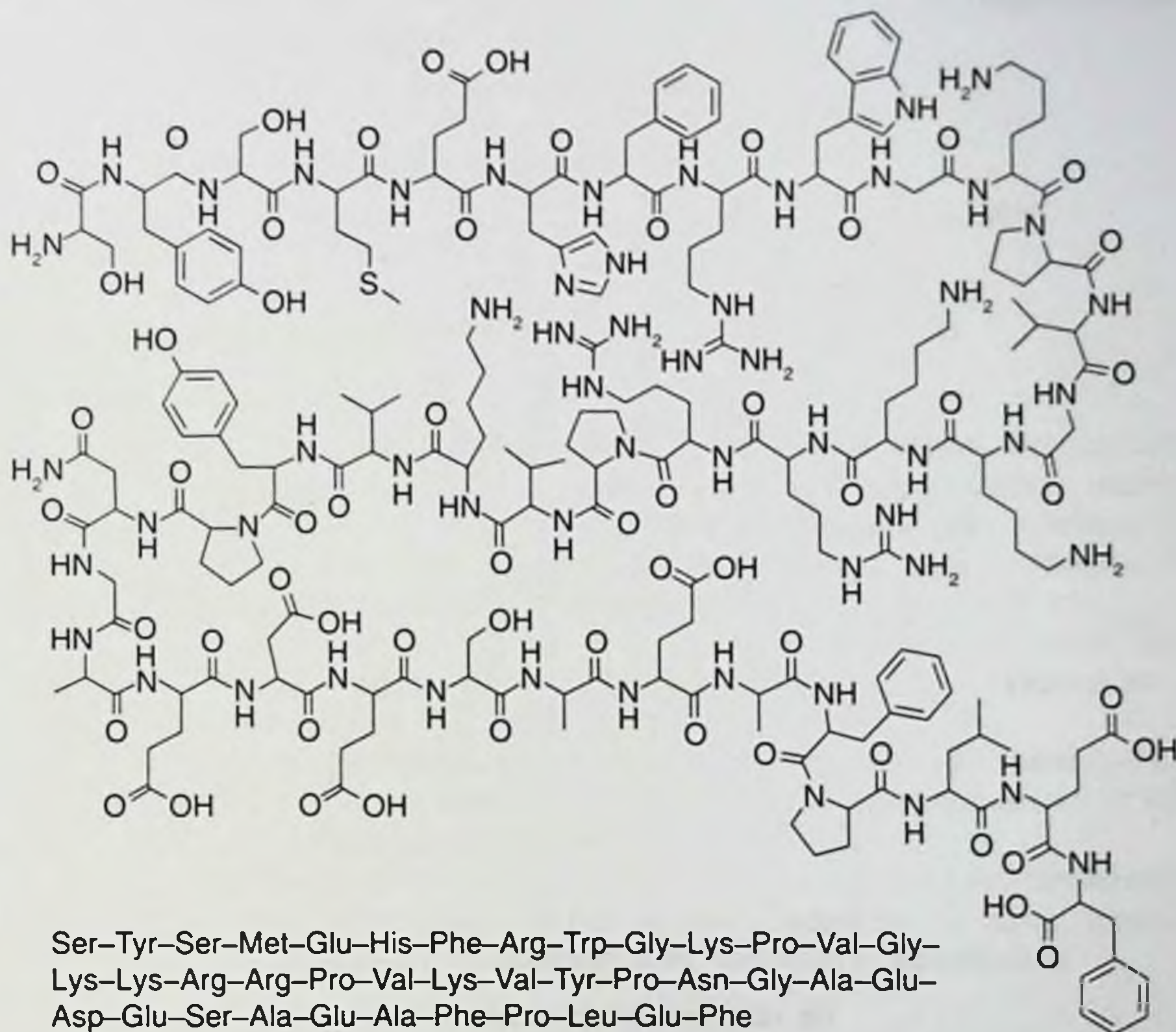


Fig. 18.10. Corticotropin structural formula

An anterior pituitary polypeptide hormone that consists of 39 amino acids. It is a physiological stimulator of the adrenal cortex. Increases the synthesis and release of GCs and androgens into the bloodstream. Its action is similar to that of GCs. For intravenous, intramuscular administration.

Therapeutic indications: adrenal insufficiency; prevention of withdrawal syndrome after long-term GC treatment, functional testing of the hypothalamic-pituitary-adrenal axis

Side effects: generalized edema, increased BP, tachycardia, increased protein metabolism with negative nitrogen balance, agitation, insomnia, hirsutism, dysmenorrhea, delayed wound healing, ulcerogenic effect, worsening of latent foci of infection, hyperglycemia, ketosis, in children — growth retardation

Contraindications: hypertension, Cushing's disease, stage III congenital heart failure, acute endocarditis, psychosis, nephritis, gastric and duodenal ulcers,

postoperative period, tuberculosis (active form in the absence of specific treatment), diabetes mellitus, pregnancy, breastfeeding

Somatotropin[®]

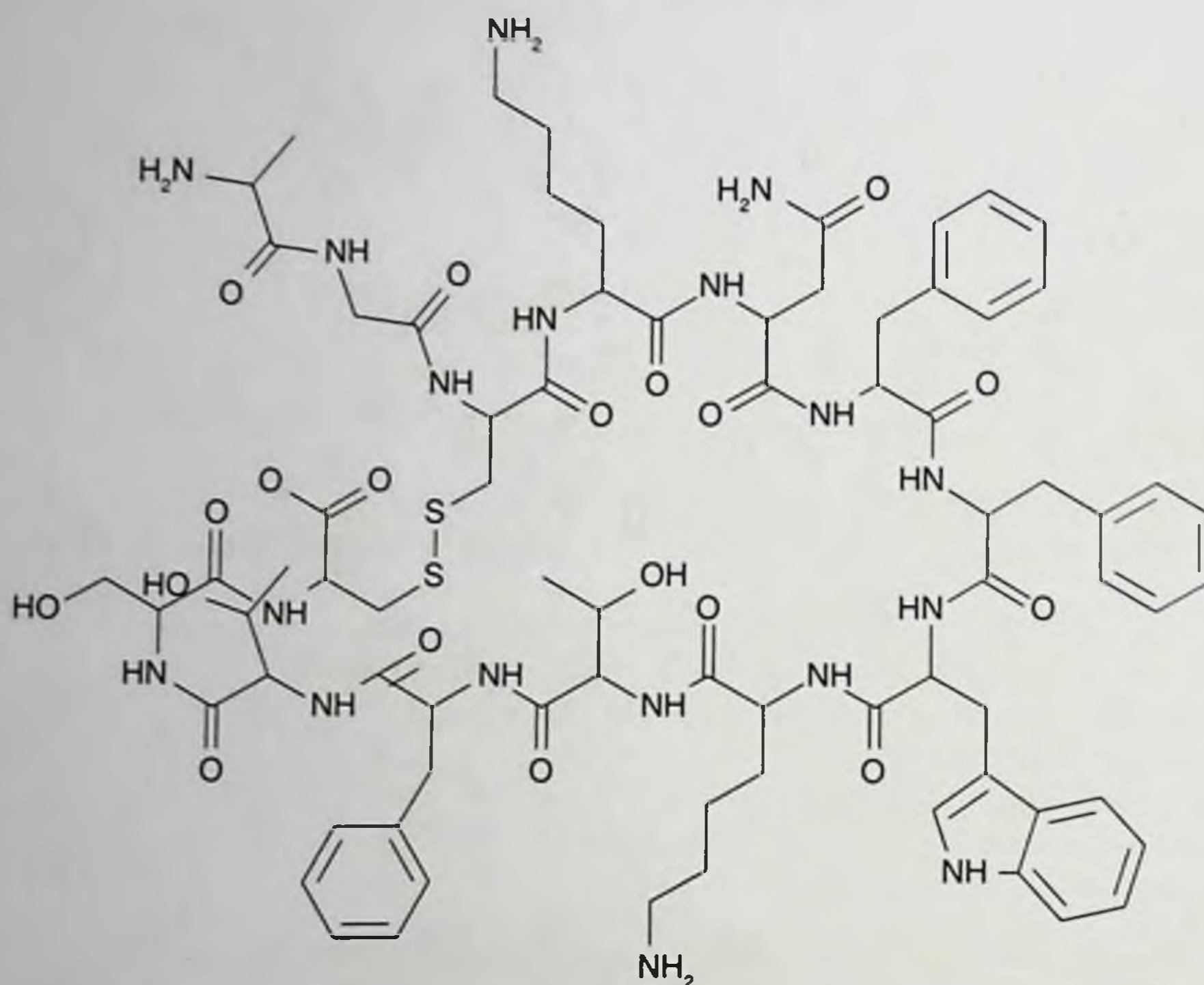


Fig. 18.11. Somatotropin structural formula

A polypeptide consisting of 191 amino acid residues. It stimulates skeletal and somatic growth and has a pronounced effect on metabolism. Somatotropin has been removed from the drug register and replaced by genetically engineered somatotropin products (genotropin, norditropin). $T_{1/2}$: 3–5 hours. For subcutaneous, intramuscular administration.

Therapeutic indications: growth retardation in children due to insufficient secretion of growth hormone, Turner syndrome, chronic kidney failure, growth hormone deficiency (as replacement therapy), osteoporosis

Side effects: headache, edema, hyperglycemia, nausea, vomiting

Contraindications: malignancies, pregnancy, breastfeeding

Gonadotropins

Product classification

1. Products that mimic follicle stimulating and luteinizing hormones (with different ratios)
 - Chorionic gonadotropin⁺
 - Menotropin (Menopausal gonadotropin⁺)
 - Urofollitropin
2. Follicle-stimulating hormone products
 - Follitropin alfa⁺
 - Follitropin beta⁺

Specifics of individual products

Chorionic gonadotropin⁺

Stimulates the production of progesterone by the corpus luteum and supports placental development. Chorionic gonadotropin has a gonadotropic, mainly luteinizing, effect: in women, it causes ovulation and stimulates the synthesis of estrogen and progesterone; in men, it stimulates spermatogenesis and production of sex steroids. $T_{1/2}$: 8 hours. For intramuscular administration.

Therapeutic indications: in women — anovulatory infertility, recurrent and threatened miscarriage, dysfunctional uterine bleeding; in men — hypogonadism, cryptorchidism, delayed puberty, spermatogenesis disorders

Side effects: excessive enlargement of the testes in the inguinal canal (which sometimes prevents testicular descent); overdose leads to hyperstimulation of the ovaries, causing an increase in their size in women

Contraindications: pituitary tumors, pelvic inflammatory diseases, hormonally active tumors, absence of reproductive glands (congenital or after surgical intervention), early menopause, thrombophlebitis, pregnancy, breastfeeding

Follitropin alfa⁺

A recombinant follicle-stimulating hormone. It stimulates the formation of follicles and has an estrogen-like effect (increases estrogen levels and stimulates endometrial proliferation). $T_{1/2}$ in first phase 2 hours; $T_{1/2}$ in second phase 24 hours. For intramuscular, subcutaneous administration.

Therapeutic indications: infertility due to hypothalamus-pituitary dysfunction; various assisted reproductive technology programs

Side effects: ovarian hyperstimulation syndrome (lower abdominal pain, nausea, vomiting, weight gain), increase or formation of ovarian cysts, ascites, thromboembolic disorders, fever, arthralgia

Contraindications: increase or formation of ovarian cysts, undiagnosed genital bleeding, tumors of the reproductive system, hypothalamus, or pituitary gland; pregnancy, breastfeeding

Posterior pituitary hormone products

Specifics of individual products

Oxytocin*

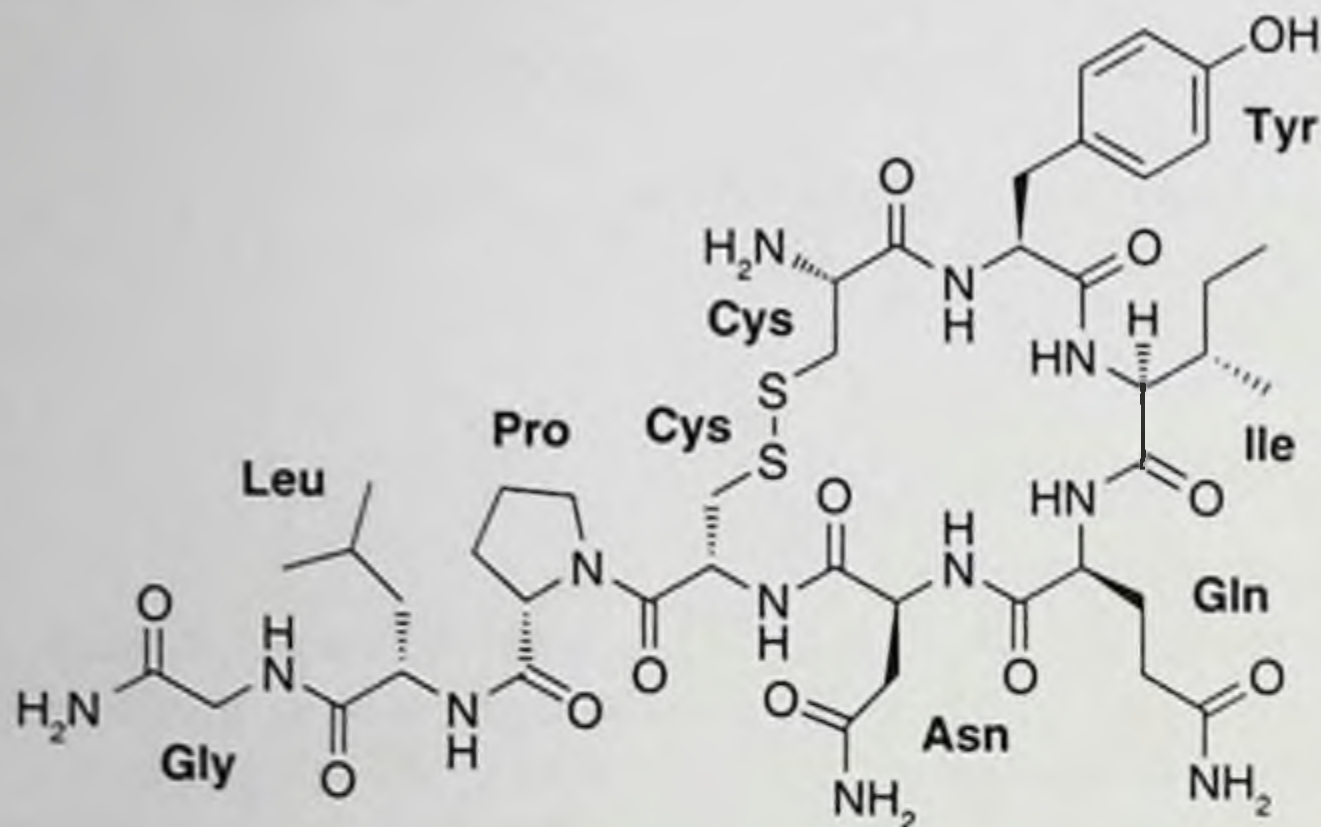


Fig. 18.12. Oxytocin structural formula

A synthetic hormonal drug whose pharmacological action is similar to endogenous oxytocin.

Pharmacological effects: uterotonic (stimulates labor), luteotropic. Virtually devoid of vasoconstrictor and antidiuretic action. $T_{1/2}$: 1–6 min (decreases during late pregnancy and breastfeeding). For intramuscular, intravenous administration.

Mechanism of action: Oxytocin increases the cell membrane's permeability to Ca^{2+} ions, increases the tone and contractile activity of the myometrium (especially at the end of pregnancy, during labor and immediately during delivery). It reduces myoepithelial cells around the alveoli of the mammary gland, stimulates the flow of milk into the large ducts and sinuses, contributing to increased milk secretion.

Therapeutic indications: stimulation of labor, prevention and treatment of hypotonic uterine bleeding, acceleration of postpartum uterine involution, hypolactation in the postpartum period

Side effects: bradycardia (with rapid intravenous injection); hyperhydration, allergic reactions, nausea, vomiting (with prolonged intravenous injection)

Contraindications: narrow pelvis, transverse and oblique fetal position, face presentation of the fetus, premature delivery, threatened uterine rupture, excessive uterine distension, uterus after multiple births, partial placenta previa, chronic kidney failure

Vasopressin[®]

Pharmacological effects

- ▶ **Antidiuretic effect:** affects water retention by increasing its reabsorption in the distal tubules and collecting ducts of the kidneys.
- ▶ **Vasopressor effect:** increased peripheral vascular resistance associated with increased circulating blood volume due to fluid retention.

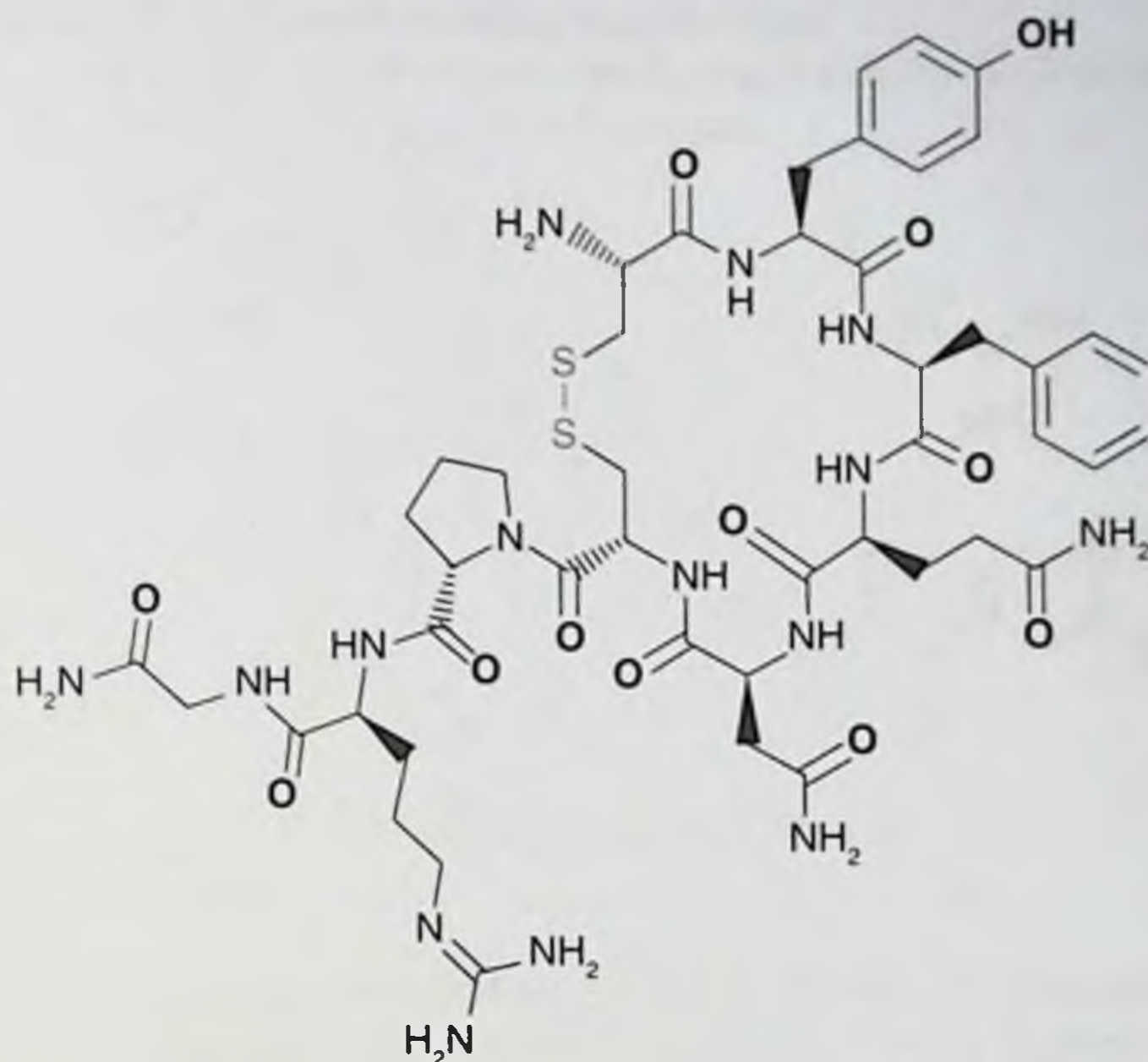


Fig. 18.13. Vasopressin structural formula

T_½: 20 min. For intramuscular, subcutaneous, intravenous, intranasal administration.

Therapeutic indications: diabetes insipidus, GI bleeding, in particular esophageal varices

Side effects: headache, dizziness, nausea, abdominal pain, allergic reactions

Contraindications: CHD, peripheral vascular disease; for intranasal application — rhinitis, maxillary sinusitis

Desmopressin⁺

A synthetic analog of the natural hormone vasopressin that has a pronounced antidiuretic effect, but minimal effects on the smooth muscle of blood vessels and internal organs. Stimulates factor VIII activity. Increases plasminogen concentration without any clinically significant increase in fibrinolysis. T_½ in the first phase: 8 min; terminal half-life: 75 min. For intranasal, subcutaneous, intramuscular, intravenous administration.

Therapeutic indications: diabetes insipidus, enuresis, hemophilia A, Von Willebrand disease (except type 2b)

Side effects: headache, nausea and vomiting, edema, increased BP, allergic reactions

Contraindications: congenital or psychogenic polydipsia, generalized edema, circulatory insufficiency, Von Willebrand disease (type 2b), CHD, pregnancy

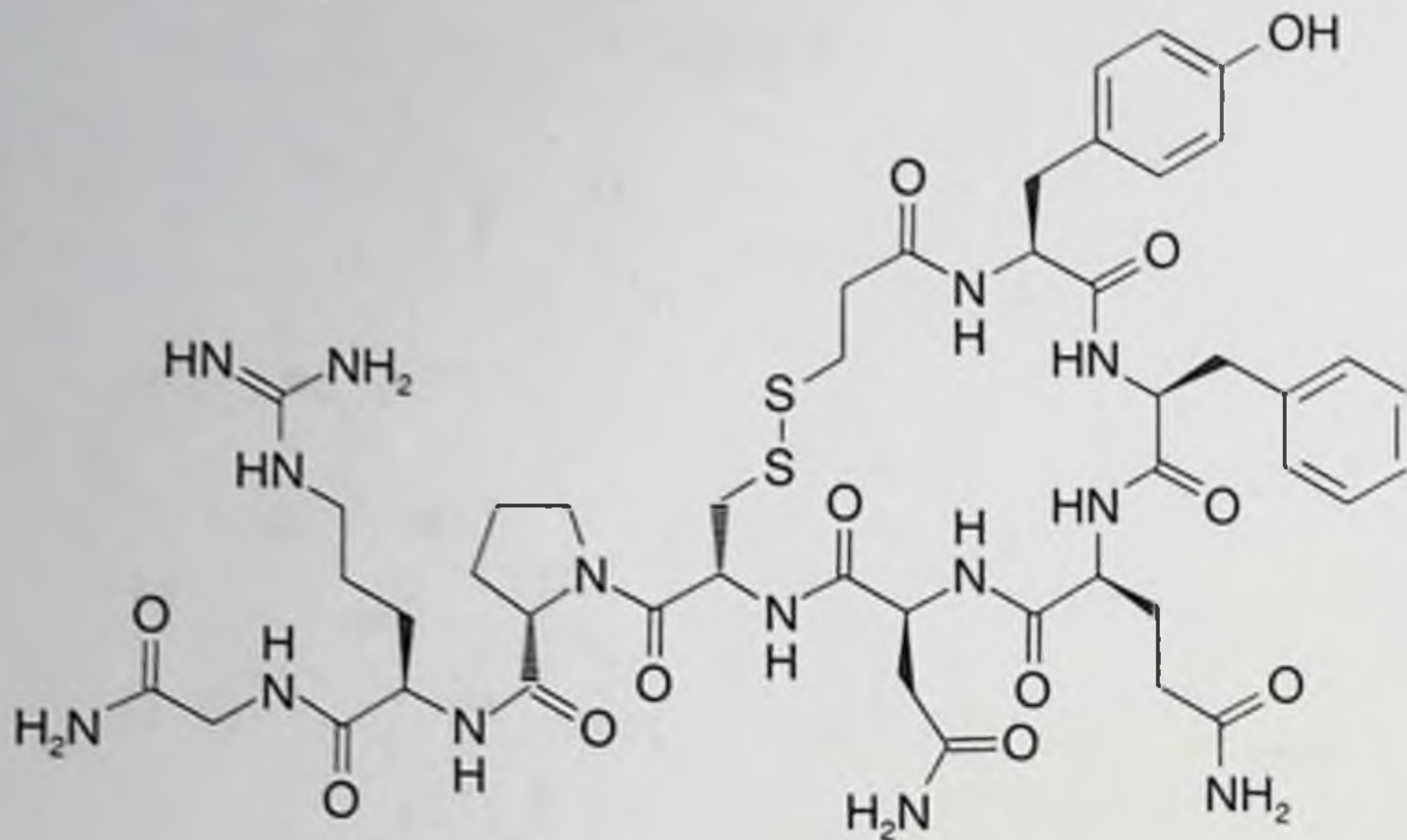


Fig. 18.14. Desmopressin structural formula

Pituitrin[®]

A hormonal product extracted from the posterior pituitary of cattle and pigs. The main active substances in pituitrin[®] are oxytocin and vasopressin. For intravenous, intramuscular administration.

Pharmacological effects

- ▶ Oxytocin: causes contraction of the uterine muscles.
- ▶ Vasopressin: increases total peripheral resistance and increases BP, helps regulate blood osmotic pressure, causing greater water reabsorption in convoluted tubules and lesser chloride reabsorption.

Therapeutic indications: diabetes insipidus, enuresis, primary and secondary dysfunctional labor, uterine subinvolution and hypotonic bleeding in the early postpartum period

Side effects: cerebral vasospasm, circulatory disorders, collapse (in large doses when administered rapidly)

Contraindications: severe atherosclerosis, hypertension, thrombophlebitis, threat of uterine rupture, fetal malpresentation

HORMONES PRODUCED BY THYROID

The thyroid gland produces two types of hormones:

- ▶ Iodine-containing thyroxine (T_4) and triiodothyronine (T_3) are produced by the follicles.
- ▶ Calcitonin is produced by parafollicular cells.

Functions of iodine-containing hormones

- ▶ Increases the basal metabolic rate: increased oxygen consumption by most tissues, increased body temperature, increased breakdown of proteins, carbohydrates, fats (decrease in blood cholesterol, body weight).

- Increases the effect of catecholamines (tachycardia).
- Participates in regulating growth and development (affects the formation of the brain, bone tissue and other organs and systems).

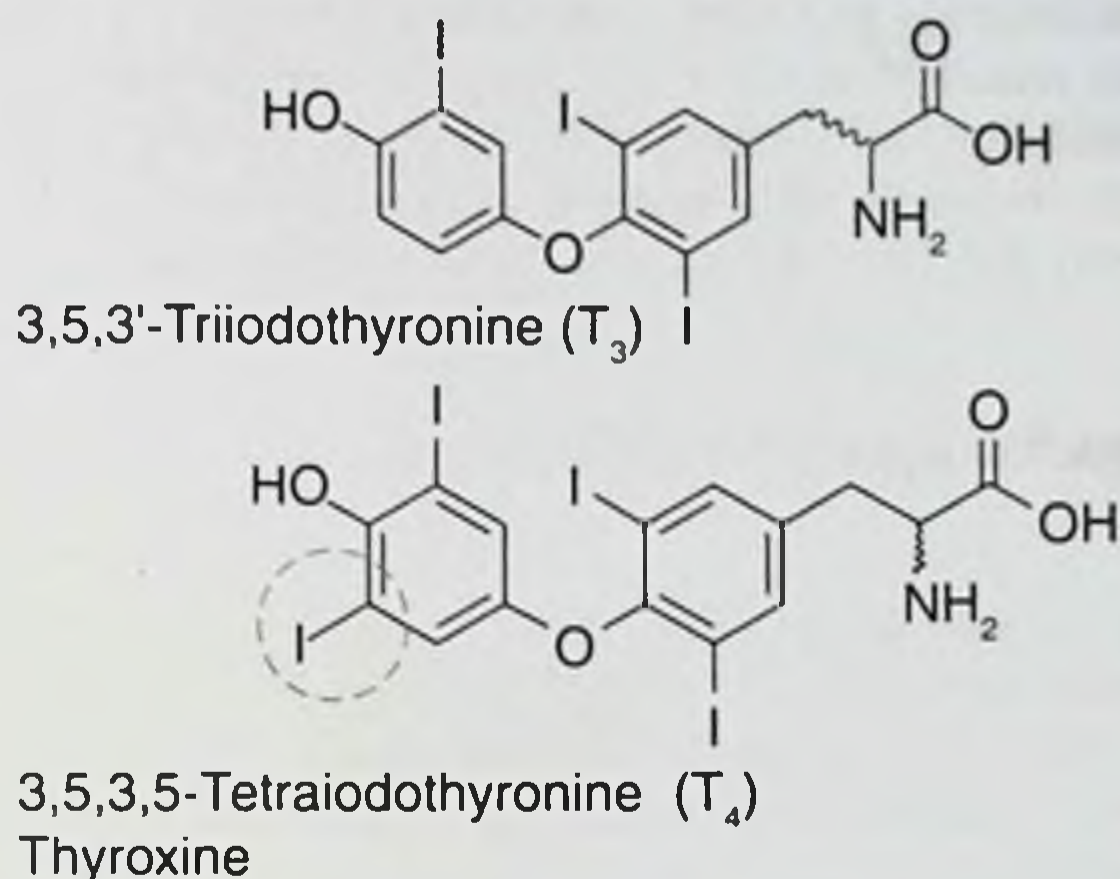


Fig. 18.15. Structural formulas of triiodothyronine and tetraiodothyronine

The synthesis of thyroxine (tetraiodothyronine) and triiodothyronine requires iodine from food. Iodides circulating in blood are absorbed by the thyroid gland, where they are oxidized to iodine, which interacts with the amino acid tyrosine. This produces mono- and diiodotyrosine, which are precursors of the thyroid hormones. The synthesized thyroxine and triiodothyronine are deposited in the follicles of the thyroid gland within thyroglobulin protein (Fig. 18.16).

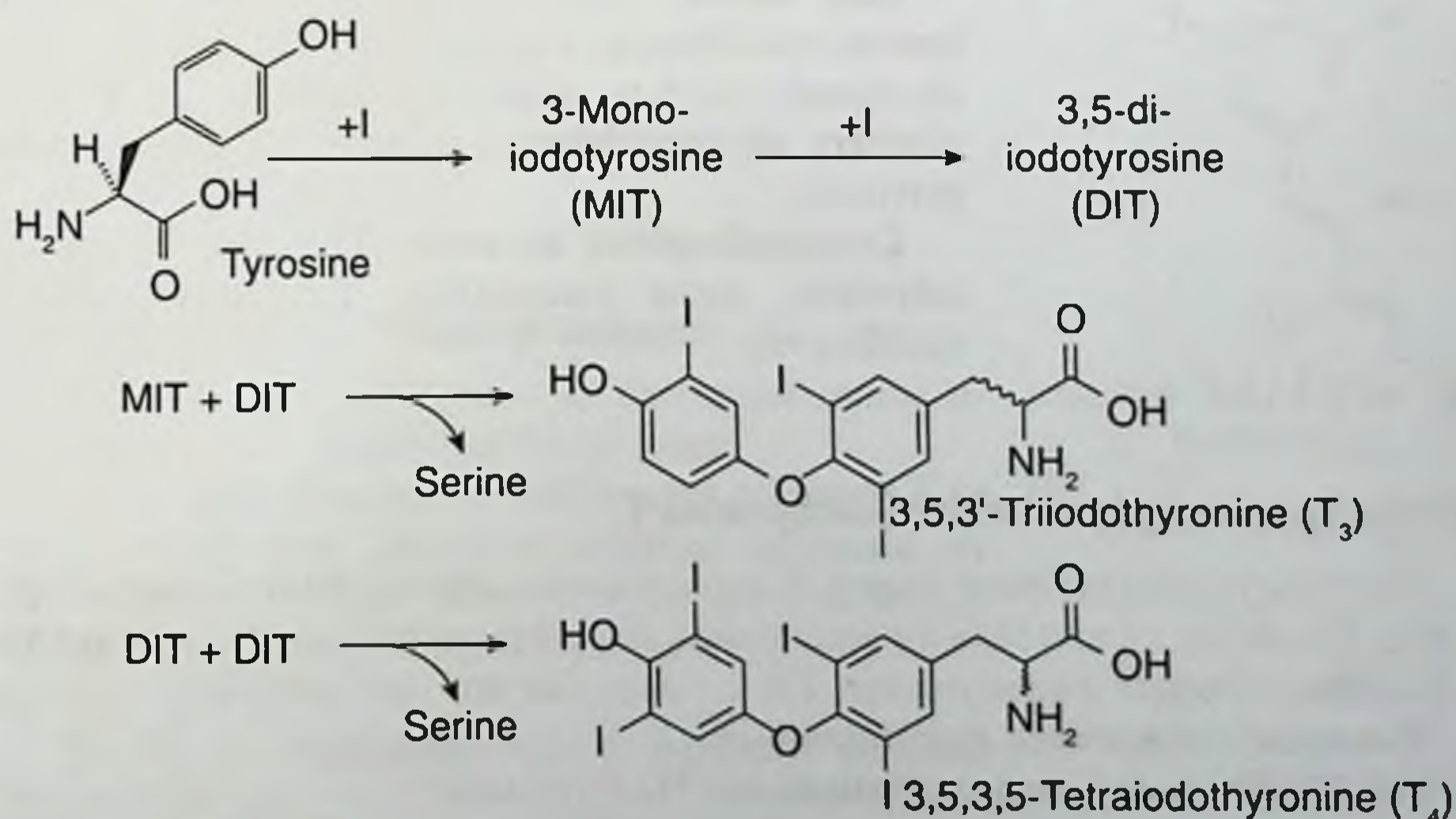


Fig. 18.16. Synthesis of triiodothyronine and tetraiodothyronine

From the thyroid, the hormones enter the bloodstream with proteases cleaving them from thyroglobulin. Iodide uptake by the thyroid, hormone synthesis and release into the bloodstream are regulated by thyroid-stimulating hormone, which is produced by the anterior pituitary. Circulating thyroxine is almost completely bound to globulin; triiodothyronine is bound to a lesser extent. Thyroxine can be considered a prohormone because it is mainly converted to triiodothyronine inside cells, which interacts with specific nuclear receptors. Receptors have a much greater affinity for triiodothyronine than for thyroxine.

Hormonal drugs for hypothyroidism

Classification

1. Monotherapy

- Levothyroxine sodium (L-Thyroxine⁺, Euthyrox⁺)
- Triiodothyronine hydrochloride⁺ (liothyronine⁺)

2. Combination therapy: Thyreocomb⁺ (levothyroxine sodium, liothyronine, potassium iodide)

Specifics of individual products

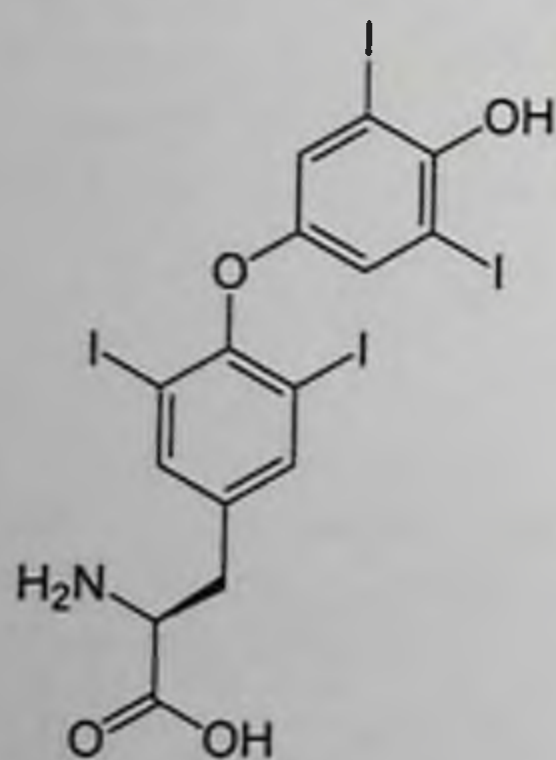


Fig. 18.17. 3,5,3',5'-Tetraiodo-L-thyronine

Levothyroxine sodium (L-Thyroxine⁺, Euthyrox⁺)

Synthetic thyroid hormone analog. $T_{1/2}$: 6–8 days. For oral administration.

Therapeutic indications: hypothyroidism

Side effects: tachyarrhythmia, retrosternal pain, tremor, restlessness, insomnia, hyperhidrosis, weight decreased, diarrhea, alopecia, adrenal dysfunction (in pituitary or hypothalamic hypothyroidism), allergic reactions

Contraindications: thyrotoxicosis, acute myocardial infarction, acute myocarditis, uncorrected adrenal insufficiency

Triiodothyronine hydrochloride⁺ (Liothyronine⁺)

Synthetic thyroid hormone analog. Faster acting than thyroxine (maximum activity within 24–48 hours) and lasts for several days. Its effect on the patient's metabolism is 3–5 times stronger than thyroxine. $T_{1/2}$: 2.5 days. For oral administration.

Therapeutic indications: hypothyroidism

For side effects and contraindications: see “L-Thyroxine”.

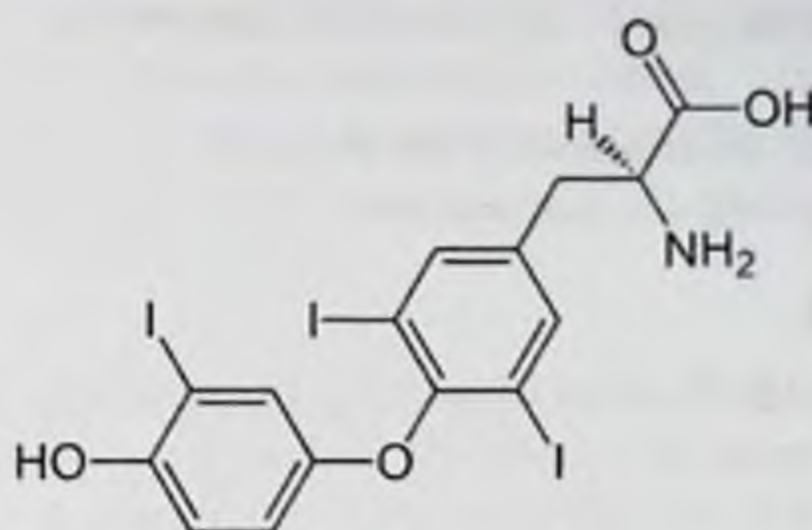


Fig. 18.18. (2S)-2-Amino-3-[4-(4-hydroxy-3-iodophenoxy)-3,5-diodophenyl]propanoic acid

Thyreocomb[®] (levothyroxine sodium, liothyronine, potassium iodide)

Therapeutic indications: hypothyroidism

For side effects and contraindications: see "L-Thyroxine".

ANTITHYROID AGENTS

Classification

1. Drugs inhibiting thyroid-stimulating hormone production by the anterior pituitary
 - Iodine[★].
 - Diiodothyrosine[★].
2. Drugs inhibiting the synthesis of thyroid hormones in the thyroid
 - Thiamazole (Mercazolyl[★])
 - Propylthiouracil[★]
3. Drugs disrupting iodine absorption by the thyroid
 - Potassium perchlorate[★]
4. Drugs destroying thyroid follicular cells
 - Radioactive iodine[★]

Specifics of individual products

Iodine is used in the form of molecular iodine or iodides. It is well absorbed in the GI tract.

Mechanism of action: It inhibits the production of thyrolyberine and thyroid-stimulating hormone by the anterior pituitary. Thyroid hormone production decreases accordingly. Iodine decreases the volume of the thyroid.

Therapeutic indications: mild to moderate forms of hyperthyroidism

Side effects: symptoms of iodism, allergic reactions to the product's components

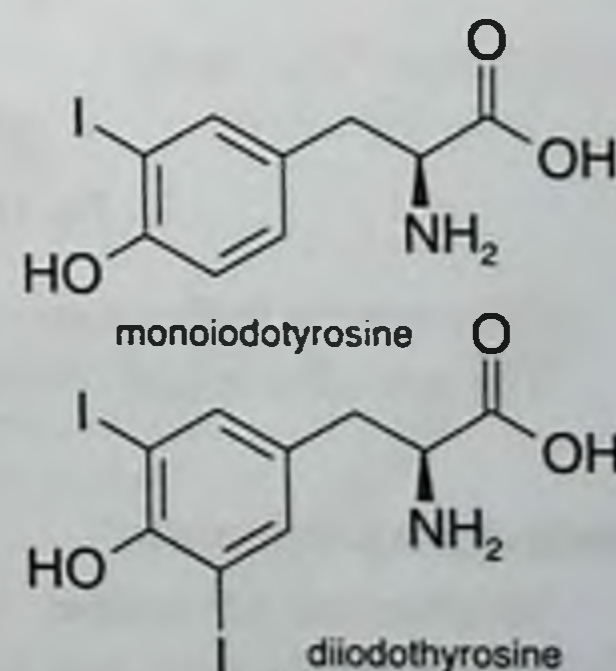


Fig. 18.19. Structural formulas of monoiodotyrosine and diiodotyrosine

Contraindications: secondary hyperthyroidism when administering iodine; pregnancy, breastfeeding

A similar mechanism of inhibition of thyroid-stimulating hormone release is observed when diiodothyrosine is administered. For oral administration.

Thiamazole (Mercazolyl⁺)

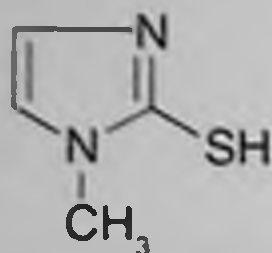


Fig. 18.20. 1-Methyl-3H-imidazole-2-thione

Mechanism of action: Thiamazole blocks thyroid hormone synthesis by inhibiting iodide peroxidase, which is involved in iodination of thyronine in the thyroid gland to form triiodo- and tetraiodothyronine (thyroxine). It reduces the internal secretion of thyroxine and the basal metabolic rate, accelerates iodide excretion from the thyroid gland, increases reciprocal synthesis and secretion of thyroid-stimulating hormone by the pituitary gland, which is accompanied by minor hyperplasia of the thyroid gland.

For oral administration.

Therapeutic indications: thyrotoxicosis

Side effects: leukopenia and agranulocytosis, goitrogenic effect [associated with increased production of the thyroid-stimulating hormone by the anterior pituitary (in response to decreased blood levels of circulating thyroid hormones)], arthralgia, allergic reactions

Contraindications: agranulocytosis, granulocytopenia (including a history thereof), cholestasis before treatment, breastfeeding

Propylthiouracil⁺

Similar to Mercazolyl in its action.

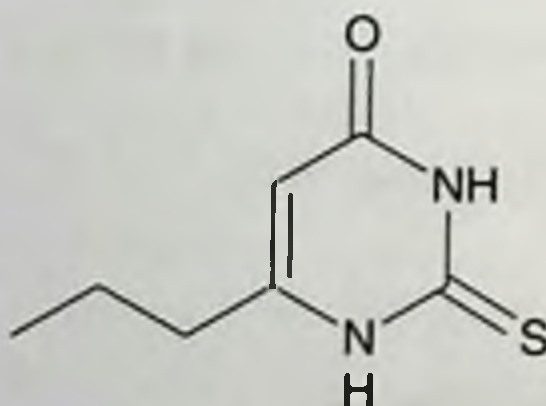


Fig. 18.21. 6-Propyl-2-sulfanylpurine-4-one

Therapeutic indications: thyrotoxicosis

For side effects and contraindications: see "Thiamazole"

Potassium perchlorate⁺

Mechanism of action: It inhibits iodine accumulation in the thyroid gland, thyroxine production, and has a thyreostatic effect.

Therapeutic indications: thyrotoxicosis

Side effects: thrombocytopenia, leukopenia, agranulocytosis, aplastic anemia, dyspepsia, liver failure, hyperthermia, goitrogenic effect

Contraindications: gastric and duodenal ulcers, hematopoietic disorders, pregnancy, breastfeeding

Radioactive iodine⁺

Mechanism of action: Destruction of thyroid cells mainly by β -rays (90% of radiation) and to a lesser extent, γ -rays.

The effect develops gradually (after 1–3 months and later). For oral administration.

Therapeutic indications: thyrotoxicosis

CALCITONIN

Calcitonin is a thyroid hormone synthesized in parafollicular cells. It is one of the major mediators of calcium and phosphorus metabolism.

Calcitonin (thyrocalcitonin⁺)

Regulates calcium and phosphorus metabolism in the body alongside parathyroid hormone and the active form of vitamin D₃ (a functional parathyroid hormone antagonist). $T_{1/2}$: 40–60 min. For intravenous, intramuscular, subcutaneous, intranasal administration.

Mechanism of action: Calcitonin suppresses Ca^{2+} release from bones; inhibits osteoclast activity and stimulates osteoblast production and activity; inhibits osteolysis, reduces elevated serum Ca^{2+} level; increases urinary Ca^{2+} , phosphorus and Na^+ excretion by reducing their reabsorption in renal tubules (Fig. 18.22).

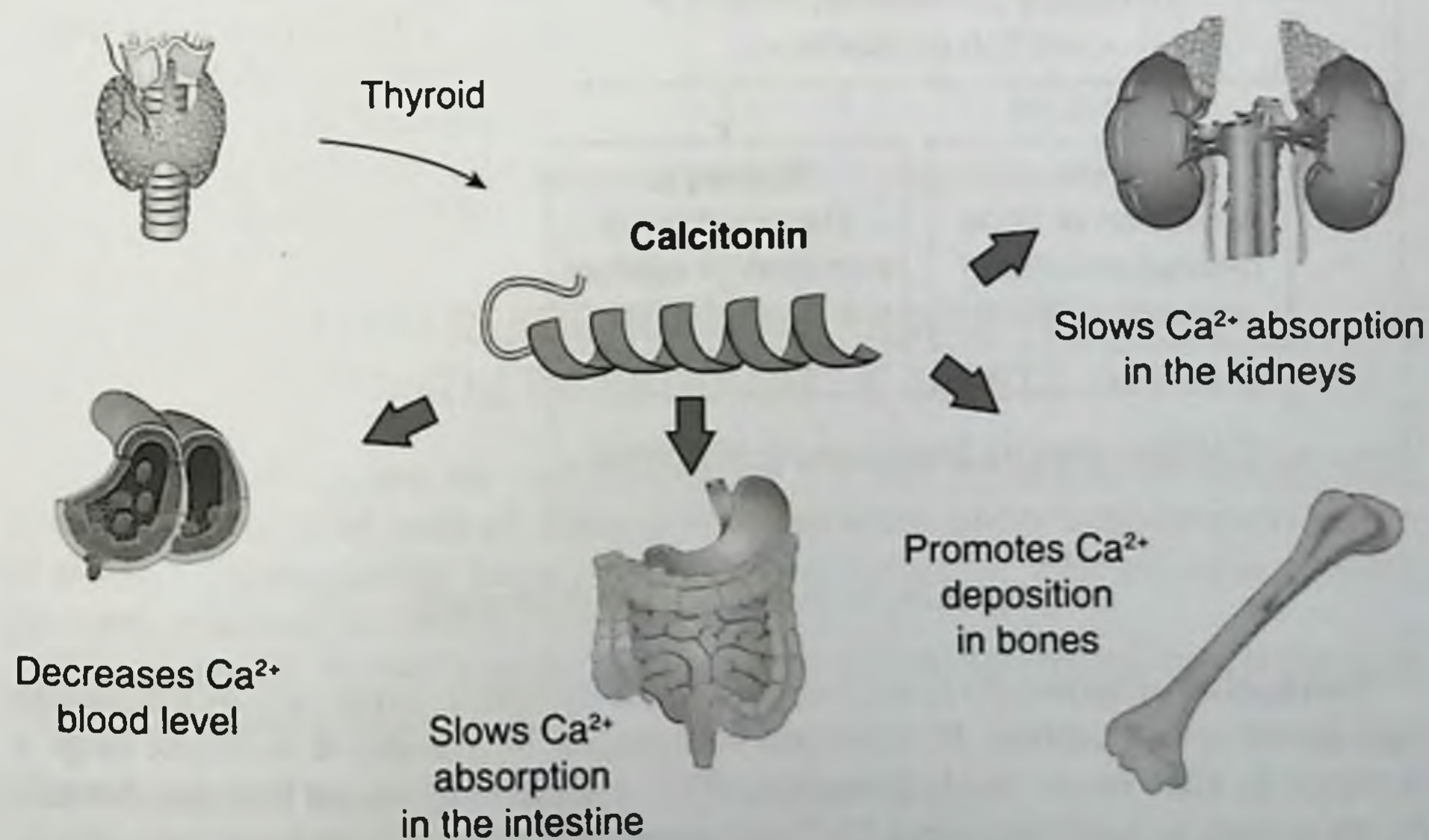


Fig. 18.22. Mechanism of action of calcitonin

Indications: osteoporosis, osteogenesis imperfecta, Paget's disease (osteitis deformans), avascular necrosis of femoral head, fibrous dysplasia, aggravation of traumatic bone lesions

Side effects: facial flushing, headache, dizziness, dysgeusia, diarrhea, nausea, lack of appetite, vomiting, arthralgia, fatigue, allergic reactions

Contraindications: hypocalcemia, pregnancy, chronic rhinitis (with intranasal drug administration)

Miacalcic is a synthetic salmon calcitonin. It is 30–40 times more active than human calcitonin and has a longer action.

PARATHYROID HORMONE PRODUCTS

Parathyroid glands secrete parathyroid hormone (PTH), a polypeptide consisting of 84 amino acid residues. Parathyroid hormone regulates Ca^{2+} and phosphorus metabolism by increasing Ca^{2+} blood levels in target organs — bones, intestine, kidneys — while phosphorus levels decrease (Fig. 18.23).

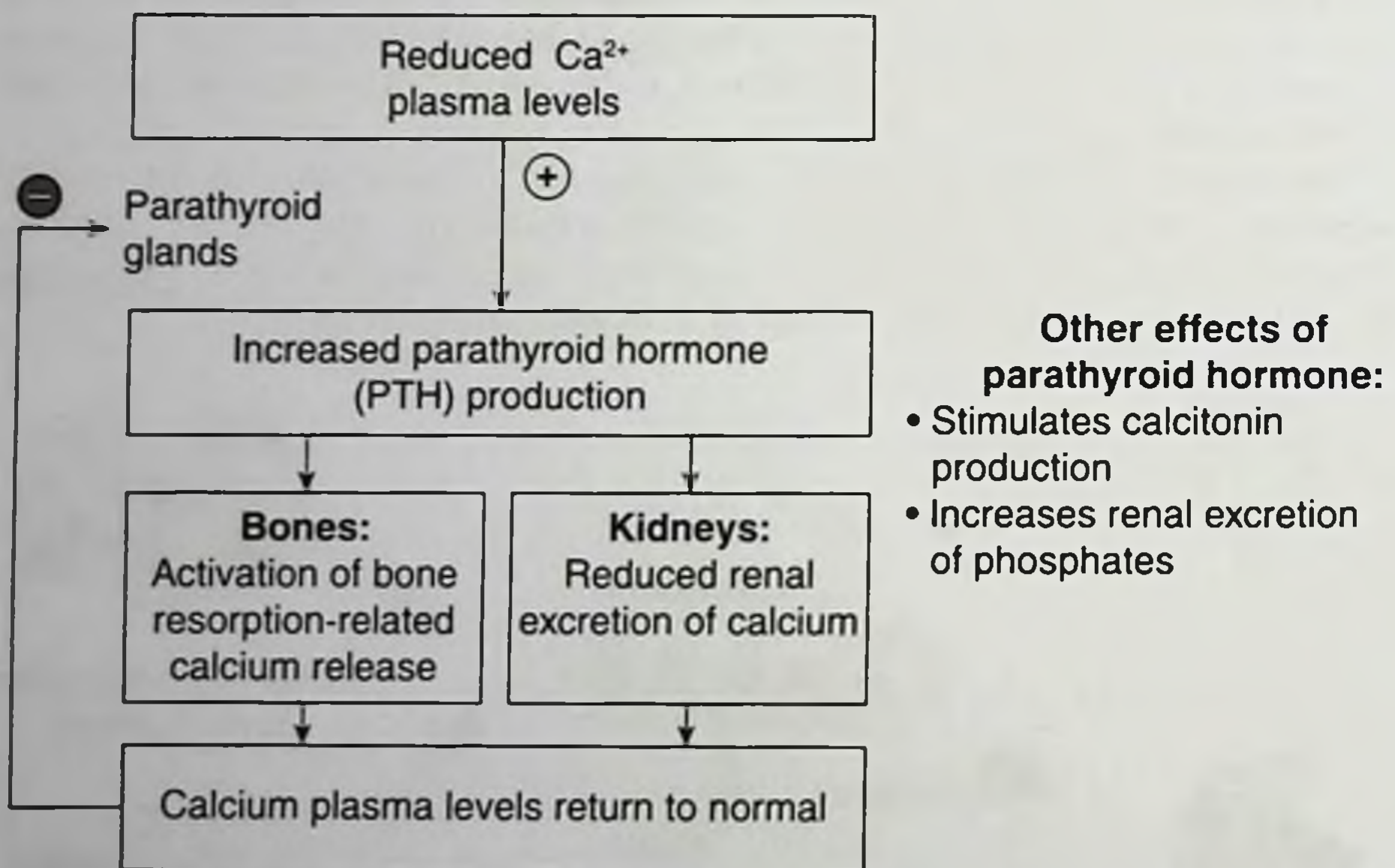


Fig. 18.23. Parathyroid hormone (PTH) effects

Mechanism of action: PTH activates adenylate cyclase in target cells by interacting with membrane receptors. Its secretion is regulated by a negative feedback loop: a decrease in Ca^{2+} blood levels stimulates PTH secretion while an increase inhibits PTHs, which in turn increases Ca^{2+} and phosphate release from bone into blood, inhibits the synthesis of collagen in osteoblasts, increases the destruction of the

mineral and organic part of bone by osteoclasts and osteocytes. PTH increases Ca^{2+} absorption from the intestine. It increases Ca^{2+} reabsorption in renal tubules and decreases phosphate reabsorption.

In medical practice, a product obtained from parathyroid glands of slaughtered cattle — **Parathyroidin*** — is used.

For subcutaneous and intramuscular administration. The onset of action occurs in 4 hours and lasts up to 24 hours.

Therapeutic indications: hypoparathyroidism, tetany, spasmophilia

Side effects: vomiting, diarrhea, adynamia, migraine, fibrous osteodystrophy, osteoporosis, allergic reactions

Contraindications: kidney failure, hypercalcemia, allergic reactions

Calcitonin and parathyroid hormone are compared in Figure 18.24.

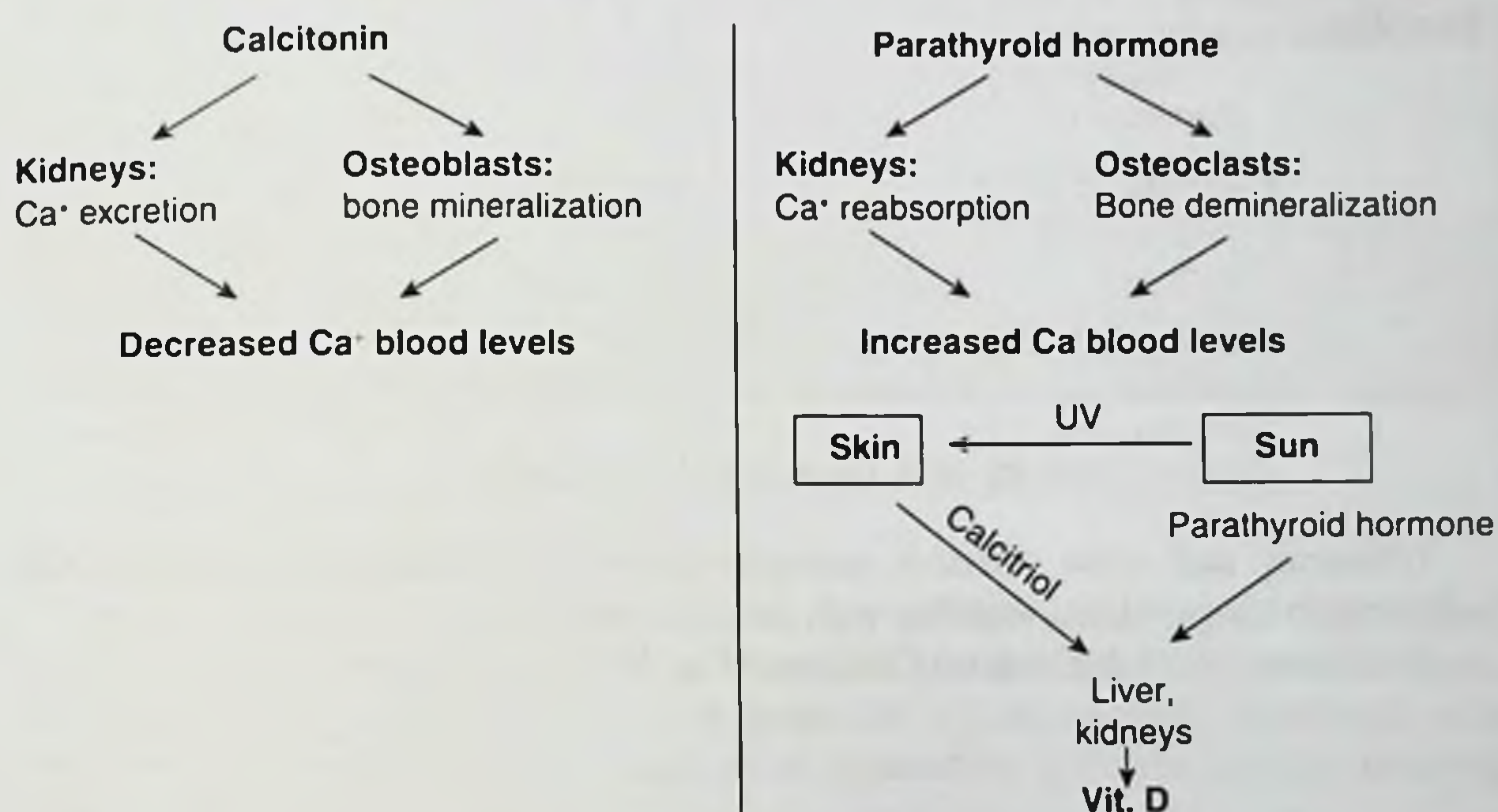


Fig. 18.24. Comparative characteristic of calcitonin and parathyroid hormone

PANCREATIC HORMONE PRODUCTS, SYNTHETIC ANTIDIABETIC AGENTS

Pancreatic hormones are very important for the regulation of carbohydrate metabolism. β -cells of islets of Langerhans (pancreatic islets) synthesize proinsulin to produce insulin, which has a pronounced hypoglycemic effect; α -cells produce glucagon, which causes hyperglycemia.

The pancreatic hormone insulin, which is used to treat diabetes mellitus, is the most critical in medical practice.

Classification of insulin products

1. Fast-acting insulin, peak effect 1–4 hours post-dose and short duration of action (4–8 hours)

- Insulin soluble [human genetically engineered] (Actrapid NM⁺, Actrapid MS⁺, Humulin Regular⁺), insulin soluble [porcine monocomponent] (Insulin S⁺)
- 2. Intermediate-acting insulin, peak effect 6–12 hours post-dose and medium duration of action (18–24 hours)
 - Insulin biphasic [human genetically engineered] (Monotard NM⁺), isophane insulin [human genetically engineered] (Protafan NM⁺, Insuman Basal GT⁺), compound insulin zinc suspension (Insulin Lente SPP⁺)
- 3. Long-acting insulin, peak effect 12–18 hours post-dose and long duration of action (24–40 hours)
 - Insulin biphasic [human genetically engineered] (Ultratard NM⁺), humulin U-L⁺, insulin glargine, insulin isophane

Insulin

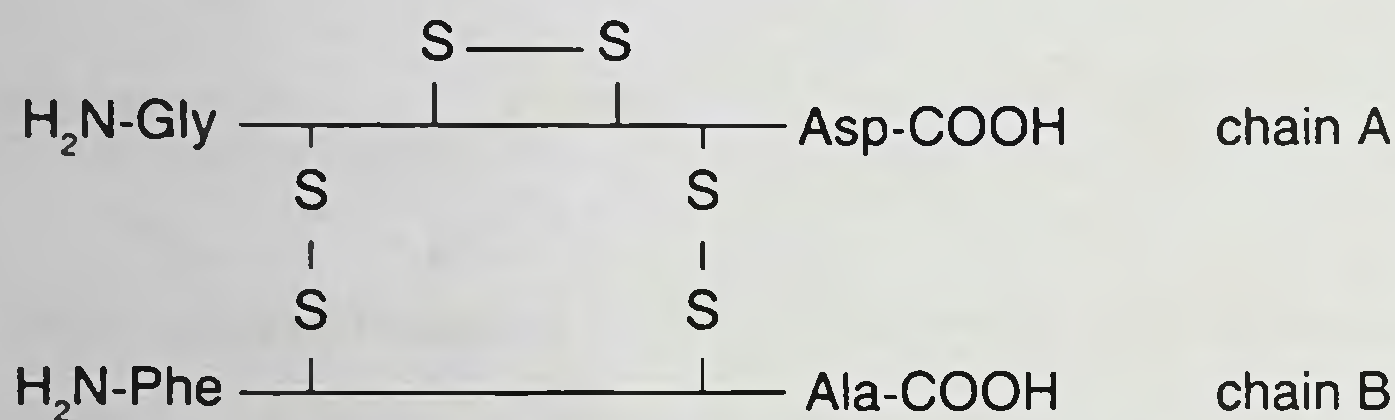


Fig. 18.25. Chemical structure of insulin

Universal and most effective antidiabetic agent. A polypeptide having two polypeptide chains linked together with disulfide bridges.

Insulin secretion depends on Ca^{2+} ions (Fig. 18.26).

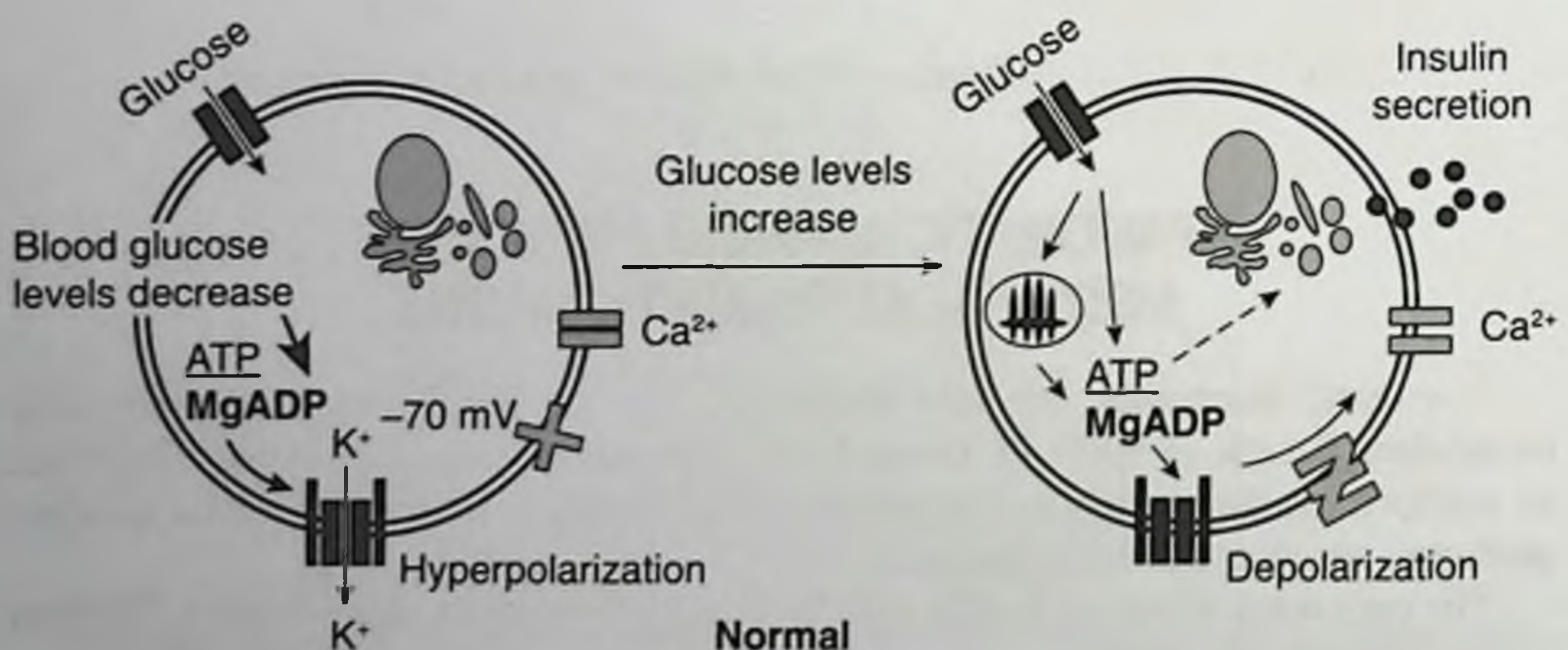


Fig. 18.26. Mechanism of insulin secretion in healthy people

Glucose triggers insulin secretion. After glucose penetrates into β -cells with the help of a special glucose transporter (GLUT), it is metabolized and increases intracellular ATP levels. By blocking ATP-sensitive potassium channels, the latter causes depolarization of the cell membrane. This promotes the uptake of Ca^{2+} ions by β -cells (through opening of voltage-gated calcium channels) and insulin exocytosis. Amino acids also stimulate insulin production. In the liver, insulin is inactivated by the enzyme insulinase.

The effects of insulin on metabolism are shown in Table 18.3.

Table 18.3. Effects of insulin on metabolism

	Liver	Adipocytes	Muscles
Carbohydrates	$\uparrow$ glycogenesis, $\uparrow$ glycolysis, $\downarrow$ glycogenolysis, $\downarrow$ gluconeogenesis, $\downarrow$ ketogenesis	$\uparrow$ glucose uptake $\uparrow$ glycerol synthesis	$\uparrow$ glucose uptake by increasing the amount and activation of GLUT-4 $\uparrow$ glucose utilization through glycogenesis $\uparrow$ glycogenolysis, $\downarrow$ glycogenolysis $\uparrow$ glycolysis
Fats	$\uparrow$ lipogenesis, $\uparrow$ antiketogenesis, $\uparrow$ free fatty acids and VLDL	$\uparrow$ triglycerides $\uparrow$ fatty acid synthesis $\downarrow$ lipolysis	
Proteins	$\downarrow$ proteolysis		$\uparrow$ amino acid uptake $\uparrow$ protein synthesis

Mechanism of anti-glycemic action of insulin

Insulin interacts with receptors on the cell surface consisting of two α - and β -subunits. The resulting insulin-receptor complex is internalized through endocytosis and the released insulin exerts its effect inside the cell. In addition, β -subunits with tyrosine kinase activity are activated upon interaction with the surface receptor (Fig. 18.27).

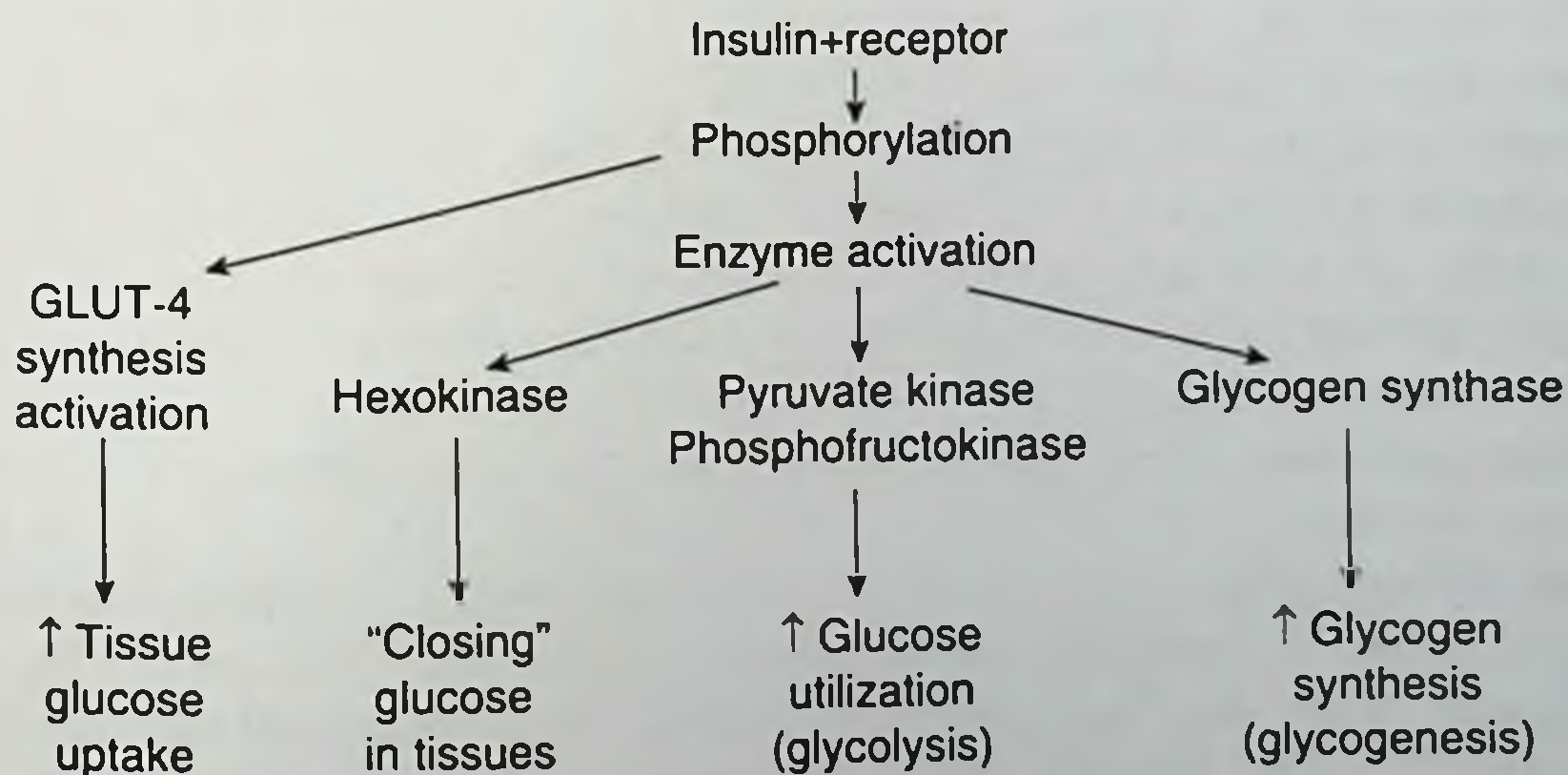


Fig. 18.27. Mechanism of anti-glycemic action of insulin

Insulin activates the transport of glucose through cell membranes and its utilization by muscles and adipose tissues. Glycogenesis increases (insulin activates glycogen synthase). In the liver and skeletal muscles, it reduces glycogenolysis. Insulin inhibits the conversion of amino acids into glucose. Decreased blood glucose levels eliminate glucosuria and the associated increased diuresis (polyuria) and thirst (polydipsia).

Insulin stimulates protein synthesis. Normalization of carbohydrate metabolism results in the normalization of protein metabolism (urinary nitrogen compound levels decrease) and fat metabolism (ketone bodies — acetone, acetoacetic acid, β -Hydroxybutyric acid — are no longer determined in blood and urine). Weight loss and extreme hunger (bulimia) associated with the breakdown of fats and intensive conversion of proteins into glucose stops.

Principles of insulin therapy

- ▶ The drug's daily dose should be as close as possible to the physiological dose. Up to 70% of the dose should be administered during the day and the remaining 30% before bedtime. This principle simulates the true pattern of hormone production by the pancreas.
- ▶ The optimal dose is selected based on the daily drug demand, which depends on the physiological characteristics of the body. For example, to break down 1 bread unit, one person needs 1/2 insulin unit, while another person might need 4 units.
- ▶ To determine the dose, blood glucose levels should be measured after a meal while taking into account the number of calories consumed. If the glucose level is higher than normal, the drug dose is raised by several units until this parameter is within the normal range.
- ▶ Doses can be adjusted according to glycemic index: for every 0.28 mmol/L of glucose over 8.25 mmol/L, 1 unit of the drug should be added, meaning that each additional unit of sugar requires 2–3 units of the drug.

For subcutaneous, intramuscular, intravenous administration (insulin is broken down by digestive enzymes when taken orally).

Short-acting insulin products exert their effect quickly, especially when administered intravenously. Intermediate- and long-acting products are absorbed more slowly from the injection site (administered subcutaneously, intramuscularly). A single injection of these formulations produces a long-lasting effect. They are not used to treat diabetic coma.

Therapeutic indications: type I diabetes, diabetic coma (short-acting drugs by intravenous route)

Side effects: hypoglycemia, post-injection lipodystrophy, pain and inflammatory reactions at the injection site, insulin resistance (associated with a reduced number of receptors, decreased affinity; production of insulin antibodies), allergic reactions

Contraindications: hypoglycemia, insulinoma, allergic reactions

Synthetic oral antidiabetic agents

Classification.

- I. Agents that increase endogenous insulin secretion by blocking ATP-sensitive potassium channels in pancreatic β -cells
 - A. Sulfonylurea derivatives
 - First generation
 - Carbutamide, tolazamide, tolbutamide, chlorpropamide
 - Second generation
 - Glibenclamide (Maninil[®]), gliclazide (Diabeton[®]), glipizide (Glynase[®]), gliquidone (Glurenorm[®])
 - Third generation
 - Glimepiride (Amaryl[®])
 - B. Benzoic acid derivatives
 - Repaglinide (NovoNorm[®])
 - C. D-phenylalanine derivatives
 - Nateglinide (starlix[®]).
- II. Agents that inhibit gluconeogenesis and promote glucose uptake by tissues
 - Biguanides.
 - Metformin (Siofor[®], Glucophage[®]).
- III. Agents that increase tissue sensitivity to insulin
 - Thiazolidinediones (glitazones)
 - Rosiglitazone (Avandia[®]), Pioglitazone (Pioglar[®])
- IV. Agents that inhibit glucose absorption in the small intestine
 - α -glucosidase inhibitors
 - Acarbose (Glucobay[®]).
- V. Glucagon production inhibitors
 - Synthetic amylin analog
 - Pramlintide[®].
- VI. Agents that inhibit glucose reabsorption in the kidneys
 - Sodium-glucose co-transporter 2 (SGLT2) inhibitors (gliflozins)
 - Dapagliflozin (Forxiga[®]), Empagliflozin (Jardiance[®]), Canagliflozin (Invokana[®])

Specifics of individual products

Glibenclamide (Maninil[®])

Glibenclamide is the main representative of oral antidiabetic sulfonylurea derivatives. It can be used in combination with biguanides. Time of action: up to 24 hours. Glibenclamide is metabolized in the liver. $T_{1/2}$: 3 to 10–16 hours. Excreted in urine and bile in approximately equal amounts.

Mechanism of action: Sulfonylurea derivatives block ATP-sensitive K^+ (KATP) channels, which causes voltage-gated Ca^{2+} -channels to open, increased intracellular

Ca^{2+} levels, and increased insulin release from β -cells. Thus, these drugs act indirectly by increasing the secretion of endogenous insulin (Fig. 18.28).

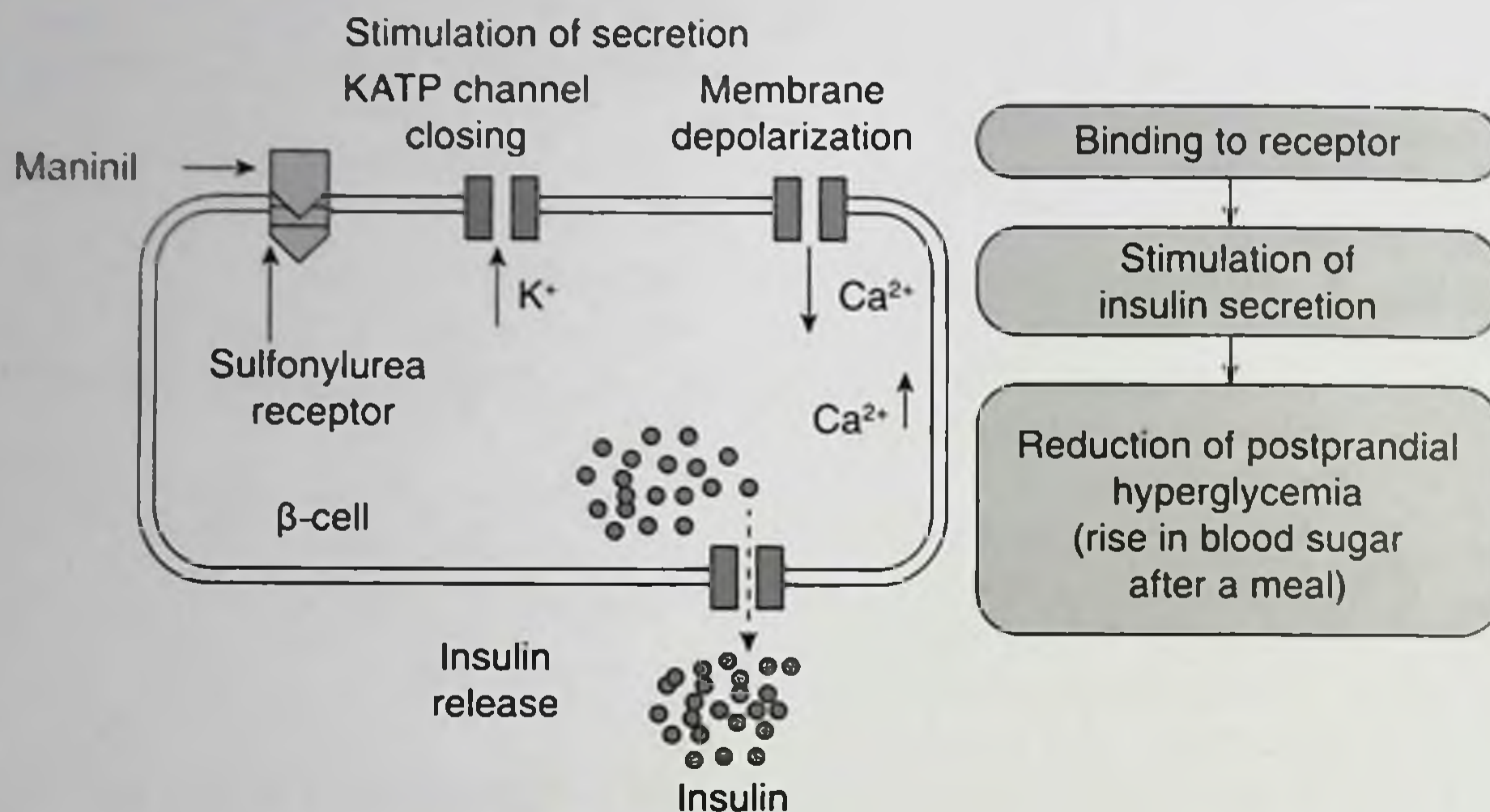


Fig. 18.28. Mechanism of action of sulfonylurea derivatives

Additional pharmacological effects: Glibenclamide improves insulin sensitivity in the target tissues and has antiaggregant and cholesterol-lowering effects.

Therapeutic indications: type 2 diabetes mellitus in patients whose response to dietary measures is inadequate. For oral administration.

Side effects: dyspepsia (nausea, vomiting, diarrhea), dysgeusia, cholestasis, liver failure, allergic reactions, suppression of hematopoiesis

Contraindications: precoma and coma, ketoacidosis, leukopenia, allergic reactions to sulfonamide drugs, less than 18 years of age, pregnancy, breastfeeding

Gliquidone (Glurenorm[®])

Gliquidone is one of the most effective and well tolerated sulfonylurea drugs. Time of action: 8–12 hours. It may be used in combination with biguanides. Metabolized in the liver. $T_{1/2}$: 1.5 hours. Metabolites are excreted in bile, which allows this drug to be used in diabetic patients with kidney disease and diabetic nephropathy.

Additional pharmacological effects: Gliquidone improves insulin sensitivity in the target tissues and has antiaggregant and lipid-lowering effects.

For the mechanism of action, therapeutic indications, side effects, and contraindications, see “Glibenclamide”.

Gliclazide (Diabeton[®])

A sulfonylurea derivative. Metabolized in the liver. $T_{1/2}$: 12–20 hours. Excreted mainly in urine. Can be used in combination with biguanides.

Additional pharmacological effects: Increases the sensitivity of peripheral tissues to insulin, has a hemovascular effect [reduces the risk of microthrombosis since it partially inhibits platelet aggregation and adhesion and reduces the concentration of platelet activation factors (β -thromboglobulin, thromboxane B_2), restores fibrinolytic activity of endothelial cells, increases tissue plasminogen activator (tPA) activity].

For the mechanism of action, therapeutic indications, side effects, and contraindications, see "Glibenclamide".

Glimepiride (Amaryl[®])

A sulfonylurea derivative. It is highly active and well tolerated. Bioavailability is absolute. Metabolized in the liver. $T_{1/2}$: 5–8 hours. Excreted as metabolites in urine (60%) and in bile (40%).

Additional pharmacological effects: anti-aggregant (selectively inhibits COX and reduces the conversion of arachidonic acid to TXA_2), lipid-lowering [normalizes lipid levels, reduces lipid peroxidation, increases endogenous α -tocopherol levels, catalyzes the activity of glutathione peroxidase and superoxide dismutase (reduces the severity of oxidative stress)].

For the mechanism of action, therapeutic indications, side effects, and contraindications, see "Glibenclamide".

Metformin (Siofor[®])

A derivative of biguanides. In combination with insulin, it is prescribed for insulin-resistant forms of diabetes, and resistance to antidiabetic drugs such as sulfonylureas. Bioavailability: 50–60%. Not metabolized. $T_{1/2}$: 6.2 hours. Excreted in urine as unchanged drug.

Mechanism of action: Metformin inhibits gluconeogenesis in the liver by activation of AMP-activated protein kinase (AMPK, adenosine monophosphate-activated protein kinase), increases tissue sensitivity to insulin, increases peripheral glucose uptake (by GLUT4 [glucose transporter, type 4] phosphorylation), increases fatty acid oxidation and reduces glucose absorption from the GI tract (Fig. 18.29).

Additional pharmacological effects: Reduces serum levels of triglycerides, cholesterol and LDL; does not change the levels of other lipoproteins. Stabilizes or reduces body weight. If there is no insulin in blood, it has no therapeutic effect. Does not cause hypoglycemic reactions. Improves fibrinolytic properties by inhibiting tissue-type plasminogen activator and plasminogen activator inhibitor-1. Metformin lowers body weight due to its anorexigenic action.

Therapeutic indications: type 2 diabetes mellitus (especially in obesity) in adults

Side effects: Lactic acidosis; GI disorders (diarrhea, nausea, flatulence, dyspepsia, metallic taste in the mouth, impaired absorption of vitamin B_{12}); skin allergic reactions

Contraindications: severe or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma; severe liver and kidney failure, pregnancy, breastfeeding

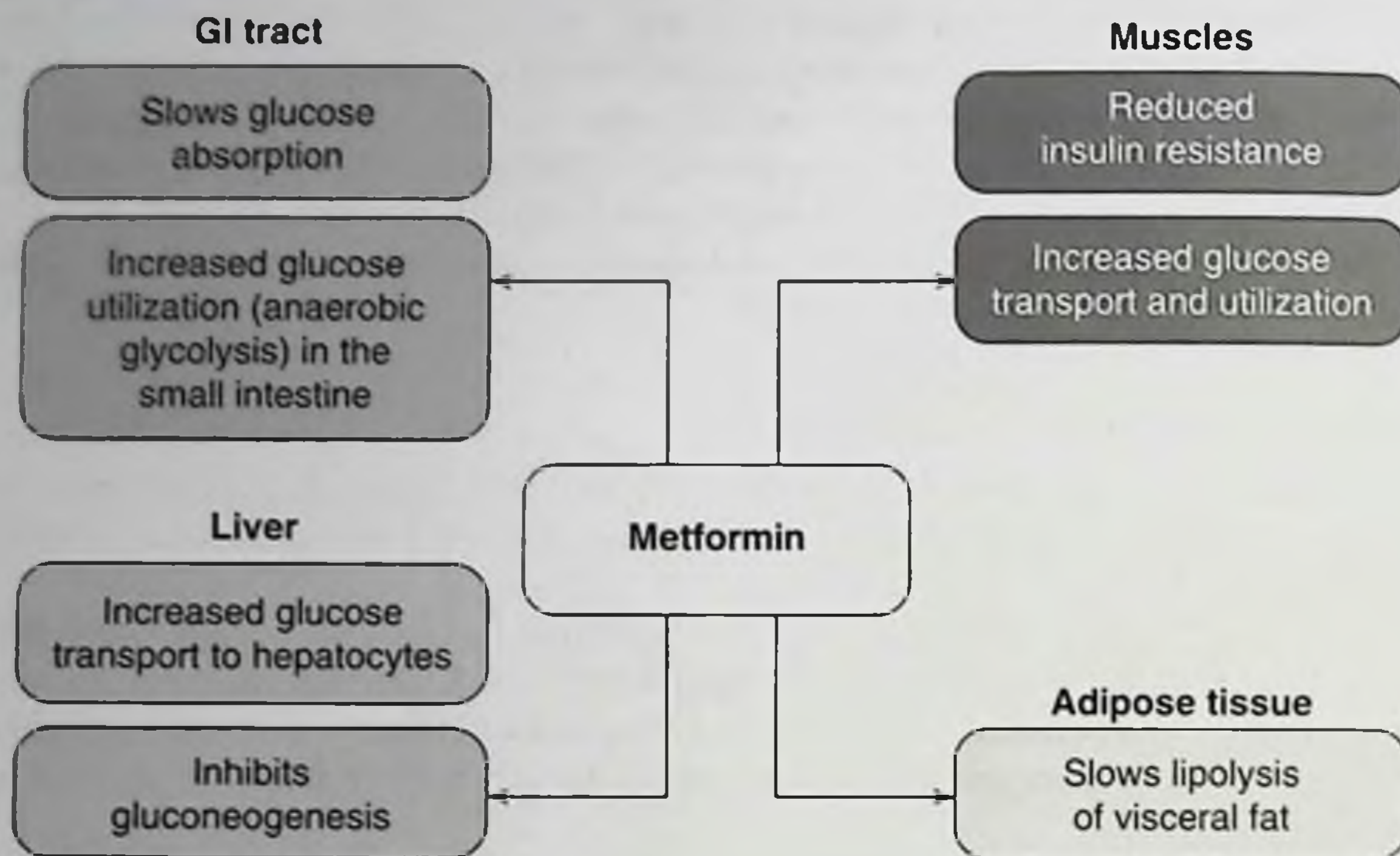


Fig. 18.29. Mechanism of action of metformin

Rosiglitazone (Avandia[®]), Pioglitazone (Pioglar[®])

Oral hypoglycemic agents from the thiazolidinedione group. Selective PPAR- γ (*Peroxisome proliferator- activated receptor gamma*) agonists. Bioavailability is absolute. Pioglitazone is metabolized in the liver to form active metabolites. Pioglitazone $T_{1/2}$: 3–7 hours, $T_{1/2}$ of metabolites: 16–24 hours. Excreted in urine and bile. Rosiglitazone is metabolized in the liver to form inactive metabolites. $T_{1/2}$: 3–4 hours. Excreted in urine and bile.

Mechanism of action: PPAR- γ is a nuclear receptor located in adipose and muscle tissues, heart muscle, liver, and kidney. It regulates the transcription of insulin-responsive genes involved in glucose production, transport and utilization, and fatty acid metabolism. Thiazolidinediones bind to PPAR- γ and increase tissue sensitivity to insulin, thus eliminating insulin resistance (Fig. 18.30).

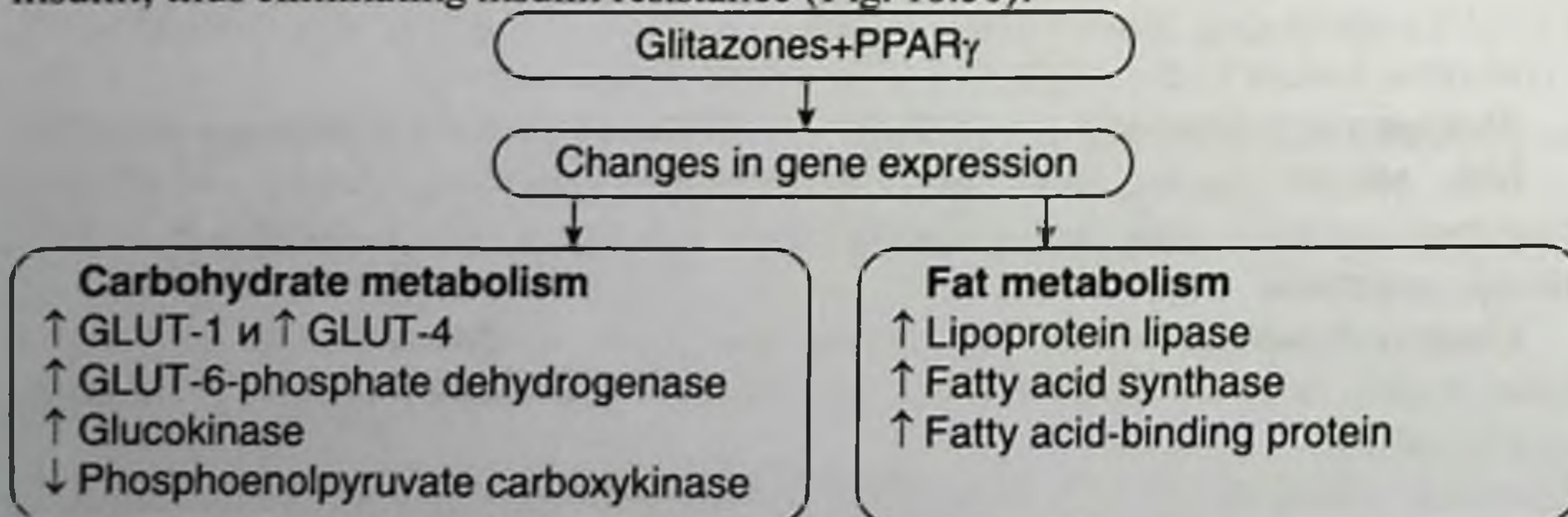


Fig. 18.30. Mechanism of action of glitazones

Therapeutic indications: type 2 diabetes mellitus

Side effects: hypoglycemia, anemia, peripheral edema, worsening of congestive heart failure, macular edema, hepatotoxicity

Contraindications: liver disease, edema of any origin, heart failure, ketoacidosis, pregnancy, breastfeeding

Acarbose (Glucobay[®])

A complex oligosaccharide, pancreatic α -amylase and intestinal α -glucosidase inhibitor. Acarbose acts locally in the GI tract and is metabolized in the GI tract, mainly by intestinal bacteria, but also by digestive enzymes. It is practically not absorbed.

Mechanism of action: Acarbose demonstrates a competitive, reversible inhibition of pancreatic α -amylase and intestinal α -glucosidase hydrolase, which delays glucose absorption and reduces postprandial hyperglycemia. Pancreatic α -amylase catalyzes the hydrolysis of complex starches to oligosaccharides in the intestinal lumen, whereas α -glucosidases associated with intestinal membranes hydrolyze oligosaccharides, trisaccharides and disaccharides to glucose and other monosaccharides in the brush borders of the intestinal lining (Fig. 18.31)..

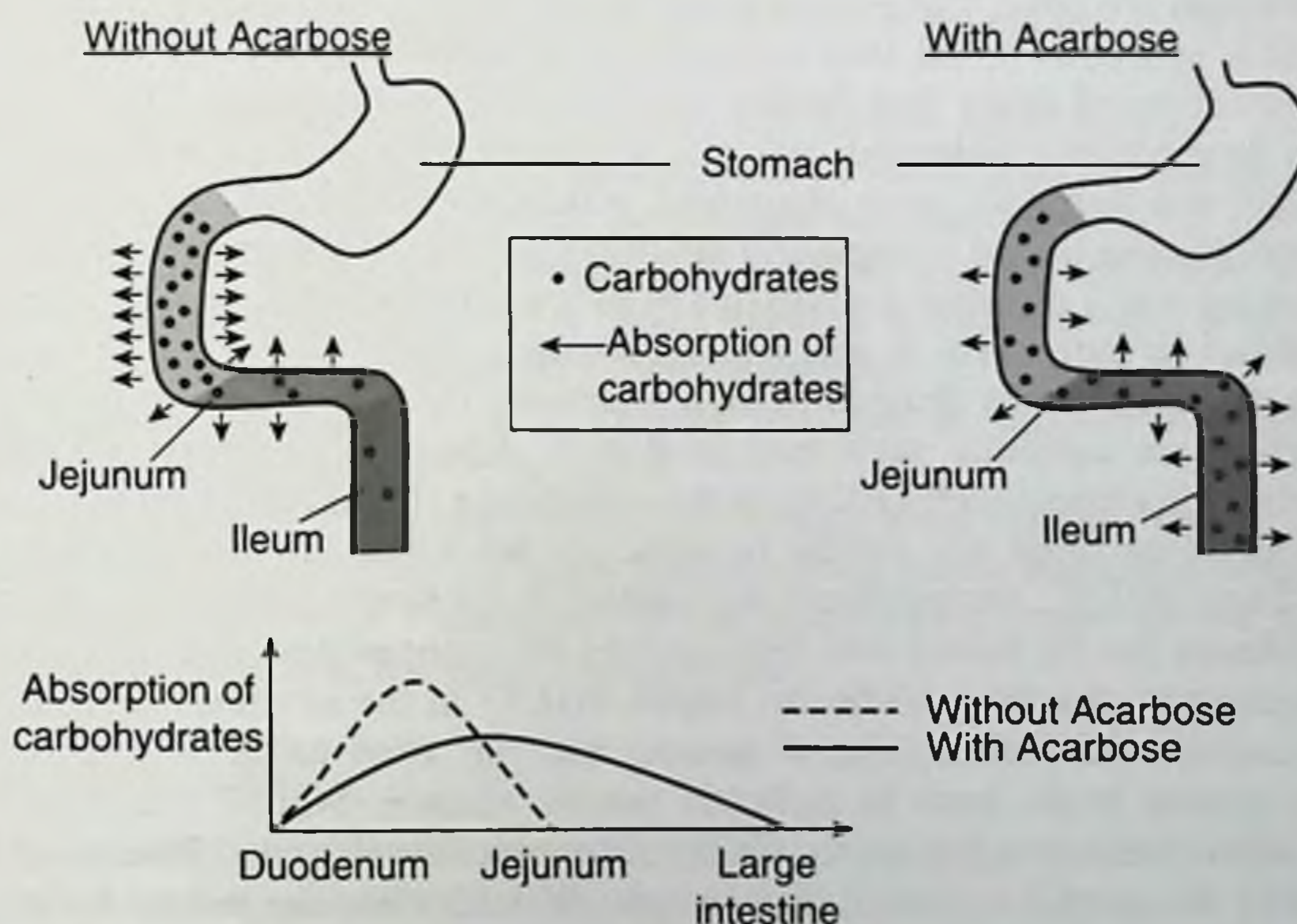


Fig. 18.31. Mechanism of action of Acarbose

Therapeutic indications: type 2 diabetes mellitus

Side effects: GI disorders (abdominal pain, diarrhea, flatulence), allergic reactions

Contraindications: diabetic ketoacidosis, liver failure, inflammatory bowel disease, pregnancy, breastfeeding, less than 18 years of age, allergic reactions

Repaglinide (NovoNorm[®]), Nateglinide (starlix[®]) – are meglitinides

oxidation and binding with glucuronic acid) to inactive metabolites. $T_{1/2}$: 1 hour. Excreted predominantly in bile (90%) and urine.

Nateglinide is a D-phenylalanine derivative. Nateglinide has a faster but less persistent effect on insulin secretion than repaglinide.

Advantages: control of postprandial hyperglycemia, rapid onset of action, can be used in persons with irregular food intake

Disadvantages: risk of hypoglycemia, weight gain

Mechanism of action: It blocks KATP channels of pancreatic β -cells, causes their depolarization, which leads to opening of calcium channels and, as a consequence, increased insulin secretion due to fusion of secretory granules with the cell membrane and release of their contents. Insulinotropic response develops after 30 min post-dose and is accompanied by a decrease in blood glucose levels during meals (insulin concentration does not increase between meals).

Therapeutic indications: type 2 diabetes mellitus May be combined with biguanides.

Side effects: hypoglycemia, abdominal pain, diarrhea, liver failure, allergic reactions

Contraindications: type 1 diabetes, diabetic coma, severe liver failure, ketoacidosis, pregnancy or breastfeeding, less than 18 years of age

Gliflozins are drugs that block glucose reabsorption in the kidneys.

A new approach to the treatment of type 2 diabetes mellitus is based on the administration of drugs that inhibit renal glucose reabsorption. The precursor of this drug group is phlorizin, which was isolated from apple tree bark in 1835. Phlorizin was found to cause glucosuria, which was due to SGLT1 and SGLT2 (sodium-glucose linked transporter) blockade. It was not suitable for clinical use for treating type 2 diabetes mellitus due to its low selectivity for renal transporters: in addition to glucosuria, it also caused diarrhea. These findings were the basis for the development of drugs with high selectivity for SGLT2. Three drugs from this group are currently registered in Russia: dapagliflozin (Forxiga[®]) (2014), empagliflozin (Jardiance[®]) (2014), and canagliflozin (Invokana[®]) (2015).

These three drugs are similar in structure but differ in their selectivity for SGLT2 and SGLT1. Dapagliflozin and empagliflozin have higher selectivity, while canagliflozin has the lowest selectivity among the registered gliflozin derivatives.

Mechanism of action: Gliflozins inhibit SGLT2 in the proximal renal tubules, which reduces the reabsorption of glucose and Na^+ from tubule lumen, reduces plasma glucose levels, leads to moderate osmotic diuresis. SGLT2 inhibitors block about 30% of glucose reabsorption. Unlike other antidiabetic agents, these drugs have an insulin-independent mechanism of action. SGLT2 inhibitors reduce fasting and postprandial plasma glucose levels. Treatment with gliflozins has an insignificant risk of hypoglycemia. This is due to the fact that SGLT2 inhibitors increase endogenous glucose production and glucagon secretion.

Non-glycemic effects: decrease in BP and uric acid blood levels, body weight, albuminuria reduction.

Side effects: hypoglycemia, urogenital infections (due to glucosuria), polyuria, increased creatinine and urea blood levels

Contraindications: type 1 diabetes, ketoacidosis, severe kidney failure, pregnancy, breastfeeding, less than 18 years of age or above 75 years

Incretin mimetics (stimulate the release of endogenous insulin)

Classification

A. Glucagon-like peptide-1 (GLP-1) receptor agonists

- ▶ Exenatide (Byetta[®])
- ▶ Liraglutide (Victoza[®])

B. Dipeptidyl peptidase-4 inhibitors inactivate glucagon-like peptide-1

- ▶ Sitagliptin (Januvia[®])
- ▶ Vildagliptin (Galvus[®])

GLP-1 (synonym: enteroglucagon) is an insulinotropic postprandial peptide hormone from the incretin family.

Specifics of individual products

Exenatide (Byetta[®])

A GLP-1 receptor agonist. Rapidly absorbed, $T_{1/2}$: 2.4 hours. Excreted in urine. For subcutaneous administration once weekly.

Advantages: low risk of hypoglycemia, BP reduction, potential protective effect on β -cells

Mechanism of action: GLP-1 receptor agonists improve β -cell function, increase glucose-dependent insulin secretion, weakly inhibit increased glucagon secretion and delay gastric emptying after they enter the systemic bloodstream from the intestine. Exenatide is a potent incretin mimetic that increases glucose-dependent insulin secretion and has other hypoglycemic effects inherent to incretins, which improves glycemic control in patients with type 2 diabetes mellitus.

Therapeutic indications: type 2 diabetes mellitus in monotherapy and in combination with oral hypoglycemic agents

Side effects: injection site reaction (pruritus), nausea, vomiting, diarrhea, decreased appetite (anorexia), dizziness, headache, hypoglycemia, gastroesophageal reflux

Contraindications: type 1 diabetes, diabetic ketoacidosis, severe kidney failure, pregnancy, breastfeeding, less than 18 years of age

Liraglutide (Victoza[®])

A human GLP-1 analog. Bioavailability: 55%. Actively metabolized in the liver, maximum blood concentrations are reached in 8–12 hours post-dose. $T_{1/2}$: 13 hours. Excreted in urine. For subcutaneous administration once daily.

For Advantages, see “Exenatide”.

Mechanism of action: Stimulates glucose-dependent insulin secretion by pancreatic β -cells. It inhibits excessive glucose-dependent glucagon secretion. In hypoglycemia, it reduces insulin secretion without affecting glucagon production. Liraglutide slightly delays gastric emptying, reduces energy expenditure, thereby reducing the amount of adipose tissue and the feeling of hunger.

Therapeutic indications: type 2 diabetes mellitus in combination with oral hypoglycemic agents

For side effects and contraindications, see "Exenatide".

Sitagliptin (Januvia*)

A highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor. Bioavailability: 87%. Essentially not metabolized. $T_{1/2}$: 12.4 hours. Excreted predominantly in urine. For oral administration once daily.

Mechanism of action: By inhibiting DPP-4, sitagliptin inhibits the hydrolysis of incretins, increasing the concentration of active forms of GLP-1 and glucose-dependent insulintropic peptide, increases insulin release and reduces glucagon secretion.

Advantages: tablet form, low risk of hypoglycemia, no effect on body weight, available in fixed-dose combinations with metformin, potential protective effect on β -cells

Therapeutic indications: type 2 diabetes mellitus — as monotherapy (as an adjunct to diet and exercise) or in combination with metformin or thiazolidinedione (PPAR)

Side effects: abdominal pain, nausea, vomiting, diarrhea

Contraindications: severe liver failure, type 1 diabetes, diabetic ketoacidosis, pregnancy, breastfeeding, less than 18 years of age

19. STEROID HORMONES

Steroid hormones are a broad group of polycyclic compounds with high biological activity; they are cyclopentanoperhydrophenanthrene derivatives (Fig. 19.1). They include adrenal hormones (glucocorticoids [GCs] and mineralocorticoids) as well as female and male sex hormones. The precursor of all steroid hormones in the human body is pregnenolone synthesized from cholesterol.

Mechanism of action: Steroid hormones easily penetrate into a cell through the cell membrane due to their lipophilicity and interact with specific receptors in the cytosol where the hormone-receptor complex is formed, which penetrates the nucleus. In the nucleus, this complex breaks down, and the hormone interacts with nuclear chromatin. This results in an interaction with DNA and then induction of messenger RNA (the first stage of the action of steroid hormones is activation of transcription). At the same time, RNA polymerase is activated, which synthesizes ribosomal RNA. As a result, additional ribosomes are formed, which bind to the endoplasmic reticulum membranes to form polysomes. Transcription and translation increase the synthesis of target proteins (Fig. 19.2).

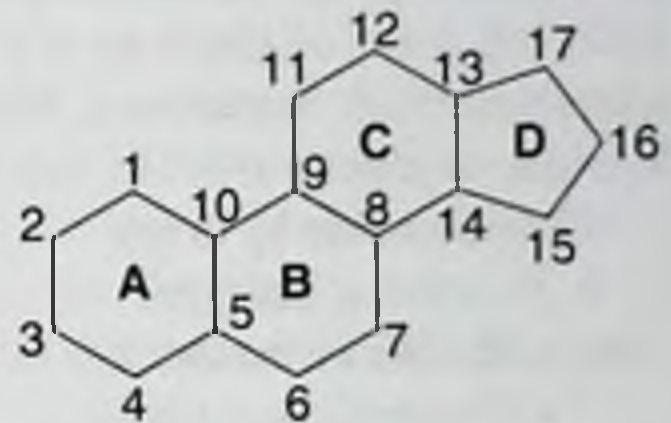


Fig. 19.1. Sterane (cyclopentanoperhydrophenanthrene) is a saturated tetracyclic hydrocarbon. Its various substituted derivatives are grouped under the general name of "steroids"

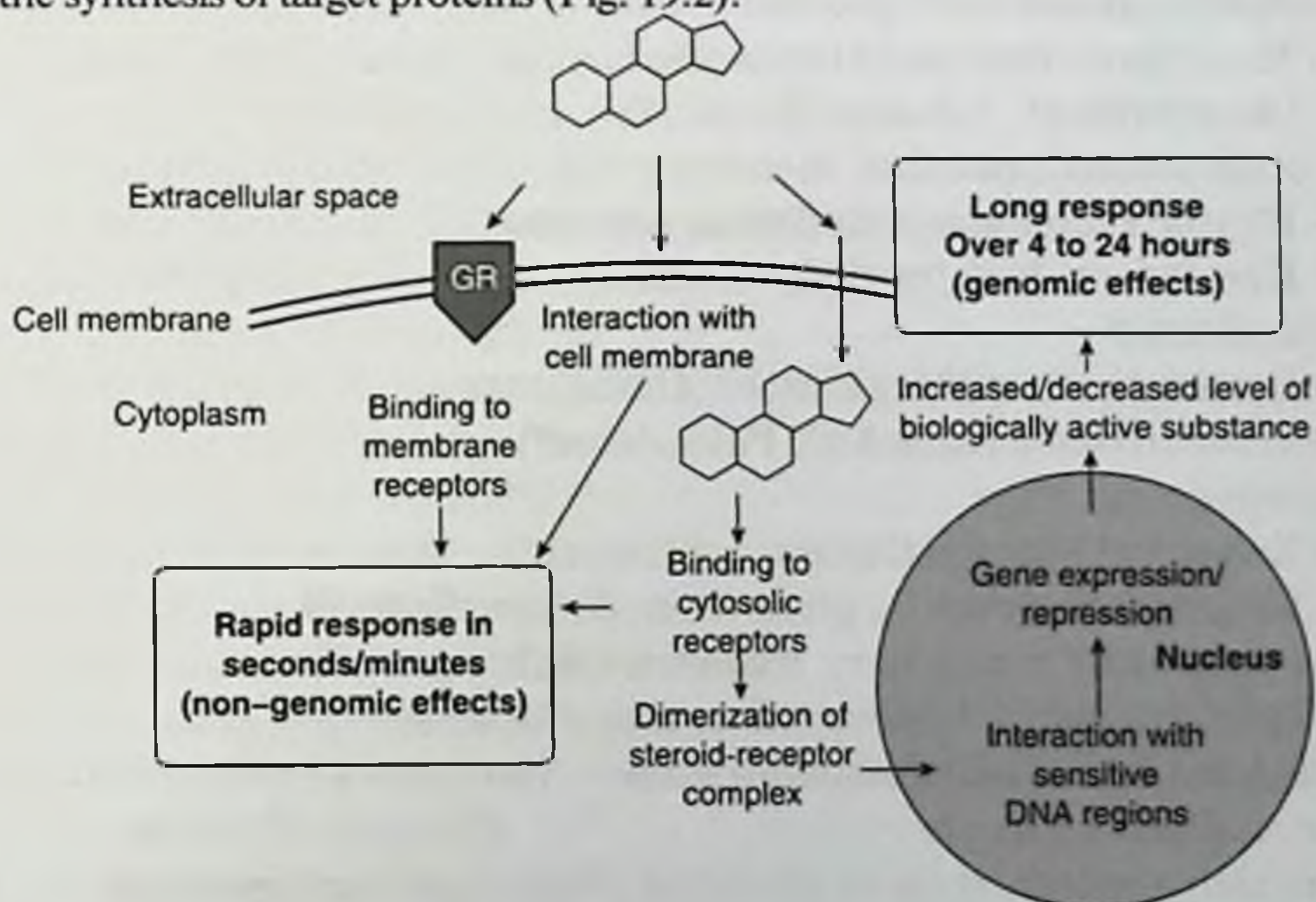


Fig. 19.2. Glucocorticoid mechanism of action. GR, hormone-receptor complex; DNA, deoxyribonucleic acid; mRNA, messenger ribonucleic acid

ADRENOCORTICAL HORMONES

Glucocorticoids

Antirheumatic substance X has been a known entity since 1929. However, corticosteroids were first isolated from the adrenal cortex in 1948 by Swiss chemist T. Reichstein and American biochemist E. Kendall. In September 1948, American physician Ph. Hensch administered cortisone to a patient with rheumatoid arthritis. In 1950, all three of them were awarded the Nobel Prize for "...discoveries concerning adrenocortical hormones, their structure and biological effects." In Russia, the founder of glucocorticoid therapy is E. M. Tareev.

Classification by origin

I. Hormone analogs

- Hydrocortisone (Cortef[®], Locoid[®], Laticort[®])
- Combination drugs
 - Targyfort[®] (hydrocortisone acetate, metronidazole, natamycin, chloramphenicol)
 - Pimafuderm[®] (hydrocortisone, natamycin, neomycin)
 - Zovirax Duo-Activ[®] (acyclovir, hydrocortisone)

II. Synthetic hydrocortisone (cortisol) derivatives

1. Non-fluorinated

- Prednisolone (Medopred[®])
- Methylprednisolone (Metypred[®], Ivecpred[®]), methylprednisolone aceponate (Komfoderm[®], Advantan[®])

• Combination drugs

- Elgyna[®] (neomycin, ornidazole, prednisolone, econazole)
- Komfoderm M2[®] (methylprednisolone aceponate, urea)

2. Fluorinated

- Dexamethasone (Megadexan[®], Dexason[®])
- Triamcinolone (Kenalog[®], Polcortolon[®])

• Combination drugs

- Rubrodex[®] (dexamethasone, tobramycin)
- Sofradex[®] (framycetin, gramicidin, dexamethasone)
- Prodetoxon[®] (naltrexone, triamcinolone)
- Polcortolone TC[®] (tetracycline, triamcinolone)

Classification by method of administration

I. Topical glucocorticoids

1. For skin application (as an ointment, cream, emulsion, powder)

- Betamethasone (Betanecin[®])
- Hydrocortisone (Cortef[®], Locoid[®], Laticort[®])
- Mometasone
- Methylprednisolone aceponate (Komfoderm[®], Advantan[®])
- Fluocinolone acetonide (Sinaflan[®], Flucinar[®])
- Flumethasone

• Combination drugs

- Lorinden A[•] (salicylic acid, flumethasone)
 - Lorinden C[•] (clioquinol, flumethasone)
 - Akriderm SK[•] (betamethasone, salicylic acid)
 - Canison Plus[•] (betamethasone, gentamicin, clotrimazole)
2. For eye and/or ear drop instillation; as an eye ointment; nasal spray
- Beclomethasone (Nasobec[•])
 - Betamethasone (Betanecin[•])
 - Budesonide (Tafen Nasal[•])
 - Hydrocortisone
 - Mometasone (Ryaltris Mono[•], Ditamal[•])
 - Fluticasone (Nazarel[•])
- Combination drugs
- Ryaltris[•] (mometasone, olopatadine)
 - Allergoferon beta[•] (betamethasone, interferon alfa-2b)
 - Candibiotic[•] (chloramphenicol, beclomethasone dipropionate, clotrimazole, lidocaine hydrochloride)
3. For intranasal or inhaled use
- Beclomethasone (Beclazone Eco[•], Beclospir[•], Clenil[•])
 - Budesonide (Pulmicort[•], Respinid[•])
 - Flunisolide (Inhacort[•])
 - Fluticasone (Flixonase[•], Flixotide[•])
- Combination drugs
- Enersair Breezhaler[•] (glycopyrronium bromide, indacaterol, mometasone)
 - Foster[•] (beclomethasone, formoterol)
 - SabaComb[•] (beclomethasone, salbutamol)
 - Trimbou[•] (beclomethasone, glycopyrronium bromide, formoterol)
4. For intra-articular and/or peri-articular administration
- Hydrocortisone
 - Triamcinolone (Kenalog[•])
 - Betamethasone (Diprosan[•], Diprometa[•], Celestone[•])
5. For rectal administration
- Budesonide (Budenofalk[•])
- II. Systemic glucocorticoids
- Hydrocortisone (Cortef[•])
 - Betamethasone (Diprosan[•], Diprometa[•])
 - Budesonide (Cortiment[•])
 - Dexamethasone (Megadexan[•], Dexason[•])
 - Prednisolone (Medopred[•])
 - Methylprednisolone (Metypred[•], Ivepred[•])
 - Triamcinolone (Kenalog[•], Polcortolon[•])

Metabolic effects

Carbohydrate metabolism: stimulate hepatic gluconeogenesis, disrupt glucose utilization by tissues, cause hyperglycemia and glucosuria, deplete the pancreatic insular apparatus.

Protein metabolism: reduce biosynthesis and increase protein catabolism in lymphoid, muscle, connective tissues, spleen; inhibit cell regeneration, antibody production; induce a negative nitrogen balance (increased urinary excretion of creatinine and amino acids).

Fat metabolism: accelerate the conversion of carbohydrates into fats; redistribute adipose tissue (lipolytic effect in the subcutaneous fat of the hands, lipogenic effect with predominant fat deposition in the anterior abdominal wall, interscapular region, face and neck); increase plasma levels of cholesterol and lipoproteins.

Water and mineral metabolism: promote the release of K^+ ions and the reabsorption of Na^+ ions in the renal tubules, thus increasing circulating blood volume, tissue hydrophilicity and blood pressure.

Calcium metabolism: inhibit the intestinal absorption of Ca^{2+} ions, promote the release of Ca^{2+} ions from bone tissue and increase its renal excretion — hypocalcemia, hypercalciuria and osteoporosis develop. In children, they disrupt bone tissue formation and delay growth.

Pharmacological effects: anti-inflammatory, anti-allergic, immunosuppressive, antishock, antitoxic

Anti-inflammatory effect: GCs inhibit the production of many factors that trigger an inflammatory response. They induce lipocortin biosynthesis in white blood cells, which inhibits phospholipase A₂ (Fig. 19.3). The production of prostanoids and leukotrienes decreases as does the expression of COX-2. The action is targeted at the main inflammation components: mediator, vascular and cellular. GCs stabilize lysosomal membranes and reduce capillary permeability, which explains their pronounced effect on the exudative phase of inflammation. Stabilization of lysosomal membranes limits the release of proteolytic enzymes and prevents destructive processes in tissues. The accumulation of inflammatory white blood cells as well as the activity of macrophages and fibroblasts are inhibited. By inhibiting the reproduction of fibroblasts and their ability to make collagen, they suppress the proliferative phase of inflammation. Inhibition of basophil maturation decreases the synthesis of mediators of immediate allergic reactions. Therefore, GCs can suppress both early and late signs of inflammation as well as proliferation reactions in chronic inflammation.

Anti-allergic effect: GCs reduce the synthesis and secretion of allergy mediators, inhibit the release of histamine and other biologically active substances from sensitized mast cells and basophils, decrease the number of circulating basophils, inhibit the proliferation of lymphoid and connective tissue, decrease the number of T cells, B cells, and mast cells, reduce the sensitivity of effector cells to allergy mediators, inhibit antibody production, and change the immune response.

Immunosuppressive effect: GCs inhibit the migration of bone marrow stem cells and B cells as well as the activity of T and B cells and the release of cytokines (interleukin-1, interleukin-2, IFN- γ) from white blood cells and macrophages, reduce the production and increase the breakdown of the complement system components, block immunoglobulin Fc receptors, suppress the functions of white blood cells and macrophages.

Antishock effect: GCs raise blood pressure by increasing the amount of circulating catecholamines, restoring the sensitivity of adrenergic receptors to catecholamines and vasoconstriction.

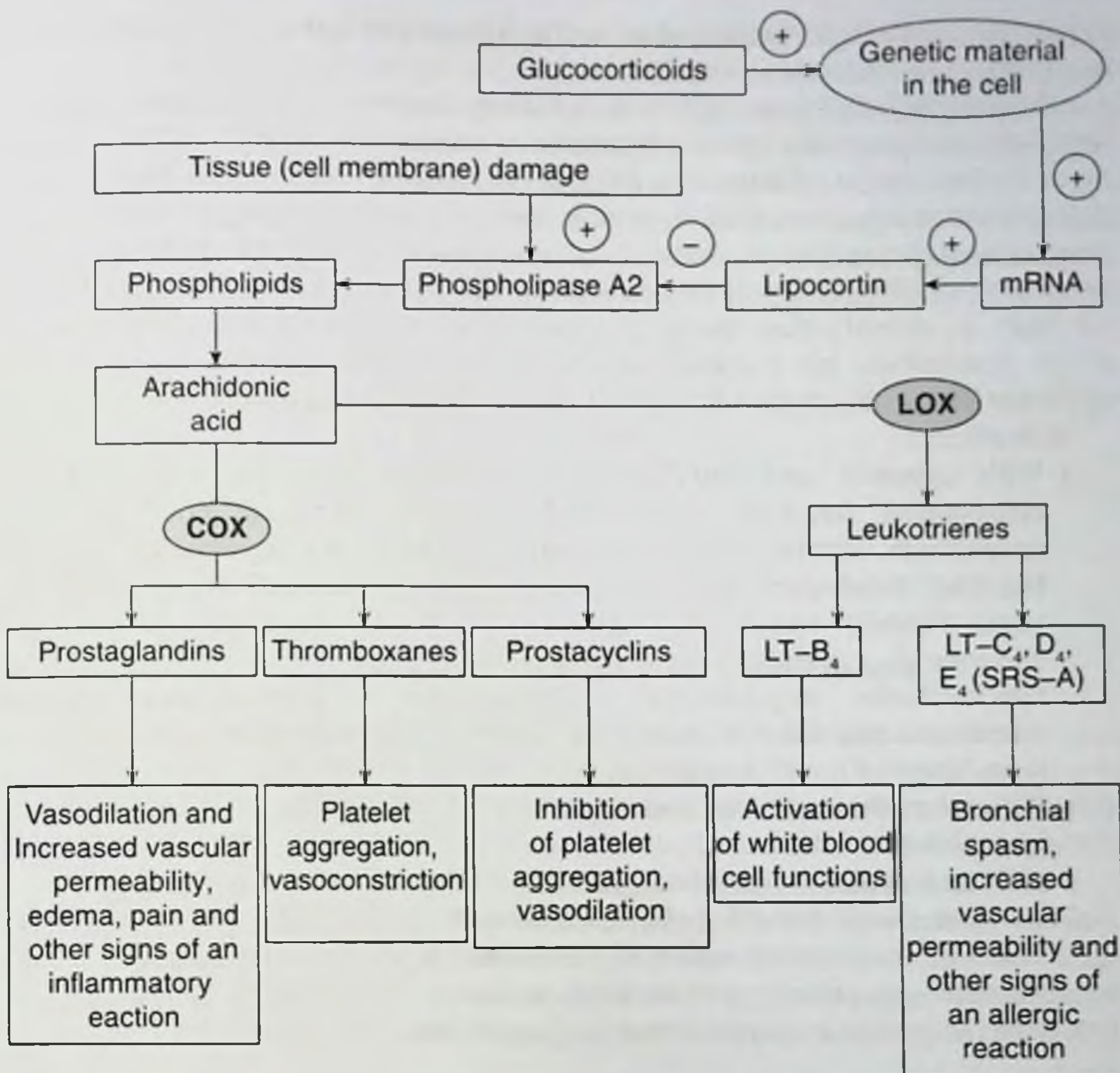


Fig. 19.3. Mechanism of anti-inflammatory action of glucocorticoids. mRNA, messenger ribonucleic acid; COX, cyclooxygenase; LOX, lipoxygenase; LT-B₄, C₄, D₄, E₄, leukotrienes; SRS-A, slow-reacting substance of anaphylaxis

Antitoxic effect: GCs activate hepatic enzymes involved in the metabolism of endo- and xenobiotics.

Pharmacokinetics: Succinates (hydrocortisone sodium succinate), hemisuccinates (hydrocortisone sodium hemisuccinate) and phosphates (hydrocortisone sodium phosphate) are water-soluble and have a rapid and acute effect when administered parenterally. Acetates (hydrocortisone acetate) and acetonides (triamcinolone acetonide) are water-insoluble; they are administered as a suspension and have a prolonged effect. Halogenated (fluorinated) GCs (dexamethasone, triamcinolone, betamethasone) have high anti-inflammatory and low mineralocorticoid activity. An increased number of fluorine atoms in the GC molecule decreases the drug's absorption through intact skin. Topical use of GCs creates a high drug concentration in the target region and significantly reduces the risk of systemic adverse reactions.

Inhalation agents in the form of an aerosol or fine powder in device-metered inhalers barely have any systemic action.

Therapeutic indications: replacement therapy for primary or secondary adrenal insufficiency, congenital adrenal hyperplasia; connective tissue diseases (systemic lupus erythematosus, rheumatoid arthritis, scleroderma, etc.); bronchial asthma, status asthmaticus; immediate hypersensitivity requiring emergency medical care; shock (burn, anaphylactic, post-traumatic, postoperative, etc.); GI disorders (ulcerative colitis, Crohn's disease); leukemia, lymphoma; prevention of graft rejection in combination therapy. Topical use: dermal diseases (contact and atopic dermatitis), eye disorders (allergic conjunctivitis, keratitis, *Herpes zoster ophthalmicus*, iritis, iridocyclitis, etc.); allergic rhinitis, sinusitis.

Side effects

- ▶ With systemic use: osteoporosis, pathological bone fractures, vertebral compression fractures, Calve–Perthes disease; increased blood pressure, arrhythmias, edema; gastric and intestinal steroid ulcers (ulcerogenic effect), GI bleeding, esophagitis, increased appetite; infectious complications (bacterial, viral, fungal); restlessness, agitation, insomnia; moderate leukocytosis, eosinopenia, lymphopenia, hyperglycemia, glucosuria, hyperlipidemia, hypocalcemia, hypokalemia, hypernatremia; Cushing disease; growth retardation and delayed puberty in children; secondary adrenal insufficiency (long-term use); withdrawal syndrome
- ▶ With inhalation use: oral and upper respiratory tract candidiasis, hoarseness, sore throat
- ▶ With topical use: atrophy, telangiectasia, steroid acne, striae, infections

Contraindications: diabetes mellitus, Cushing disease; gastroduodenal ulcer, severe kidney and/or liver failure; severe hypertension, decompensated congestive heart failure; severe osteoporosis; systemic mycosis, immunodeficiency states (including in HIV-infected patients); mental illness; pregnancy, breastfeeding

Specific properties of individual drugs

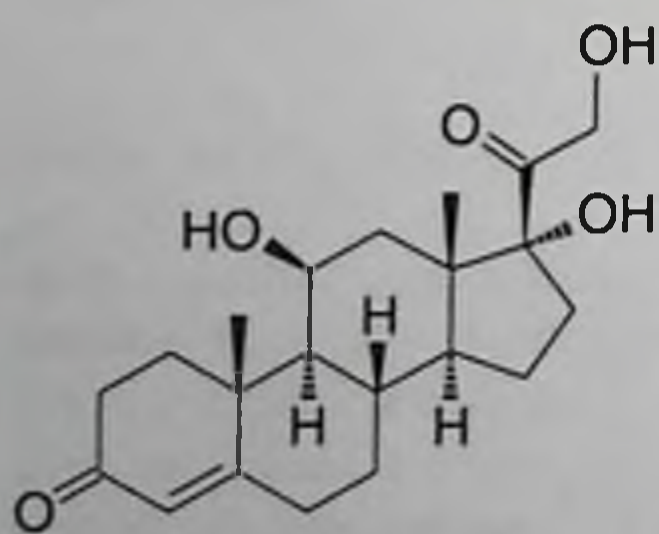


Fig. 19.4. (11 β)-11,17,21-Trihydroxypregn-4-ene-3,20-dione (as acetate, sodium hemisuccinate)

Hydrocortisone (Cortef®)

▶ Analog of the natural hormone cortisol. Natural hydrocortisone or its esters (hydrocortisone acetate and hydrocortisone sodium hemisuccinate) are for systemic and topical use. Its anti-inflammatory activity is 4-fold inferior to prednisolone but its mineralocorticoid activity is superior to other GCs. After intraarticular administration, the therapeutic effect occurs within 6–24 hours and lasts for several days to several weeks. After intramuscular administration, it is absorbed for 24–48 hours. After intravenous administration, the effect occurs in 1 hour.

The administered dose is excreted within 12 hours. In order to maintain high plasma concentrations, administration every 4–6 hours is recommended. When

using an ophthalmic ointment (such as hydrocortisone acetate), it penetrates the intraocular fluid through the cornea poorly but penetrates the epidermis and mucosal epithelium. Following skin application (such as hydrocortisone acetate and hydrocortisone 17-butyrate), it accumulates in the epidermis. It can be marginally absorbed through the skin and have a systemic effect.

- ▶ Metabolized in the liver. Excreted mainly in urine as inactive metabolites. Hydrocortisone acetate is administered intramuscularly, intraarticularly, intrasynovially, topically; hydrocortisone sodium hemisuccinate is administered intravenously and intramuscularly.

Prednisolone (Medopred*)

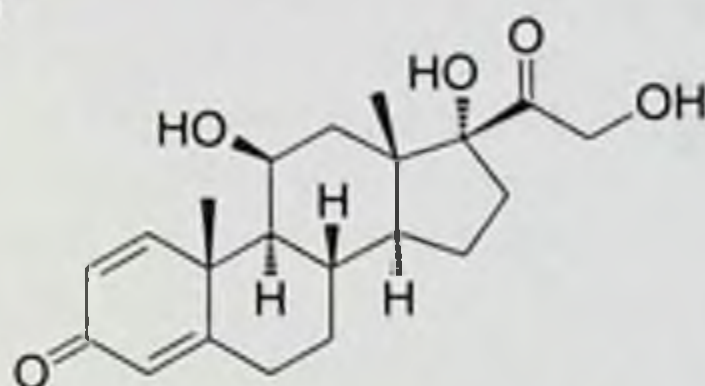


Fig. 19.5. (11-β)-11,17,21-Trihydroxypregna-1,4-diene-3,20-dione

- ▶ A synthetic, non-fluorinated analog of hydrocortisone. Easily penetrates the skin and mucous membranes. Its anti-inflammatory activity is 3–4-fold superior to hydrocortisone. It has a less pronounced mineralocorticoid effect. Well absorbed in the GI tract, maximum blood concentration reached within 1.0–1.5 hours. Crosses the placental barrier and excreted into breast milk (less than 1%).
- ▶ Metabolized in the liver to inactive metabolites. Plasma $T_{1/2}$: 2–4 hours, tissue $T_{1/2}$: 18–36 hours, $T_{1/2}$ after topical use: 3 hours. Excreted as metabolites in bile and urine, with 20% excreted as unchanged drug in urine. Prednisone is administered orally, hemisuccinate is administered intravenously, intramuscularly; topically.

Dexamethasone (Megadexan*, Dexason*)

- ▶ A fluorinated prednisolone derivative that has a long-term systemic effect. A fluorine atom in the molecule makes its anti-inflammatory activity 10-fold superior to prednisolone with almost no effect on mineral metabolism. It activates catabolic processes more than prednisolone; therefore short-term administration is recommended, only in cases of disease exacerbation and intolerance to prednisolone. After administration, it is rapidly and completely absorbed. Easily crosses the blood-tissue barriers, excreted into breast milk. When used topically in ophthalmology, it is absorbed through the cornea with intact epithelium into the aqueous humor of the anterior eye chamber. The absorption rate increases when the ocular tissue is inflamed or the mucous membrane is damaged.
- ▶ Metabolized in the liver (mainly by conjugation with glucuronic and sulfuric acids) to inactive metabolites. Plasma $T_{1/2}$: 3.0–4.5 hours, tissue $T_{1/2}$: 36–54 hours.

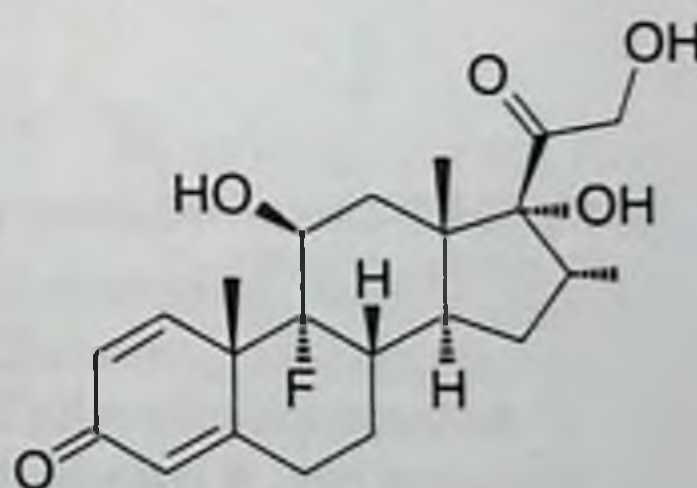


Fig. 19.6. (11-β,16-α)-9-Fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione

Excreted in urine and bile. For oral, intravenous, intramuscular, intravitreal, intraarticular, periarticular, and topical administration.

Triamcinolone (Kenalog[®], Polcortolon[®])

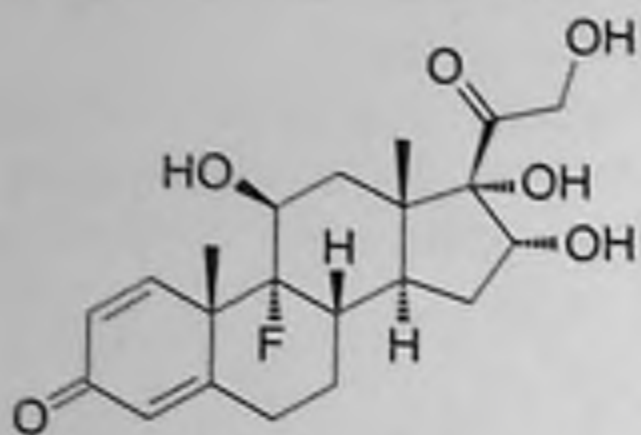


Fig. 19.7. (11 β ,16 α)-9-Fluoro-11,16,17,21-tetrahydroxypregna-1,4-diene-3,20-dione

► Its chemical structure, action and indications are similar to those of dexamethasone. Unlike the latter, it contains a hydroxy group instead of a methyl group at position 16. Its anti-inflammatory activity is about 5-fold superior to hydrocortisone but is inferior to dexamethasone. It barely affects the excretion of Na⁺, Cl⁻, K⁺ and water ions. It activates catabolic processes more than prednisolone, similarly to dexamethasone, thus is used short-term, only in cases of inflammatory flareups and intolerance to prednisolone. After oral administration, the maximum effect is observed

in 1–2 hours, after intramuscular administration in 24–48 hours. The time of action depends on the method of administration: 2.5 days (orally), 1–6 weeks (intramuscularly) or several weeks (intraarticularly).

- Metabolized in the liver to form inactive metabolites. Plasma T_{1/2}: 5 hours, tissue T_{1/2}: 18–36 hours. Excreted mainly in urine. For oral, intramuscular, intraarticular, periarticular, and topical administration.

Beclomethasone (Beclazone Eco[®], Beclospir[®], Clenil[®])

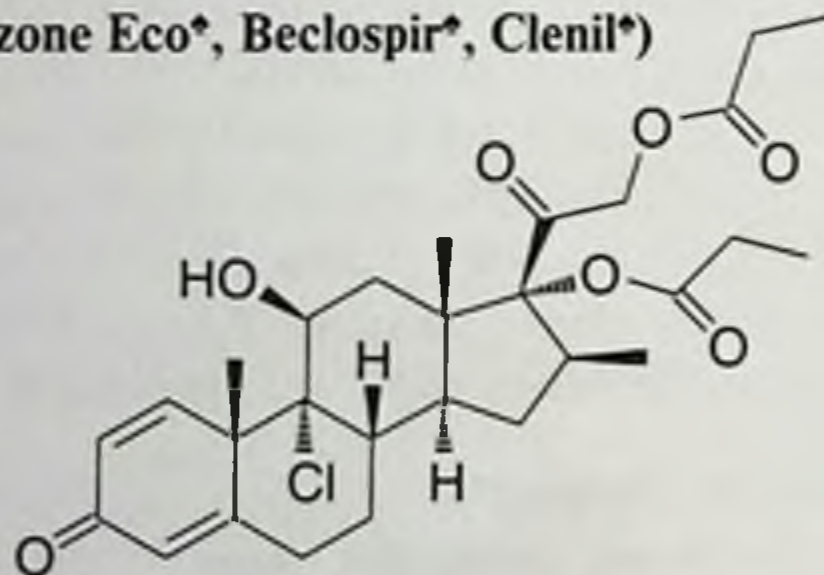


Fig. 19.8. 9-Chloro-11 β hydroxy-16 β -methyl-3,20-dioxopregna-1,4-diene-17,21-dipropionate

- For topical administration. Before pulmonary absorption, beclomethasone is extensively metabolized to the active metabolite beclomethasone 17-monopropionate with a pronounced topical anti-inflammatory effect. In the bronchial tree, it reduces the number of mast cells as well as epithelial edema and mucus secretion by the glands, decreases bronchial hyperreactivity, improves mucociliary transport and indicators of external respiration function. When administered intranasally, it eliminates edema and hyperemia of the nasal mucosa. Therapeutic doses do not cause the side effects typical of systemic GCs. It does not stop bronchospasm; the therapeutic effect occurs after 5–7 days of treatment.
- Systemic absorption of beclomethasone 17-monopropionate occurs in the lungs (36%) and in the GI tract (26% when swallowed). Metabolized in the liver. Most of the drug (35–76%) is excreted in bile predominantly as metabolites, with 10–15% excreted in urine. For inhalation and intranasal administration.

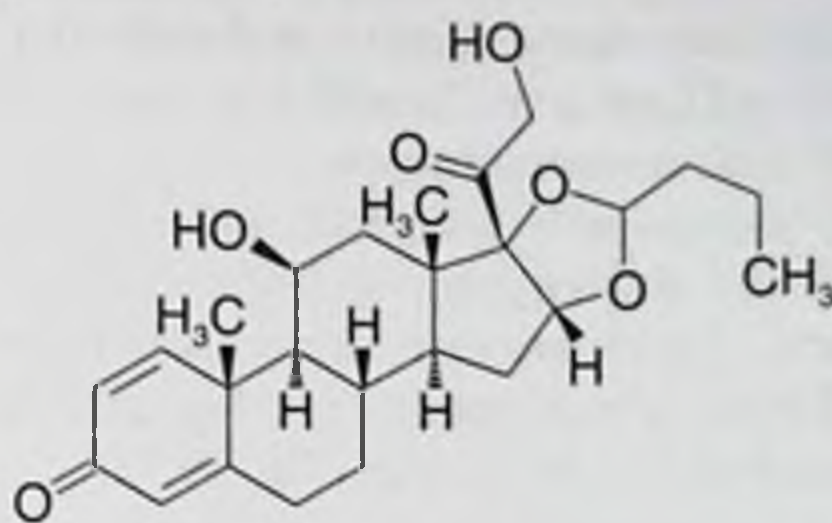
Budesonide (Cortiment*, Pulmicort*, Respid*)

Fig. 19.9. (11 β , 16 α)-16,17-(Butylidene-bis(oxy))-11,21-dihydroxypregna-1,4-diene-3,20-dione

- ▶ Similar to triamcinolone in structure, although one fluorine atom in the molecule is absent. It does not have a pronounced systemic effect when inhaled and is not metabolized in the lungs. The maximum therapeutic effect occurs in 1–2 weeks. When taken orally, bioavailability is low. It has a more pronounced anti-inflammatory effect than other GCs, mainly in the intestine.
- ▶ Metabolized in the liver to form metabolites with low glucocorticoid activity. $T_{1/2}$ for inhalation administration is 2–3 hours. Excreted in urine and bile as metabolites. For oral, topical administration.

Fluticasone (Flixonase*, Flixotide*)

- ▶ Synthetic trifluorinated compound with high affinity for GC receptors for topical use. The therapeutic effect after inhalation occurs within 24 hours, reaching a maximum within 1–2 weeks or more after treatment initiation. When administered intranasally, it has a rapid anti-inflammatory effect on the nasal mucosa; the anti-allergic effect occurs 2–4 hours after the first use. When applied topically, bioavailability is very low due to limited absorption through the skin.
- ▶ Metabolized in the liver to form an inactive carboxyl metabolite. $T_{1/2}$: 3 hours. Excreted mainly in bile. For inhalation, intranasal and topical administration.

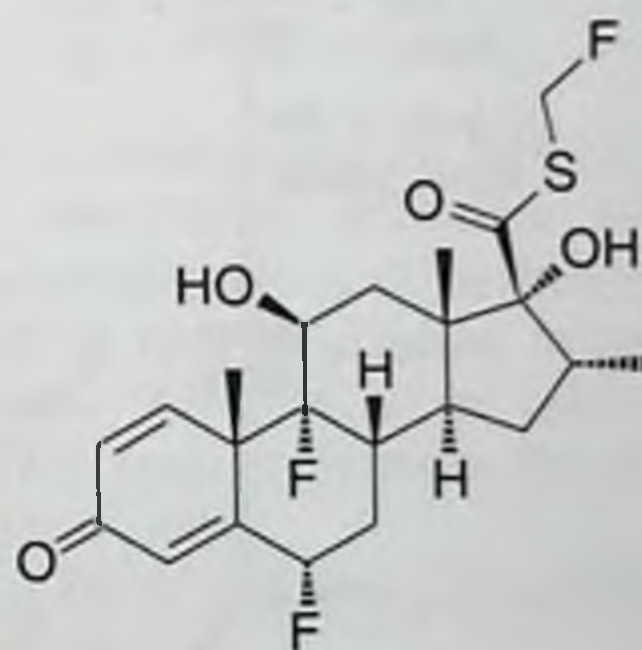


Fig. 19.10. (6 α , 11 β , 16 α , 17 α)-6,9-Difluoro-11,17-dihydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carbothioic acid S-(fluoromethyl) ester

Mineralocorticoids

Natural mineralocorticoids — aldosterone and 11-deoxycorticosterone — barely have any glucocorticoid activity. The effect of aldosterone on electrolyte metabolism is 20–30-fold superior to 11-deoxycorticosterone. Their main function is to retain Na^+ ions in the body and maintain the physiological osmolarity of the internal environment.

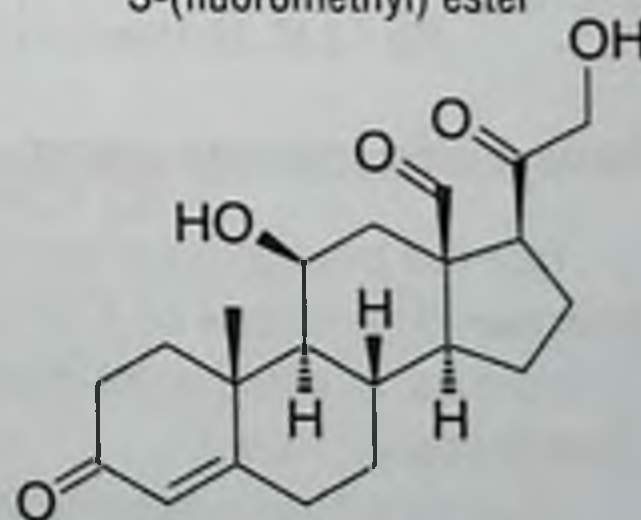


Fig. 19.11. Structural formulas of aldosterone and deoxycorticosterone

The main target of these hormones is the kidney where they increase active reabsorption of Na^+ ions in the distal convoluted tubules and collecting ducts, stimulating the expression of the Na^+/K^+ -ATPase gene. In addition, mineralocorticoids promote the renal excretion of K^+ , H^+ and ammonium ions.

By interacting with intracellular receptors and stimulating protein synthesis, aldosterone 1) increases the reabsorption of Na^+ ions from urine; 2) induces the synthesis of tricarboxylic acid cycle enzymes, whose activity ensures ATP production; 3) activates Na^+/K^+ -ATPase, which maintains a low intracellular concentration of Na^+ ions and a high concentration of K^+ ions (Fig. 19.12).

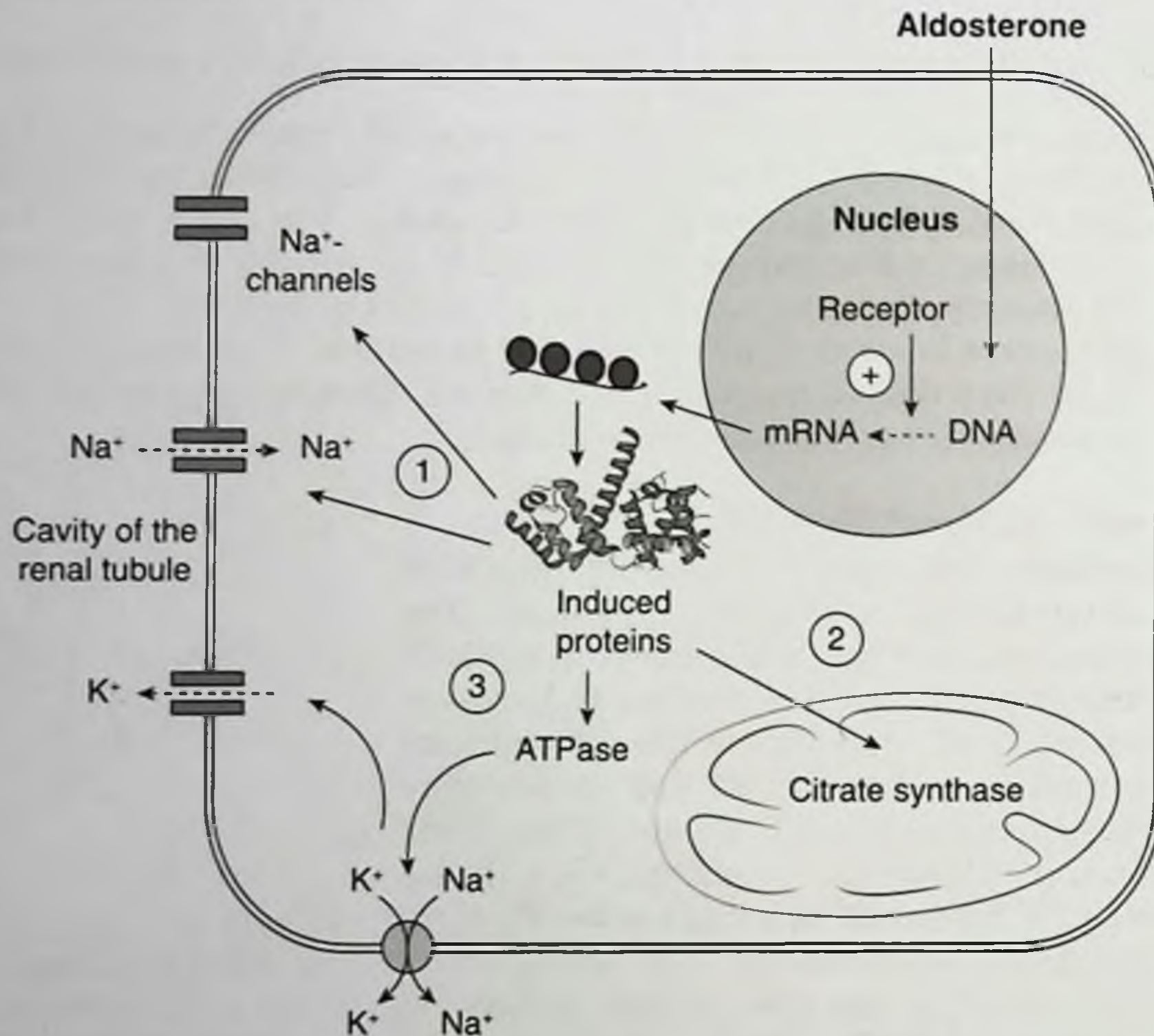


Fig. 19.12. Mechanism of action of mineralocorticoids as illustrated by aldosterone

Deoxycorticosterone acetate¹⁹

Has the properties of an adrenocortical hormone: retains Na^+ ions in the body and increases the release of K^+ ions, leading to fluid accumulation in tissues. It promotes an increase in plasma volume and blood pressure, increases muscle tone and improves muscle performance.

Fludrocortisone is currently used as a drug with mineralocorticoid activity.

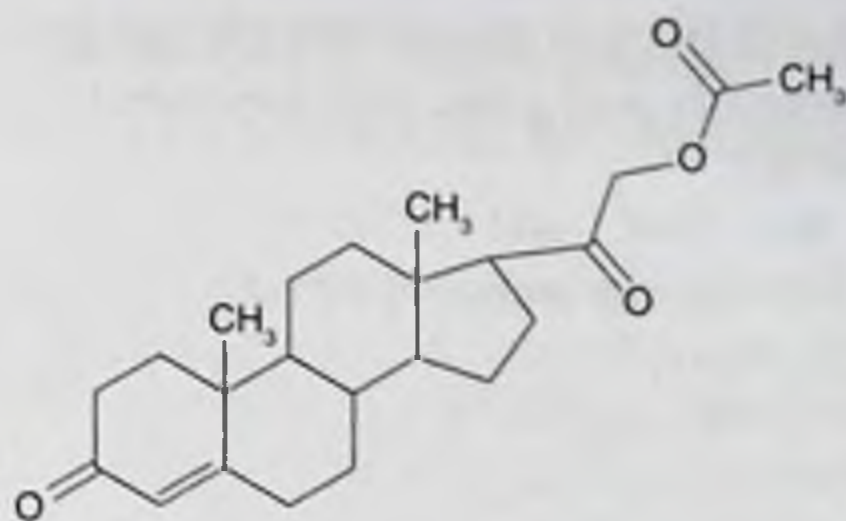


Fig. 19.13. 11-Deoxycorticosterone 21-acetate; 21-acetoxypregn-4-ene-3,20-dione

Fludrocortisone (Cortineff®)

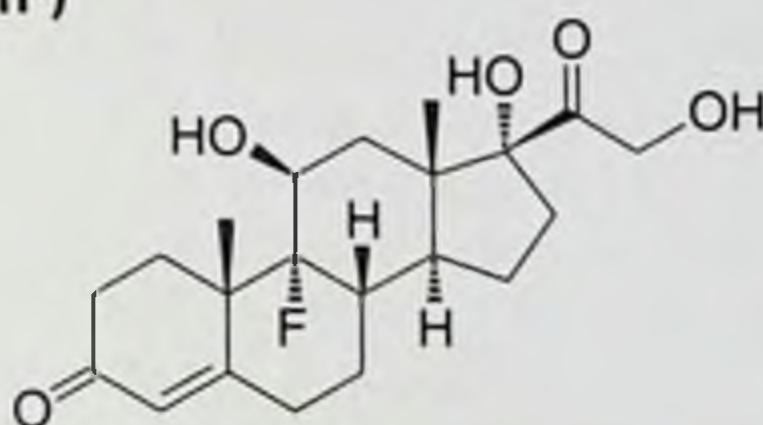


Fig. 19.14. (11β)-9-Fluoro-11,17,21-trihydroxypregn-4-ene-3,20-dione (and as 21-acetate)

- ▶ Fludrocortisone is currently used as a drug with mineralocorticoid activity. Synthetic adrenocortical hormone analog, a fluorinated derivative of hydrocortisone, whose mineralocorticoid activity is comparable to aldosterone. It has 100-fold more potent mineralocorticoid effect and 10–15-fold more potent anti-inflammatory effect than hydrocortisone. Effective when taken orally. Rapidly and completely absorbed in the GI tract, maximum blood concentration reached in 1.7 hours. Excreted into breast milk.
- ▶ Metabolized in the liver. Plasma $T_{1/2}$: 3.5 hours, tissue $T_{1/2}$: 18–36 hours. Excreted in urine as inactive metabolites. For oral administration.

Therapeutic indications: Addison's disease (replacement therapy), temporary adrenal suppression (hypocorticism); myasthenia, asthenia

Side effects: hypernatremia, edema, increased blood pressure

Contraindications: hypertension, cardiac decompensation, severe liver and/or kidney disease, breastfeeding

CORTICOSTEROID ANTAGONISTS

Mitotane, spironolactone (Verospiron®) and eplerenone either inhibit the synthesis of adrenocortical hormones or block their receptors.

Mitotane®

- ▶ Non-selective inhibitor of corticosteroid synthesis. Bioavailability: 35–40%. It penetrates all body tissues, is deposited in adipose tissue, and a small

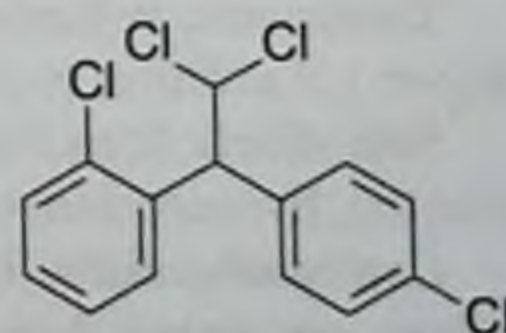


Fig. 19.15. 1-Chloro-2-[2,2-dichloro-1-(4-chlorophenyl)ethyl]benzene

amount crosses the BBB as a metabolite. It reduces the concentration of 17-hydroxycorticosteroids 2–3 days after treatment initiation; the antitumor effect occurs in 6 weeks.

- ▶ Metabolized in the liver and kidneys to water-soluble compounds. $T_{1/2}$: 18–159 days. Excreted in urine and bile. For oral administration.

Mechanism of action: It has a cytotoxic effect on adrenal cells, inhibits adrenocortical function; changes the peripheral metabolism of steroids, extra-adrenal metabolism of cortisol, thus decreasing blood concentration of 17-hydroxycorticosteroids.

Therapeutic indications: functional adrenal tumors, treatment of Cushing disease

Side effects: adrenal insufficiency (skin darkening, diarrhea, dizziness, somnolence, loss of appetite, depression, nausea and vomiting, skin rash, asthenia)

Contraindications: pregnancy, breastfeeding, allergic reactions

Spironolactone is a non-selective aldosterone receptor antagonist used as a diuretic (see section “Diuretics”).

Eplerenone (Inspra®)

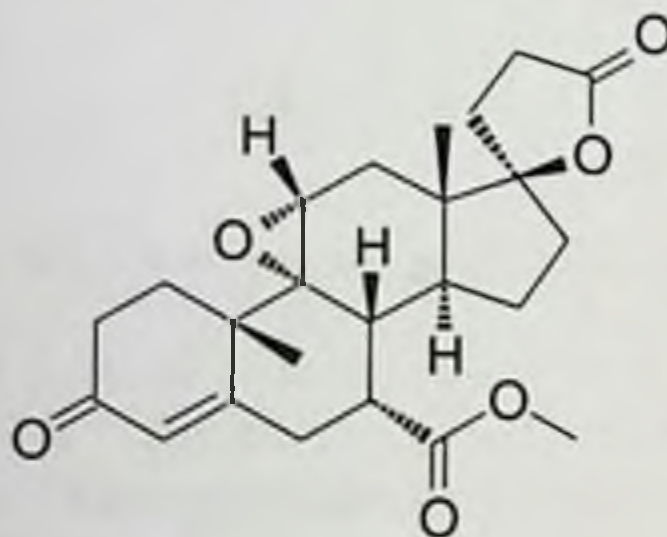


Fig. 19.16. Methyl(4aS,4bR,5aR,6aS,7R,9aS,9bR,10R)-4a,6a-dimethyl-2,5'-dioxo-2,4,4',4a,5',5a,6,6a,8,9,9a,9b,10,11-tetradecahydro-3H,3'H-spiro[cyclopenta[7,8]phenanthro[4b,5-b]oxirene-7,2'-furan]-10-carboxylate

- ▶ Highly selective aldosterone antagonist
- ▶ Bioavailability: 69%. Food intake does not affect absorption. Metabolized in the liver. $T_{1/2}$: 3–5 hours. Excreted in urine and bile. For oral administration.

Mechanism of action: It selectively blocks aldosterone receptors, prevents aldosterone from binding to mineralocorticoid receptors, which is involved in blood pressure regulation and pathogenesis of cardiovascular diseases. It persistently increases in plasma concentration of renin and aldosterone. Subsequently, renin secretion is suppressed by aldosterone through a feedback loop. It has virtually no effect on glucocorticoid and androgen receptors.

Therapeutic indications: hypertension (in combination therapy), congestive heart failure (in addition to standard therapy)

Side effects: hyperkalemia, hypercholesterolemia, hypertriglyceridemia; dizziness, fainting, hypotension; calf cramps, musculoskeletal pain; dyspepsia; allergic reactions

Contraindications: hyperkalemia, kidney failure in patients with congestive heart failure, pregnancy, breastfeeding, less than 18 years of age

SEX HORMONAL AGENTS, THEIR DERIVATIVES, SYNTHETIC SUBSTITUTES AND ANTAGONISTS

Preparations of female gonadal hormones

In 1902, gynecologist L. Fraenkel suggested that there was a corpus luteum hormone. G. W. Corner, W. M. Allen, A. Butenandt, U. Westphal, M. Hartmann and A. Wettstein are some of the scientists who, since 1928, have been studying and synthesizing the corpus luteum hormone (progesterone). In 1933, E. Schwenk and F. Hildebrandt derived the female gonadal hormone — estradiol — from estrone. It was described in 1935 by E. Doisy.

Female sex hormones are produced by the ovaries. Ovarian follicles produce estrogen, the activity of which is associated with the development of secondary sexual characteristics and the proliferative phase in the first half of the menstrual cycle. Follicle development and estrogen secretion are stimulated by follicle-stimulating hormone from the anterior pituitary gland. Through a negative feedback loop, estrogens inhibit the production of follicle-stimulating hormone and gonadotropin-releasing hormone from the hypothalamus.

In the middle of the cycle, levels of luteinizing hormone increase, which stimulates ovulation: an ovum is released from a mature follicle and enters the uterine cavity through the fallopian tubes. The corpus luteum is formed at the site of the destroyed follicle and begins to produce progestin hormones. At the same time, the production of estrogens decreases sharply, the secretory phase of the cycle occurs. If the ovum is fertilized and pregnancy occurs, the corpus luteum develops and continues to secrete progestin hormones into the bloodstream to help maintain the pregnancy. Through a negative feedback loop, progestins inhibit the production of luteinizing hormone from the anterior pituitary and gonadotropin-releasing hormone from the hypothalamus (Fig. 19.17). If the ovum is not fertilized, the corpus luteum atrophies and the blood levels of progestins decrease. At the end of the cycle, estrogen levels rise, which promotes the onset of menstruation.

Estrogens

Classification

I. Steroids

- Estrone (Folliculinum^o)
- Estriol (Ovestin⁺, Ovanelia⁺, Orniona⁺)
- Estradiol (Climara⁺, Estrogel⁺)
- Estradiol valerate (Progynova⁺)

II. Non-steroidal hormones (synthetic)

- Hexestrol (Synoestrol⁺)
- Ethinylestradiol (Microfollin⁺)

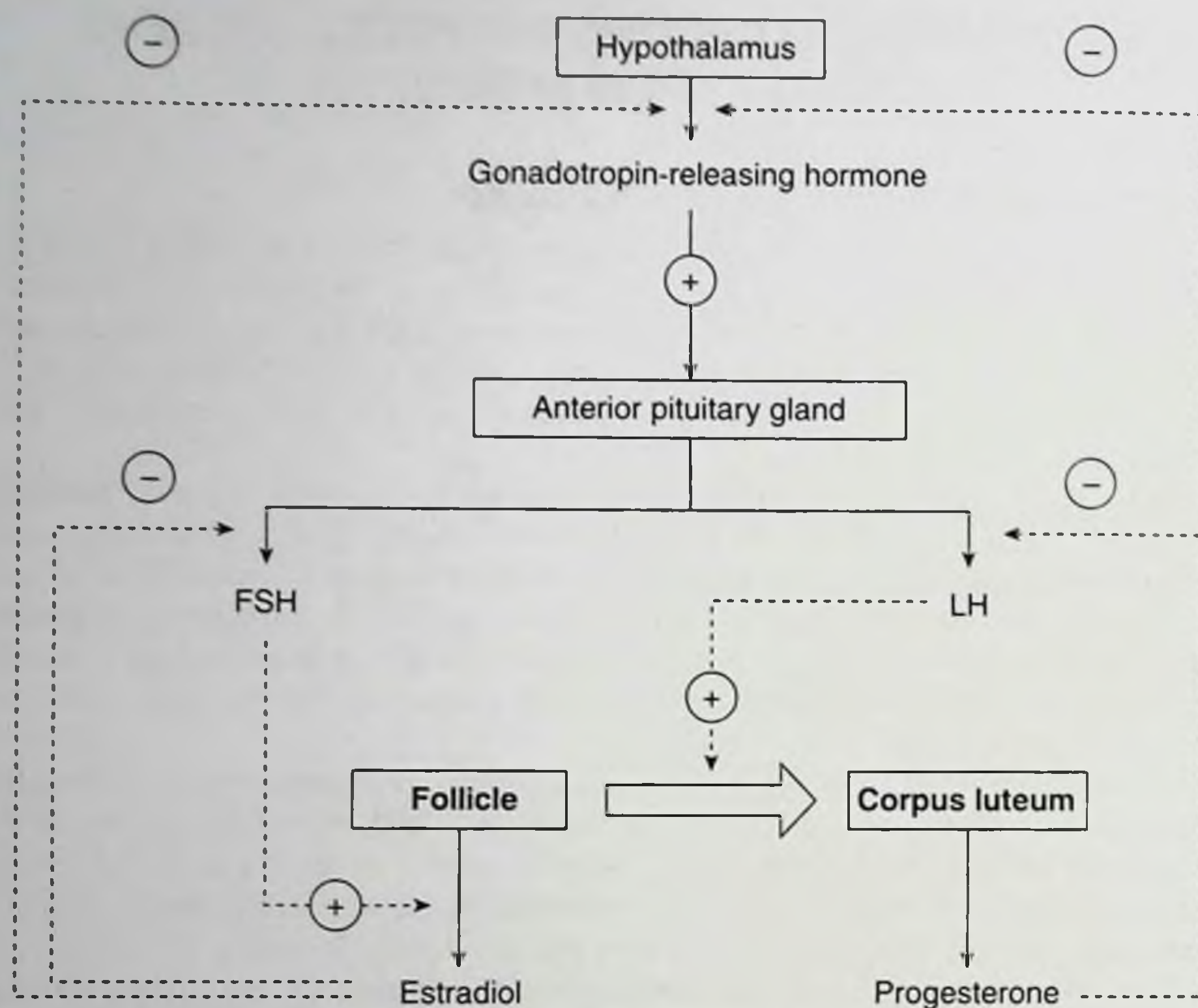


Fig. 19.17. Regulation of female sex hormone secretion. FSH, follicle stimulating hormone; LH, luteinizing hormone

Therapeutic indications: hormone therapy for primary ovarian insufficiency and related disorders (genital hypoplasia, delayed menstruation, etc.), menopause (used in combination with gestagens to prevent and eliminate menopausal disorders); hormonal contraception; metastatic breast cancer; prostate cancer

Side effects: edema and weight gain, increased blood pressure due to retention of Na^+ ions and water; increased risk of thrombosis and thromboembolism; breast engorgement and soreness; dysfunctional uterine bleeding; increased risk of endometrial cancer, breast cancer and cancer of other estrogen-dependent reproductive organs; nausea, vomiting, anorexia; cholelithiasis due to increased cholesterol levels in bile; gynecomastia, decreased potency

Contraindications: liver disease; history of thromboembolic diseases; cerebrovascular disorders; endometriosis; pregnancy; breastfeeding.

Specific properties of individual drugs

Estrone (Folliculinum[®])

This is a natural follicular hormone. For intramuscular administration once daily. It is metabolized and inactivated mainly in the liver (estriol is a weakly active metabolite), excreted in bile, reabsorbed in the intestine to re-enter the liver through the portal system.

Pharmacological effects: It stimulates the growth of the uterus and fallopian tubes, the development of secondary sexual characteristics when they are underdeveloped; causes proliferative changes in the endometrium; involved in the formation and maintenance of bone tissue (maintains the balance between osteoblasts and osteoclasts, reduces bone tissue resorption and stimulates its formation); regulates nitrogen metabolism; reduces the blood level of lipids and cholesterol

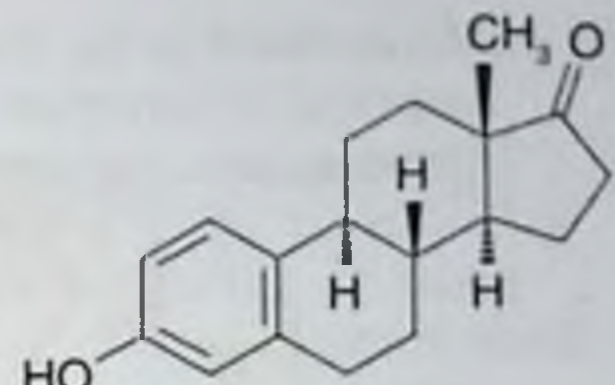


Fig. 19.18. 1,3,5-Estratrien-3-ol-17-one

Estriol (Ovestin[®], Ovanelia[®], Orniona[®])

- ▶ A natural short-acting estrogen that substitutes for the reduced estrogen production in postmenopausal women, alleviating the postmenopausal symptoms. Estriol is most effective when used for treating urinary and genital disorders (e.g., atrophic vaginitis). In case of mucosal atrophy of the lower urinary and genital tract, estriol induces the recovery of the vaginal, cervical and urethral epithelium, thus stimulating the restoration of normal vaginal microflora and pH. As a result, it increases the resistance of the urogenital tract epithelium to infection and inflammation; reduces mucosal dryness and vaginal itching, painful intercourse, risk for vaginal and urinary tract infections. Estriol therapy contributes to the normalization of urination and prevents urinary incontinence. If the recommended dosing regimen is observed, endometrial proliferation does not occur. Therefore, periodic use of progestogens is not necessary, postmenopausal withdrawal bleeding does not occur. After oral administration, it is rapidly and almost completely absorbed from the GI tract. Intravaginal administration ensures optimal availability at the site of action.
- ▶ Metabolized in the liver. $T_{1/2}$: 6–9 hours. Excreted mainly in urine as a conjugate. For oral and intravaginal administration.

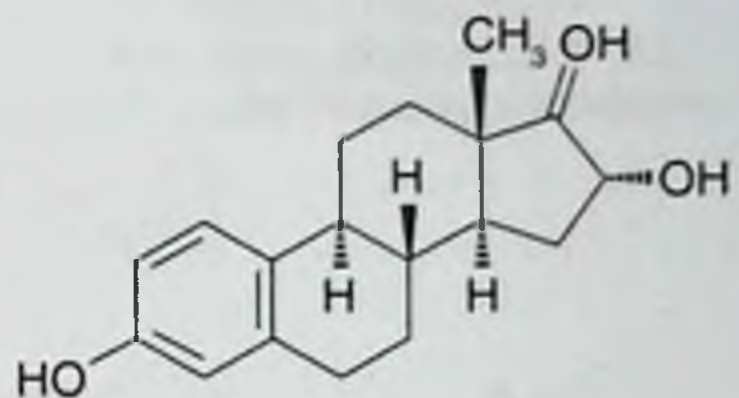


Fig. 19.19. (16 α ,17 β)-Estra-1,3,5(10)-triene-3,16,17-triol

Estradiol (Climara[®], Estrogel[®])

- ▶ An estrogen steroid hormone, identical to endogenous estradiol, that is more active than estrone and has longer duration of action. When taken orally, bioavailability is low. Before entering the systemic circulation, it is metabolized with the involvement of microflora in the intestinal lumen and wall, and in the liver to less-active metabolites — estrone and estriol — and only a small portion enters the blood as free substance. It has high lipophilicity (well absorbed from the skin's surface).

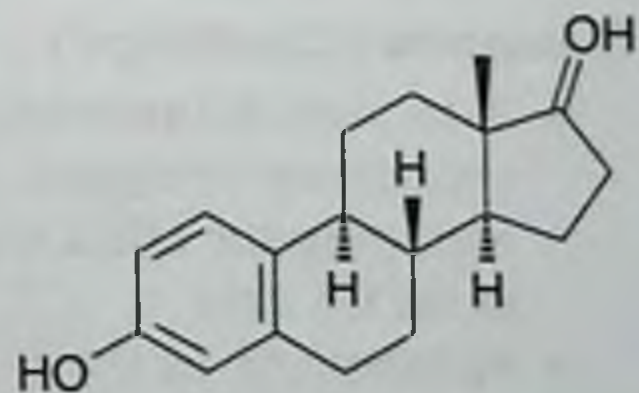


Fig. 19.20. (17 β)-Estra-1,3,5(10)-triene-3,17-diol

- ▶ Metabolized in the liver. Excreted in urine as sulfates and glucuronides; trace amounts of estradiol, estrone and estriol are also detectable in urine. For intramuscular, intranasal, topical (TTS) administration.

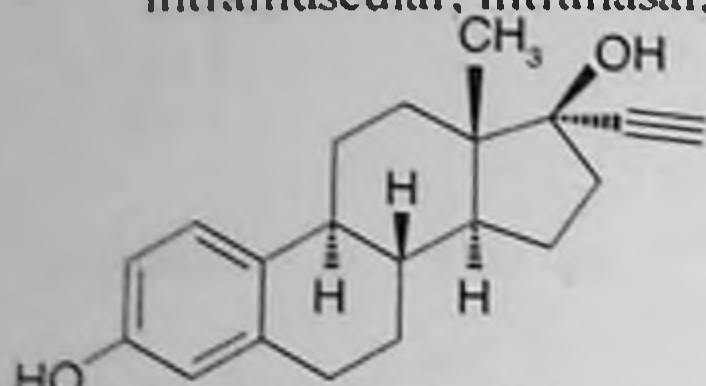


Fig. 19.21. (8R,9S,13S,14S,17R)-17-Ethynyl-13-methyl-7,8,9,11,12,14,15,16-octahydro-6H-cyclopenta[a]phenanthrene-3,17-diol

Ethinylestradiol (Microfollin®)

- ▶ A synthetic form of estrogen that is similar to estradiol in its structure and action. It has high bioavailability compared to natural estrogens. It undergoes enterohepatic recirculation with the first-pass effect in the liver where it undergoes oxidation to form 2-OH-ethinyl estradiol and 2-methoxy-ethinyl estradiol and subsequent glucuronidation and sulfonation.
- ▶ Metabolized in the liver to form hydroxylated and methylated metabolites. Excreted as metabolites in urine (40%) and bile (60%). For oral, intramuscular administration.

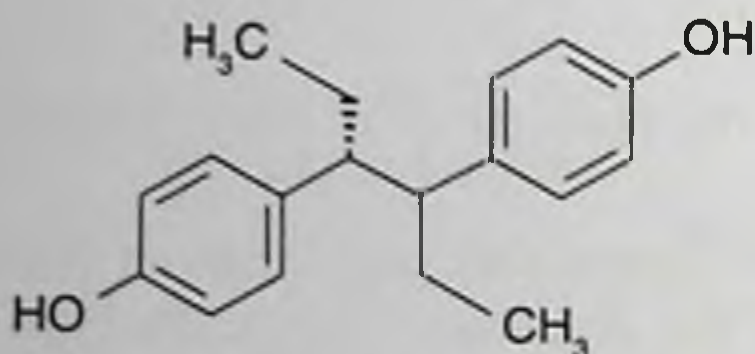


Fig. 19.22. 4, 4'-(1, 2-Diethyl-1,2-ethanediyl)bisphenol (as diacetate or didecanoate)

Hexestrol (Synoestrol®)

- ▶ A stilbene derivative, a synthetic non-steroidal estrogen. Its estrogenic activity is equivalent to that of estrone (natural follicular hormone). Well absorbed in the GI tract.
- ▶ Metabolized in the liver. Excreted in urine. For oral, intramuscular administration.

Antiestrogens

Synthetic non-steroidal substances

Mechanism of action: These drug products suppress the effects of estrogens by blocking estrogen receptors involved in regulating the hypothalamus (release of luteinizing hormone-releasing hormone) and the pituitary gland (release of gonadotropins). This disrupts the negative feedback. As a result, more gonadotropins are released, which increases the size of the ovaries and their function (Fig. 19.23).

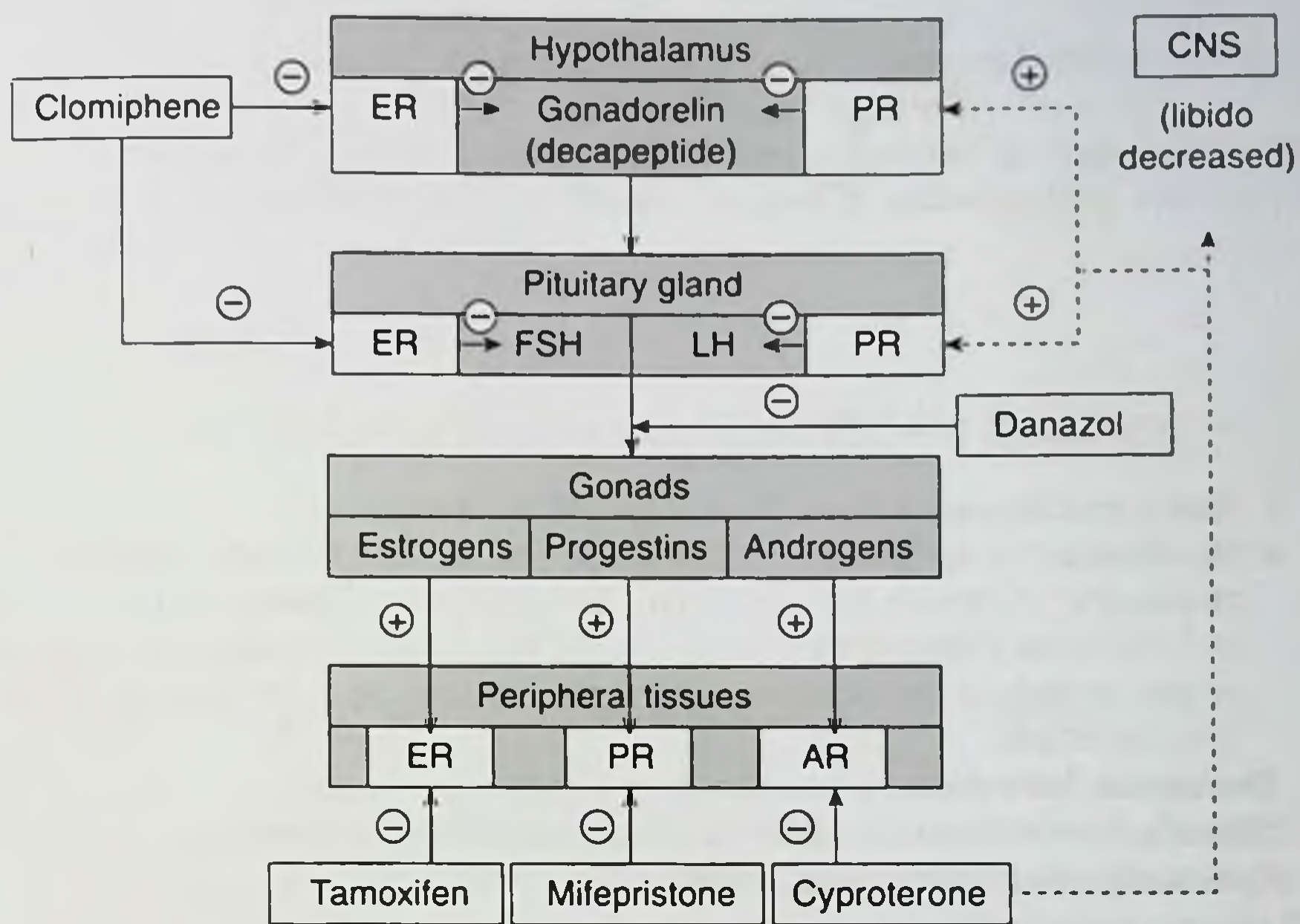
Clomiphene (Clostilbegyt®)

- ▶ Non-steroidal antiestrogen. Similar to tamoxifen in its chemical structure. It has a moderate estrogenic effect when estrogens levels are low in the body and an antiestrogenic effect when they are high. When taken orally, it is well absorbed in the GI tract.
- ▶ Metabolized in the liver. $T_{1/2}$: 5–7 days. Excreted mainly in bile. For oral administration 1–2 times daily.

Therapeutic indication: anovulatory infertility

Side effects: hot flashes, blurred vision, menstrual disorders

Contraindications: metrorrhagia of unknown etiology, visual impairment, genital neoplasms, endometriosis, ovarian cyst, thyroid or adrenal dysfunction, liver and/or kidney failure



ER, estrogen receptor PR, progestin receptor AR, androgen receptor

FSH, follicle-stimulating hormone

LH, luteinizing hormone

⊖ — inhibitory action

⊕ — stimulating action

Fig. 19.23. Main mechanism of action of sex hormone antagonists on the reproductive system (D. A. Kharkevich, 2021)

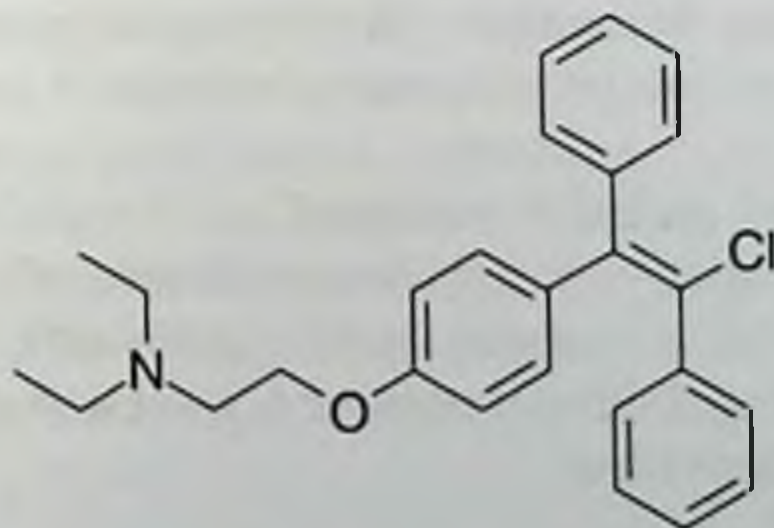


Fig. 19.24. 2-[4-(2-Chloro-1,2-diphenylvinyl)phenoxy]triethylamine dihydrogen citrate

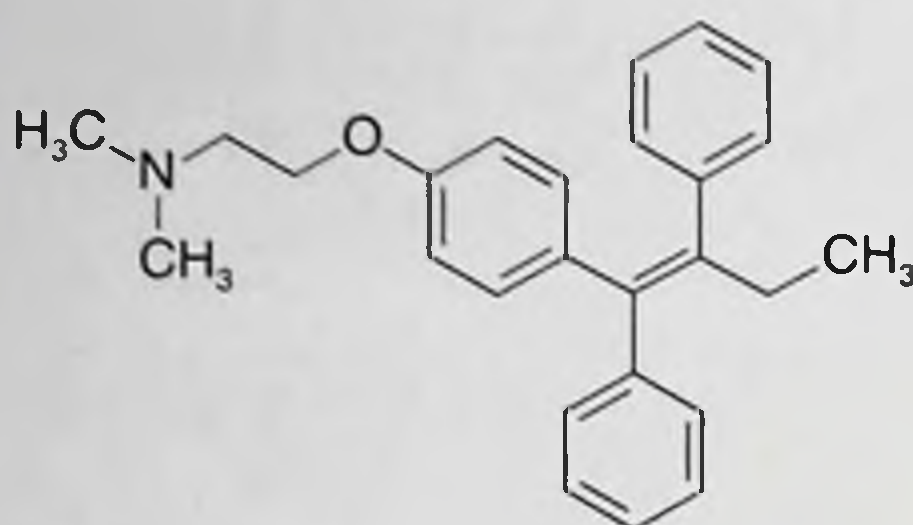
Tamoxifen (Sinfen[†])

Fig. 19.25. (Z)-2-[4-(1,2-Diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine

- ▶ Non-steroidal antiestrogen. Well absorbed in the GI tract.
- ▶ Metabolized in the liver by hydroxylation and demethylation to form the active metabolite, N-desmethyl tamoxifen. Elimination is biphasic with initial $T_{1/2}$ of 7–14 hours followed by slow terminal $T_{1/2}$ of 7 days. Excreted predominantly in bile, mainly as metabolites, with small portions excreted in urine. For oral administration.

Therapeutic indications: breast cancer in women and in men

Side effects: hot flashes, vaginal bleeding, alopecia, bone pain

Contraindications: pregnancy, breastfeeding, allergic reactions

Progestins

Classification

I. Natural

- Progesterone (Prolus[®], Vanel[†], Mirajel[®])

II. Synthetic

1. Progesterone derivatives

- Medroxyprogesterone (Provera[†]), Divina[†] (medroxyprogesterone, estradiol)
- Dydrogesterone (Duphaston[†])
- Cyproterone (Antiandren[†], Androcur Depot[†])

2. 19-nortestosterone derivatives (19-norprogestogens), compounds in which a methyl group in the progesterone molecule at position C₁₉ is replaced by hydrogen

A. With an ethynyl radical at position C₁₇

- Estrane derivative — norethisterone (Norcolut[†]), tibolone (Ladybon[†])
- Gonane derivative — levonorgestrel (Lalinola[†]), Desogestrel[†], Gestodene[†]

B. Without an ethyl residue at position C₁₇ — Dienogest[†]

3. Spironolactone derivatives

- Drospirenone[†].

Pharmacological effects: gestagen; estrogenic effect in norethisterone since metabolites with estrogenic activity are formed during its first passage through the liver; antiestrogenic (except Drospirenone); androgenic effect of 19-nortestosterone derivatives (except Dienogest); antimineralocorticoid effect of Drospirenone.

Therapeutic indications: infertility, hormone replacement therapy in menopause, all endocrine causes of miscarriage, endometrial hyperplasia, endometriosis, contraception

Side effects: menstrual disorders, weight gain, increased blood pressure, thromboembolism

Contraindications: thromboembolic conditions, diagnosed or suspected breast and genital malignancies, severe liver disease, pregnancy, breastfeeding, less than 18 years of age

Progesterone (Prolus[®], Vanel[®], Mirajel[®])

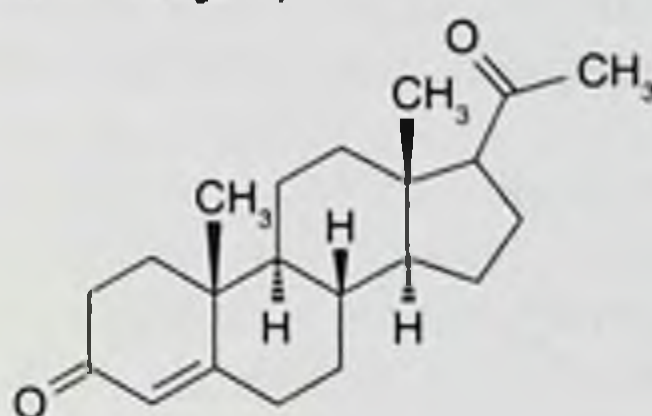


Fig. 19.26. (8S,9S,10R,13S,14S,17S)-17-Acetyl-10,13-dimethyl-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-3-one

- ▶ Corpus luteum hormone. It ensures the endometrium's transition from the proliferation phase caused by follicle-stimulating hormone to the secretory phase; after fertilization, it supports a transition to the state necessary for the development of a fertilized egg. It reduces muscular excitability and contractility of the uterus and fallopian tubes. It stimulates the development of the terminal end buds. It prevents gonadotropin-releasing hormone from stimulating the release of luteinizing and follicle-stimulating hormones, inhibits the production of gonadotropins by the pituitary gland and ovulation.
- ▶ Metabolized in the liver, excreted in urine. For oral, intramuscular, topical administration.

Norethisterone (Norcolut[®])

- ▶ A progestogen that promotes the endometrium's transformation from the proliferative phase to the secretory one. Inhibits the secretion of gonadotropins by the pituitary gland, preventing the maturation of follicles and ovulation. Well absorbed after oral administration.
- ▶ Metabolized in the liver. Initial $T_{1/2}$: 2.5 hours, terminal $T_{1/2}$: 8 hours. Excreted in urine.

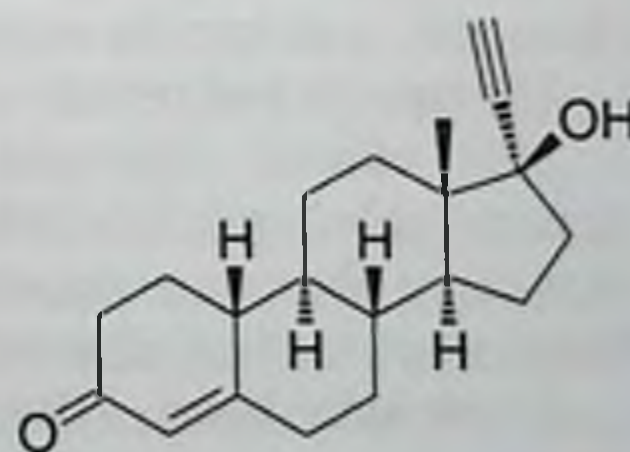


Fig. 19.27. (17 α)-17-Hydroxy-19-norpregn-4-en-20-yn-3-one (and as acetate or enanthate)

Anti-progestins

Mifepristone (Mifegyne[®]) is a synthetic steroidal antiprogestogen (progesterone receptor antagonist). It inhibits the effect of progesterone on the endometrium and myometrium. It increases myometrial contractility by stimulating the release

of interleukin-8 in choriodecidual cells, increasing myometrial sensitivity to progesterone (to enhance the effect, it is used in combination with a synthetic analog of progesterone). The drug induces decidual desquamation and ovum expulsion.

Therapeutic indication: termination of early uterine pregnancy (up to 42 days)

Side effects: uterine bleeding, lower abdominal discomfort and pain

Contraindications: pregnancy for more than 42 days, adrenal insufficiency, anemia

Parenteral and implantable contraceptives

A group of drugs used for birth control. They are used not only to prevent unwanted pregnancy, but also to plan the time of pregnancy (depending on the parent's health and age), the interval between children, the number of children in a family, etc.

Classification.

I. Oral estrogen-progestin combinations

1. Monophasic (fixed doses of estrogens and progestins): Diane-35⁺ (cyproterone, ethinylestradiol), Jeanine⁺ (dienogest, ethinylestradiol), Logest⁺ (gestodene, ethinylestradiol), Regulon⁺ (desogestrel, ethinylestradiol), Minizistone⁺ (levonorgestrel, ethinylestradiol)
2. Biphasic (estrogen and progestin content varies): Anteovin⁺.
3. Triphasic (estrogen and progestin content varies): Trisiston⁺ (levonorgestrel, ethinylestradiol)

II. Single component contraceptives (progestins)

1. Oral: levonorgestrel (Microlut⁺), Micronor⁺, desogestrel (Cerazette⁺)
2. Subdermal implants: levonorgestrel (Norplant⁺)

III. Postcoital contraceptives: levonorgestrel (Postinor⁺), mifepristone

Oral estrogen-progestin combinations

Mechanism of action: They inhibit the production of follicle-stimulating and luteinizing hormones of the pituitary gland and gonadotropin-releasing hormone from the hypothalamus, which stimulates their biosynthesis and release; change the endometrium, prevent ovum implantation (premature regression in the proliferative phase, etc.); change the cervical mucus composition, thus decreasing sperm motility.

Therapeutic indications: contraception

Side effects: increased blood clotting (risk of venous thrombosis and thromboembolism), liver failure, headache, dizziness, breast lumpiness (engorgement), changes in libido, nausea, vomiting, intermenstrual spotting, weight gain, increased blood pressure, hyperglycemia

Contraindications: thromboembolic diseases, cerebrovascular disorders; reproductive system and breast tumors; liver failure, diabetes mellitus, pregnancy, breastfeeding

Single component contraceptives (progestins)

They can be administered to women with contraindications to estrogens or during breastfeeding.

Mechanism of action: They change the composition and amount of the cervical mucus, making it difficult for sperm to penetrate through it; they reduce the rate

of ovum transport through the fallopian tubes and prevent the implantation of a fertilized ovum.

The lack of estrogens and the low progestin doses explain the lesser severity or absence of a number of side effects typical of estrogen-progestin contraceptives (effects on metabolism, risk of thrombophlebitis). Fertility is restored 3 months after discontinuation of progestin-only contraceptives.

Side effects: irregular menstrual cycle, intermenstrual spotting, nausea, headache, depression

Contraindications: allergic reactions, pregnancy, thromboembolic diseases, liver failure, hormone-sensitive cancers, vaginal bleeding of unknown etiology, breast cancer, hepatic cancer

To reduce the systemic side effects of progestins, the Mirena device was proposed, which is an intrauterine hormone-releasing system. It consists of a depot that continuously releases levonorgestrel, which has a local contraceptive effect, for 5 years, making the cervical mucus thick and suppressing the process of ovum implantation in the endometrium. Mirena is a highly reliable contraceptive and is well-suited for women suffering from menorrhagia and dysmenorrhea because of the decreased frequency and volume of menstrual bleeding.

There are also drugs containing high doses of estrogens or progestins that are used in the first 24 to 48 hours after intercourse (postcoital contraceptives), such as levonorgestrel (Postinor[®]) (contains levonorgestrel).

Preparations of male gonadal hormones (androgens)

In 1849, A. Berthold suggested that an extract from seminal vesicles contained highly active substances, although their structures were unidentified at that time. In 1889, Ch. Brown-Séquard published his personal experience with subcutaneous injection of testicular extracts of animals and reported being rejuvenated. He called it the elixir of life. In 1932, A. Butenandt isolated three sex hormones in their pure form: estradiol, androsterone and testosterone. He found that all three hormones had the same structure, a molecule called steroid. In 1939, he was awarded the Nobel Prize. The Prize was also awarded to L. Ruzicka for the discovery of testosterone's molecular structure and the partial synthesis of androsterone and testosterone from cholesterol.

Interstitial Leydig cells (testicular glandulocytes) in the testes produce the hormone testosterone. A significant portion of testosterone is converted in many organs (e.g., the prostate gland) into dihydrotestosterone (by 5 α -reductase), which has the highest affinity for intracellular androgen receptors. Testosterone promotes the development of the male genitalia and secondary sexual characteristics, and also controls spermatogenesis. Testosterone also has a pronounced effect on protein synthesis (anabolic effect) and it increases the reabsorption of water, Ca²⁺, Na⁺, Cl⁻ ions in the renal tubules, etc. Testosterone production is regulated by the luteinizing hormone of the anterior pituitary gland (Fig. 19.28).

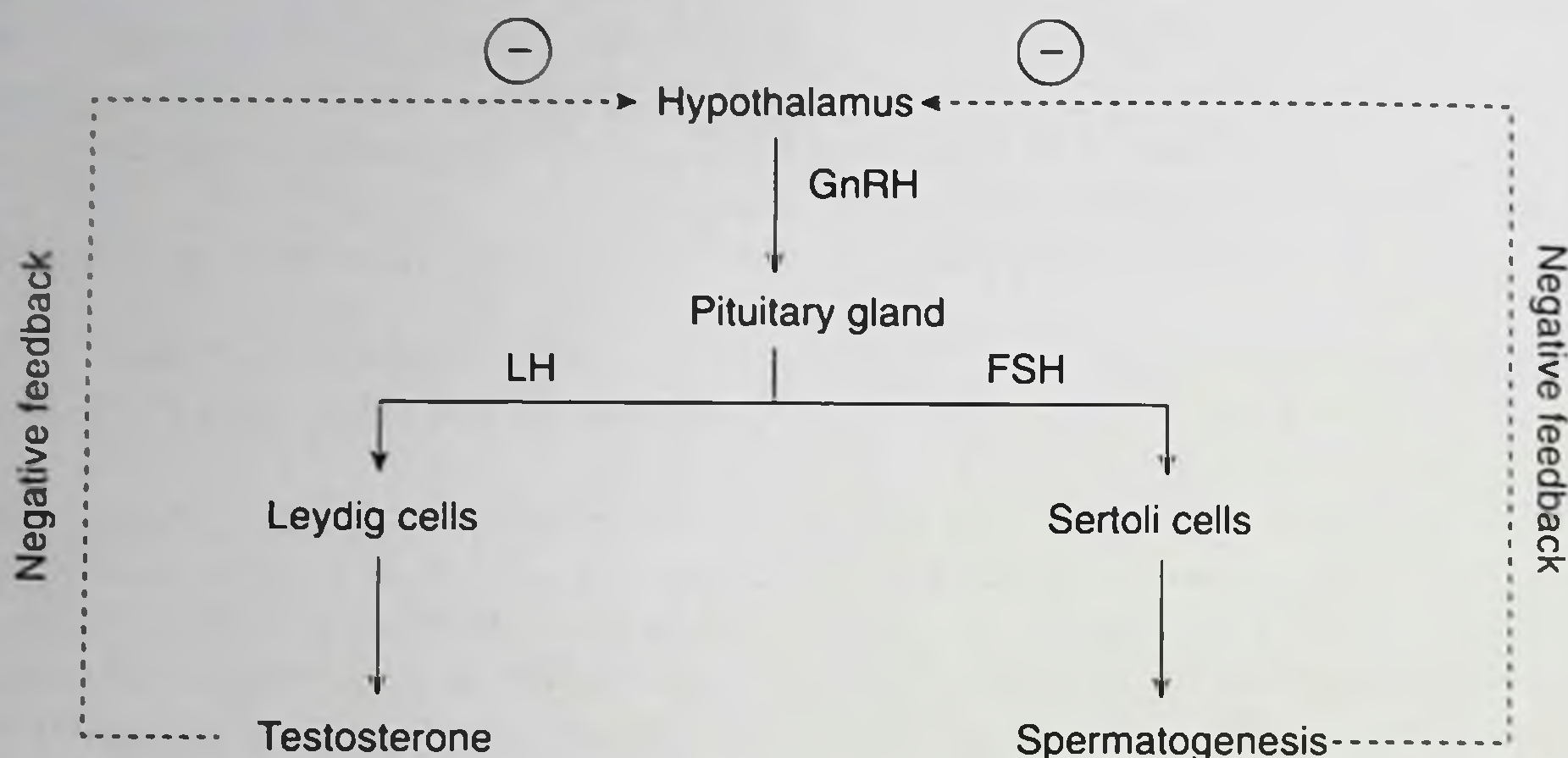


Fig. 19.28. Regulation of testes function by gonadotropins through a feedback loop. LH: luteinizing hormone, FSH: follicle stimulating hormone, GnRH: gonadotropin-releasing hormone

Classification

- ▶ Testosterone (Nebido[†], Androgel[†])
- ▶ Testosterone esters — Testosterone propionate[†] and Testosterone enanthane[†]
- ▶ 17-alkylandrogens — methyltestosterone

Preparations of male sex hormones have androgenic and anabolic effects.

Androgenic action promotes sexual maturation and the formation of primary and secondary male sexual characteristics, controls spermatogenesis, develops the male mind and sexuality, and maintains sexual potency. Anabolic properties of androgens activate protein synthesis in muscle and bone tissue and promote the deposit of Ca^{2+} ions in the bones.

When taken orally, testosterone is rapidly metabolized in the liver, so it can only be used in dosage forms that allow it to enter the systemic circulation, bypassing the liver. For example, it is used as a gel for topical use (Androgel) or a solution for intramuscular administration (Nebido). When used daily, these dosage forms ensure the blood concentration of the drug is maintained at a physiological level. Testosterone esters (testosterone propionate and testosterone enanthane) have high lipophilicity, which promotes the deposition of esters in fat depots and, accordingly, prolongs their action. In the body, testosterone esters are hydrolyzed to form testosterone. Synthetically produced 17- α -alkylandrogens (methyltestosterone) are resistant to liver degradation.

Therapeutic indications: hormone replacement therapy for primary or secondary hypogonadism in men, delayed puberty; impotence caused by testosterone deficiency; postcastration syndrome, spermatogenesis disorders; metastatic breast cancer

Side effects: excessive sexual drive, edema, dizziness, nausea, masculinization (voice deepening, hirsutism, hypomastia); methyltestosterone can cause jaundice

Contraindications: prostate cancer, liver tumors, puberty

Specific properties of individual drugs

Testosterone (Nebido⁺, Androgel⁺)

- ▶ Gel for topical use. After transdermal delivery, testosterone enters the systemic circulation at relatively constant concentrations within 24 hours. Serum testosterone concentration increases from the first hour after drug administration, reaching a constant level on the 2nd day of treatment. Daily variations in concentrations have the same amplitude as the changes in endogenous testosterone levels observed due to circadian rhythms. With transdermal administration, there are no supraphysiological peaks in the blood testosterone concentration like the ones that occur with injection.
- ▶ Metabolized in the liver. The main active metabolites of testosterone are dihydrotestosterone and estradiol. Excreted mainly in urine and bile as conjugated testosterone metabolites.

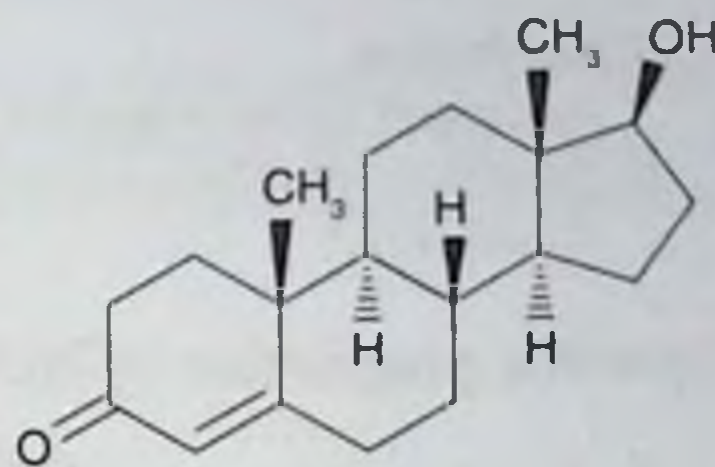


Fig. 19.29. (17 β)-17-Hydroxyandrost-4-en-3-one

Testosterone (Testosterone propionate⁺)

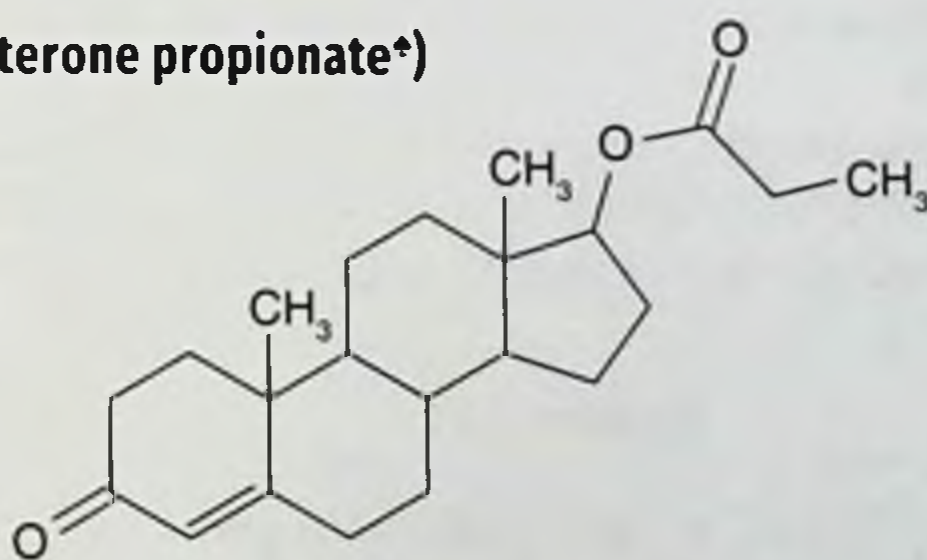


Fig. 19.30. (17 β)-17-Hydroxyandrost-4-en-3-one

A synthetic androgenic agent that is absorbed more slowly and thereby persists better in the body. It has an anabolic effect: involved in skeletal growth, increases skeletal muscle mass, causes the retention of nitrogen, phosphorus, sulfur, K^+ ions necessary for protein synthesis. It inhibits the production and release of luteinizing and follicle-stimulating hormones by the pituitary gland. After injection, the effect occurs immediately and lasts 24 hours.

Metabolized in the liver to form weakly active androsterone and inactive etiocholanolone. $T_{1/2}$: 3–4 hours. Excreted mainly in urine, with about 6% excreted in bile as unchanged drug. For intramuscular administration.

Methyltestosterone

A synthetic testosterone analog that is 3–4-fold less active than testosterone propionate. Short-acting (4–6 hours). For oral administration.

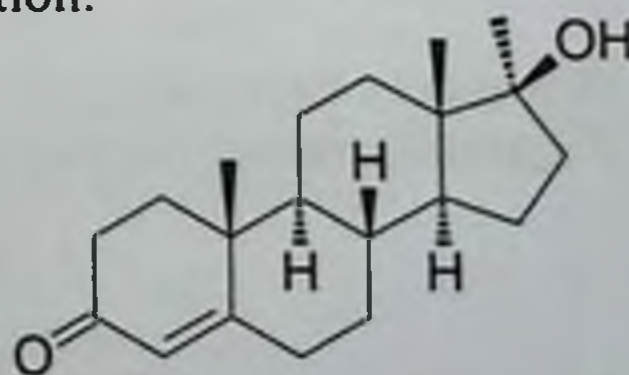


Fig. 19.31. (17-Methyltestosterone, 17 α -methylandrosten-4-ol-17 β -one-3

Antiandrogens

Classification

- I. Androgen receptor blockers: Cyproterone⁺, Flutamide⁺
- II. 5α -reductase inhibitors (inhibit testosterone conversion to dihydrotestosterone): Finasteride⁺

Specific properties of individual drugs

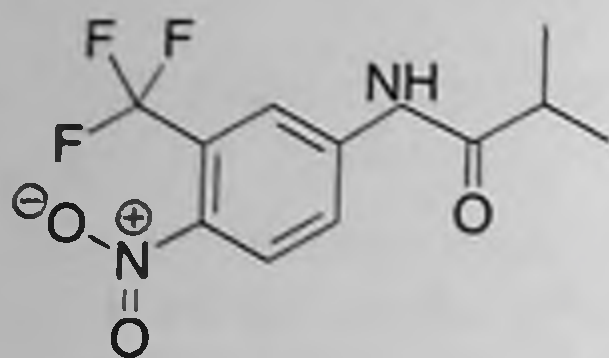


Fig. 19.32. 4'-Nitro-3'-trifluoromethylisobutyranilide

Flutamide⁺

- ▶ A non-steroidal antiandrogen. It reduces the size and density of the prostate gland, prevents metastasis from developing.
- ▶ Metabolized in the liver. $T_{1/2}$: 6–8 hours. Excreted mainly in urine. For oral administration 3 times daily.

Mechanism of action: It competitively blocks the interaction of androgens with their cellular receptors, suppresses the biological effects of endogenous androgens, which disrupts tumor cell replication.

Therapeutic indications: prostate cancer, differential diagnosis of hypogonadism in men

Side effects: gynecomastia, galactorrhea, fluid retention, decreased libido, impotence, liver and/or kidney failure, spermatogenesis inhibition

Contraindications: severe liver, kidney disease

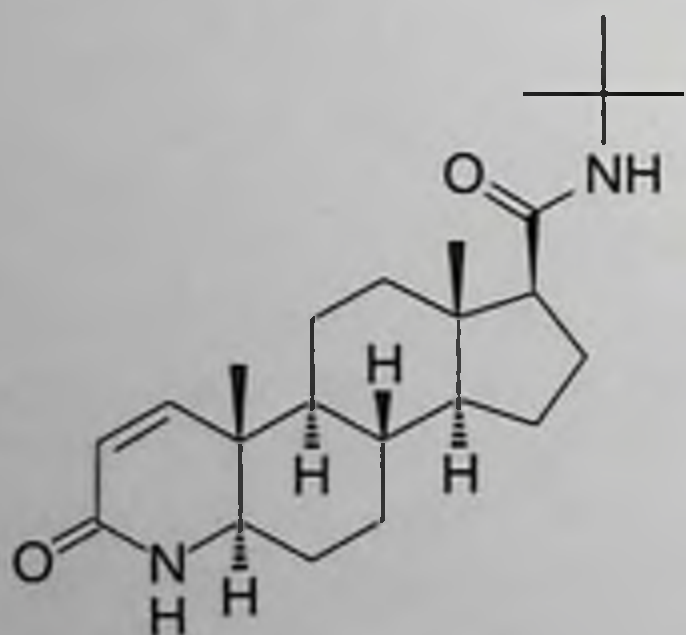


Fig. 19.33. N-tert-Butyl-3-oxo-4-aza-5 α -androst-1-en-17 β -carboxamide

Finasteride⁺

- ▶ An inhibitor of 5α -reductase, an enzyme that converts testosterone to more active dihydrotestosterone. It lowers the level of dihydrotestosterone in the blood and prostate tissue. It reduces the size of the prostate gland when enlarged, improves urine flow. It is well absorbed and penetrates tissues and bodily fluids. Bioavailability: 80%, regardless of food intake.
- ▶ Metabolized in the liver. $T_{1/2}$: 6–8 hours. Excreted as metabolites in urine and bile. For oral administration once daily.

Therapeutic indications: benign prostatic hyperplasia

Side effects: impotence, decreased libido, ejaculate volume reduction, gynecomastia

Contraindications: obstructive uropathy, prostate cancer

ANABOLIC STEROIDS

They increase skeletal muscle mass, the volume of certain parenchymal organs and bone tissue density (total body weight increases in this case); delay the release of nitrogen, phosphorus and Ca^{2+} ions from the body, enhance male sexual characteristics.

Classification

I. Androstane derivatives

- Methandienone (Methandrostenolone[®]).

II. Estren derivatives.

- Nandrolone (Retabolil[®]).
- Nandrolone phenylpropionate[®] (Phenobolin[®]).

Therapeutic indications: muscular dystrophy, osteoporosis, cachexia

Side effects (associated with their androgenic effect): dyspeptic symptoms, transient jaundice, edema, voice deepening, gynecomastia; in women — menstrual disorders, virilization, increased libido, liver disease

Contraindications: nephrotic syndrome; prostate cancer, breast cancer in men; prostatitis; liver failure; metastatic breast cancer; hypercalcemia (including history thereof), pregnancy, breastfeeding

Specific properties of individual drugs

Methandienone (Methandrostenolone[®])

Similar to testosterone and its analogs in its chemical structure and biological action. It has a pronounced anabolic effect. Its androgenic activity is 100-fold inferior to testosterone propionate. Short-acting. For oral administration 1–2 times daily.

Nandrolone phenylpropionate[®] (Phenobolin[®])

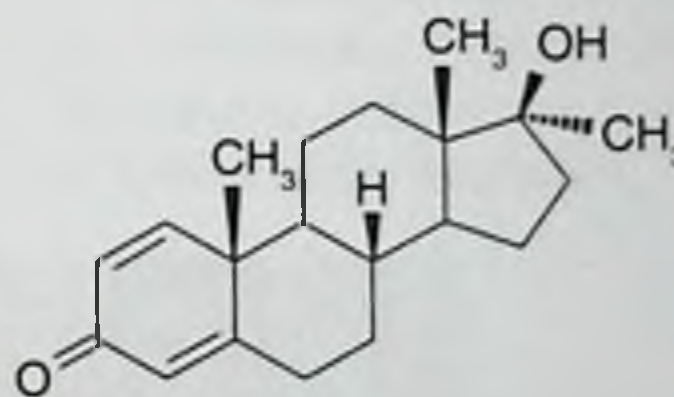


Fig. 19.34. (8S,9S,10S,13S,14S,17S)-17-Hydroxy-10,13,17-trimethyl-7,8,9,11,12,14,15,16-octahydro-6H-cyclopentophenanthren-3-one

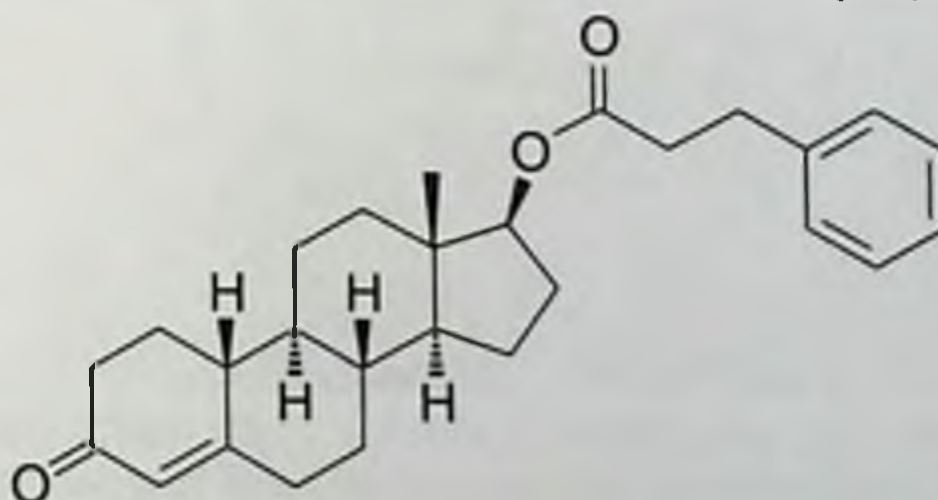


Fig. 19.35. 19-Nortestosterone 17 β -phenylpropionate

A long-acting anabolic steroid. After a single injection, the effect persists for 7–15 days. For intramuscular administration as an oil-based solution.

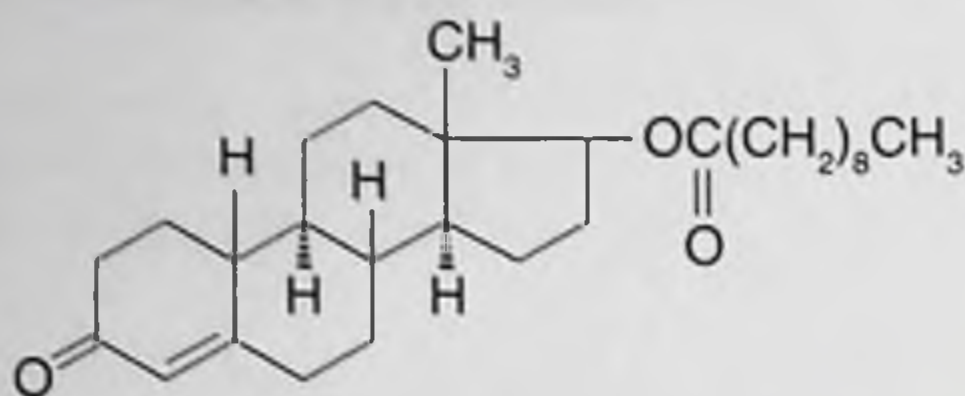
Nandrolone decanoate (Retabolil®)

Fig. 19.36. 19-nor-4-androsten-3-one, 17 β -ol or 4-estren-17 β -ol-3-one

A synthetic testosterone derivative. It has a pronounced and long-lasting anabolic effect. It has a less androgenic (virilizing) effect than Phenobolin[®]. After injection, the effect develops over the first 3 days, reaching a maximum by the 7th day and lasts at least 3 weeks.

Metabolized in the liver. $T_{1/2}$: 4.3 hours. Excreted in urine. For intramuscular administration.

20. GENERAL PRINCIPLES OF PHARMACOTHERAPY / SYNTHETIC ANTIMICROBIALS

References to the therapeutic use of mold are found in the writings of Arab philosopher and physician Avicenna (2nd century) and German alchemist/physician Paracelsus (14th century). In 1963, Bolivian ethnobotanist E. O. Poblete described the use of mold by Indian healers in the Inca era (15th–16th centuries). In 1896, Italian physician B. Gosio, who was studying the causes of mold damage to rice, developed an antibiotic formula similar to that of penicillin. At the end of the 19th century, French military doctor E. Duchesne described the destructive effect of mold on the typhoid bacillus. In 1913, American scientists C. Alsberg and O. F. Black produced an acid with antimicrobial properties from mold. In 1928, British scientist A. Fleming conducted an experiment to study the human body's resistance to bacterial infections (Fig. 20.1). He found that some colonies of staphylococcal cultures he had left in Petri dishes were infected with the *Penicillium Notatum* mold strain. Around the mold spots, Fleming noticed an area without bacteria. This led him to conclude that this mold produced a bacteria-killing substance, which he called "penicillin".



Fig. 20.1. Alexander Fleming (1881–1955), a British microbiologist, and member of the Royal Society of London and the Paris Academy of Sciences. He graduated from St. Mary's School of Medicine at the University of London

Oxford scientists H. Florey and E. Chain continued his work. In 1940, they isolated the pure drug substance and studied its therapeutic properties. On February 12, 1941, penicillin was first administered to a patient by injection. In 1943, H. Florey transferred the technology for obtaining the new drug to American scientists, and

mass production of the antibiotic was launched in the USA. In 1945, A. Fleming, H. Florey and E. Chain were awarded the Nobel Prize in Physiology or Medicine.

In the 1870s, molds were studied by Russian physicians A. Polotebnov and V. Manassein who found they blocked the growth of other microorganisms. Polotebnov recommended these molds be used in medicine, in particular, for the treatment of skin diseases. In the Soviet Union, the first samples of penicillin were obtained by microbiologists Z. V. Ermolyeva and T. I. Balezina (Fig. 20.2). In 1942, they discovered the penicillin-producing strain *Penicillium Crustosum*. In 1945, penicillin testing was initiated in the Soviet Union. The production of penicillin was mastered by the Research Institute of Epidemiology and Hygiene of the Red Army under the direction of N. Kopylov.



Fig. 20.2. Zinaida Vissarionovna Ermolyeva (1898–1974), a Soviet microbiologist and epidemiologist, full member of the USSR Academy of Medical Sciences, creator of the first domestic penicillin (1942). Laureate of the First Degree Stalin Prize

GENERAL PRINCIPLES OF PHARMACOTHERAPY

For successful treatment, it is important to identify a pathogen and determine its sensitivity to those drugs that can be used as pharmacotherapeutic agents. If the pathogen is known, drugs with the appropriate antibacterial action are selected. If the pathogen is not known, it is advisable to use broad-spectrum drugs or a combination of two drugs, the total spectrum of which includes the probable pathogens. Treatment should be started as early as possible. At disease onset, there are fewer microbial cells and they are in a state of vigorous growth and reproduction. At this stage, microbes are most sensitive to pharmacotherapeutic agents. Drug

doses should be sufficient to produce bacteriostatic or bactericidal concentrations in bodily fluids and tissues. At the initiation of treatment, a loading dose is sometimes administered that exceeds subsequent ones (e.g., sulfonamides). The duration of therapy should be sufficient to suppress pathogen activity. It should be noted that clinical improvement (temperature decrease and other symptoms) is not a reason to discontinue the drug. If the prescribed course of treatment (usually 7–14 days) is not completed, the disease can return. Choosing the route of administration also plays a significant role in the treatment's efficacy, taking into account the fact that some substances are not completely absorbed in the GI tract, poorly cross the BBB, etc. Combination therapy is the simultaneous administration of 2–3 drugs with different mechanisms of action to prevent antibiotic resistance, increase the treatment's efficacy and reduce the risk of side effects.

SULFONAMIDES

Sulfonamides are antimicrobial agents derived from sulfanilic acid amide. The first drug from this group was obtained in 1908 when trying to synthesize a good dye for textile materials, related to the well-known dye aniline. About 20 years later, the azo dye prontosil was synthesized, and its activity against streptococci was discovered. The antibacterial effect of this substance was discovered by German scientist G. Domagk who was continuing the research of J. Klarer and F. Mietzsch, which, in turn, was based on the work by P. Ehrlich on the use of dyes as antibiotics.

Classification

- I. Drugs with systemic action (well absorbed in the GI tract)
 - A. Intermediate-acting (4–6 hours)
 - Sulfadimidine (Sulfadimesine[†])
 - Sulfaethidole (Ethazol-sodium[†])
 - Sulfacarbamide (Urosulfan[®])
 - Sulfathiazole (Norsulfazol[®])
 - B. Long-acting (12–24 hours)
 - Sulfapyridazin[®]
 - Sulfadimethoxine[†]
 - C. Ultra-long-acting (> 7 days)
 - Sulfalene[†]
- II. Drugs acting within the intestinal lumen (poorly absorbed in the GI tract)
 - Phthalylsulfathiazole (Phtalazol[†])
- III. Topical drug products
 - Sulfacetamide (Sulfacyl-sodium[†])
 - Silver sulfadiazine (Argedin[†])
 - Silver sulfathiazole (Argosulfan[†])
- IV. Combination drugs with trimethoprim

- Co-trimoxazole [sulfamethoxazole, trimethoprim] (Bactrim[®], Biseptol[®])
- V. Combination drugs with salicylic acid
 - Sulfasalazine (Salazosulfapyridine[®])
 - Salazopyridazine[®] (Salazodin[®])
 - Salazodimethoxine[®]

The mechanism of antimicrobial action is associated with competitive antagonism with para-aminobenzoic acid (PABA) (Fig. 20.3). The latter is included in the structure of dihydrofolic acid, which is synthesized by many microbes.

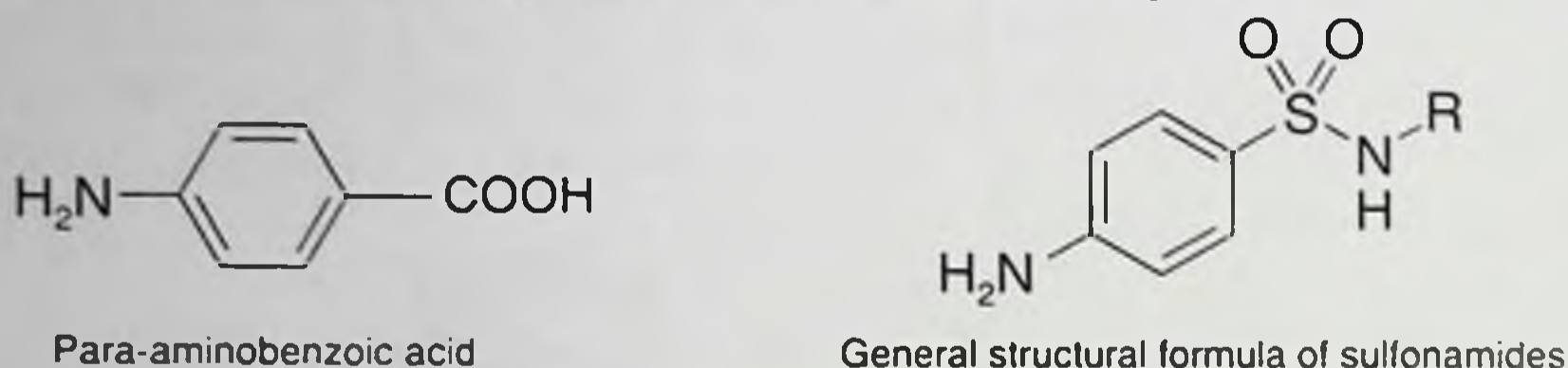


Fig. 20.3. General structural formula of sulfonamides and chemical structure of para-aminobenzoic acid

Due to their chemical similarity to PABA, sulfonamides prevent its incorporation into dihydrofolic acid and competitively inhibit dihydropteroate synthetase. Disturbance of dihydrofolic acid synthesis reduces the production of tetrahydrofolic acid, which is necessary for the synthesis of purine and pyrimidine bases. This inhibits the synthesis of nucleic acids and the reproduction of microbes (bacteriostatic action) (Fig. 20.4).

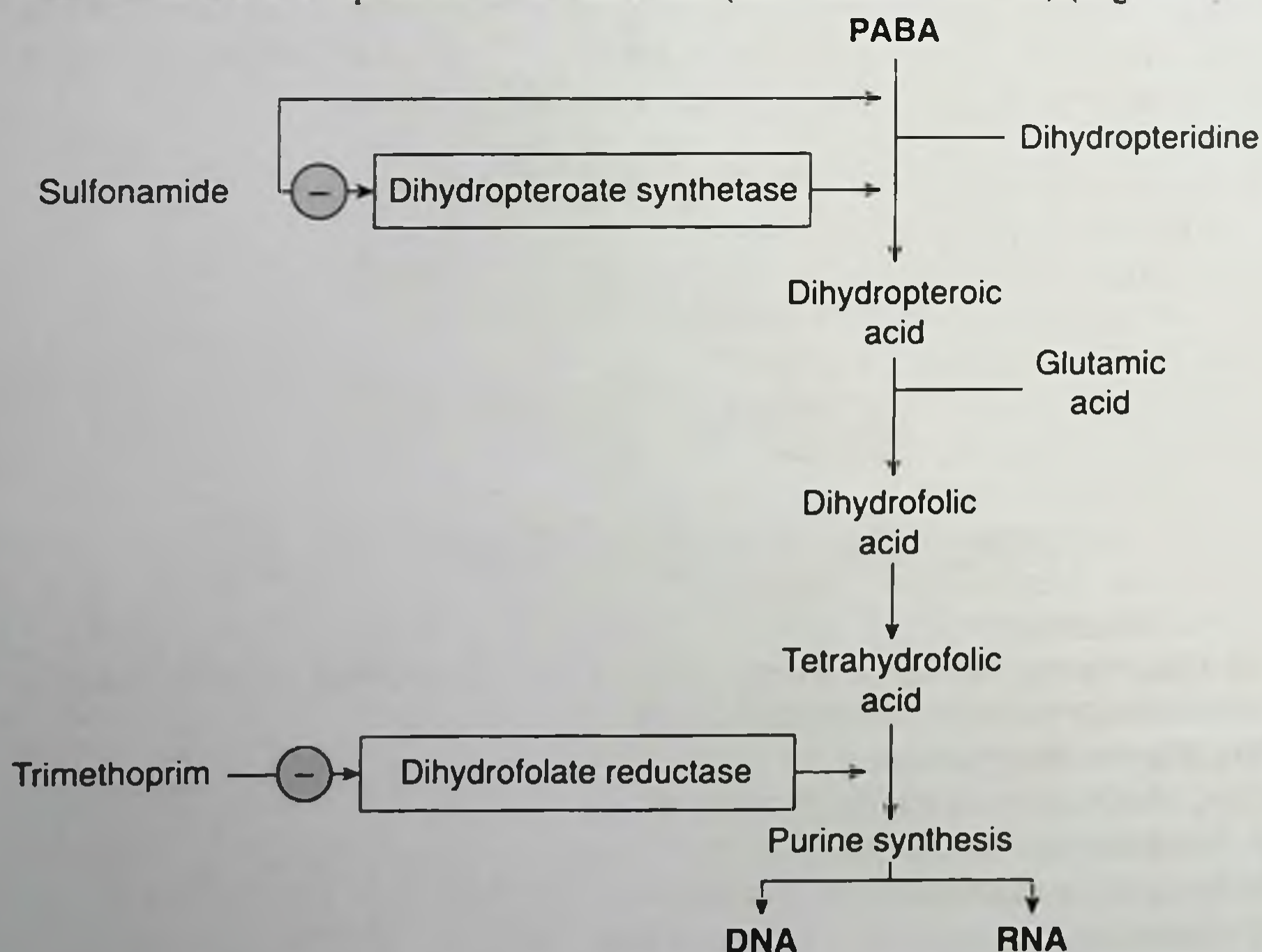


Fig. 20.4. Mechanism of action of sulfonamides and trimethoprim

Spectrum of activity

Bacteria: gram-positive (except MRSA) and gram-negative cocci, coliform bacterium (*Escherichia coli*), dysentery pathogens (*Shigella species*), cholera bacillus (*Vibrio cholerae*), gas gangrene pathogens (*Clostridium perfringens*), anthrax pathogens (*Bacillus anthracis*), diphtheria pathogens (*Corynebacterium diphtheriae*)

Chlamydia: trachoma pathogens (*Chlamydia trachomatis*), ornithosis pathogens (*Chlamydophila psittaci*), lymphogranuloma venereum pathogens (*Chlamydia trachomatis*)

Actinomycetes: nocardiosis (*Nocardia asteroides*) and micromonosporosis (*Micromonospora parva* Jensen and *M. monospora*) pathogens

Protozoa: toxoplasmosis pathogen (*Toxoplasma gondii*), malaria parasites (*Plasmodium species*)

Enterococci, *Pseudomonas aeruginosa*, *Bordetella pertussis*, *Corynebacterium diphtheriae*, *Mycobacterium tuberculosis*, *Treponema pallidum*, leptospira and most anaerobes have natural resistance to sulfonamides.

Indications for sulfonamide administration are currently limited since sulfonamides are significantly inferior to modern synthetic antimicrobials and antibiotics in their activity, have high toxicity and acquired resistance.

Side effects: leukopenia, hypoplastic anemia, thrombocytopenia, agranulocytosis, pancytopenia; crystalluria (more often caused by poorly soluble sulfonamides: sulfadiazine, sulfadimethoxine, sulfalene), hematuria, interstitial nephritis; hepatitis; headache, dizziness, lethargy, abdominal pain, nausea, vomiting, diarrhea; photosensitivity, allergic reactions. When used topically: burning, pruritus, application site pain; allergic reactions

Contraindications: allergic reactions to sulfanilamides, furosemide, thiazide diuretics, carbonic anhydrase inhibitors and sulfonylurea derivatives; kidney failure, severe liver diseases, hematopoiesis suppression, pregnancy, breastfeeding

Characteristics and principles of treatment

- ▶ Loading doses are used in the initial stage of treatment.
- ▶ Their antimicrobial activity is significantly inferior to antibiotics.
- ▶ They are administered in case of intolerance to antibiotics or the development of antibiotic resistance.

Specific properties of individual drugs

Systemic action

They are rapidly and completely absorbed in the GI tract, partially bound to plasma albumin. They are distributed in all tissues, cross the BBB and the placental barrier, accumulate in the serous cavities of the body. The main pathway for conversion of sulfonamides in the body is acetylation, which occurs in the liver. The resulting compounds have no antibacterial activity. Acetylated metabolites are less soluble than the parent sulfonamides and may cause crystal formation at acidic urine pH (crystalluria). Sulfonamides and their metabolites are excreted mainly in urine

by filtration. Some portion of the sulfonamides is reabsorbed. Small amounts are excreted in feces, sweat and saliva.

They differ mainly in the duration of their antibacterial effect.

Intermediate-acting drugs are well absorbed and relatively rapidly excreted. Following enteral administration, maximum plasma concentrations are reached in 2–3 hours. To maintain bacteriostatic concentrations, they are administered every 4–6 hours.

The concentration of Sulfapyridazin[®] and sulfadimethoxine in the cerebrospinal fluid is 5–10% of the plasma concentration. This distinguishes them from intermediate-acting sulfonamides, which accumulate in the cerebrospinal fluid in relatively large amounts: 50–80% of the plasma concentration.

Sulfapyridazin[®] and sulfadimethoxine are administered orally 1–2 times daily.

Bacteriostatic concentrations of the ultra-long-acting drug sulfalene are maintained in the body for up to 1 week.

In case of urinary tract infection, sulfonamides such as sulfacarbamide (Urosulfan[®]) and sulfaethidole (Ethazol-sodium[®]), which are poorly acetylated and excreted in urine as free substance, are administered.

Sulfacarbamide (Urosulfan[®]) is excreted unchanged in urine and reaches high urine concentrations.

Sulfalene is used in the following cases:

- ▶ Acute or rapidly developing infections — orally daily (1 g on the 1st day, then 0.2 g daily, the treatment course is 7–14 days).
- ▶ Chronic infections and long-term prophylaxis (rheumatic fever, chronic bronchitis, etc.) — once every 7–10 days (2 g once a week for 1–15 months).

Slow elimination of sulfalene is associated with intensive drug reabsorption in the renal tubules.

Sulfonamides with a systemic effect can be used for coccal infections, respiratory diseases, urinary and biliary tract infections, etc.

Acting within the intestinal lumen

These drugs are poorly absorbed in the GI tract and reach high concentrations in the intestinal lumen. Phthalylsulfathiazole has an antimicrobial effect after phthalic acid elimination in the small intestine, amino group release and sulfathiazole formation. For oral administration 4–6 times daily. Preferably used in combination with B vitamins because the growth and reproduction of *E. coli* involved in the synthesis of these vitamins is suppressed. It can be used to treat intestinal infections (dysentery, colitis, gastroenteritis, etc.).

For topical administration

Sulfacetamide (Sulfacyl-sodium[®]) is used in ophthalmology to treat and prevent gonorrheal eye damage in newborns and adults, in conjunctivitis, blepharitis, corneal ulcers, etc. It has a local irritant effect.

Combination with salicylic acid

Sulfasalazine (Salazosulfapyridine[®])

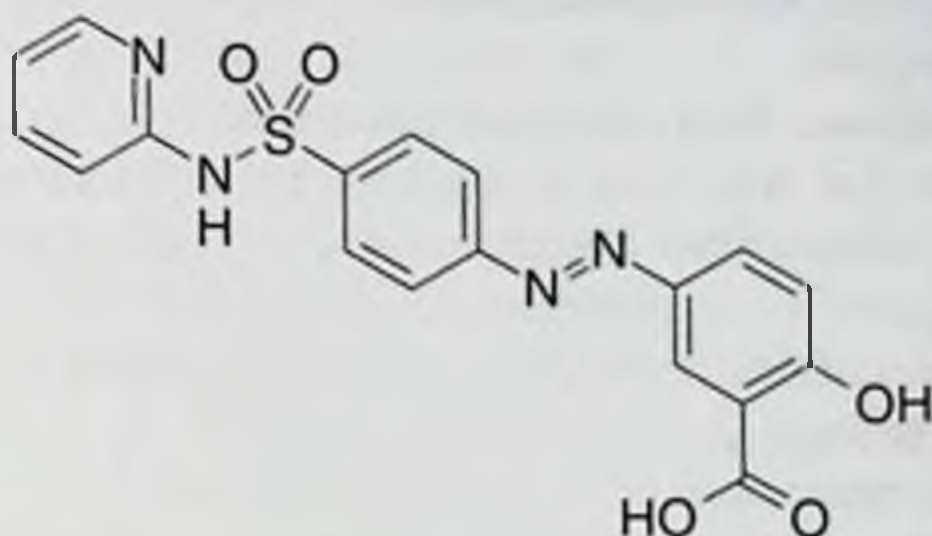


Fig. 20.5. 4-[Pyridyl-(2)-amidosulfonyl]-3-carboxy-4-hydroxyazobenzene

Selectively accumulates in the intestinal connective tissue with the release of 5-aminosalicylic acid which has anti-inflammatory activity and sulfapyridine which has antimicrobial bacteriostatic activity. Maximum plasma concentration is reached in 3–12 hours.

Metabolized in the liver by hydroxylation to form inactive metabolites, 5-aminosalicylic acid, by acetylation. $T_{1/2}$ of sulfasalazine: 5–10 hours, sulfapyridine: 6–14 hours, 5-aminosalicylic acid: 0.6–1.4 hours. 5% of sulfapyridine and 67% of 5-aminosalicylic acid are excreted in bile, 75–91% of sulfasalazine are excreted in urine (within 3 days). For oral administration.

Therapeutic indications: ulcerative colitis (treatment of exacerbations and maintenance therapy in remission); Crohn's disease (mild and moderate forms in the acute phase)

Combination with trimethoprim

Co-trimoxazole [sulfamethoxazole, trimethoprim] (Bactrim[®], Biseptol[®])

An antimicrobial combination drug consisting of five parts sulfamethoxazole and one part trimethoprim. Sulfamethoxazole (intermediate-acting sulfonamide), similar to PABA in its structure, disrupts dihydrofolic acid synthesis in bacterial cells, preventing the incorporation of PABA into its molecule. Trimethoprim enhances sulfamethoxazole action by inhibiting dihydrofolate reductase, disrupts the reduction of dihydrofolic acid to tetrahydrofolic acid, the active form of folic acid responsible for protein metabolism and microbial cell division. It is a broad-spectrum bactericidal drug.

When taken orally, both drug components are completely absorbed in the GI tract. The maximum concentration of the active ingredients is reached in 1–4 hours.

Trimethoprim crosses cell membranes and tissue barriers readily (lungs, kidneys, prostate gland, bile, saliva, sputum, cerebrospinal fluid). $T_{1/2}$: 8.6–17.0 hours. Excreted mainly in urine with 50% excreted as unchanged drug. $T_{1/2}$ of sulfamethoxazole: 9–11 hours. Excreted mainly in urine with 15–30% excreted as an active substance.

Spectrum of activity: gram-positive (staphylococci, some streptococci) and gram-negative anaerobes (*meningococci*, *M. catarrhalis*, *H. influenzae*, *E. coli*, many species of *Klebsiella*, *Citrobacter*, *Enterobacter*, *Salmonella*, *Shigella*). It is active against *Toxoplasma gondii*, *Haemophilus ducreyi*, *Burkholderia cepacia*, *S. maltophilia*, nocardia and pneumocysts.

Therapeutic indications: treatment and prevention of pneumocystis pneumonia in HIV patients; intestinal infections (shigellosis, salmonellosis, travelers' diarrhea); community-acquired urinary tract infections (acute cystitis, chronic relapsed cystitis, pyelonephritis); staphylococcal infections of the skin and soft tissues; infections caused by *Stenotrophomonas maltophilia* and *Burkholderia cepacia*; nocardiosis; toxoplasmosis; brucellosis

Side effects: dyspeptic symptoms (nausea, vomiting, anorexia, diarrhea), allergic reactions (rash, urticaria, pruritus), hematopoietic depression (leukopenia, agranulocytosis, thrombocytopenia, megaloblastic anemia); liver/kidney failure

Contraindications: severe liver and kidney failure, hematopoiesis disorders, aplastic anemia, B₁₂ deficiency anemia, agranulocytosis, leukopenia, pregnancy, breastfeeding

FLUOROQUINOLONES

The first quinolone — nalidixic acid — was discovered in 1962. In the 1980s, fluorinated compounds appeared (presence of a fluorine atom at ring 6 position) that provided a fundamentally new level of antimicrobial activity and had pharmacokinetic properties ensuring high bioavailability. The first drug of this group was norfloxacin, which has activity against gram-negative bacteria and urinary tract infections. Further development of fluoroquinolones resulted in the introduction of ofloxacin and ciprofloxacin to the pharmaceutical market in the mid-1980s. Compounds containing an additional fluorine atom at ring 8 position (lomefloxacin, sparfloxacin) were subsequently synthesized.

Classification.

- ▶ First generation: ciprofloxacin (Ciprolet*), ofloxacin (Tarivid*), lomefloxacin (Maxaquin*), norfloxacin (Nolicin*), pefloxacin (Abaktal*)
- ▶ Second generation (respiratory): levofloxacin (Tavanic*), sparfloxacin (Sparflo*)
- ▶ Third generation (respiratory-anaerobic): moxifloxacin (Avelox*)

Mechanism of action: They inhibit DNA gyrase (topoisomerases II and IV responsible for packaging chromosomal DNA in a supercoil around nuclear RNA), disrupt DNA biosynthesis, bacterial growth and division, cause pronounced morphological changes (including the cell wall and membranes) and rapid cell death (bactericidal action). Highly active broad-spectrum antibacterial agents.

Side effects: arthropathy, arthralgia, myalgia, tendinitis, tenosynovitis, tendon ruptures; crystalluria, transient nephritis; cardiotoxicity; headache, dizziness, visual disturbances, paresthesia; rash, pruritus, angioedema; photosensitivity; oral and/or vaginal candidiasis; nausea, vomiting, diarrhea; pseudomembranous colitis

Contraindications: tendon injury, allergic reactions, less than 18 years of age, pregnancy, breastfeeding

Specific properties of individual drugs

Ciprofloxacin (Ciprolet⁺)

A broad-spectrum drug with high activity against gram-negative bacteria, including *Pseudomonas aeruginosa*. Food intake slows absorption but does not change bioavailability. It penetrates tissues, fluids and cells, reaching high concentrations in the kidneys, gall bladder, liver, lungs, bronchial and sinus mucosa, female genitalia, urine, sputum; detectable in the prostate gland, cerebrospinal fluid, saliva, skin, muscles, bones; crosses the placental barrier. Bioavailability: 60–80%. $T_{1/2}$ for oral administration: 3.5–5.0 hours, with intravenous administration: 5–6 hours. Metabolized in the liver (15–30%) to form weakly active metabolites (diethylciprofloxacin, sulfociprofloxacin, oxociprofloxacin, formilciprofloxacin). Excreted mainly in urine as unchanged drug and as metabolites in bile. It causes pseudomembranous colitis more often than other drugs. For oral, intravenous and topical administration twice daily.

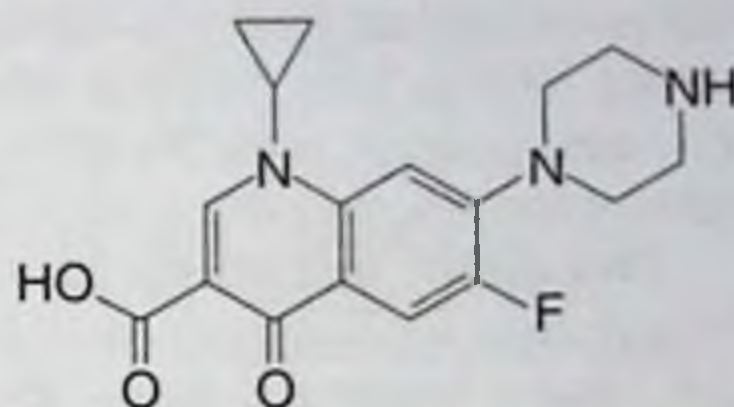


Fig. 20.6. 1-Cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-quinoline-3-carboxylic acid

Spectrum of activity: It is moderately active against gram-positive bacteria in the division phase but has no effect on anaerobes. It is effective against coliform bacterium (*Escherichia coli*), meningococcus (*Neisseria meningitidis*), gonococcus (*Neisseria gonorrhoeae*), salmonella (*Salmonella species*), shigella (*Shigella species*), klebsiella (*Klebsiella species*), proteus (*Proteus species*), blue pus bacillus (*Pseudomonas aeruginosa*), Hemophilus influenzae, staphylococcus (*Staphylococcus species*), chlamydia (*Chlamydia species*), legionella (*Legionella pneumophila*), brucella (*Brucella species*), and Mycobacterium tuberculosis.

Therapeutic indications: ENT infections (otitis, antritis, sinusitis, tonsillitis, pharyngitis), lower respiratory tract (bronchitis, pneumonia), pelvic organs and urinary system (cystitis, pyelonephritis, prostatitis, endometritis), bone tissue, joints (osteomyelitis, arthritis), skin and soft tissues (infected ulcers, wounds, burns, abscesses), abdominal organs (bacterial infections of the GI tract, prevention of postoperative infections during surgical interventions); infectious and inflammatory eye diseases (keratitis, conjunctivitis, blepharitis), combined treatment of tuberculosis

Ofloxacin (Tarivid⁺)

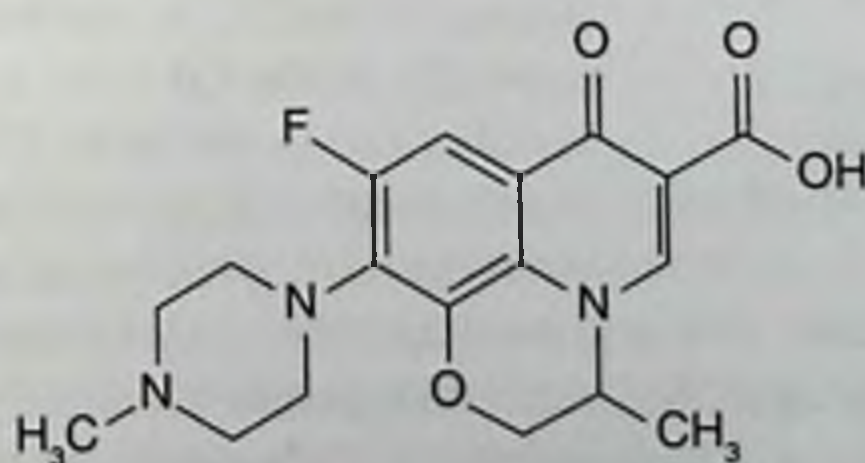


Fig. 20.7. (±)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid

Less potent than ciprofloxacin, effective against *Pseudomonas aeruginosa*.

It penetrates organs and tissues well, accumulates in various organ secretions, crosses well the BBB and placental barrier, excreted into breast milk. It penetrates the cerebrospinal fluid (14–60%). Bioavailability: > 95%. Metabolized in the liver (about 5%) to form N-oxide ofloxacin and dimethylofloxacin. $T_{1/2}$: 4.5–7.0 hours. Excreted in urine, with 75–90 % excreted as unchanged drug. For oral, intravenous administration, for topical administration 1–2 times daily.

Therapeutic indications: infections of the respiratory tract (pneumonia, acute bronchitis), ENT organs (sinusitis, pharyngitis, otitis media, tracheitis), skin and soft tissues, bones and joints, abdominal cavity, pelvic organs, kidneys and urinary tract (pyelonephritis, cystitis, urethritis), genitalia (gonorrhea, prostatitis); combined treatment of tuberculosis

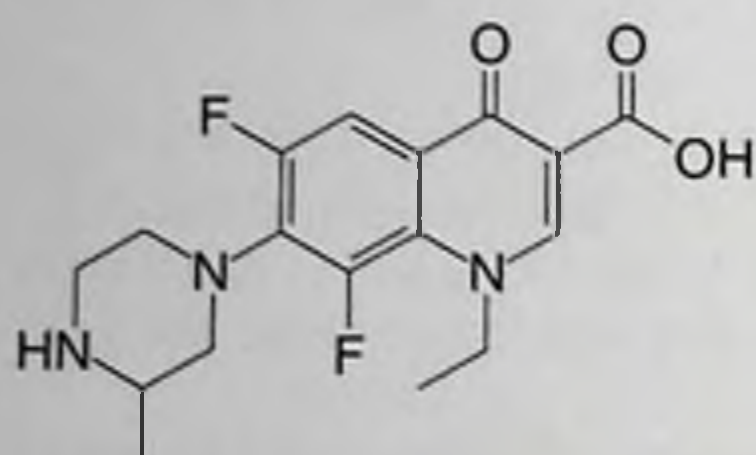


Fig. 20.8. 1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid (as hydrochloride or mesylate)

Lomefloxacin (Maxaquin*)

It has less antimicrobial activity than other fluoroquinolones, but has anti-tuberculosis activity, acting both on extra- and intracellular *Mycobacterium tuberculosis*. It causes photosensitivity more often than other fluoroquinolones.

Bioavailability: 95–98%. It penetrates organs and tissues well (respiratory tract, ENT organs, soft tissues, bones, joints, abdominal and pelvic organs) where the concentration is 2–7 times higher than in plasma. For oral (once daily) and topical (2–3 times daily) administration.

A small portion of the drug is metabolized. $T_{1/2}$: 8–9 hours. 70–80% excreted in urine (mainly as unchanged drug, 9% as glucuronides, 5% as other metabolites); 20–30% in bile.

For therapeutic indications, see “Ofloxacin (Tarivid*)”.

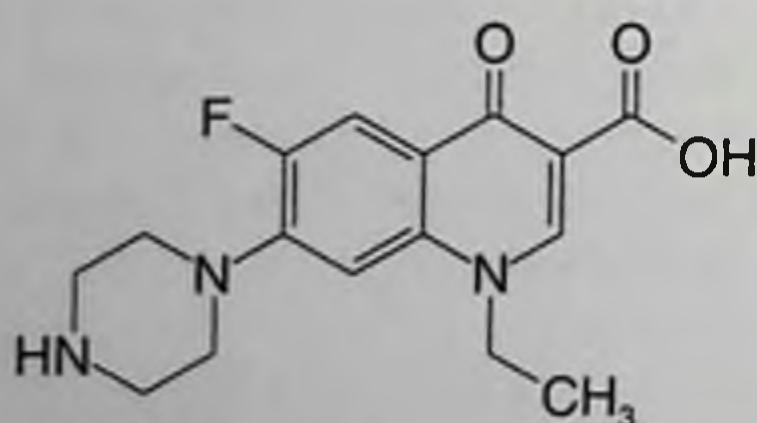


Fig. 20.9. 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid (as hydrochloride)

Norfloxacin (Nolicin*)

A synthetic pyridonecarboxylic analog of nalidixic acid, a metabolite of pefloxacin, differing in the absence of a methyl group at the piperazine core. Rapidly absorbed, bioavailability: 30–40%. Crosses the BBB and placental barrier. Unlike other fluoroquinolones, it reaches high concentrations primarily in the GI tract and genitourinary tract. Metabolized in the liver. $T_{1/2}$: 3–4 hours. Excreted mainly in urine. For oral (2 times daily) and topical (4 times daily) administration.

Therapeutic indications: For oral administration: acute and chronic urinary tract infections (pyelonephritis, cystitis, urethritis), genital infections (prostatitis, cervicitis, endometritis, gonorrhea), GI tract infections (salmonellosis, shigellosis). For topical administration: otitis externa and otitis media; eye infections (conjunctivitis, keratitis, blepharitis)

Pefloxacin (Abaktal*)

Its activity is slightly inferior to ciprofloxacin and ofloxacin. Bioavailability: 90%. It penetrates bodily tissues and fluids well (including the cerebrospinal fluid). Metabolized in the liver. Excreted in urine and bile. It can cause tendonitis more often than other fluoroquinolones. For oral, intravenous administration 1–2 times daily.

Therapeutic indications: infections of the respiratory tract and ENT organs, kidneys and urinary tract; intestinal infections, pelvic infections, gonorrhea, chlamydia, chancroid, infections of bones, joints, skin and soft tissues, intra-abdominal infections, sepsis, endocarditis, meningitis, meningoencephalitis

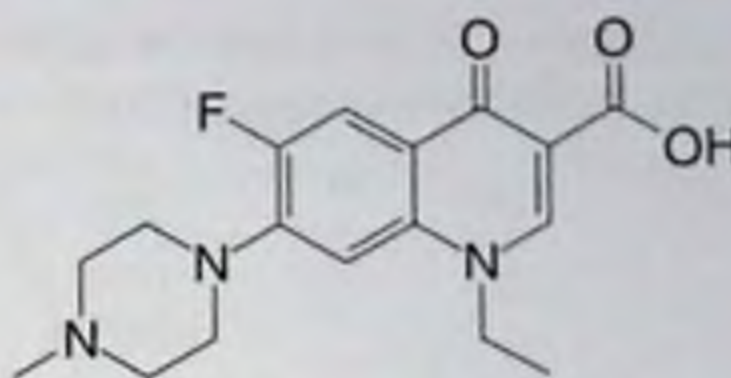


Fig. 20.10. 1-Ethyl-6-fluoro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid (as mesylate)

Levofloxacin (Tavanic*)

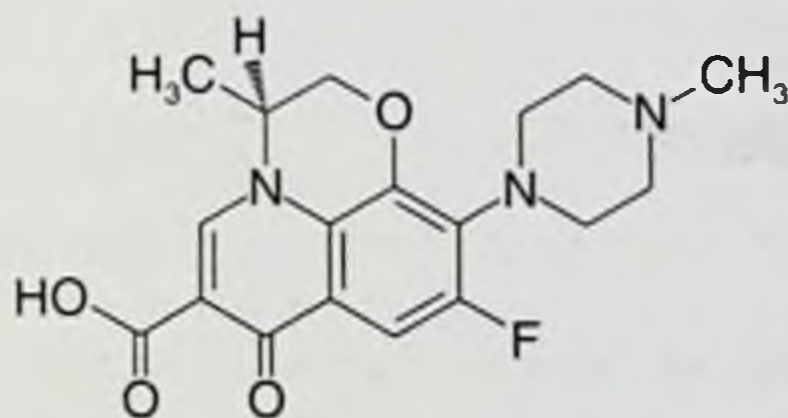


Fig. 20.11. (-)-(S)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]1,4-benzoxazine-6-carboxylic acid hemihydrate

A levorotatory isomer of ofloxacin. It is the main representative of the respiratory fluoroquinolones and has higher activity (compared to the first generation fluoroquinolones) against pneumococcus *Streptococcus pneumoniae* (including penicillin-resistant strains) and other respiratory tract pathogens — *Hemophilus influenzae*, *Moraxella catarrhalis* — as well as mycoplasmas and chlamydia, while maintaining a bactericidal effect on gram-negative bacteria. Bioavailability is absolute. It accumulates in high concentrations in the respiratory tissues and fluids (higher concentrations than in plasma). Barely metabolized, excreted mainly as unchanged drug in urine and bile. $T_{1/2}$: 6–8 hours. For oral, intravenous administration once daily, for topical administration.

Therapeutic indications: infections of the upper and lower respiratory tract; urinary tract; chronic bacterial prostatitis; infections of the skin and soft tissues; as part of the combined treatment for drug-resistant forms of tuberculosis; prevention and treatment of anthrax. Topically (eye drops): eye infections; prevention of complications after surgical and laser eye surgeries.

Moxifloxacin (Avelox*)

High bactericidal activity against streptococci, staphylococci, including MRSA, listeria (*Listeria species*), corynebacteria (*Corynebacterium diphtheriae*), chlamydia (*Chlamydia species*), mycoplasmas (*Mycoplasma species*), ureaplasmas (*Ureaplasma species*) and non-spore-forming anaerobes (including *B. fragilis*) bacteroides and, to a lesser extent, enterococci (*Enterococcus species*).

It has pronounced activity against *Mycobacterium tuberculosis*. Bioavailability: 90%. It undergoes biotransformation, without the involvement of cytochrome P450, by

conjugation to form inactive metabolites. Excreted in urine and bile. $T_{1/2}$: 12 hours. For oral, intravenous administration once daily.

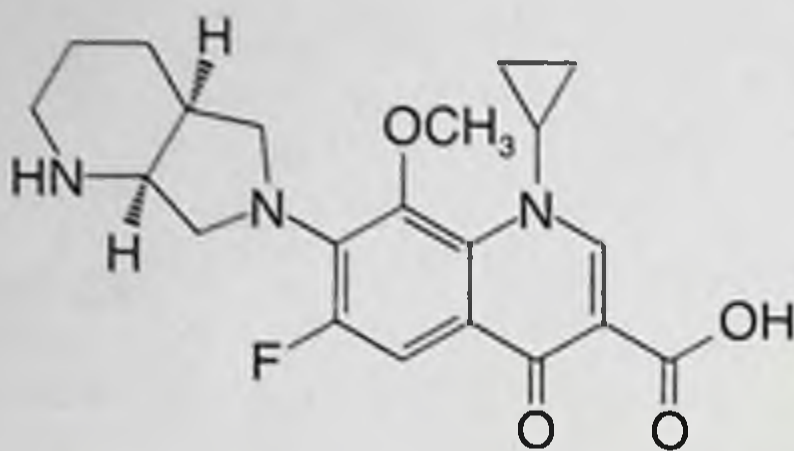


Fig. 20.12. 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid (as hydrochloride)

Therapeutic indications: infections of the upper and lower respiratory tract, skin and soft tissues (including diabetic foot infections); complicated intra-abdominal infections, including polymicrobial infections, including intra-abdominal abscesses

5-NITROIMIDAZOLE DERIVATIVES (NITROIMIDAZOLES)

Metronidazole (Flagyl⁺, Trichopol⁺), tinidazole (Fasigyn⁺), ornidazole (Tiberal⁺), nimorazole (Naxogin⁺)

DNA-tropic drugs with selective action against bacteria having enzyme systems (nitroreductases) that are capable of reducing the nitro group.

Mechanism of action: After penetrating into the microbial cell, influenced by cellular nitroreductases, they turn into highly toxic metabolites that disrupt DNA replication, the synthesis of nucleic acids and proteins, and inhibit cellular respiration (bactericidal action).

Spectrum of activity Gram-negative and gram-positive anaerobes: bacteroides (including *Bacteroides fragilis*), clostridia (including *Clostridium difficile*), fusobacteria (*Fusobacterium species*), peptostreptococci (*Peptostreptococcus species*), *Peptococcus niger*, *Gardnerella vaginalis*, *Helicobacter pylori*. Protozoa: *Trichomonas vaginalis*, dysentery amoeba (*Entamoeba histolytica*), giardia (*Giardia lamblia*, *Giardia intestinalis*), leishmania (*Leishmania species*).

Therapeutic indications:

► Anaerobic or aerobic-anaerobic infections: lower respiratory tract infections (aspiration pneumonia, pleural empyema, lung abscess); CNS infections (meningitis, brain abscess); intra-abdominal infections, including pelvic infections; oral infections; pseudomembranous colitis; perioperative prophylaxis for intra-abdominal and gynecological interventions. Protozoal infections: trichomoniasis, giardiasis, balantidiasis, amoebic dysentery and extraintestinal amoebiasis. *Helicobacter pylori* eradication in gastroduodenal ulcer (metronidazole)

► For topical use: vaginitis, bacterial vaginosis, seborrheic eczema, dermatitis

Side effects: nausea, vomiting, diarrhea, anorexia, metallic taste in the mouth, epigastric pain; headache, dizziness, irritability, sleep disturbances; arthralgia, leukopenia, allergic reactions; disulfiram-like reactions (metronidazole and tinidazole)

Contraindications: allergic reactions, pregnancy (1st trimester), breastfeeding

Metronidazole (Flagyl[®], Trichopol[®])

It penetrates bodily tissues and fluids well, reaching bactericidal concentrations in saliva, seminal fluid, and vaginal secretions; crosses the BBB, placental barrier and is excreted into breast milk. Bioavailability: > 80%, regardless of food intake. Metabolized by hydroxylation, side chain oxidation and conjugation with glucuronic acid to form inactive and active (2-hydroxymetronidazole) metabolites. $T_{1/2}$: 8 hours. Excreted in urine (60–80%) and bile. For intravenous, oral, topical administration.

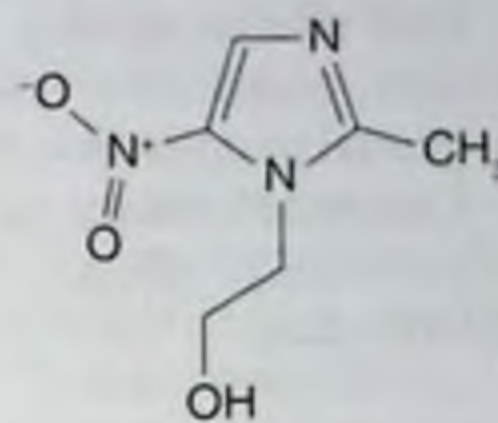


Fig. 20.13. 2-Methyl-5-nitro-1H-imidazole-1-ethanol

NITROFURAN DERIVATIVES

Nitrofurantoin (Furacin[®]), nitrofurantoin (Furadonin[®]), furazidin (Furagin[®]), Furazolidone[®], nifuroxazide (Enterofuryl[®]), nifuratel (Macmiror[®])

The clinical efficacy of nitrofurans is inferior to most antibiotics.

For oral administration. Do not reach high concentrations in the blood and tissues. Cross the BBB, placental barrier, and are excreted into breast milk.

Nifuroxazide is barely absorbed in the GI tract; it has an antibacterial effect only in the intestinal lumen. High concentrations of nitrofurantoin, furazidin, nifuratel accumulate in urine. Furazolidone is poorly absorbed in the GI tract and reaches high concentrations in the intestinal lumen. Nitrofurantoin is used primarily as an antiseptic.

Mechanism of action: Being oxygen acceptors, they disrupt cellular respiration in bacteria, inhibit the biosynthesis of nucleic acids. Depending on the concentration, they can have a bacteriostatic or bactericidal effect.

Spectrum of activity

- ▶ Active against gram-negative (*Escherichia coli*, *Klebsiella pneumoniae*, etc.) and gram-positive bacteria, some anaerobes, yeasts of the genus *Candida* (*Candida species*). Enterococci (*Enterococcus species*) are less sensitive. Blue pus bacillus (*Pseudomonas aeruginosa*), most strains of proteus (*Proteus species*), serratia (*Serratia species*), providencia (*Providencia species*), acinetobacter (*Acinetobacter species*) are resistant.
- ▶ Furazolidone and nifuratel are active against some protozoa [lamblia (*Giardia lamblia*), trichomonas (*Trichomonas species*)]; nifuratel is effective against *Helicobacter pylori*.

Therapeutic indications: acute cystitis (nitrofurantoin, furazidin); prevention of infection-related complications during urological surgeries, cystoscopy, bladder catheterization (nitrofurantoin, furazidin); acute infectious diarrhea, enterocolitis (nifuroxazide, nifuratel); giardiasis and trichomoniasis (nifuratel, furazolidone); gastroduodenal ulcer associated with *Helicobacter pylori* with resistance to metronidazole (nifuratel); topically — bathing of wounds and cavities, treatment and prevention of purulent-inflammatory processes (blepharitis, conjunctivitis, stomatitis, gingivitis, etc.) (furazidin, nitrofurantoin)

Side effects: nausea, vomiting; transient elevation of transaminases, cholestasis; broncho-obstructive syndrome; dizziness, headache, general fatigue, somnolence, peripheral neuropathy; allergic reactions

Contraindications: severe kidney and/or liver failure (nitrofurantoin, furazidin, furazolidone), allergic reactions, pregnancy — 3rd trimester (nitrofurantoin), breastfeeding

8-OXYHINOLLINE DERIVATIVES

Nitroxoline (5-HOK*), chlorchinaldol (Chlorchinaldin*)

They have antibacterial, antiprotozoal and antifungal activity.

Mechanism of action: Selectively inhibit bacterial DNA synthesis, form complexes with metal-ion-containing enzymes of microbial cells (bacteriostatic action). Decrease the adhesion of uropathogenic strains to epithelial cells of the urinary tract.

Spectrum of activity: coliform bacterium (*Escherichia coli*), salmonella (*Salmonella species*), shigella (*Shigella species*), proteus (*Proteus species*) and yeasts of the genus *Candida* (*Candida species*), some types of protozoa.

Therapeutic indications: acute uncomplicated cystitis (nitroxoline); dysentery, salmonellosis, food-borne illnesses, amebiasis, giardiasis, vaginal infection and inflammation (chlorquinaldol)

Side effects: headache, dizziness, paresthesia, polyneuropathy, myelopathy; nausea, vomiting, loss of appetite; elevation of transaminases; allergic reactions (rash, pruritus). Vaginal itching and burning (chlorquinaldol)

Contraindications: peripheral neuropathy, severe liver disease, kidney failure, pregnancy, breastfeeding

21. ANTIBIOTICS

Antibiotics (from the Ancient Greek *anti*, meaning “against”, *bios*, meaning “life”) are drugs based on natural or synthetic chemical compounds that have a selective damaging (bacteriostatic) or destructive (bactericidal) effect on microorganisms.

In the 19th century, J. Lister and E. Duchesne — a French medical student — used mold to treat infections. In 1908, A. Fleming received a M.B. B.S. with gold medal at the University of London. His research focused on the antibacterial action of bodily fluids (including blood and tears). In the 1920s, Fleming discovered lysozyme, an enzyme present in tears that has an antibacterial effect. In the 1930s, A. Fleming, E. Chain, and H. Florey isolated penicillin; they were awarded the Nobel Prize in physiology or medicine in 1945.

Antibiotics are curative drugs. To reach their targets, antibiotics must first penetrate the surface layers of the cell. The main barrier for the drug is the cell wall. Bacteria are divided into gram-positive and gram-negative depending on the structure of their cell wall, which has a significant impact on their sensitivity to antimicrobial agents. The cell wall of gram-negative bacteria has an outer membrane, which makes it less permeable than that of gram-positive bacteria (Fig. 21.1).

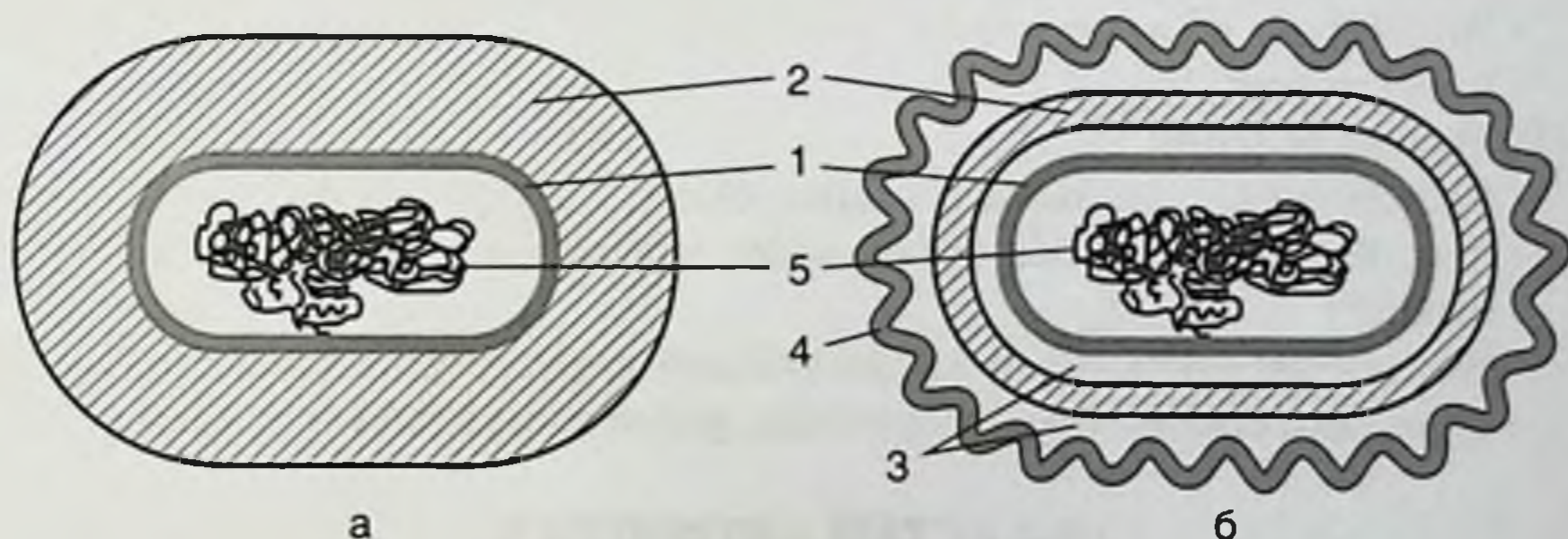


Fig. 21.1. Schematic of the cell wall of gram-positive (a) and gram-negative (b) bacteria: 1 — cytoplasmic membrane; 2 — peptidoglycan; 3 — periplasmic space; 4 — outer membrane; 5 — nucleoid

The targets of antibacterial drugs can be enzymes involved in biosynthetic pathways; components of the cytoplasmic membrane that maintain the cell's internal environment; components that help transfer information transfer from DNA to RNA or are involved in complex processes of protein synthesis. Antibiotics are produced by actinomycetes (ray fungi), molds, and certain bacteria (e.g., those belonging to the *Bacillus* genus and non-spore-forming bacteria from the *Pseudomonas* genus).

Classification of antibiotics:

I. By chemical structure

- β -lactam antibiotics (contain a β -lactam ring): penicillins, cephalosporins, carbapenems, monobactams
- Macrolides and azalides (contain a macrocyclic lactone ring)

- Tetracyclines (contain a multifunctional hydronaphthacene nucleus containing four rings), glycyclines
- Aminoglycosides (molecule that contains amino sugar linked to an aminocyclic ring by a glycosidic bond)
- Polymyxins (cyclic peptides)
- Glycopeptides (contain glycans and amino acid residues)
- Lipoglycopeptides (lipophilic side-chains linked to glycopeptides)
- Lincosamides (pyrrolidine ring linked to a pyranose moiety [methylthiolincosamide] via an amide bond)
- Oxazolidinones (class of compounds containing 2-oxazolidone)
- Cyclic lipopeptides (contain 13 amino acid residues)
- Levomycetins (amphenicols, dioxyaminophenylpropane derivatives)
- Other: rifampicin (Rimpin*), fusidic acid (Sodium fusidin*), fosfomycin (Monural*), etc.

II. By mechanism of action

- Antibiotics that inhibit cell wall synthesis: β -lactam antibiotics, glycopeptides, fosfomycin
- Antibiotics that inhibit cytoplasmic membrane function: polymyxins
- Antibiotics that inhibit protein and nucleic acid synthesis: levomycetins, tetracyclines, glycyclines, lincosamides, macrolides, azalides, oxazolidinones, aminoglycosides, fusidic acid (Sodium fusidin*), rifampicin
- Antibiotics with combined mechanism of action: cyclic lipopeptides, lipoglycopeptides

III. By type of action

- Bacteriostatic antibiotics: tetracyclines, glycyclines, amphenicols, macrolides and azalides, lincosamides, oxazolidinones, fusidic acid (Sodium fusidin*)
- Bactericidal antibiotics: β -lactam antibiotics, glycopeptides, aminoglycosides, cyclic lipopeptides, lipoglycopeptides, polymyxins, fosfomycin, rifampicin

B-LACTAM ANTIBIOTICS

Mechanism of action: The bacterial cell wall is mainly composed of mucopeptide or murein (contains N-acetylglucosamine, N-acetylmuramic acid, and peptide chains). Beta-lactam antibiotics have similarities with N-acetylmuramic acid, which inhibits murein synthesis or disrupts the bonds between murein (peptidoglycan) chains, leading to cell death (bactericidal action) (Fig. 21.2). β -lactam antibiotics act at the stage of interpeptide bond formation. These antibiotics are active against young dividing cells.

β -lactamases are bacterial enzymes that serve as the bacterium's main defense against β -lactam antibiotics (they break β -lactam rings) and the main cause of antibiotic resistance in microorganisms, e.g., pathogens such as *Staphylococcus aureus*, *Hemophilus influenzae*, *Moraxella catarrhalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Bacteroides fragilis*, etc.

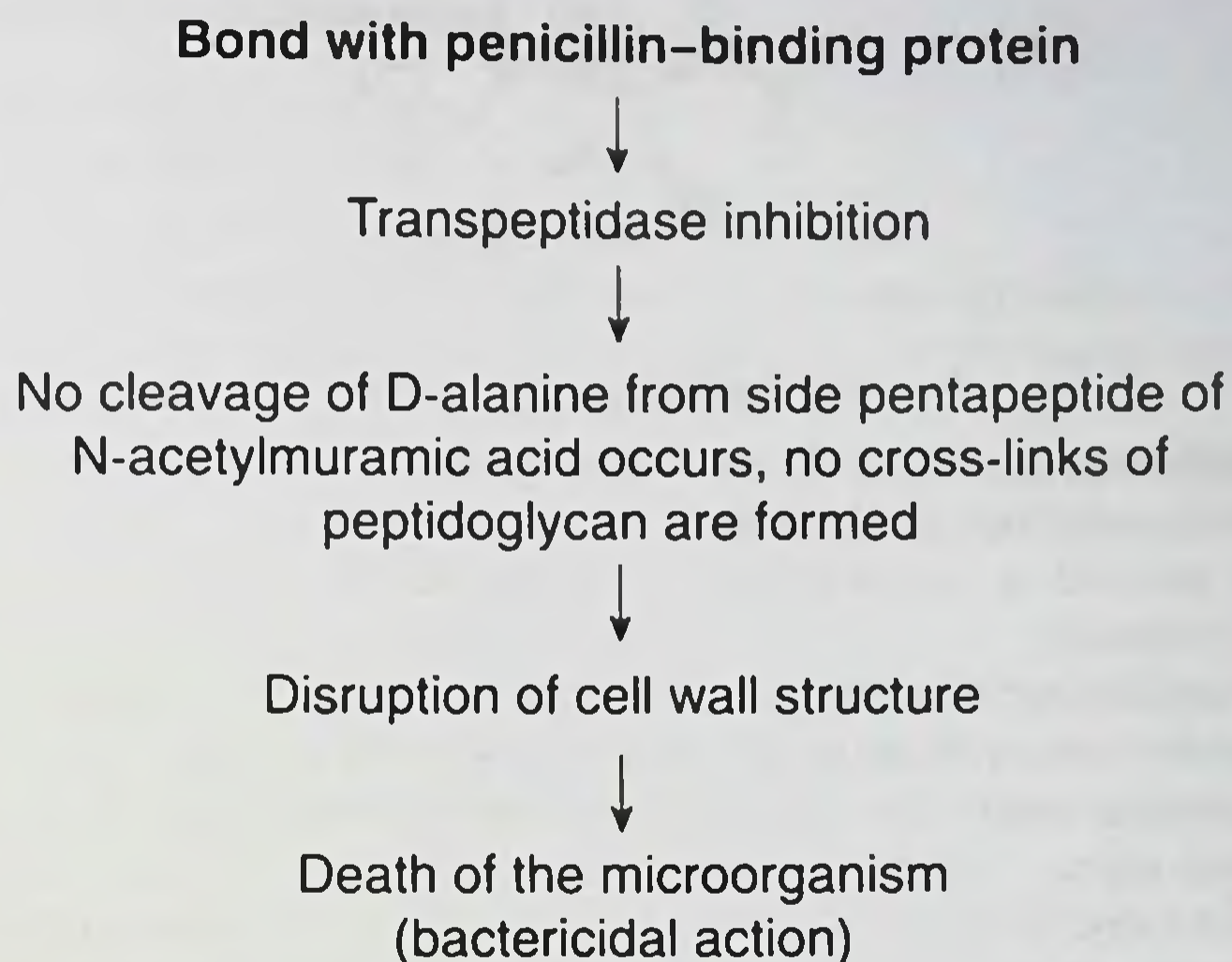


Fig. 21.2. Mechanism of action of β -lactam antibiotics

β -lactamase inhibitors were developed to overcome antibiotic resistance (Fig. 21.3):

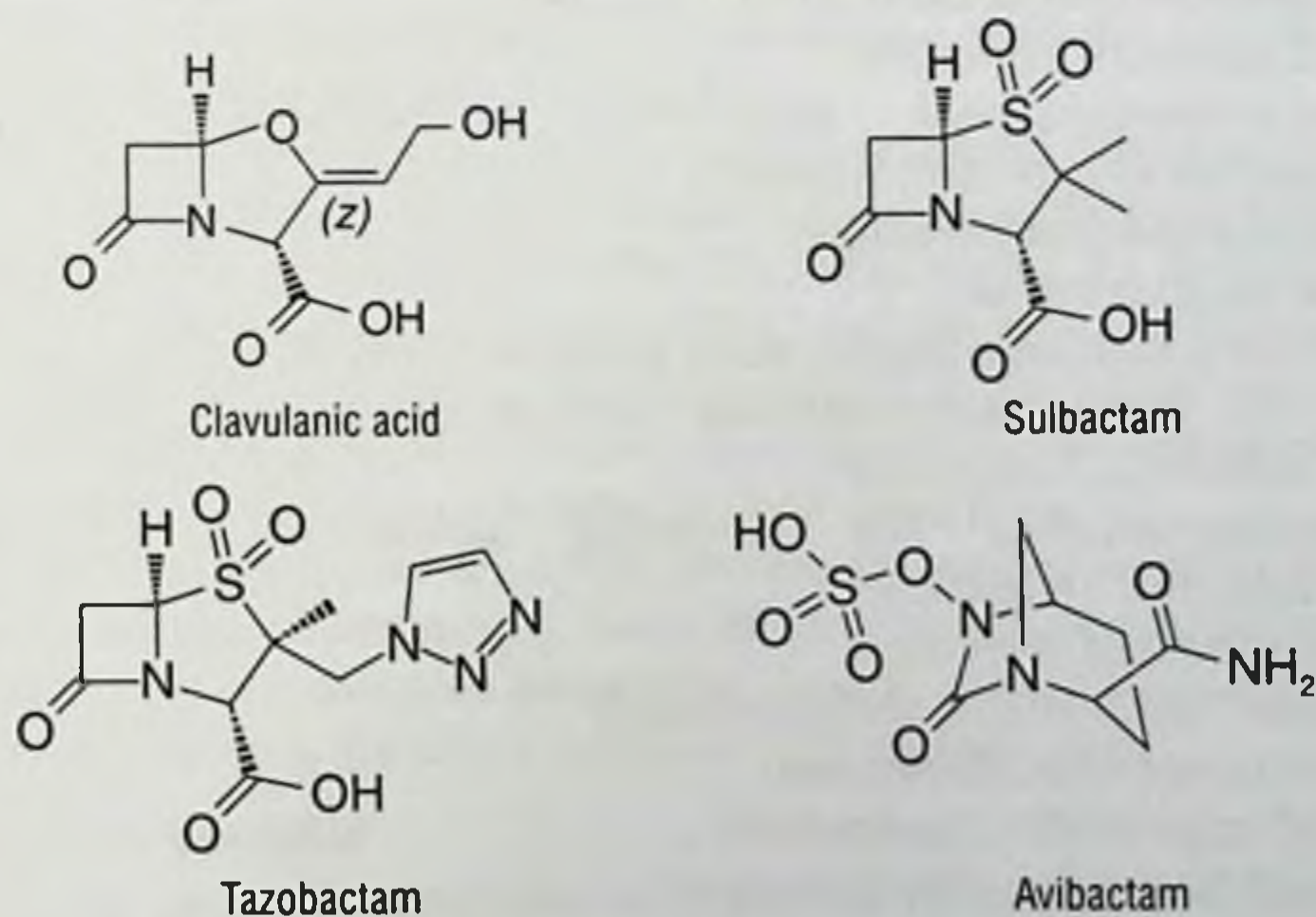


Fig. 21.3. β -Lactamase inhibitors

Penicillins

Some drugs are obtained from cell culture, where certain strains of mold fungi (*Penicillium*) that are penicillin producers (i.e., natural penicillins) grow. A number of semisynthetic drugs were created by chemical modification of 6-aminopenicillanic acid, which is the structural base of semisynthetic penicillins (Fig. 21.4).

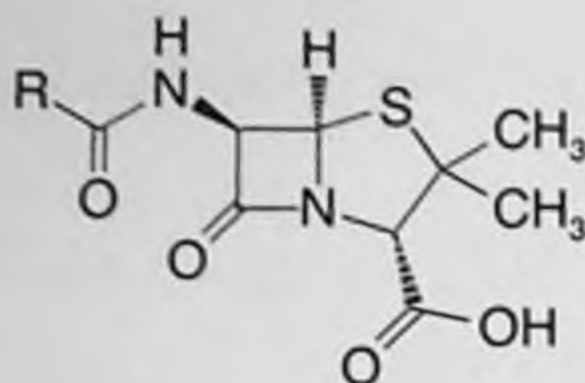


Fig. 21.4. Structure of penicillins

Classification

I. Naturally occurring penicillins

- For parenteral administration (break down in the stomach's acidic environment):
 - a) short-acting: benzylpenicillin (Benzylpenicillin sodium salt⁺) (for intravenous, intramuscular, subcutaneous administration), benzylpenicillin potassium salt⁺ (for intramuscular, subcutaneous administration)
 - b) long-acting (for intramuscular administration): benzylpenicillin (Benzylpenicillin novocaine salt⁺), benzathine benzylpenicillin (Bicillin-1⁺), Bicillin-5⁺ (benzathine benzylpenicillin, procaine benzylpenicillin)
- For enteral administration (acid-resistant): Phenoxymethylpenicillin⁺

II. Semisynthetic penicillins

- A. Penicillinase-resistant (antistaphylococcal) penicillins Isoxazolyl penicillins: oxacillin (Oxacillin sodium salt⁺), Nafcillin⁺
- B. Broad spectrum penicillins
 - Non-antipseudomonal penicillins: aminopenicillins: Ampicillin⁺, amoxicillin (Flemoxin⁺, Amosin⁺)
 - Antipseudomonal penicillins:
 - a) carboxypenicillins:
 - for parenteral administration: carbenicillin disodium salt⁺, Ticarcillin⁺
 - for enteral administration (acid-resistant): carbenicillin indanyl sodium⁺, Carfecillin⁺
 - b) ureidopenicillins (for parenteral administration): Piperacillin⁺, Mezlocillin⁺, Azlocillin⁺
- Inhibitor-protected penicillins
 - Amoxiclav⁺ (amoxicillin, clavulanic acid)
 - Unasyn⁺ (ampicillin, sulbactam)
 - Tazocin⁺ (piperacillin, tazobactam)
 - Timentin⁺ (ticarcillin, clavulanic acid)

The combination of penicillins with β -lactamase inhibitors restores the natural activity of penicillins against most staphylococci, non-spore-forming anaerobes, and expands their antibacterial spectrum to include a number of gram-negative bacteria (*Klebsiella*, etc.) that are naturally penicillin-resistant.

Specific properties of drugs by group

Naturally occurring penicillins

Spectrum of activity

- ▶ Predominantly gram-positive bacteria
 - Gram-positive cocci: non-penicillinase-producing staphylococci, streptococci, pneumococci, enterococci; gram-positive rods: *Corynebacterium diphtheriae*, *Bacillus anthracis*, *Listeria*, *Leptospira*
 - Gram-positive anaerobes: gas gangrene and tetanus pathogens (*Clostridium*).
- ▶ Gram-negative cocci (meningococci, gonococci), *Treponema pallidum*, *Borrelia*
- ▶ Some pathogenic fungi (actinomycetes)

Natural penicillins are not active against *Hemophilus influenzae*, *Enterobacteriaceae* (*Escherichia coli*, *Klebsiella*, *Salmonella*, *Shigella*), non-fermenting gram-negative bacteria (*Pseudomonas aeruginosa*, *Acinetobacter*), *Mycobacterium tuberculosis*, rickettsioses, viruses, protozoa.

Benzylpenicillin

Monobasic acid. Benzylpenicillin is poorly soluble in water and unstable as a free acid, so it is used in the form of well-soluble sodium and potassium salts. Short-acting (3–4 hours). $T_{1/2}$: 30–60 min. Penetrates well into all tissues and bodily fluids, except the brain, eye, and serous and synovial membranes; however, during inflammation, the permeability of the meninges and other membranes increases. Crosses the placental barrier. Excreted in urine as unchanged drug.

Poorly soluble benzylpenicillin salts are administered intramuscularly: 2–3 times daily for benzylpenicillin (Benzylpenicillin novocaine salt*), once every 7 or 14 days for benzathine benzylpenicillin (Bicillin-1*), once a month for Bicillin-5* (benzathine benzylpenicillin, procaine benzylpenicillin); they are slowly absorbed at the site of administration. The penetration into fluids is high, while the penetration into tissues is low. Does not cross the BBB. Crosses the placental barrier and excreted into breast milk. Excreted predominantly in urine as unchanged drug.

Therapeutic indications: tonsillitis, pharyngitis, laryngitis, otitis media, sinusitis, community-acquired pneumonia, bacterial endocarditis, wound infections, skin, soft tissue, and mucosal infections (erysipelas, furunculosis, abscess, etc.), scarlet fever, leptospirosis, anthrax, syphilis, prophylaxis of rheumatic fever

Phenoxymethylpenicillin*

Stable in an acidic environment. Absorbed in the small intestine: 30–60 %, circulates in the blood for a long time, penetrates slowly into tissues. Therapeutic blood concentrations are reached within 30 min and last 3–6 hours. Metabolized in the liver. $T_{1/2}$: 30–45 min. Excreted in urine as unchanged drug (25 %) and as metabolites (35 %), with about 30 % excreted in bile.

Therapeutic indications: lower respiratory tract infections (bronchitis, pneumonia), ear, nose and throat infections (tonsillitis, laryngitis, otitis media, sinusitis), skin and soft tissue infections (abscess, phlegmon, erysipelas, impetigo, migratory erythema, furunculosis, erysipeloid), scarlet fever

Side effects

- ▶ Allergic side effects: anaphylactic shock (up to 10 % mortality), skin rash, mucosal edema, dermatitis, fever, arthritis, arthralgia, kidney injury, erythroderma, etc.
- ▶ Non-allergic side effects: with oral administration — glossitis, stomatitis, pharyngitis, loss of appetite, dry mouth, dysgeusia, nausea, vomiting, diarrhea; with intramuscular administration — pain at the injection site, infiltration and aseptic muscle necrosis; with intravenous administration — phlebitis and thrombophlebitis
- ▶ Extremely high doses of sodium salt may result in neurotoxicity (arachnoiditis, encephalopathy).

Contraindications: history of allergic reactions to penicillins, bronchial asthma, urticaria, hay fever and other allergic diseases; epilepsy (intralumbar administration); hyperkalemia (for potassium salt); aphthous stomatitis and pharyngitis

Semisynthetic penicillins**Antistaphylococcal penicillins****Oxacillin (Oxacillin sodium salt*)**

Not inactivated by penicillinase and effective against strains of penicillinase-producing staphylococci. Penetrates well into various tissues and organs. $T_{1/2}$: 30 min. Time to reach maximum concentrations following intramuscular injection: 1–2 hours. Does not cross the BBB. Crosses the placental barrier and is excreted into breast milk. Excreted in urine and bile. For oral administration 4–6 times daily; for intravenous, intramuscular administration.

Therapeutic indications: staphylococcal infections (except MRSA), pneumonia, endocarditis, skin and soft tissue infections, bone and joint infections

Side effects: allergic reactions; nausea, vomiting, diarrhea; with intravenous administration — phlebitis, thrombophlebitis

Contraindications: history of allergic reactions to penicillins and allergic diseases

Nafcillin*

Crosses the BBB, time of action: 4–6 hours. For oral, intravenous, intramuscular administration.

Therapeutic indications: osteomyelitis, sepsis, infective endocarditis, CNS infections caused by strains of β -lactamase-producing staphylococci

Side effects and contraindications: see "Oxacillin"

Aminopenicillins**Ampicillin***

Ampicillin is resistant to acid. The bioavailability is low; therefore it is administered via intramuscular, intravenous injection. $T_{1/2}$: 1–2 hours. Poorly penetrates the BBB. Metabolized in the liver. Excreted predominantly in urine (70–80 %), partially excreted in bile, breast milk. Administered at 4–8 hours intervals.

Has a broader spectrum of activity than natural penicillins, mainly due to its effects on gram-negative microflora. Less active than benzylpenicillin against gram-positive microflora.

Spectrum of activity:

- ▶ Gram-positive aerobic bacteria: staphylococci (except penicillinase-producing strains), streptococci (including enterococci), *Listeria*
- ▶ Gram-negative aerobic bacteria: gonococci, meningococci, *Escherichia coli*, *Proteus*, *Shigella*, *Salmonella*, certain strains of *Hemophilus influenzae*

Therapeutic indications: respiratory tract infections, ear, nose and throat infections, urinary tract infections, GI infections, skin and soft tissue infections, musculoskeletal infections, bacterial endocarditis

Side effects: allergic reactions (rash, urticaria, angioedema, anaphylactic shock), pain at the administration site, infiltrates following intramuscular administration, nausea and diarrhea, dysbiosis, candidiasis

Contraindications: see "Oxacillin"

Amoxicillin (Flemoxin⁺, Amosin⁺)

Semisynthetic penicillin, 4-hydroxyl analog of ampicillin. The bioavailability is 95 %, does not depend on the time of food intake. Poorly penetrates the BBB. Partially (10–20 %) metabolized to form inactive metabolites. $T_{1/2}$: 1.0–1.5 hours. 50–70 % is excreted in urine as unchanged drug, with 10–20 % excreted in bile. Excreted in small amounts into breast milk. For oral administration 2–3 times daily.

Spectrum of activity: gram-positive (staphylococci, except penicillinase-producing strains; streptococci; *Listeria*) and gram-negative bacteria (*Escherichia coli*, *Proteus*, *Shigella*, *Salmonella*, *Campylobacter*, *Hemophilus influenzae*, *Bordetella pertussis*, *Leptospira*, *Helicobacter pylori*)

Therapeutic indications: respiratory tract infections, ear, nose and throat infections, biliary and urinary tract infections, GI infections, endometritis, skin and soft tissue infections, leptospirosis, listeriosis, gastric and duodenal ulcer associated with *Helicobacter pylori*

Side effects: allergic reactions, dyspepsia, insomnia, agitation, dizziness, dysbiosis, candidiasis

Contraindications: see "Oxacillin"

Carboxypenicillins**Carbenicillin⁺**

Semisynthetic penicillin derivative. Crosses the placental barrier and is excreted into breast milk. Only a small portion (about 2 %) undergoes biotransformation in the liver. $T_{1/2}$: 1.0–1.5 hours. Excreted mainly in urine (60–90 % as unchanged drug), where it reaches high concentrations. For oral administration 4–6 times daily; for intramuscular, intravenous administration.

Spectrum of activity: Carbenicillin is active against gram-negative and gram-positive bacteria (including *Pseudomonas aeruginosa*, *Hemophilus influenzae*, certain anaerobic bacteria). It does not act on the strains of penicillinase-producing staphylococci.

Therapeutic indications: diseases caused by gram-negative bacteria (predominantly by *Pseudomonas aeruginosa*): urinary and biliary tract infections; infections

of abdominal, pelvic organs; skin, soft tissue, bone and joint infections; sepsis, endocarditis, wound infections, infected burns, etc.

Side effects: allergic reactions; dyspepsia, dysbiosis; leukopenia, neutropenia, thrombocytopenia; at the administration site: thrombophlebitis, pain, erythema and/or infiltration, hematoma

Contraindications: history of allergic reactions to penicillins and allergic diseases

Carfecillin*

Phenyl ester of carbenicillin for oral administration. Inferior to ampicillin in its activity against *Salmonella* and *Shigella*; equivalent to carbenicillin in other respects.

Used mainly for the treatment of urinary tract infections caused by *Pseudomonas aeruginosa* and *Proteus mirabilis*; the other therapeutic indications are the same as for carbenicillin.

Ticarcillin*

For parenteral administration only. The spectrum of antibacterial activity is similar to carbenicillin, but it has greater activity against *Pseudomonas aeruginosa*.

Ureidopenicillins

Piperacillin*

Belongs to penicillins with marked activity against *Pseudomonas aeruginosa*. Its spectrum of activity is similar to carbenicillin, superior to carbenicillin and equivalent to ticarcillin. Easily crosses the blood-tissue barriers and penetrates all bodily tissues and fluids (including the bones, prostate, heart, bile). $T_{1/2}$: 35–70 min. Excreted predominantly in urine as unchanged drug, partially excreted in bile. For intravenous administration 2–4 times daily; for intramuscular administration.

Therapeutic indications: severe inflammatory infections of the urinary system (acute and chronic pyelitis, cystitis, pyelonephritis, prostatitis, epididymitis, urethritis), abdominal cavity (peritonitis, cholangitis, empyema of the gallbladder, intra-abdominal abscess); pelvis (endometritis, pelvic abscess, salpingitis, adnexitis, postpartum infections), lower respiratory tract (bronchitis, pneumonia, lung abscess, pleural empyema); ear, nose and throat; skin and soft tissues, bones and joints; bacteremia, sepsis, endocarditis

Side effects: allergic reactions; headache, increased fatigue, somnolence, paresthesia, increased neuromuscular excitability and seizures (intravenous administration); eosinophilia, leukopenia, neutropenia, thrombocytopenia; nausea, vomiting, diarrhea, cholestatic hepatitis, increased activity of liver transaminases, hyperbilirubinemia, dysbiosis; at the administration site: thrombophlebitis, pain, erythema and/or infiltration, hematoma

Contraindications: history of allergic reactions to penicillins and allergic diseases, hemorrhages, severe liver disease

Mezlocillin*, Azlocillin*

Broad spectrum penicillins with marked antipseudomonal activity; more effective against *Klebsiella* than carboxypenicillins. For parenteral administration.

Therapeutic indications: respiratory tract infections, urinary tract infections, sepsis, peritonitis, endometritis, skin and soft tissue infections, infected burns, etc.

Amoxiclav[®] (amoxicillin, clavulanic acid)

Combination drug containing amoxicillin and clavulanic acid. Bioavailability: about 70 %. Does not cross the BBB, crosses the placental barrier. Amoxicillin is mainly excreted in urine, while clavulanic acid is eliminated through renal and extrarenal excretion. $T_{1/2}$: 1 hour. For oral administration 2–3 times daily; for intravenous administration.

Spectrum of activity: staphylococci (except MRSA), streptococci, enterococci, gonococci, *Escherichia coli*, *Proteus*, *Klebsiella*, *Gardnerella*, *Salmonella*, *Bordetella pertussis*, etc. *Acinetobacter*, *Citrobacter*, *Legionella*, *Morganella morganii*, *Pseudomonas aeruginosa* are naturally resistant.

Therapeutic indications: respiratory tract infections, ear, nose and throat infections, biliary and urinary tract infections, infections of abdominal, pelvic organs, skin and soft tissue infections, bone and connective tissue infections

Unasyn[®] (ampicillin, sulbactam)

Combination of ampicillin and sulbactam. Poorly penetrates the BBB. $T_{1/2}$: about 1 hour. Both ingredients are predominantly excreted in urine as unchanged substances. For intravenous administration 2 times daily; for intramuscular administration.

Spectrum of activity: gram-positive and gram-negative bacteria (see “Ampicillin”), including penicillin-resistant strains. The following bacteria are resistant to Unasyn[®]: MRSA, *Citrobacter*, most *Enterobacter* strains, *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis*, *Clostridium*, *Mycoplasma*, *Chlamydia trachomatis*.

Therapeutic indications: respiratory tract infections, ear, nose and throat infections, urinary tract infections, intra-abdominal infections, skin and soft tissue infections

Cephalosporins

7-Aminocephalosporanic acid is at the core of the chemical structure. Cephalosporins have a similar structure to penicillins (Fig. 21.4). Both groups of antibiotics contain a β -lactam ring; the structure of penicillins includes a thiazolidine ring, while the structure of cephalosporins includes a dihydrothiazine ring (Fig. 21.5).

The main features of cephalosporins compared with penicillins are their greater resistance to β -lactamases; however, having high antibacterial activity, they are not fully resistant to β -lactamases. Numerous semisynthetic derivatives of cephalosporins have been synthesized to increase their resistance, expand the spectrum of antibacterial activity, and improve their pharmacokinetic parameters. Combination drugs contain cephalosporins with inhibitors of enzymes that destroy them.

The spectrum of activity is broad, but enterococci and *Listeria* are resistant to the action of cephalosporins of all groups.

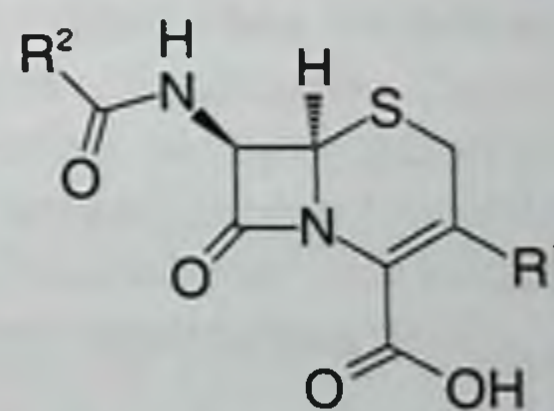


Fig. 21.5. Structure of cephalosporins

Classification▶ **First generation**

- Parenteral (for intramuscular, intravenous administration): cefazolin (Cefamezin*), cephalothin (Keflin[®]); oral: Cephalexin*, cefadroxil (Duricef*)

▶ **Second generation**

- Parenteral (for intramuscular, intravenous administration): cefuroxime (Zinacef*), cefamandole (Cefamabol*); oral: Cefaclor*, cefuroxime (Zinnat*)

▶ **Third generation**

- Parenteral (for intramuscular, intravenous administration): ceftriaxone (Rocephin*), cefotaxime (Cefabol*, Claforan*), cefoperazone (Operaz*, Cefobid*), ceftazidime (Fortum*), ceftizoxime (Cefzoxime J*), Moxalactam* (Moxam[®]); oral: cefixime (Suprax*), cefibuten (Cedex[®]).

▶ **Fourth generation**

- Parenteral (for intramuscular, intravenous administration): cefepime (Maxipime*), cefpirome (Cefactive*)

▶ **Fifth generation**

- Parenteral (for intravenous administration): ceftaroline fosamil (Zinforo*)

▶ **Protected cephalosporins**

- Sulperazon* (cefoperazone, sulbactam) (for intravenous, intramuscular administration)
- Zavicefta* (ceftazidime, avibactam) (for intravenous administration)

Cephalosporins exhibit bactericidal action. Their mechanism of action is associated with damage to the bacterial cell membrane (inhibition of peptidoglycan layer synthesis) at the reproduction stage (see the mechanism of action of β -lactam antibiotics).

Oral cephalosporins are used for the same therapeutic indications as parenteral cephalosporins, but usually for moderate-to-severe infections.

Side effects: allergic reactions (less common than with penicillins), cross-sensitization with penicillins; tenderness and infiltration following intramuscular administration; phlebitis following intravenous administration; per os: dyspepsia, dysbiosis and superinfection (candidiasis), nephrotoxicity (first-generation drugs, ceftazidime), hypoprothrombinemia, reversible neutropenia, leukopenia, thrombocytopenia (cefamandole, cefoperazone, Moxalactam*), Teturam-like effect (cefoperazone, cefamandole), increased activity of liver transaminases (cefoperazone), cholestasis, pseudocholelithiasis (ceftriaxone)

Contraindications: history of allergic reactions to cephalosporins, penicillins

Specific properties of drugs by generation**First generation**

First-generation cephalosporins exhibit high activity against gram-positive cocci, including *Staphylococcus aureus* (except MRSA), β -hemolytic *Streptococcus*, *Streptococcus pneumoniae*. They are stable against the action of staphylococcal β -lactamase but hydrolyzed by β -lactamases of gram-negative bacteria.

Therapeutic indications: perioperative antibiotic prophylaxis, skin and soft tissue infections, bone and joint infections, respiratory tract infections, genitourinary system infections

Second generation

Second-generation cephalosporins exhibit higher antibacterial activity against gram-negative bacteria of the Enterobacteriaceae family (*Escherichia coli*, *Proteus*, *Klebsiella*, etc.), as well as *Hemophilus influenzae*, gonococci, and meningococci. All drugs in this group are less active than first-generation cephalosporins on gram-positive cocci.

They penetrate most tissues better than first-generation cephalosporins.

Therapeutic indications: respiratory infections, ear, nose and throat infections (acute otitis media and sinusitis), urinary and biliary tract infections, skin and soft tissue infections, bone and joint infections, infections of abdominal and pelvic organs, wound infections

Third generation

This generation is characterized by a broader spectrum of activity. In contrast to first- and second-generation cephalosporins, third-generation cephalosporins are more active against gram-negative bacteria and not inactivated by most β -lactamases produced by gram-negative bacteria. They are inferior to first- and second-generation cephalosporins with respect to staphylococci (although cefotaxime and ceftriaxone are superior to other cephalosporins with respect to streptococci, acting against a lot of penicillin-resistant strains). A number of third-generation cephalosporins are effective against *Pseudomonas aeruginosa* (ceftazidime, cefoperazone). Ceftizoxime and Moxalactam* exhibit antianaerobic activity (*Bacteroides*).

An important property of third-generation cephalosporins (ceftriaxone, cefotaxime, ceftazidime) is their ability to cross the BBB.

Therapeutic indications: respiratory tract infections, urinary tract infections, infections of abdominal, pelvic organs, ear, nose and throat infections, skin and soft tissue infections, bone and joint infections, sepsis, endocarditis, meningitis and Lyme borreliosis, acute gonorrhea, etc.

Sulperazon* (cefoperazone, sulbactam)

- ▶ Sulbactam helps to increase the stability, antibacterial activity, and efficacy of the antibiotic.
- ▶ Well distributed in various tissues and fluids. Crosses the placental barrier.
T_{1/2}: about 1–1.7 hours. Excreted in urine and bile. For intravenous administration 2–3 times daily, for intramuscular administration.

Spectrum of activity: the combination of sulbactam and cefoperazone is active against all microorganisms susceptible to cefoperazone, has synergy with respect to various microorganisms, particularly *Hemophilus influenzae*, *Bacteroides*, staphylococci (except MRSA), *Acinetobacter*, *Enterobacter*, *Escherichia coli*, *Proteus*, *Klebsiella*, *Citrobacter*.

Therapeutic indications: respiratory tract infections, urinary and biliary tract infections, infections of abdominal and pelvic organs, skin infections, bone and joint infections, soft tissue infections, sepsis

Zavicefta[®] (ceftazidime, avibactam)

- ▶ Combination drug: ceftazidime, avibactam. Cefazidime is a broad spectrum antibiotic that is active against many gram-negative and gram-positive pathogenic bacteria.
- ▶ Easily crosses the placental barrier and is excreted into breast milk. Is not metabolized. $T_{1/2}$: 2 hours. Excreted in urine as unchanged drug. For intravenous administration 3 times daily.

Therapeutic indications: complicated intra-abdominal infections; complicated urinary tract infections; hospital-acquired pneumonia, including ventilator-associated pneumonia

Fourth generation

Fourth-generation cephalosporins are characterized by high activity against *Pseudomonas aeruginosa* and other gram-negative bacteria (including β -lactamase-producing strains), anaerobes (in contrast to other first-, second- and most of third-generation cephalosporins) and higher activity against gram-positive flora compared with third-generation (but not first-generation) drugs. Similar to second- and third-generation cephalosporins, they are resistant to the β -lactamases of gram-negative bacteria.

Therapeutic indications: severe lower respiratory tract infections, urinary tract infections, infections of abdominal organs, skin and soft tissue infections, sepsis, gynecological infections

Fifth generation

Ceftaroline fosamil (Zinforo[®])

- ▶ Exhibits bactericidal action against MRSA and penicillin non-susceptible *Streptococcus pneumoniae*. The spectrum of activity also includes *Escherichia coli*, *Hemophilus influenzae*, *Klebsiella*, *Morganella morganii*.
- ▶ Ceftaroline fosamil is a prodrug that is rapidly converted to active ceftaroline by phosphatases in the plasma. Metabolism does not involve cytochrome P450 isoenzymes. $T_{1/2}$: 2.5 hours. Excreted predominantly in urine. For intravenous administration 2 times daily.

Therapeutic indications: complicated skin and soft tissue infections, community-acquired pneumonia

Carbapenems

Carbapenems are highly effective inhibitors of bacterial cell wall synthesis that exhibit bactericidal action (see the mechanism of action of β -lactam antibiotics).

Specific properties

- ▶ Carbapenems are structurally similar to other β -lactam antibiotics, but in contrast, they are characterized by high resistance to the action of extended

spectrum β -lactamases (ESBLs) and a broader spectrum of activity, including *Pseudomonas aeruginosa* (except ertapenem) and non-spore-forming anaerobes.

- ▶ They are active against many strains of gram-negative bacteria which are resistant to third-, fourth-, and fifth-generation cephalosporins.
- ▶ They are only intended for parenteral administration in moderate and severe infections at various locations, including nosocomial infections, often as second-line drugs, but in life-threatening infections they can be considered for first-line empiric therapy.

Classification

- ▶ First generation: imipenem, Tienam[®] (Grimipenem[®], Primaxin[®])
- ▶ Second generation: meropenem (Meronem[®]), doripenem (Doriprex[®])
- ▶ Third generation: ertapenem (Invanz[®]), biapenem (Bianem-AF[®])

Imipenem

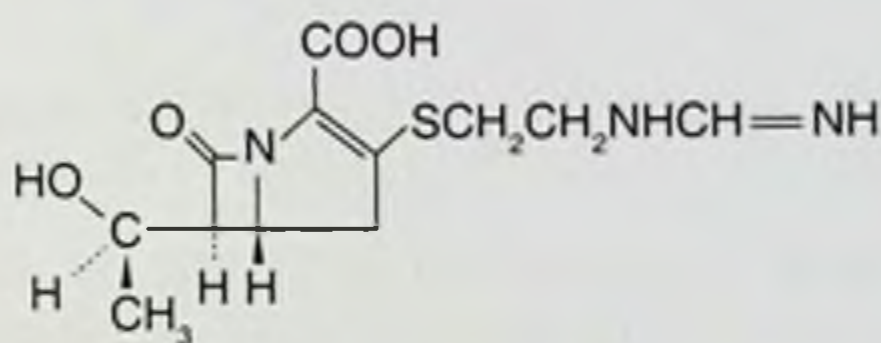


Fig. 21.6. (5R,6S)-6-[(1R)-1-Hydroxyethyl]-3-[(2-[(iminomethyl)amino]ethyl)thio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

Thienamycin derivative, semisynthetic drug. Resistant to destruction by bacterial β -lactamase, which makes it effective against multiple microorganisms, such as *Staphylococcus aureus* (except *MRSA*), *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Serratia spp.*, *Enterobacter spp.*, and anaerobes (*Bacteroides spp.*, *Fusobacterium spp.*, etc.). Destroyed by dehydropeptidase-1 of the proximal tubules, which explains low drug concentrations in the urine. Cilastatin, a dehydropeptidase-1 inhibitor, was synthesized. Administered in combination with cilastatin, a dehydropeptidase-1 inhibitor.

Tienam[®] (Grimipenem[®], Primaxin[®])

- ▶ Tienam[®] is a 1:1 combination of imipenem and cilastatin. Cilastatin inhibits dehydropeptidase-1 that is produced in the kidneys. Tienam is a highly effective inhibitor of bacterial cell wall synthesis and exerts bactericidal action (see the mechanism of action of β -lactam antibiotics) against a wide range of pathogens, gram-positive and gram-negative, aerobic and anaerobic.
- ▶ $T_{1/2}$: 1 hour. Excreted predominantly in urine. For intravenous administration 4 times daily.

Therapeutic indications: lower respiratory tract infections, urinary tract infections, intra-abdominal infections, gynecological infections, bacterial septicemia, bone and joint infections, skin and soft tissue infections, infective endocarditis

Side effects: eosinophilia; seizures, myoclonus, dizziness, somnolence; thrombophlebitis; diarrhea, vomiting, nausea; increased activity of serum transaminases, increased activity of alkaline phosphatase; allergic reactions

Contraindications: history of allergic reactions to any other β -lactam antibiotics, severe kidney failure

Meropenem (Meropenem*)

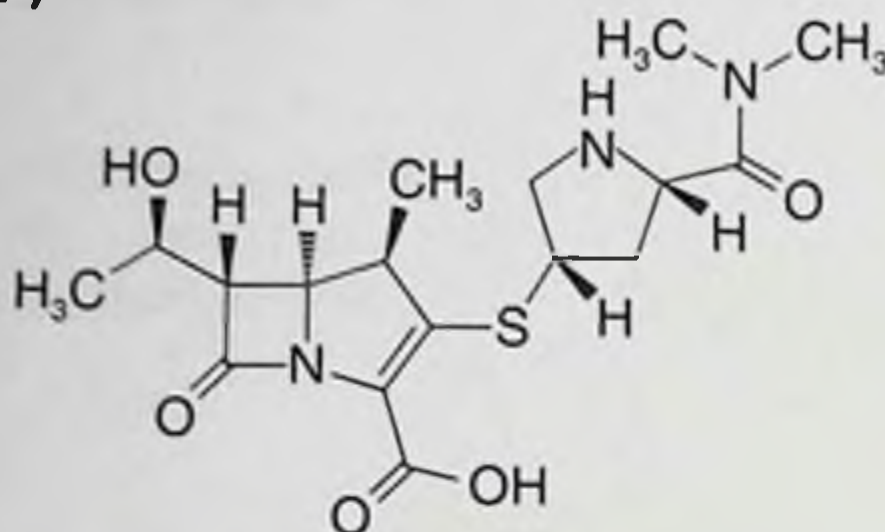


Fig. 21.7. [4R-[3(3S*, 5S*) 4 α , 5 β , 6 β (R*)]]-3-[[5-[(Dimethylamino)carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0.]hept-2-ene-2-carboxylic acid trihydrate

- ▶ Many characteristics of meropenem are similar to those of Tienam, but meropenem is resistant to dehydropeptidase-1. The spectrum of activity of meropenem differs from Tienam in that meropenem is more active against gram-negative microflora, less active against staphylococci and streptococci, and does not exert any action against enterococci.
- ▶ Metabolized in the liver. $T_{1/2}$: 1.5 hours. Easily crosses the blood-tissue barriers. Excreted mainly in urine. For intravenous administration 2–3 times daily.

Therapeutic indications: lower respiratory tract infections, urinary tract infections, skin and soft tissue infections, gynecological infections, sepsis, meningitis, including severe nosocomial infections caused by polyresistant strains of microorganisms. Empiric therapy of patients with febrile neutropenia.

Side effects: nausea, vomiting, diarrhea, increased activity of liver transaminases, alkaline phosphatase, serum bilirubin; thrombocytosis; allergic reactions; thrombophlebitis

Contraindications: see "Tienam"

Doripenem (Doriprex*)

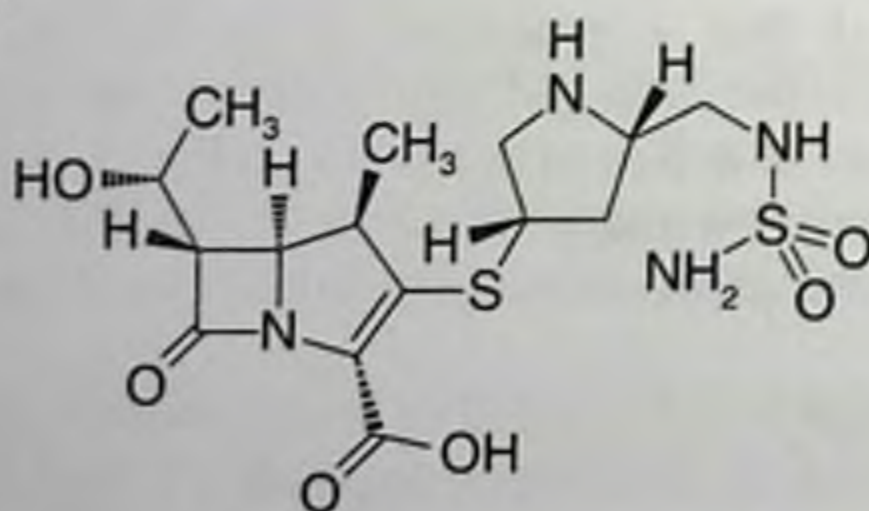


Fig. 21.8. (4R,5S,6S)-6-(1-Hydroxyethyl)-4-methyl-7-oxo-3-(((5S)-5-((sulfamoylamino)methyl)pyrrolidin-3-yl)thio)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

- ▶ Exhibits marked activity against aerobic and anaerobic gram-positive and gram-negative bacteria. It is 2–4 times more active against *Pseudomonas aeruginosa* than Tienam and meropenem.
- ▶ Metabolized by cytochrome P450 isoenzymes. Excreted in urine. For intravenous administration 3 times daily.

Therapeutic indications: hospital-acquired pneumonia, complicated intra-abdominal infections, complicated urinary system infections

Side effects and contraindications: see “Meropenem”

Ertapenem (Invanz*)

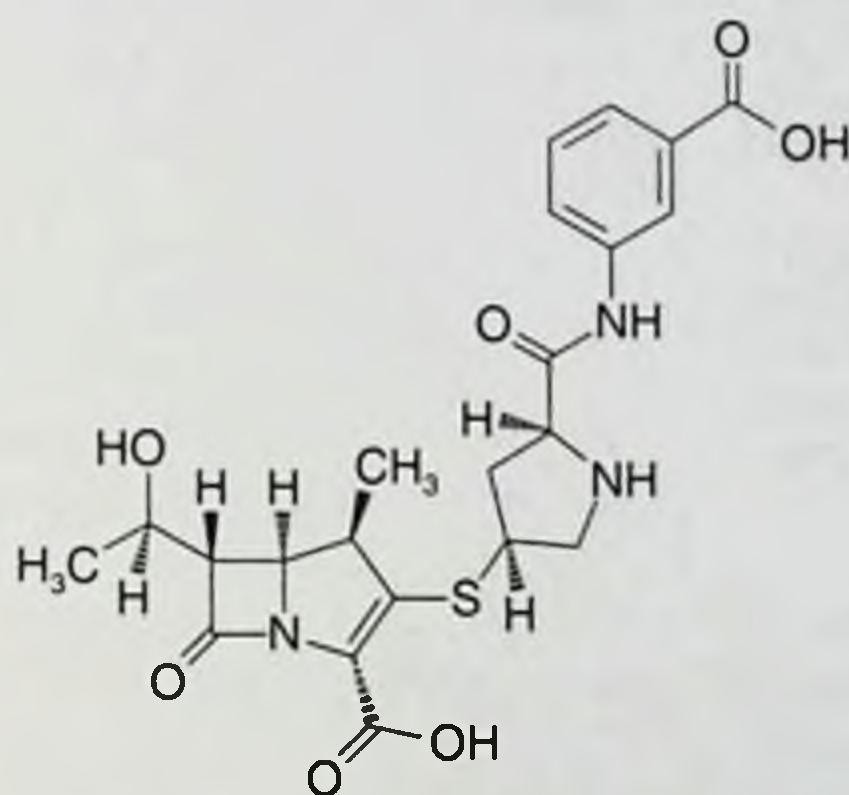


Fig. 21.9. (4R,5S,6S)-3-[(3S,5S)-5-[(3-Carboxyphenyl)carbamoyl]pyrrolidin-3-yl]sulfanyl-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

- ▶ Active against a wide range of gram-positive and gram-negative aerobic and anaerobic bacteria. Not active against *Pseudomonas aeruginosa*.
- ▶ Its main advantage is that it is suitable for intramuscular and intravenous administration once daily. Its major metabolite is an open ring derivative formed by hydrolysis of the β -lactam ring. $T_{1/2}$: 4 hours. Excreted in urine.

Therapeutic indications: community-acquired pneumonia, urinary tract infections, skin and soft tissue infections, intra-abdominal infections, infections of pelvic organs, bacterial septicemia

Side effects and contraindications: see “Meropenem”

A new carbapenem named biapenem was registered in the Russian Federation in 2021. Ertapenem exerts bactericidal action against a broad spectrum of aerobic gram-positive, gram-negative, and anaerobic bacteria, including *Pseudomonas aeruginosa* resistant to imipenem, meropenem, ceftazidime, ofloxacin, gentamicin and *Bacteroides fragilis*.

Therapeutic indications: pneumonia, urinary system infections (complicated cystitis, pyelonephritis), peritonitis, chronic respiratory disease

Contraindications: history of allergic reactions to carbapenems and to any antibacterial drugs with the β -lactam structure; less than 18 years of age

Monobactams

Aztreonam (Azactam*)

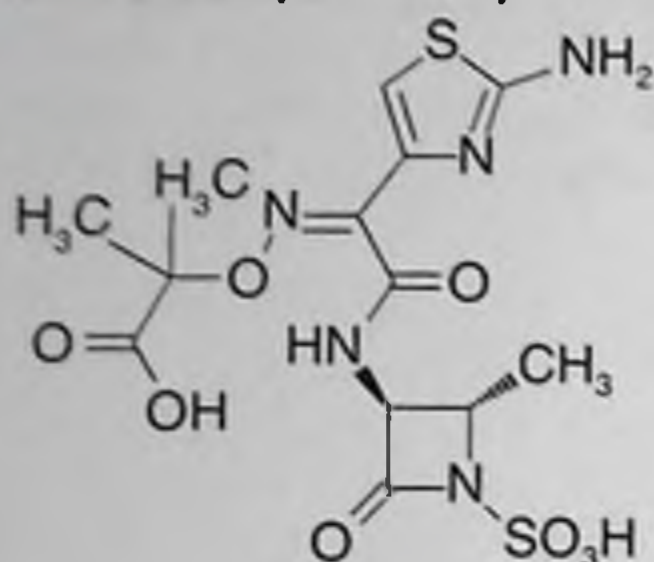


Fig. 21.10. [2S-[2 α ,3 β (Z)]]-2-[[[1-(2-Amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]amino]oxy]-2-methyl propionic acid

Monocyclic β -lactam antibiotic. Its structure differs from other β -lactam antibiotics: the core of the molecule is α -methyl-3-aminomonobactamic acid. Inhibits cell wall synthesis, exerts bactericidal action (see the mechanism of action of β -lactam antibiotics).

Poorly penetrates the BBB. Crosses the placental barrier and is excreted into breast milk at low concentrations. Negligible amounts (less than 6 % of administered dose) are metabolized in the liver. $T_{1/2}$: 1.7 hours (1.5–2.0 hours). Excreted predominantly in urine. For intramuscular administration 2–3 times daily; for intravenous administration.

Spectrum of activity: gram-negative bacteria (*Escherichia coli*, *Salmonella*, *Shigella*, *Proteus*, *Hemophilus influenzae* and *Pseudomonas aeruginosa*, meningococcus, gonococcus, *Citrobacter*, *Enterobacter*, *Serratia*). Highly resistant to β -lactamases (including penicillinases and cephalosporinases) of gram-negative bacteria.

Therapeutic indications: sepsis, peritonitis, nosocomial pneumonia, urinary tract infections, skin and soft tissue infections, gynecological infections

Side effects: allergic reactions; nausea, diarrhea; leukopenia, thrombocytopenia; increased activity of liver transaminases, alkaline phosphatase, hyperbilirubinemia; headache, dizziness; with intravenous administration — phlebitis; with intramuscular administration — tenderness at the administration site

Contraindications: pregnancy, breastfeeding, history of allergic reactions to any other β -lactam antibiotics

MACROLIDES AND AZALIDES

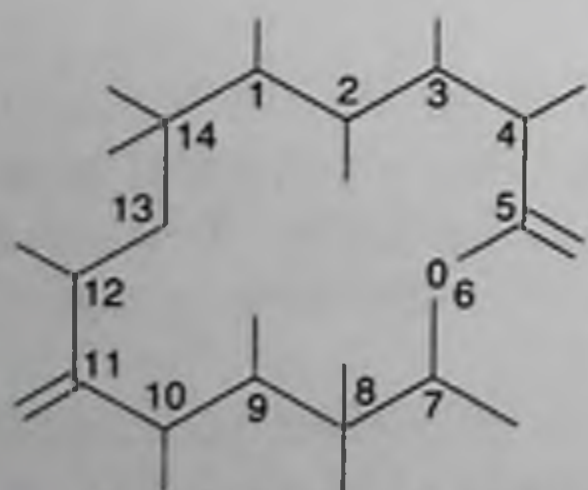


Fig. 21.11. Structure of macrolide nucleus as illustrated by erythromycin

This is a group of antibiotics (natural and semisynthetic) that include a macrocyclic lactone ring with one or more carbohydrate residues in their chemical structure. Depending on the number of carbon atoms in the ring, macrolides are divided into 14-, 15- (azalides), and 16-membered (Fig. 21.11).

Classification

I. Natural

- 14-membered: erythromycin (erythran[®])*.

- 16-membered: spiramycin (Rovamycin[•])^{**}, josamycin (Wilprafen[•])^{**}, midecamycin (Macropen[•])^{**}

II. Semisynthetic

- 14-membered: clarithromycin (Klacid[•])^{**}, roxithromycin (Rulide[•])^{**}
- 15-membered (azalides): azithromycin (Sumamed[•])^{**}

* Older generation

** Newer generation

Mechanism of action: Macrolides inhibit protein synthesis in microbial cell ribosomes by reversible binding to the 50S ribosomal subunit (without affecting nucleic acid synthesis) and inhibit peptide translocase (bacteriostatic type of action) (Fig. 21.12).

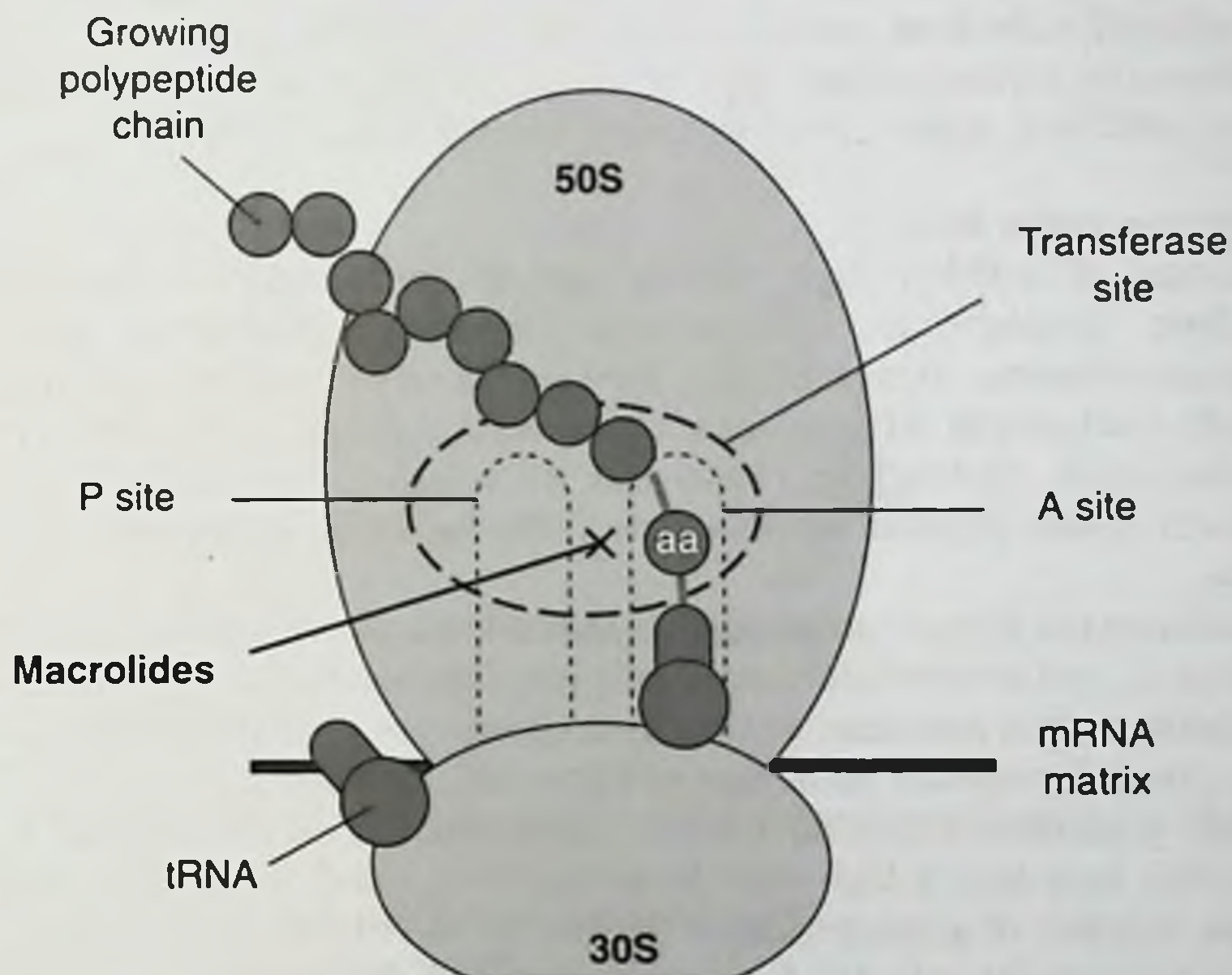


Fig. 21.12. Mechanism of action of macrolides and azalides: block translocase, inhibit mRNA movement along the ribosome, from the acceptor (A) site to the peptide (P) site

They can have bactericidal action on Group A β -hemolytic *Streptococcus*, *Streptococcus pneumoniae*, *Bordetella pertussis*, and *Corynebacterium diphtheriae* at high concentrations. Macrolides are tissue antibiotics because their serum concentrations are significantly lower than tissue concentrations and vary between drugs. They are well distributed in the body and reach high concentrations in various tissues and organs, especially during inflammation. They poorly penetrate the BBB and blood-ocular barrier, easily cross the placental barrier, and are excreted into breast milk.

They are cytochrome P450 inhibitors and are excreted in bile and urine. Macrolides are prescribed for oral and parenteral administration; no cross-reactivity with β -lactam antibiotics. They exhibit anti-inflammatory action (inhibit the diapedesis

of lipopolysaccharide-activated white blood cells and transendothelial migration of neutrophils and monocytes into the infection site).

Erythromycin (Erythran®)

Microorganisms rapidly develop resistance, second-line antibiotic.

Spectrum of activity: the most sensitive bacteria are gram-positive cocci [staphylococci (except MRSA), streptococci, including pneumococci]; *Corynebacterium diphtheriae*, *Bacillus anthracis*; pathogenic spirochetes; gram-negative cocci; *Rickettsia*, *Chlamydia trachomatis*, *Mycoplasma*, *Legionella*

Therapeutic indications

- ▶ Infections in patients who are allergic to penicillins (tonsillopharyngitis, scarlet fever, prophylaxis of rheumatic fever), community-acquired pneumonia, orodental infections (periodontitis, etc.), skin and soft tissue infections, chlamydia, mycoplasmosis, legionellosis — for oral, intravenous administration.
- ▶ Eye infections, acne — as an ointment for topical administration.

Newer generation drugs

Spectrum of activity: high activity against gram-positive cocci [Group A β -hemolytic *Streptococcus* (*Streptococcus pyogenes*), *Streptococcus pneumoniae*, *Staphylococcus aureus*, except MRSA]; exert action on intracellular microorganisms: *Chlamydia trachomatis*, *Mycoplasma*, *Ureaplasma*, *Legionella*; *Bordetella pertussis*, *Corynebacterium diphtheriae*; *Moraxella catarrhalis*, *Campylobacter*, *Listeria*, *Helicobacter pylori*, atypical mycobacteria (*Mycobacterium avium complex*), certain protozoa.

Clarithromycin is more active against *Helicobacter pylori*, atypical mycobacteria, staphylococci, and streptococci compared with other macrolides; spiramycin is more active against certain protozoa; azithromycin is superior to all other macrolides in its activity against *Hemophilus influenzae* and gram-negative cocci.

Specific properties: Meals do not affect bioavailability; easily absorbed in the GI tract; reaches long-lasting high concentrations in the blood, tissues, and cells, which allows the number of administrations per day to be reduced (1–2 times), remains in immunocompetent cells for 8–12 days after 3–5 day oral treatment courses at standard doses (postantibiotic effect).

Therapeutic indications: upper and lower respiratory tract infections (tonsillopharyngitis, sinusitis, exacerbation of chronic bronchitis, community-acquired pneumonia), sexually transmitted infections (chlamydia, ureaplasmosis, mycoplasmosis), eradication of *Helicobacter pylori* (clarithromycin), legionellosis, orodental infections (periodontitis, periostitis), skin and soft tissue infections, toxoplasmosis (spiramycin), cryptosporidiosis (spiramycin, roxithromycin), prophylaxis and treatment of mycobacteriosis caused by *Mycobacterium avium* in HIV patients (clarithromycin, azithromycin)

Side effects: abdominal pain or discomfort, nausea, vomiting, diarrhea, transient increase in transaminase activity, cholestatic hepatitis, which may manifest as jaundice, fever, malaise, weakness, abdominal pain, nausea, vomiting; cardiotoxicity (prolonged QT interval) (erythromycin, spiramycin, clarithromycin, roxithromycin,

azithromycin), phlebitis and thrombophlebitis following intravenous administration caused by local irritation; headache, dizziness, allergic reactions

Contraindications: severe liver failure, pregnancy (erythromycin, clarithromycin, midecamycin, roxithromycin), breastfeeding (erythromycin, clarithromycin, midecamycin, roxithromycin, spiramycin), history of allergic reactions

TETRACYCLINES

Tetracyclines are a group of antibiotics that belong to the class of polyketides with a structure having four fused 6-membered rings (Fig. 21.13).

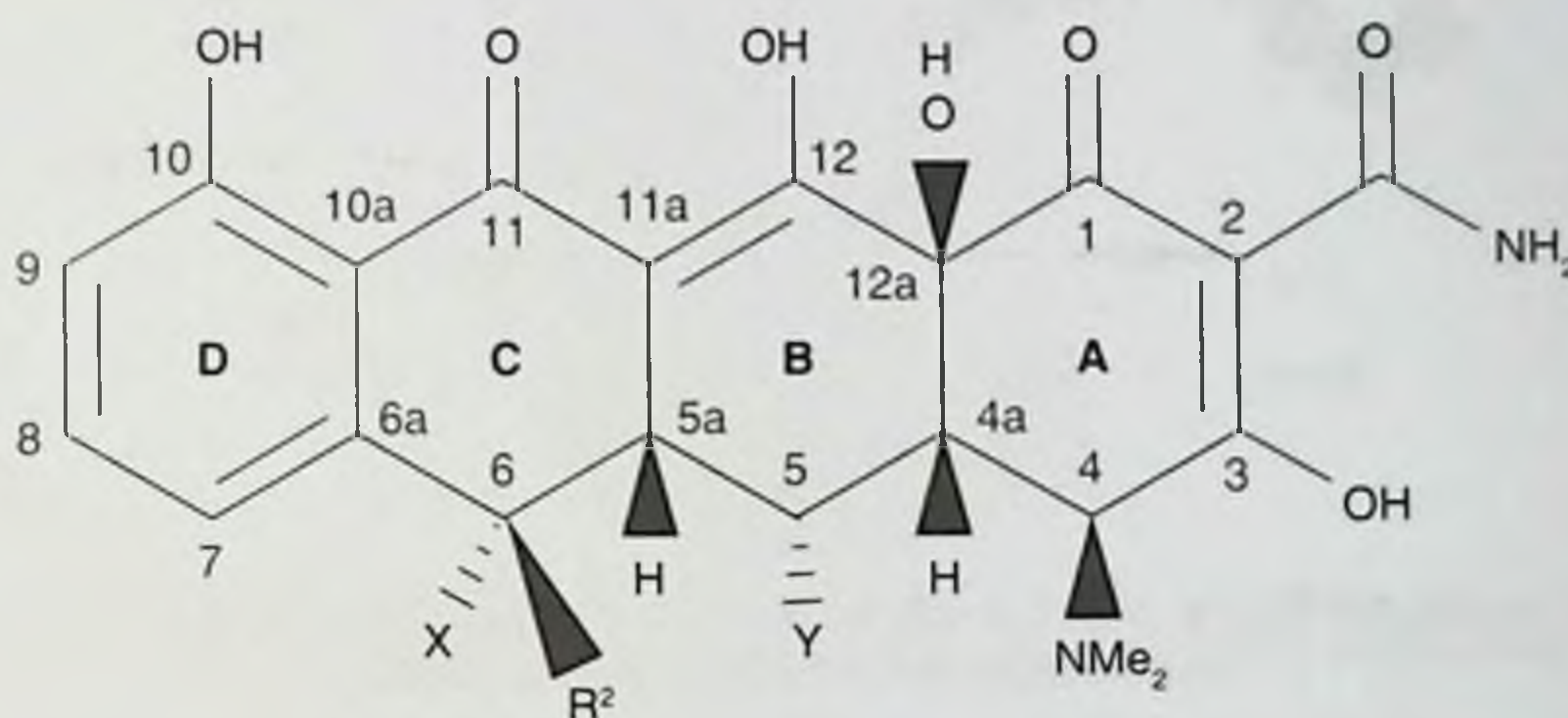


Fig. 21.13. Structure of tetracyclines

Classification

I. Naturally occurring

- Tetracycline (Deschlorobiomycin[®]), Oxytetracycline dihydrate[®] (Tetran[®])

II. Semisynthetic

- Doxycycline (Unidox Solutab[®], Vibramycin[®])
- Methacycline (Randomycin[®])

Mechanism of action: Tetracyclines inhibit protein synthesis by binding to the 30S ribosomal subunit (bacteriostatic action) (Fig. 21.14). They are capable of forming chelate complexes with metal ions (Ca^{2+} , Mg^{2+} , Fe , Al^{3+} , etc.).

Spectrum of activity: gram-positive cocci (currently there is evidence of high resistance of pneumococci, streptococci, and most staphylococci); gram-positive rods (*Listeria*, *Bacillus anthracis*); gram-negative bacteria (*Campylobacter*, *Brucella*, *Hemophilus*, *Vibrio cholerae*, *Yersinia pestis*, *Francisella tularensis*); anaerobes (*Clostridium*, except *Clostridium difficile*; *Fusobacterium*); spirochetes, *Rickettsia*, *Chlamydia trachomatis*, *Mycoplasma*; actinomycetes; *Helicobacter pylori* (tetracycline); *Plasmodium*, *Borrelia*

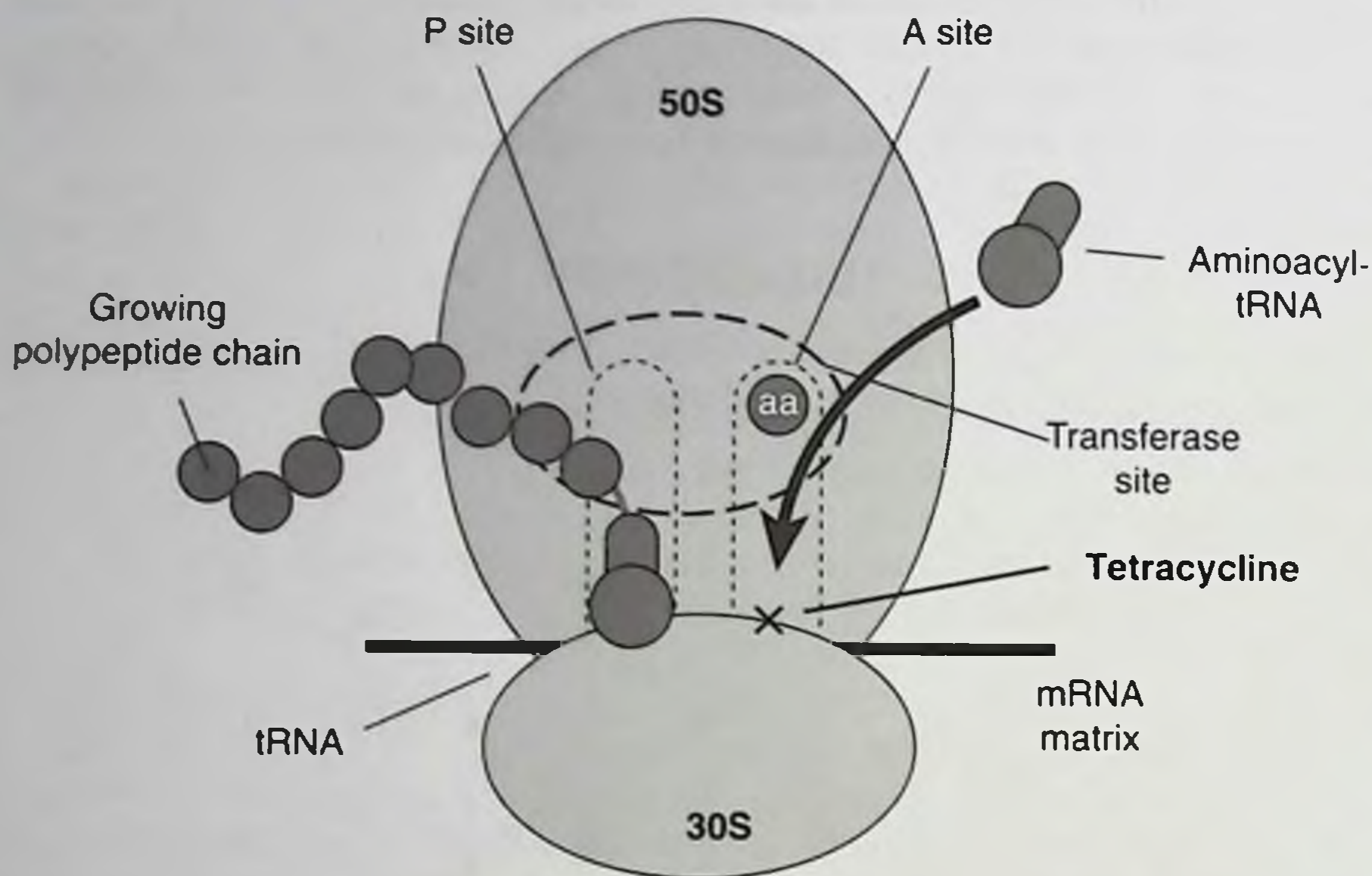


Fig. 21.14. Mechanism of action of tetracyclines: they block the acceptor (A) site, disrupting the attachment of aminoacyl-tRNA to the 30S ribosomal subunit

Specific properties:

- ▶ Broad spectrum of activity, with high secondary resistance in many bacteria, cross-resistance of microorganisms to the entire drug group.
- ▶ High toxicity. Easily penetrate bodily tissues and fluids, poorly penetrate the BBB, easily cross the placental barrier. Excreted in bile and urine.
- ▶ For topical administration (ointments), oral administration, and intravenous drip.

Their use is now limited because of the emergence of a large number of tetracycline-resistant microorganisms and numerous adverse reactions that are unique to these drugs.

Therapeutic indications: sexually transmitted infections (chlamydia, ureaplasmosis, mycoplasmosis) (doxycycline); biliary and urinary tract infections, orodental infections (periodontitis) (doxycycline), yersiniosis (doxycycline); eradication of *Helicobacter pylori* in gastric and duodenal ulcer (tetracycline in combination with other antibiotics); syphilis (in patients allergic to β -lactams); rickettsioses; especially dangerous infections (plague, cholera, brucellosis, tularemia) (doxycycline); zoonoses (Lyme disease, leptospirosis, tropic malaria) (doxycycline); trachoma, conjunctivitis, blepharitis, and other eye infections (topically administered tetracycline). In addition, doxycycline is considered for second-line treatment of upper and lower respiratory tract infections.

Side effects: Since they form chelate complexes with Ca^{2+} ions, tetracyclines are deposited in the calcification zone of bone and dental enamel, which disrupts the formation of bone and dental tissue, resulting in slower linear bone growth, enamel

defects; they cross the placental barrier and are deposited in fetal bone tissues, causing delays in growth and development (teratogenic effect); inhibition of protein synthesis (antianabolic effect); dyspepsia, leukopenia, thrombocytopenia, hemolytic and aplastic anemia, allergic reactions (photosensitization), dysbiosis, candidiasis, hepatotoxicity, nephrotoxicity, thrombophlebitis (intravenous administration)

Contraindications: less than 8 years of age, pregnancy, breastfeeding, severe kidney and/or liver failure, history of allergic reactions

Glycylcyclines

Tigecycline (Tygacil®)

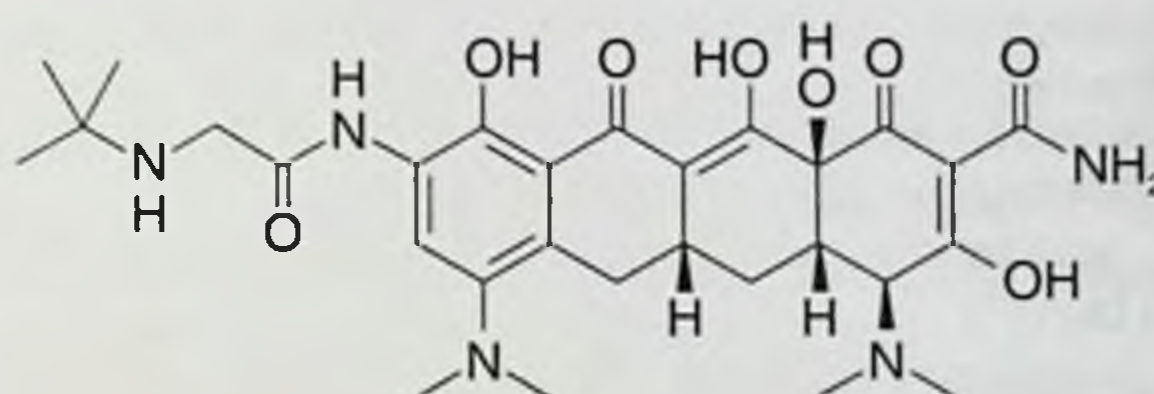


Fig. 21.15. (4S,4aS,5aR,12aS)-9-[2-(Tert-butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

- ▶ Its structure is similar to that of tetracyclines. Does not cross the BBB.
- ▶ Less than 20 % is metabolized. Excreted in urine and bile.

For intravenous administration 2 times daily.

Mechanism of action: Tigecycline inhibits bacterial protein translation by binding to the 30S ribosomal subunit and inhibiting the penetration of aminoacyl-tRNA to the ribosomal A site, which prevents the incorporation of amino acid residues into growing peptide chains (bacteriostatic action).

Spectrum of activity: gram-positive and gram-negative bacteria, including MRSA and enterococci. Tigecycline exerts bactericidal action against *Streptococcus pneumoniae*, *Legionella pneumophila*, *Hemophilus influenzae*. *Acinetobacter*, *Pseudomonas aeruginosa*, *Morganella morganii*, *Proteus* are resistant.

Therapeutic indications: complicated skin and soft tissue infections, complicated intra-abdominal infections, community-acquired pneumonia

Side effects: increased activated partial thromboplastin time, increased prothrombin time, anemia, thrombocytopenia; dizziness, headache; phlebitis, thrombophlebitis; nausea, vomiting, diarrhea, abdominal pain; increased AST, ALT activity, hyperbilirubinemia; allergic reactions

Contraindications: history of allergic reactions to tetracyclines

AMINOGLYCOSIDES

Aminoglycosides are a group of antibiotics that have a core structure of amino sugars connected via glycosidic linkages to an aminocyclic ring in the molecule (Fig. 21.16).

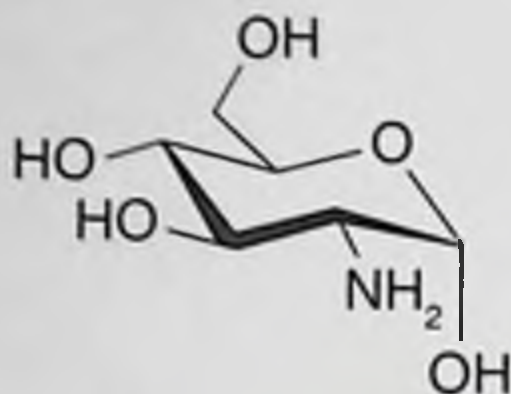


Fig. 21.16. Glucosamine in the structure of aminoglycosides

Classification.

- ▶ First generation: streptomycin (Streptomycin sulfate[®]), kanamycin (umecan[™]), neomycin (Neomycin sulfate[®], kolimycin[™])
- ▶ ▶ Second generation: gentamicin (Gentamicin sulfate[®], Garamycin[®]), framycetin (Isofra[®])
- ▶ ▶ Third generation: amikacin (Amikacin sulfate[®], mikacin[™]), tobramycin (tobracin[™], obrex[®]), sisomicin sulfate[™] (extramycin[™]), netilmicin (Netromycin[®])

Mechanism of action: Aminoglycosides disrupt the synthesis of bacterial cell proteins by penetrating the bacterium's cytoplasmic membrane and binding to bacterial 30S ribosomal subunits (Fig. 21.17). They inhibit the function of cytoplasmic membranes at higher concentrations (bactericidal action [dose-dependent]).

Aminoglycosides must penetrate into the bacterium for the antibacterial effect to develop. This process can be impaired in an anaerobic environment or when the pH is reduced. The administration of antibiotics that inhibit cell wall synthesis enhances the antibacterial effect of aminoglycosides.

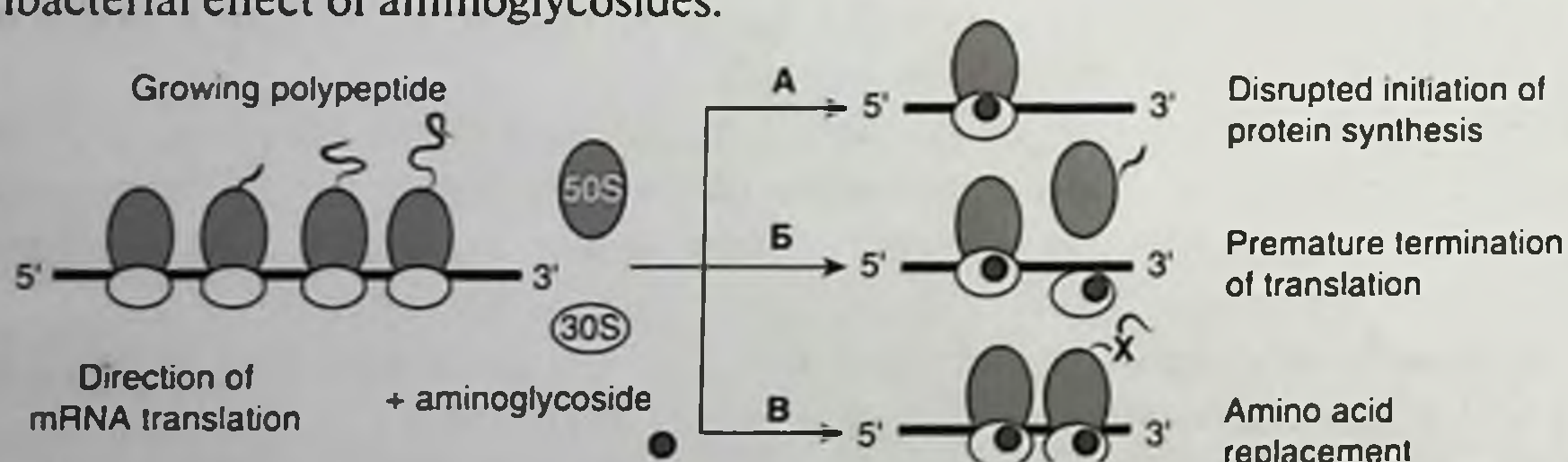


Fig. 21.17. Mechanism of action of aminoglycosides: ribosome binding to mRNA, ribosome subunits detach from mRNA before completion of protein synthesis, disrupt the recognition of the mRNA codon by the tRNA anticodon, abnormal proteins are synthesized

Specific properties:

- ▶ Broad spectrum of activity
- ▶ Poorly absorbed in the GI tract, poorly penetrates the CNS and eye
- ▶ Well distributed in the extracellular fluid, penetrates into body cavities and serous fluids

- ▶ For intramuscular, intravenous administration, inhalation (tobramycin), intranasal (framycetin), oral (kanamycin, neomycin), topical (neomycin in combination drugs, tobramycin) administration
- ▶ High frequency of side effects

Spectrum of activity

- ▶ First generation: most active against *Mycobacterium tuberculosis* (streptomycin, kanamycin); pathogens causing especially dangerous infections: plague, tularemia, brucellosis (streptomycin); gram-positive (staphylococci except MRSA, pneumococci) and gram-negative (*Escherichia coli*, *Shigella dysenteriae*, *Proteus*) bacteria (neomycin)
- ▶ Second and third generations: staphylococci except MRSA; aerobic gram-negative bacteria (third generation is most active): *Enterobacteriaceae* family [*Escherichia coli*, *Proteus*, *Klebsiella*, *Enterobacter*, *Serratia*]; non-fermenting gram-negative bacteria [*Pseudomonas aeruginosa*, *Acinetobacter*]; amikacin is highly active against atypical mycobacteria (*Mycobacterium avium*)

Therapeutic indications

- ▶ First generation: mycobacterial infections (tuberculosis), plague, tularemia, brucellosis; topical administration: neomycin for infected eczema, ulcers, first- and second-degree burns and frostbite, etc.
- ▶ Second and third generations: nosocomial pneumonia, sepsis, peritonitis, bacterial endocarditis, complicated urinary tract infections, meningitis caused by gram-negative bacteria resistant to β -lactam antibiotics, blepharitis, conjunctivitis, keratoconjunctivitis, keratitis, iridocyclitis (tobramycin for topical administration), rhinitis, rhinopharyngitis, sinusitis [framycetin, Polydexa⁺ (dexamethasone, neomycin, polymyxin B) for topical administration], tuberculosis (amikacin as a second-line drug)

Side effects: ototoxicity, vestibular disorders (nausea, vomiting, dizziness), nephrotoxicity, disruption of nerve impulse transmission (curare-like effect) due to inhibition of Ca^{2+} release, resulting in shallow breathing

Contraindications: vestibular neuritis, myasthenia gravis, chronic kidney failure, pregnancy, breastfeeding, less than 14 years of age, history of allergic reactions

Combination drugs with aminoglycosides

Baneocin⁺ (bacitracin, neomycin) (ointment, powder): skin and soft tissue infections

Polydexa⁺ (dexamethasone, neomycin, polymyxin B) (spray): ear, nose and throat infections

Polygynax⁺ (neomycin, nystatin, polymyxin B) (vaginal capsules): bacterial and fungal infections of female genitalia

Tobradex⁺ (dexamethasone, tobramycin) (eye ointment): eye infections

LEVOMYCETINS (AMPHENICOLS)

Dioxyaminophenylpropane derivatives (Fig. 21.18)

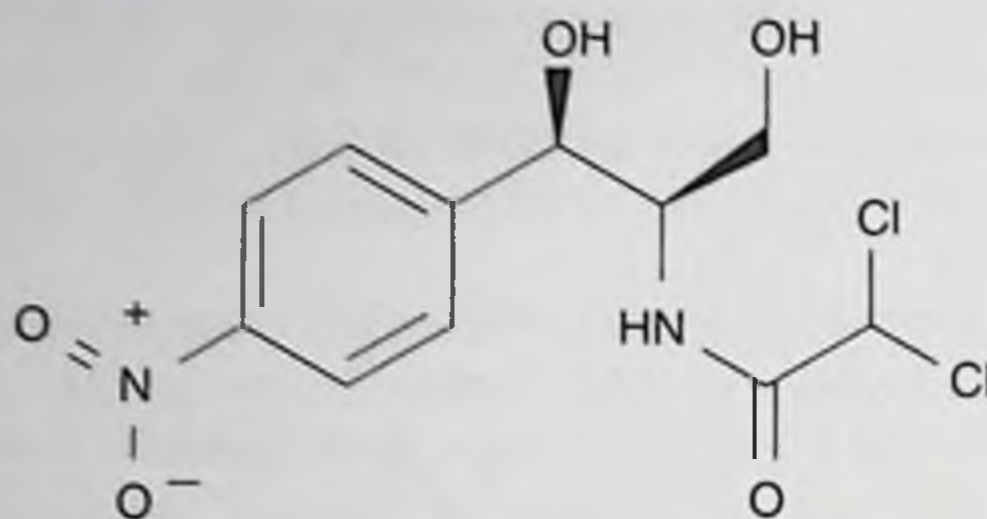


Fig 21.18. Structure of chloramphenicol

Classification

I. Naturally occurring: chloramphenicol (Levomycetin[®]) — for oral, topical administration [ingredient of Levomecol[®] (dioxomethyltetrahydropyrimidine, chloramphenicol)]; levomycetin succinate[®] (chloricide C[®]) — for intravenous, intramuscular, subcutaneous administration; levomycetin stearate[®] (eulevomycetin[®]) — for oral administration

II. Semisynthetic: D,L-chloramphenicol (Synthomycin[®]) — suppositories, ointment

Mechanism of action: Levomycetins reversibly bind to the 50S ribosomal subunit, inhibit peptidyl transferase, disrupt the incorporation of amino acids into polypeptides and protein synthesis in microorganisms (bacteriostatic action) (Fig. 21.19).

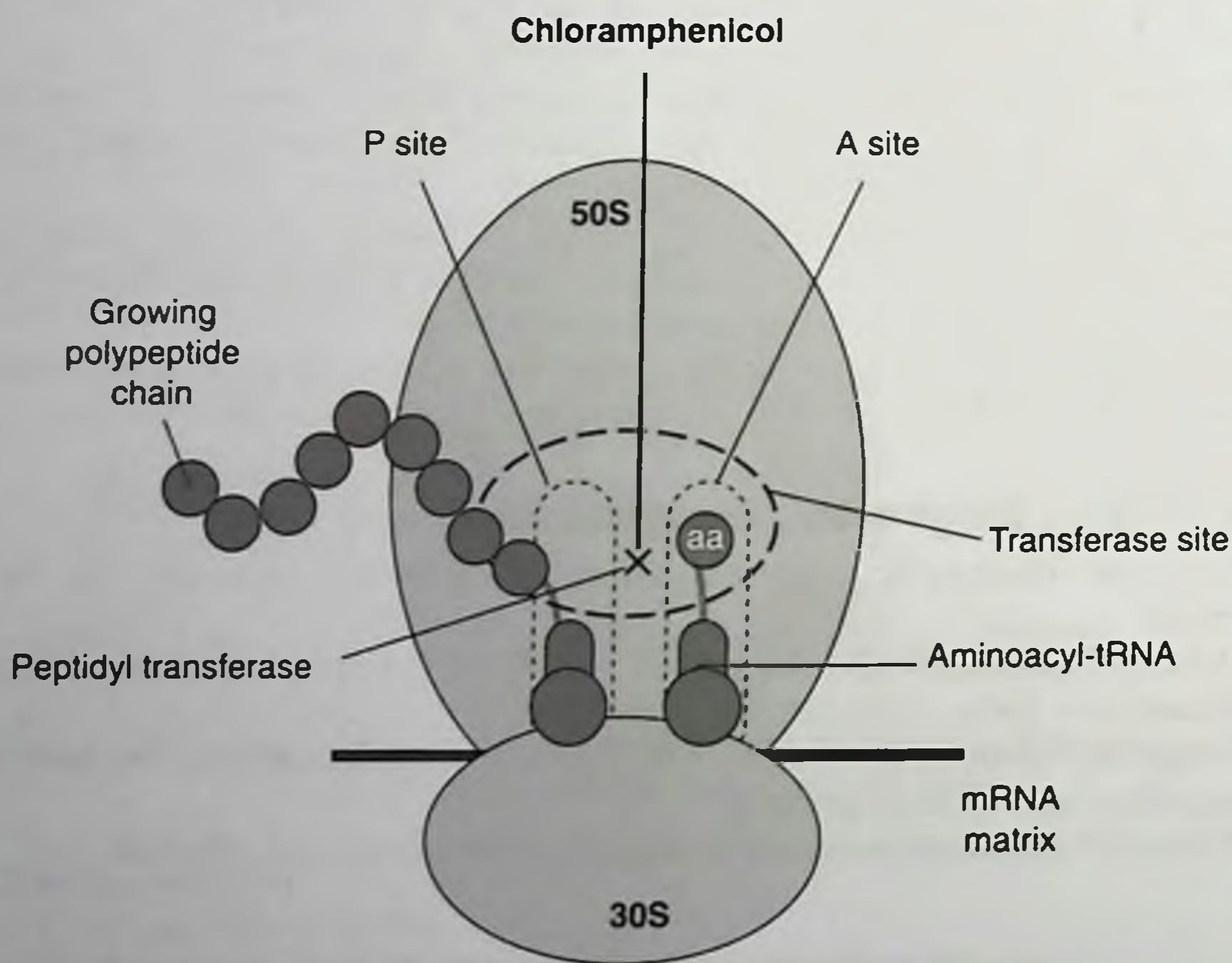


Fig. 21.19. Mechanism of action of chloramphenicol

Specific properties

- ▶ Broad spectrum of activity. Bactericidal action against *Streptococcus pneumoniae*, meningococcus, and *Hemophilus influenzae* and bacteriostatic action against other sensitive microflora.
- ▶ Its use is limited due to severe adverse reactions (primarily hematological) and secondary resistance in many pathogens.
- ▶ Well absorbed in the GI tract. Crosses the BBB and blood–ocular barrier; high concentrations reached in brain tissue, bronchial secretions, and bile.
- ▶ Bioavailability: 80 %. Metabolized in the liver. Hydrolyzed in the intestine by bacteria to form inactive metabolites. Excreted mainly in urine. Administered 3–4 times daily.

Spectrum of activity: gram-positive cocci [streptococci, including pneumococci (except penicillin-resistant ones), staphylococci (many strains are resistant), enterococci]; gram-negative cocci [meningococci, gonococci, *Moraxella*]; gram-negative bacilli [*Hemophilus influenzae* (including ampicillin-resistant strains), *Escherichia coli*]; *Salmonella*, *Shigella*, *Brucella*, *Yersinia*, *Rickettsia*, anaerobes [*Clostridium*, anaerobic cocci, *Bacteroides*]

Therapeutic indications: bacterial meningitis, cerebral abscess, intra-abdominal and pelvic infections, generalized forms of salmonellosis, typhoid fever, rickettsiosis, gas gangrene, sepsis

Levomycetins are widely used topically for the prophylaxis and treatment of infectious and inflammatory eye diseases and purulent wounds.

Given the high frequency and risk of adverse reactions, levomycetins are considered a second-line treatment for all of the above therapeutic indications.

Side effects (not typically reported with topical administration):

- ▶ Hematological:
 - a) reversible: reticulocytopenia, thrombocytopenia, leukopenia
 - b) irreversible: aplastic anemia
- ▶ Dysbiosis, candidamycosis, vitamin B deficiency
- ▶ Neurotoxicity (disorders of consciousness at high doses): psychosis, hallucinations. Decreased visual acuity and hearing
- ▶ Hepatotoxicity, dyspepsia
- ▶ Gray baby syndrome — poisoning with unmetabolized chloramphenicol. Cardiovascular instability (collapse, cyanosis), hypothermia, and irregular respiration occur. Supportive measures: no antidote, exchange transfusion.

Contraindications: bone marrow suppression, psoriasis, eczema, pregnancy, breastfeeding, history of allergic reactions; less than 3 years of age and body weight < 20 kg for oral administration; less than 4 weeks of age for parenteral administration

LINCOSAMIDES

Classification

- I. Naturally occurring: lincomycin hydrochloride (lincocyn[®])
- II. Semisynthetic: clindamycin (Dalacin[®])

Mechanism of action: Lincosamides inhibit protein synthesis in ribosomes, reversibly bind to the 50S ribosomal subunit, and inhibit peptidyl transferase at the

peptide (P) site (bacteriostatic action) (Fig. 21.21). The bactericidal action can occur at high concentrations against highly susceptible microorganisms.

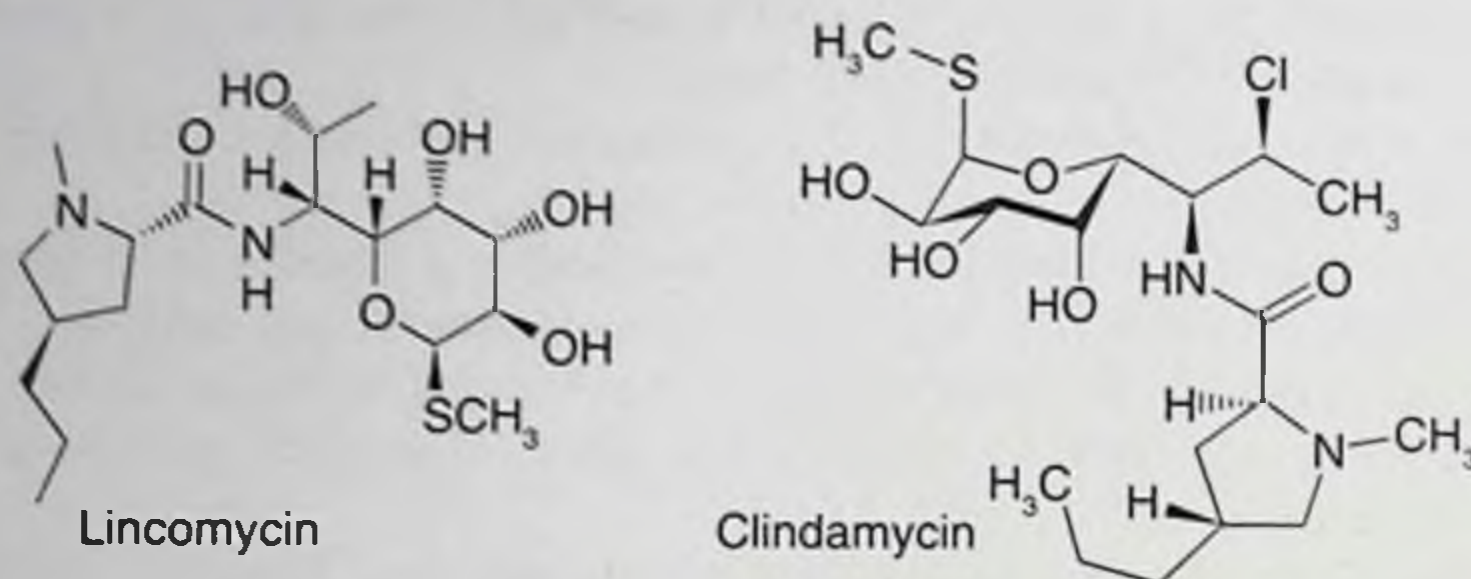


Fig. 21.20 Structural formulas of lincosamides

Spectrum of activity: staphylococci (except *MRSA*), streptococci, anaerobes (*Bacteroides fragilis*, etc.). Clindamycin is moderately active against certain protozoa: *Toxoplasma gondii*, *Pneumocystis jirovecii*, *Plasmodium*.

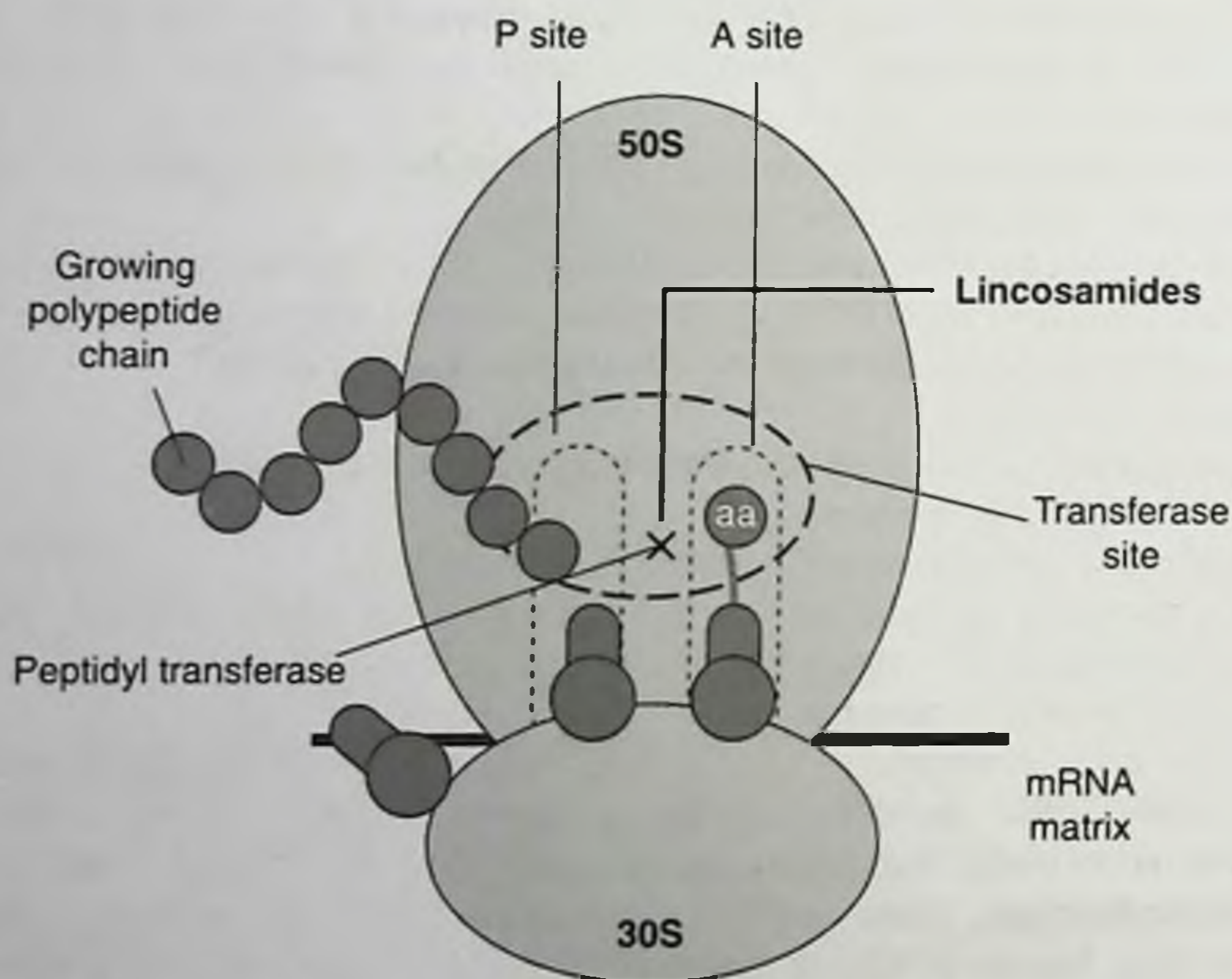


Fig. 21.21. Mechanism of action of lincosamides

Specific properties: high bioavailability (food intake does not affect absorption), with clindamycin being better absorbed in the GI tract; penetrates well into organs and tissues (reaching high concentrations in the bronchial secretions, bones, bile), placenta and breast milk, poorly penetrates the BBB. Excreted in urine and bile. For oral administration 3–4 times daily; for intramuscular, intravenous, topical administration.

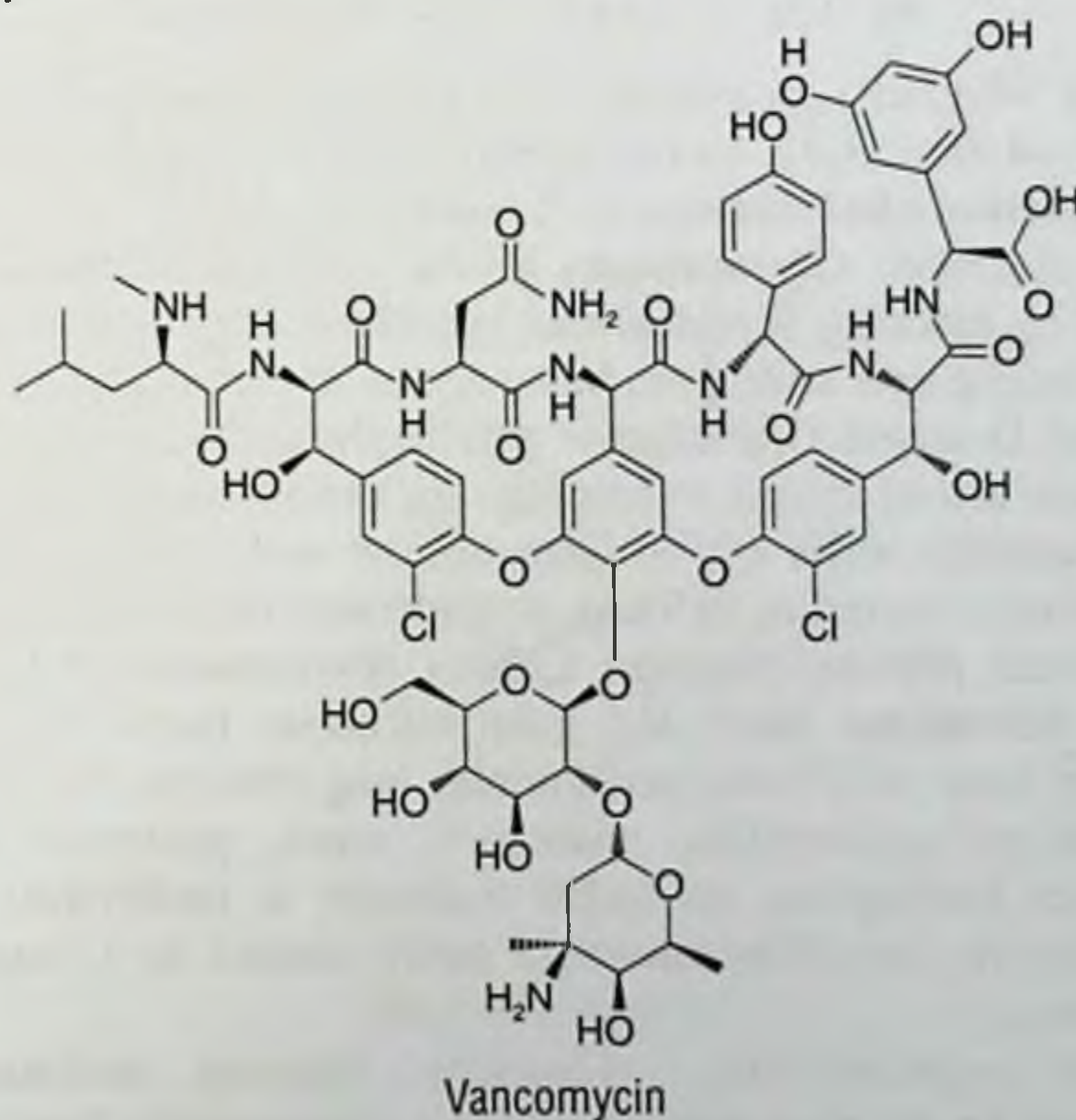
Therapeutic indications: bone and joint infections (osteomyelitis, prosthetic joint infection); lower respiratory tract infections (aspiration pneumonia, lung abscess, pleural empyema; skin and soft tissue infections, including diabetic foot; intra-abdominal infections (peritonitis, abscess); infections of pelvic organs (endometritis, adnexitis, salpingitis, non-gonococcal tubo-ovarian abscess, pelvic cellulitis, postoperative anaerobic vaginal infections); chloroquine-resistant tropic malaria and toxoplasmosis (clindamycin)

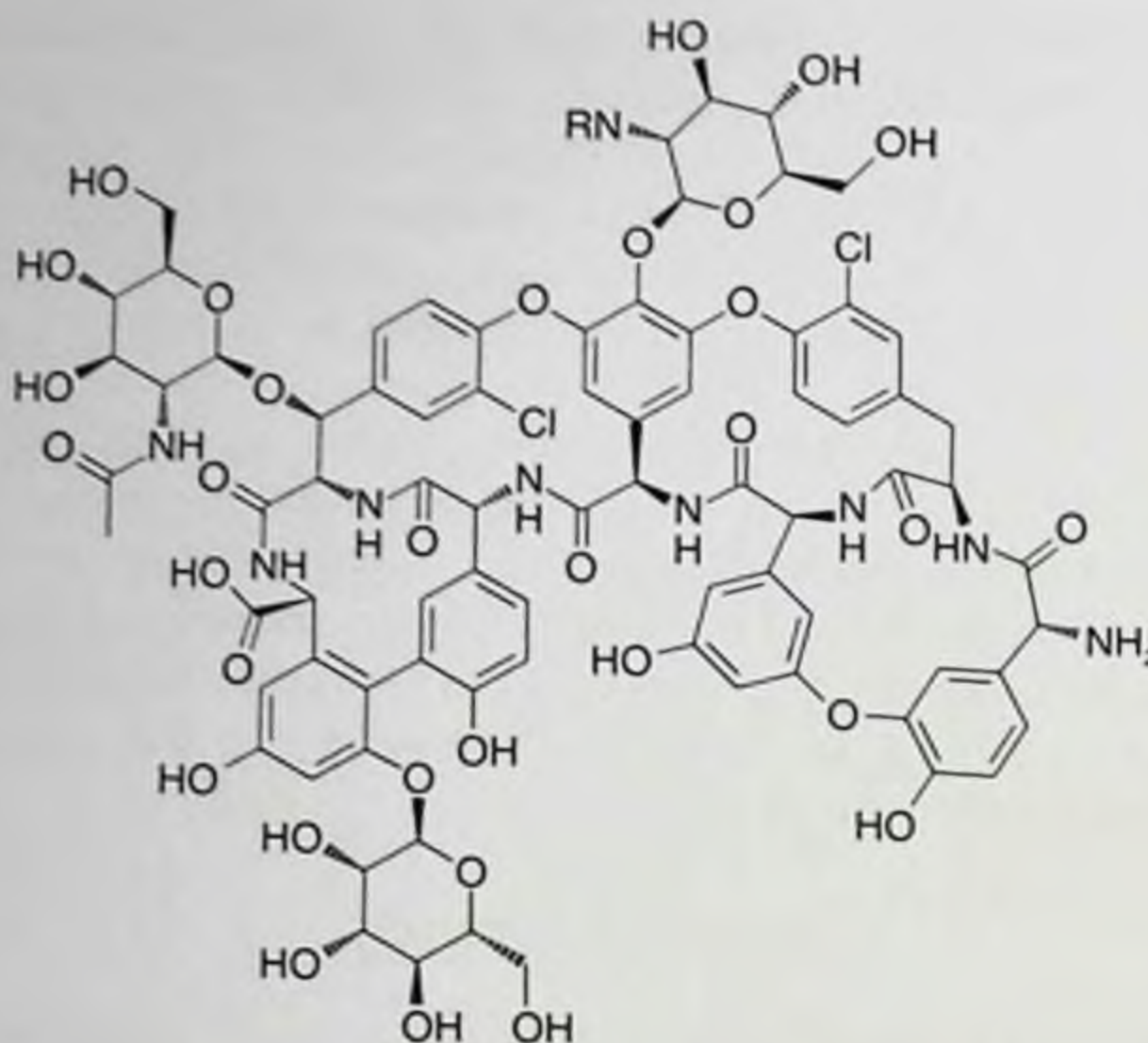
Side effects: pseudomembranous colitis, collapse following intravenous administration (clindamycin), neuromuscular blockade, hepatotoxicity (jaundice), neutropenia, leukopenia, thrombocytopenia, tenderness at the intramuscular injection site; thrombophlebitis, allergic reactions (intravenous administration)

Contraindications: history of GI disorders (non-specific ulcerative colitis, enteritis or colitis associated with antibiotics); end-stage kidney or liver disease; pregnancy, breastfeeding; history of allergic reactions

GLYCOPEPTIDES

Glycopeptides are a group of antibiotics that contain carbohydrate fragments (glycans) linked through a covalent bond with side chains of amino acid residues that make up the peptide.





Teicoplanin

Fig. 21.22. Structural formulas of glycopeptides

Classification Naturally occurring: vancomycin (Vancorus[®]) for intravenous administration 3–4 times daily, for oral administration; Teicoplanin[®] for intravenous drip, for intramuscular administration 1–2 times daily

Mechanism of action: Glycopeptides inhibit cell wall synthesis in susceptible microorganisms by blocking peptidoglycan synthesis. They bind to cell wall amino acids, thus preventing new units from being added to peptidoglycans. In particular, they bind to acyl-D-alanyl-D-alanine in peptidoglycan (bactericidal action). They exert bacteriostatic action against enterococci and certain streptococci.

Spectrum of activity: active against gram-positive aerobic and anaerobic bacteria, such as staphylococci (including MRSA), streptococci (including penicillin-resistant strains), enterococci, peptostreptococci, *Listeria*, corynebacteria, *Clostridium*

Therapeutic indications: bone and joint infections (including osteomyelitis), lower respiratory tract infections (pneumonia, lung abscess), skin and soft tissue infections, infectious endocarditis, meningitis, sepsis, peritoneal dialysis-related peritonitis, febrile neutropenia (if initial treatment is ineffective), perioperative antibiotic prophylaxis; pseudomembranous colitis caused by *Clostridium difficile* (oral administration)

Side effects: nephrotoxicity, ototoxicity (hearing problems, vestibular disorders), redness on the face and upper torso (vancomycin flushing syndrome), hematological reactions (reversible leukopenia, thrombocytopenia), transient increase in transaminases, alkaline phosphatase, local reactions (pain, burning at the administration site, phlebitis), allergic reactions, dyspepsia

Contraindications: vestibular neuritis, kidney failure, first trimester of pregnancy, breastfeeding, history of allergic reactions

LIPOGLYCOPEPTIDES

Lipoglycopeptides are a group of semisynthetic antibiotics with lipophilic side chains linked to glycopeptides.

Telavancin (Vibativ[®]), dalbavancin (Xydalba[®]), oritavancin[®]

Mechanism of action:

- ▶ By binding to the terminal dipeptide that is part of the peptidoglycan precursor — the main component of the bacterial cell wall — the drugs block the last stages of peptidoglycan synthesis.
- ▶ The lipophilic side chain of lipoglycopeptides interacts with the lipid bilayer of the bacterial cell membrane, which depolarizes the bacterial membrane and disrupts its integrity (bactericidal action) (Fig. 21.26).

Spectrum of activity: staphylococci, including MRSA, streptococci, enterococci; oritavancin[®] is active against vancomycin-resistant strains of enterococci; dalbavancin and telavancin do not exhibit such activity; telavancin is one of the most active drugs against *Clostridium spp.*

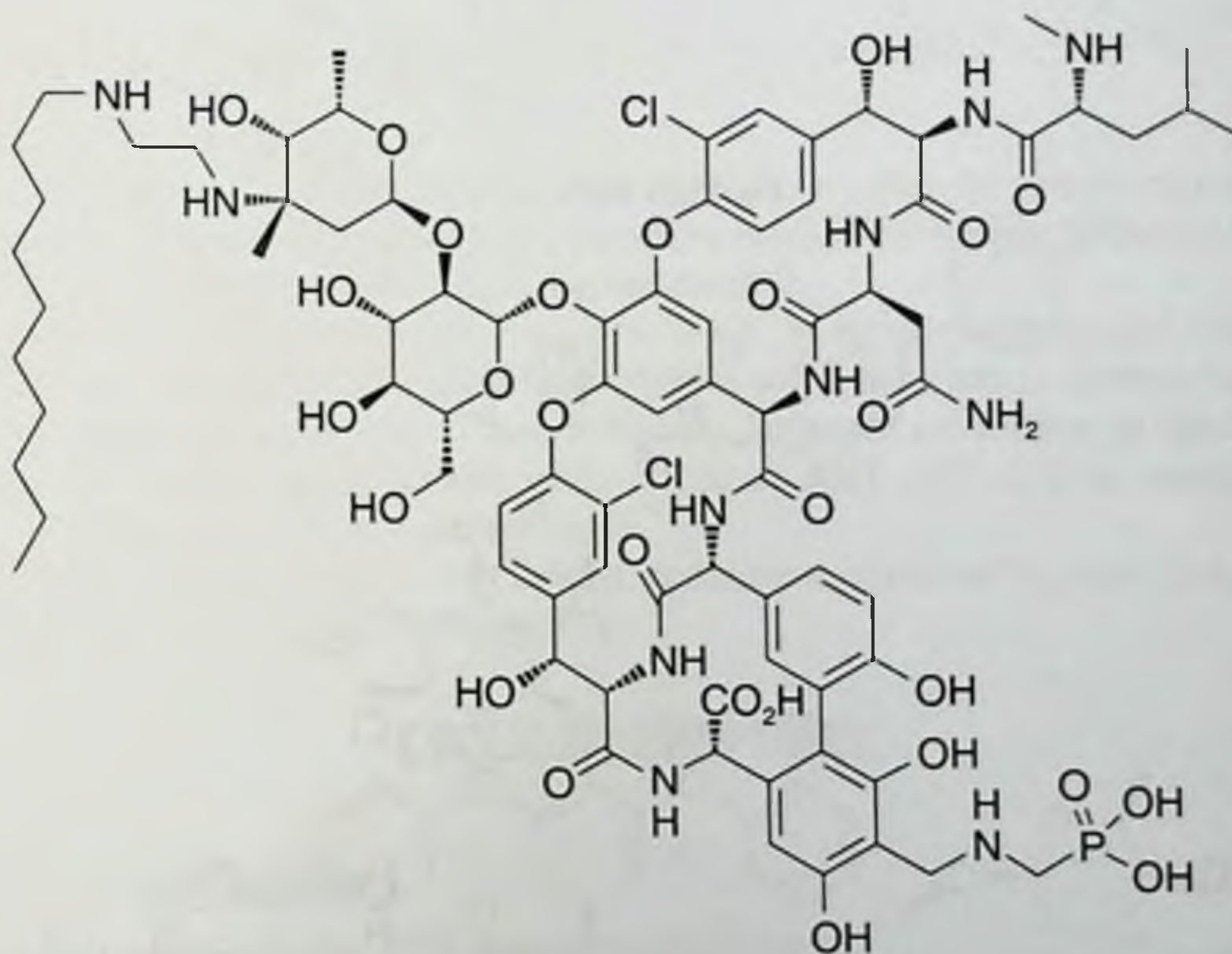


Fig. 21.23. Telavancin

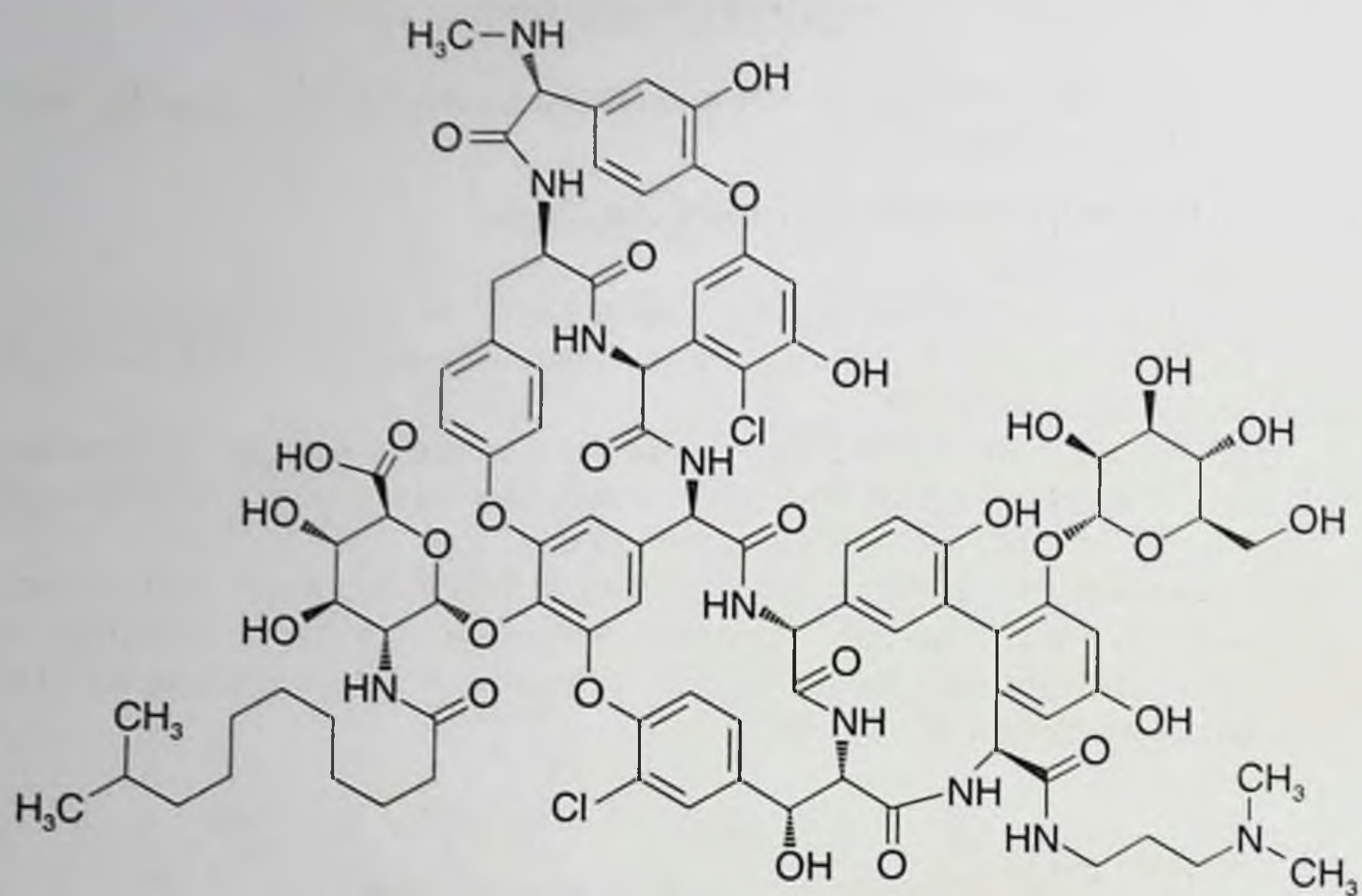
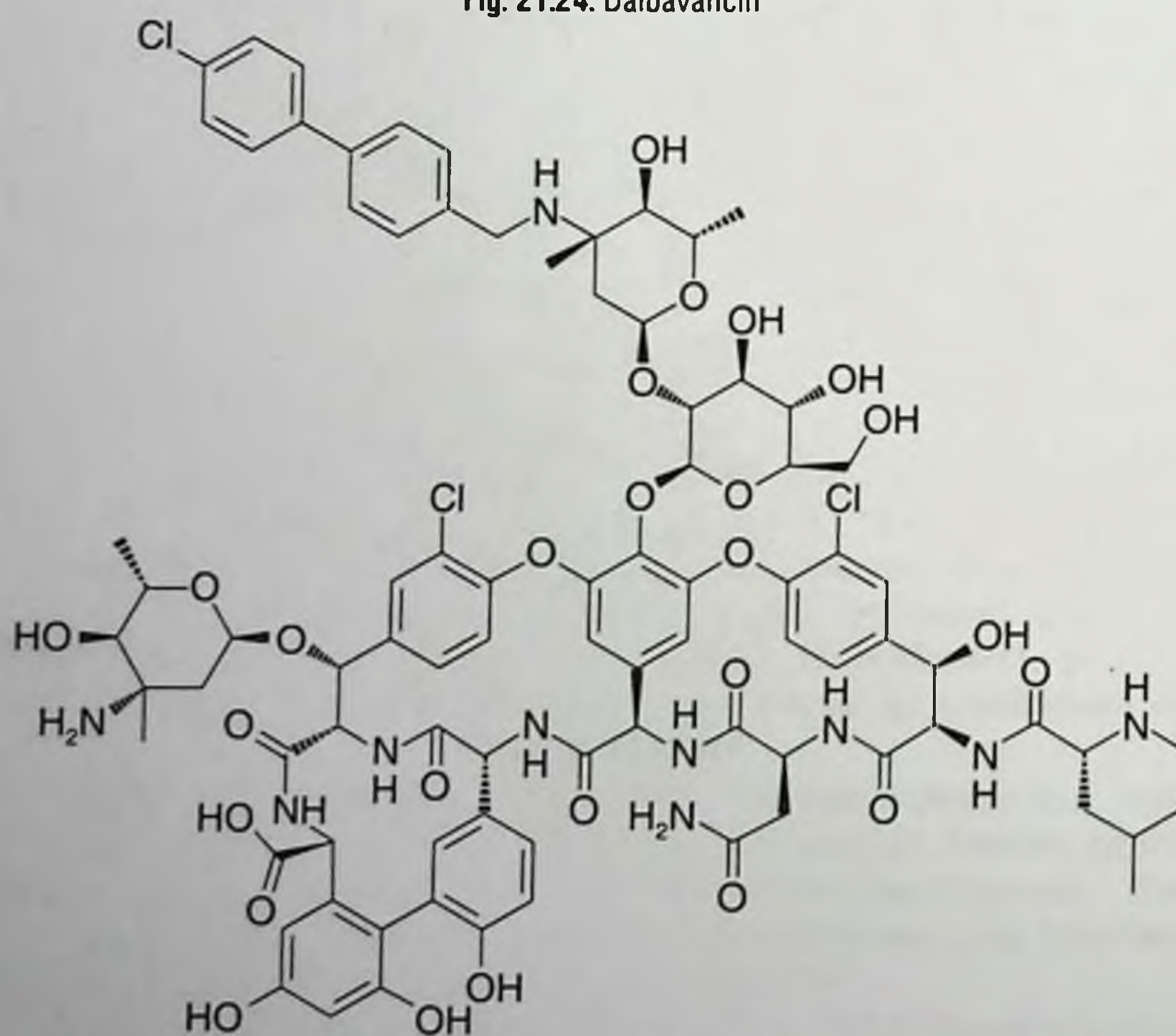


Fig. 21.24. Dalbavancin

Fig. 21.25. Oritavancin[®]

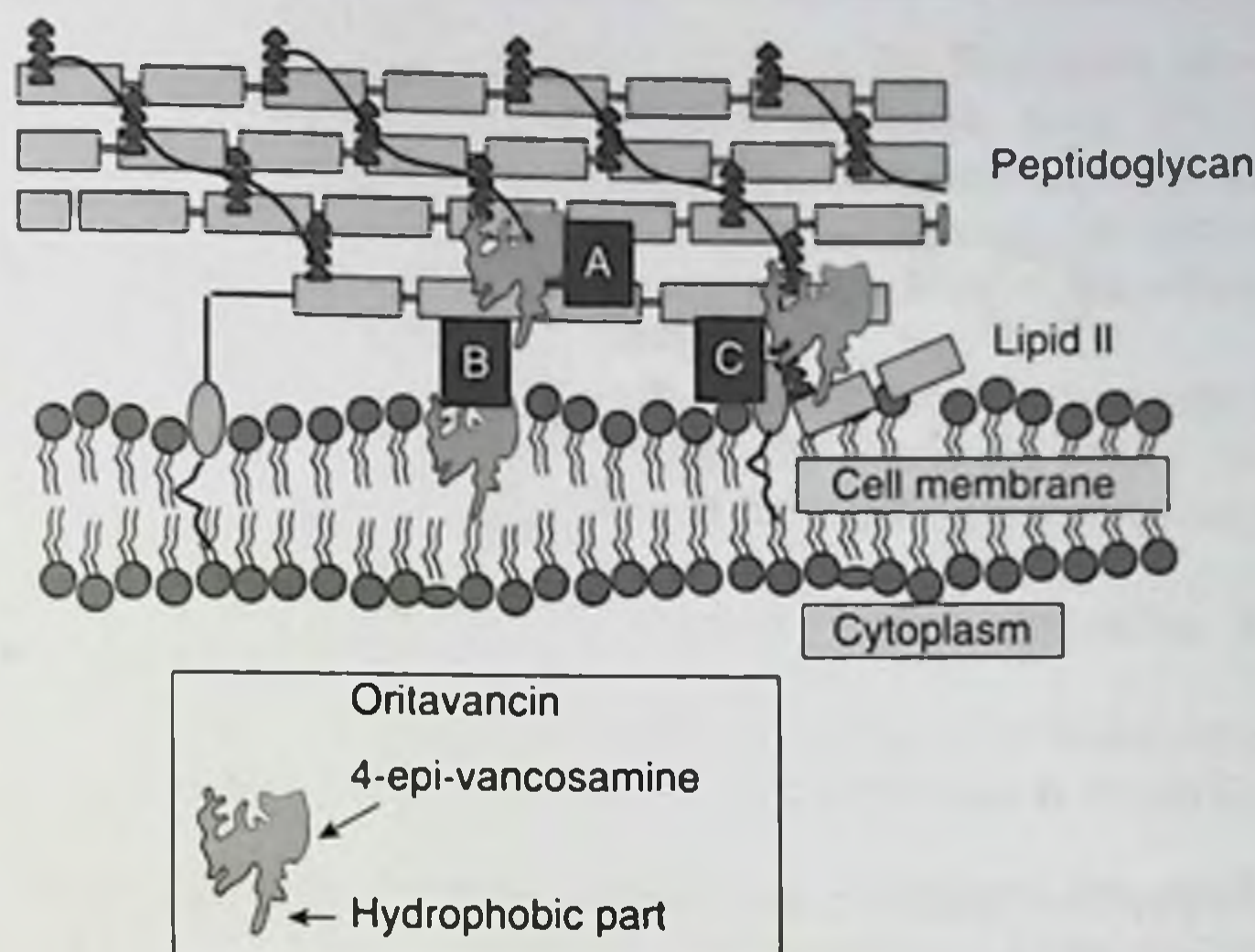


Fig. 21.26. Mechanism of action of lipoglycopeptides

Therapeutic indications

- ▶ Telavancin is used in complicated skin infections, hospital-acquired and ventilator-associated pneumonia caused by susceptible strains of *Staphylococcus aureus* (intravenous administration once daily).
- ▶ Dalbavancin and Oritavancin[®] are used to treat complicated skin and subcutaneous tissue infections (intravenous administration 1–2 times daily).

Side effects: insomnia, headache, dizziness, dysgeusia (distortion of the sense of taste), nausea, vomiting, abnormal stools, increased ALT, AST activity, acute kidney failure, fungal infections, allergic reactions

Contraindications: acute kidney failure, pediatric age (below 18 years), pregnancy, breastfeeding, history of allergic reactions

CYCLIC LIPOPEPTIDES

Daptomycin (Cubicin[®])

- ▶ Poorly penetrates the BBB and placental barrier.
- ▶ Excreted in urine and bile. For intravenous administration once daily.

Mechanism of action: This molecule is a cyclic lipopeptide consisting of 13 amino acid residues that has a hydrophilic core and a hydrophobic tail. The hydrophobic tail binds irreversibly to the cell membrane of gram-positive bacteria through a calcium-dependent mechanism. A channel is formed, causing rapid depolarization of the cell membrane due to the release of K^+ and possibly other ions present in the cytoplasm, which inhibits protein, DNA, and RNA synthesis. As a result of a major disruption of macromolecule synthesis, the bacterial cell dies (bactericidal action).

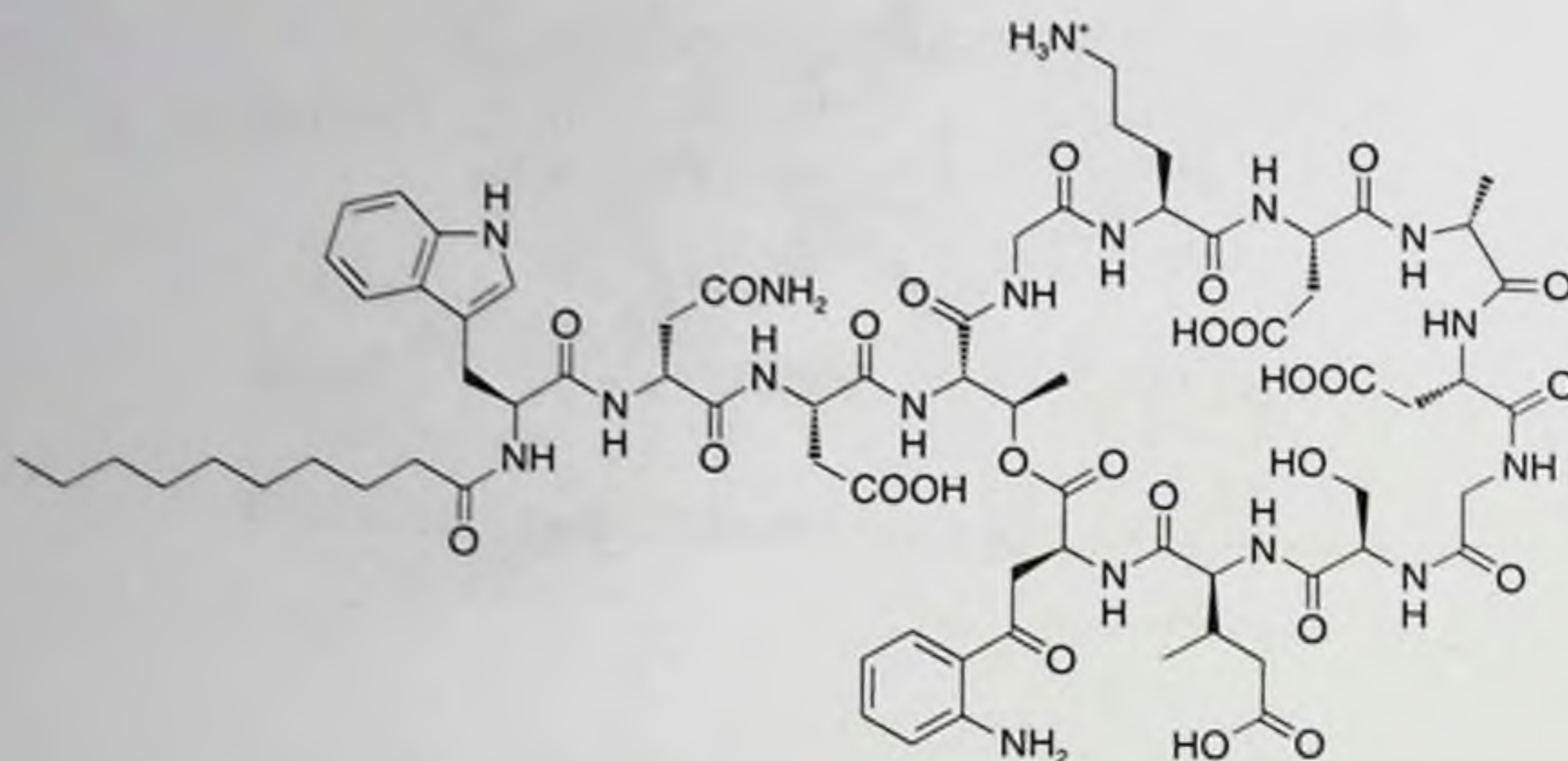


Fig. 21.27. N-Decanoyl-L-tryptophyl-L-asparaginyl-L-aspartyl-L-threonylglycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-threo-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine [egr]1-lactone

Mechanism of action: This molecule is a cyclic lipopeptide consisting of 13 amino acid residues that has a hydrophilic core and a hydrophobic tail. The hydrophobic tail binds irreversibly to the cell membrane of gram-positive bacteria through a calcium-dependent mechanism. A channel is formed, causing rapid depolarization of the cell membrane due to the release of K^+ and possibly other ions present in the cytoplasm, which inhibits protein, DNA, and RNA synthesis. As a result of a major disruption of macromolecule synthesis, the bacterial cell dies (bactericidal action).

Spectrum of activity: high activity against gram-positive bacteria, including susceptible and polyresistant staphylococci (including MRSA) and enterococci

Therapeutic indications (intravenous administration): complicated skin and soft tissue infections (wound infections, subcutaneous abscess); bacteremia caused by *Staphylococcus aureus*; infective endocarditis

Side effects: fungal infections; anemia; labile hypertension; anxiety, insomnia, dizziness, headache; dyspepsia, increased activity of creatine phosphokinase, AST, ALT, and alkaline phosphatase; allergic reactions

Contraindications: history of allergic reactions

OXAZOLIDINONES

Linezolid (Zyvox®)

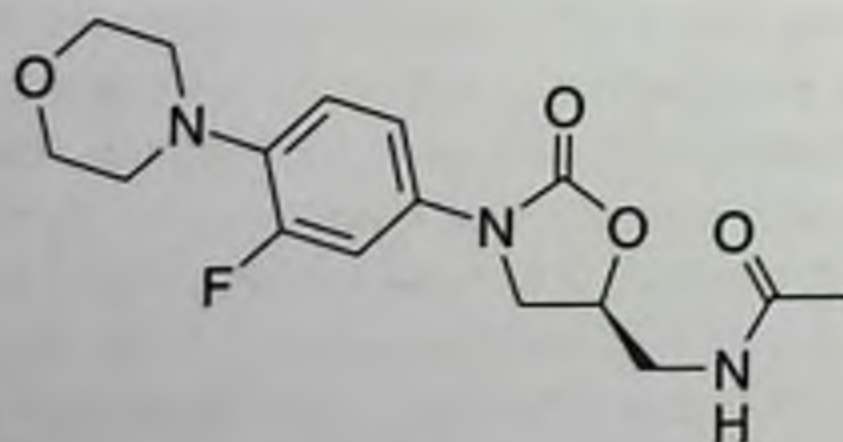


Fig. 21.28. (S)-N-([3-[3-Fluoro-4-(morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl]methyl)acetamide

Crosses the BBB. Metabolic oxidation results in the formation of two inactive metabolites: hydroxyethyl glycine and aminoethoxyacetic acid. $T_{1/2}$: 5–7 hours. Excreted in urine as hydroxyethyl glycine (40 %), aminoethoxyacetic acid (10 %), and as unchanged drug (30–35 %). Excreted in bile as hydroxyethyl glycine (6 %) and aminoethoxyacetic acid (3 %). For oral administration 2 times daily; for intravenous administration.

Mechanism of action: Linezolid selectively inhibits protein synthesis in bacteria. By binding to bacterial ribosomes, it prevents the formation of the 70S initiation complex, which is an important component of the translation process during protein synthesis (bacteriostatic action).

Spectrum of activity: aerobic gram-positive bacteria (including *MRSA*) and anaerobic microorganisms

Therapeutic indications: community-acquired and hospital-acquired pneumonia, skin and soft tissue infections, infections caused by vancomycin-resistant *Enterococcus faecium* and *MRSA*

Side effects: reversible anemia, thrombocytopenia, leukopenia; dysgeusia, nausea, vomiting, diarrhea, abdominal pain, flatulence; changes in total bilirubin, ALT, AST, alkaline phosphatase; headache; candidiasis; allergic reactions

Contraindications: history of allergic reactions

POLYMYXINS

Polymyxins are a group of antibiotics represented by complex organic compounds with a cyclic polypeptide serving as the base.

Classification

- ▶ Polymyxin M: for oral, topical administration
- ▶ Polymyxin B (Vilimiksin®): for intravenous, intramuscular administration
- ▶ Polymyxin E^p (Colistin®): for inhalation

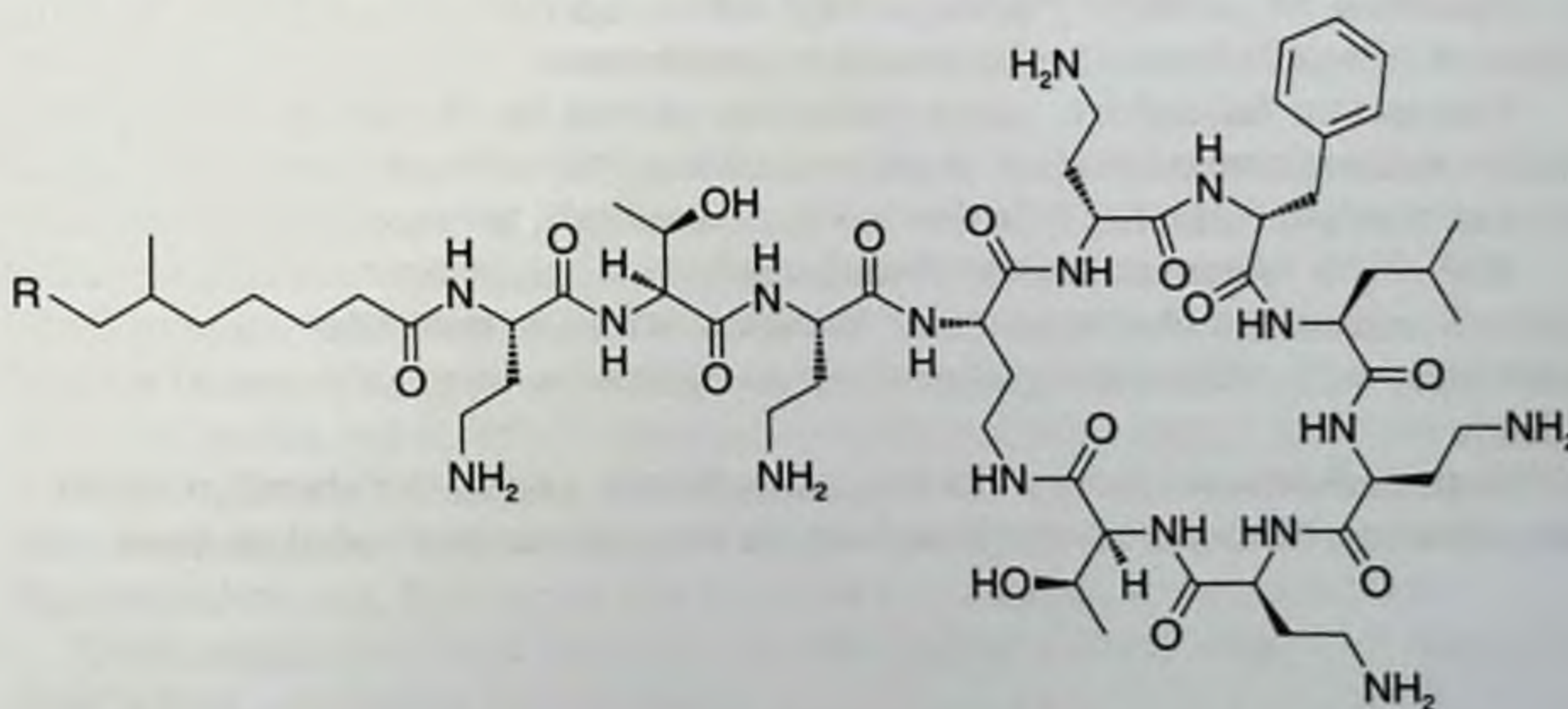


Fig. 21.29. Polymyxin B

Mechanism of action: Polymyxins disrupt the integrity of the cytoplasmic membrane, causing the components of the bacterial cell cytoplasm leak out, which leads to bacterial cell lysis (bactericidal action).

Specific properties:

- ▶ Not absorbed in the GI tract, poorly penetrates tissue barriers after parenteral administration, do not cross the BBB; reaches low concentrations in the pleural and synovial fluid. Rapidly inactivated in the presence of pus.
- ▶ Excreted in urine and bile, resistance develops slowly.

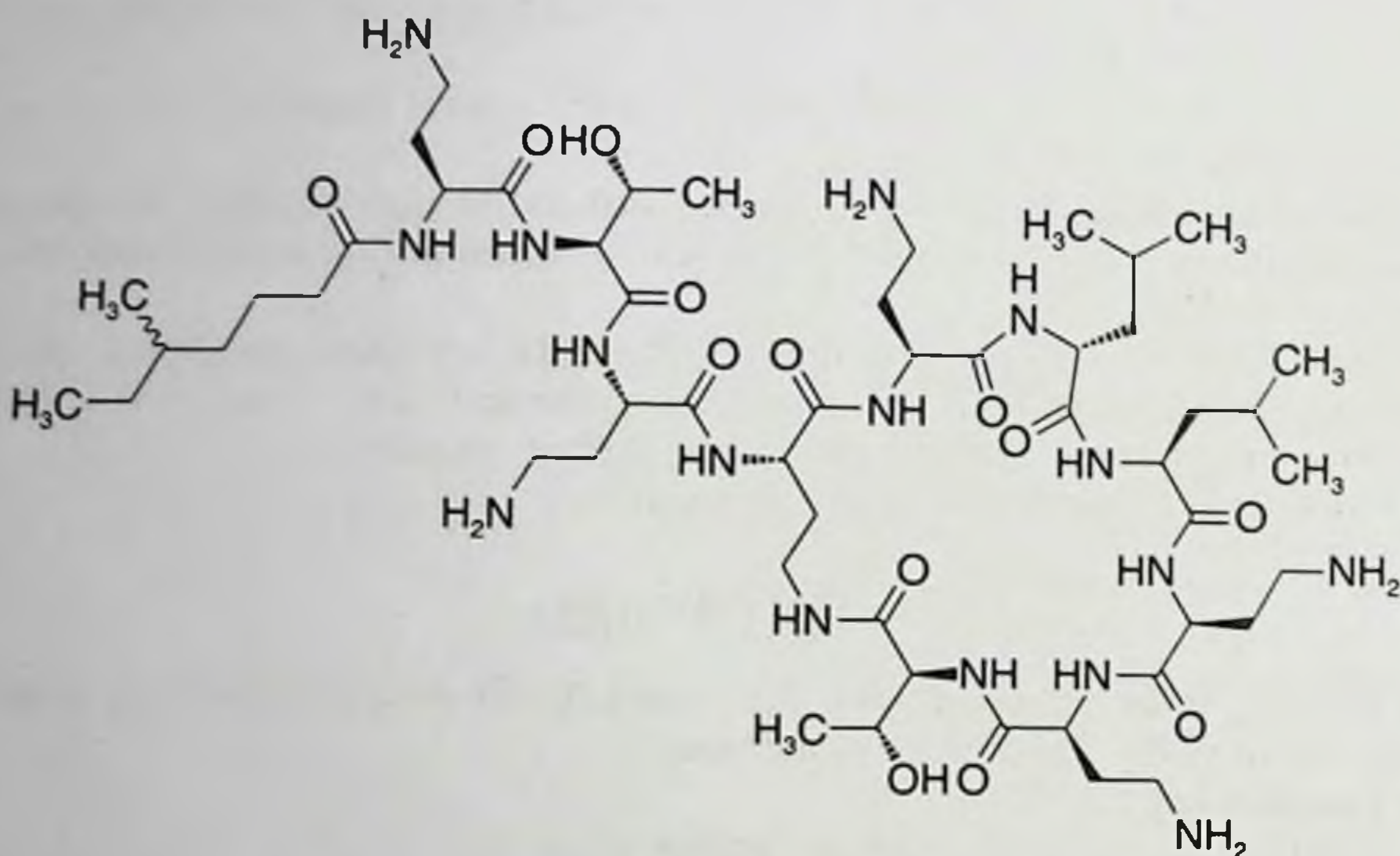


Fig. 21.30. Polymyxin E

Spectrum of activity Predominantly active against gram-negative bacteria, especially *Pseudomonas aeruginosa* and *Acinetobacter*.

Therapeutic indications: severe infections caused by *Pseudomonas aeruginosa*, *Acinetobacter baumani* or gram-negative multidrug resistant pathogens; sepsis; topical treatment of pseudomonas infection in infected wounds, burns, otitis (polymyxin M)

Side effects (parenteral dosage forms): nephrotoxic and neurotoxic effects, in rare cases — neuromuscular conduction blockade; with intramuscular administration: infiltrates; with intravenous administration: phlebitis, dyspepsia, superinfection, allergic reactions

Contraindications: kidney failure, myasthenia gravis, botulism, pregnancy, breastfeeding, history of allergic reactions; for external use: perforated eardrum

RIFAMYCINS

Rifampicin (Rimpin[®])

- ▶ Semisynthetic broad spectrum antibiotic, first-line antituberculosis drug. Polyketide belongs to the chemical class of compounds with a heterocyclic structure. Food intake decreases the absorption of rifampicin.

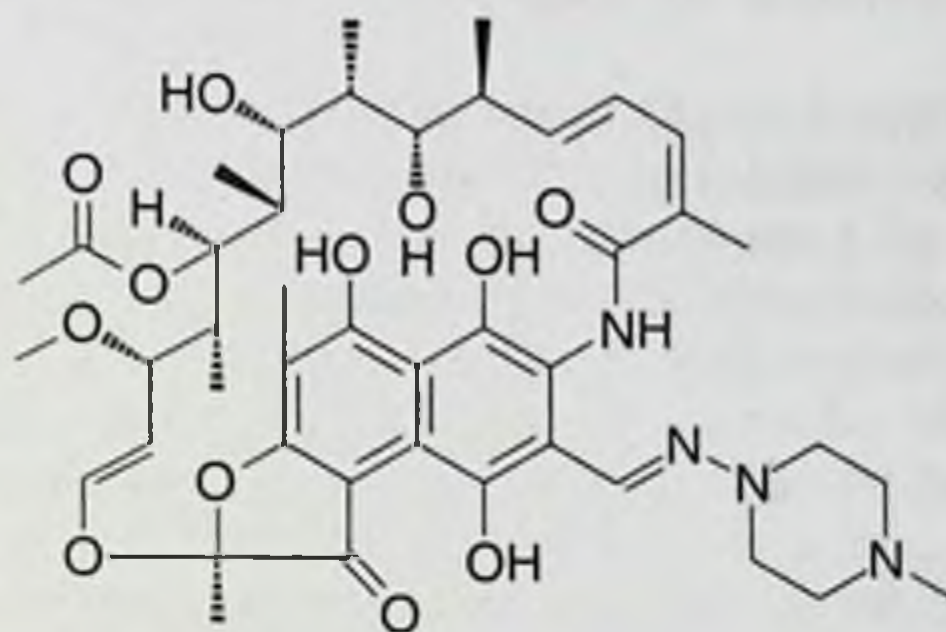


Fig. 21.31. (7S,11S,12R,13S,14R,15R,16R,17S,18S)-2,15,17,27,29-Pentahydroxy-11-methoxy-3,7,12,14,16,18,22-heptamethyl-26-[(E)-N-(4-methylpiperazin-1-yl)carboximidoyl]-6,23-dioxo-8,30-dioxa-24-azatetracyclo[23.3.1.14.7.05.28]triaconta-1,3,5(28),9,19,21,25(29),26-octaen-13-yl acetate

Poorly penetrates the BBB. Crosses the placental barrier and is excreted into breast milk. Metabolized in the liver to form the active metabolite 25-O-desacetyl rifampicin. Hepatic microsomal enzyme inducing drug. Excreted in bile and urine, with small amounts excreted in tears, saliva, sweat, sputum, and other biological fluids staining them orange-red. For oral administration 2–3 times daily; for intravenous, intramuscular, topical (ear drops) administration.

Mechanism of action: Rifampicin disrupts RNA synthesis in bacterial cells by binding to the β -subunit of DNA-dependent RNA polymerase, preventing its attachment to DNA and inhibiting RNA transcription (bactericidal action). Rifampicin is active against intracellular and extracellular microorganisms.

Spectrum of activity: *Mycobacterium tuberculosis*, gram-positive cocci [staphylococci, hemolytic streptococci, pneumococci]. At high concentrations, rifampicin is active against certain gram-negative bacteria.

Therapeutic indications: tuberculosis (both forms) as part of combination therapy, leprosy, infectious diseases caused by sensitive microorganisms (if they are resistant to other antibiotics and as part of combination antimicrobial therapy)

Side effects: nausea, vomiting, diarrhea, anorexia, erosive gastritis, pseudomembranous enterocolitis, increased activity of serum liver transaminases, hyperbilirubinemia, leukopenia, dysmenorrhea, headache, allergic reactions

Contraindications: viral hepatitis, chronic kidney failure, stage 2–3 congestive heart failure, pregnancy, breastfeeding

22. ANTIFUNGALS

Antifungals (antimycotics) are drugs used for the prophylaxis and treatment of fungal infections.

In 1954, the antifungal activity of the polyene antibiotic nystatin, known since the late 1940s, was discovered. The antibiotic griseofulvin, which was first isolated in 1939 and used in fungal plant diseases, proved to be a highly effective antifungal. It was introduced in medical practice in 1958. Another polyene antibiotic, amphotericin B (obtained in the purified form in 1956), began to be used for the treatment of deep (visceral) fungal infections. In the late 20th century, imidazole derivatives were synthesized and introduced into practice: clotrimazole (1969), miconazole, ketoconazole (1978), itraconazole (1980), fluconazole (1982), terbinafine (1983), etc. In recent decades, fungal infections have become an important clinical problem.

The fungal cell wall is 90 % carbohydrates: chitin, glucans, mannans. The cytoplasmic membrane of fungi is rich in sterols, unlike other biological membranes (ergosterol) (Fig. 22.1).

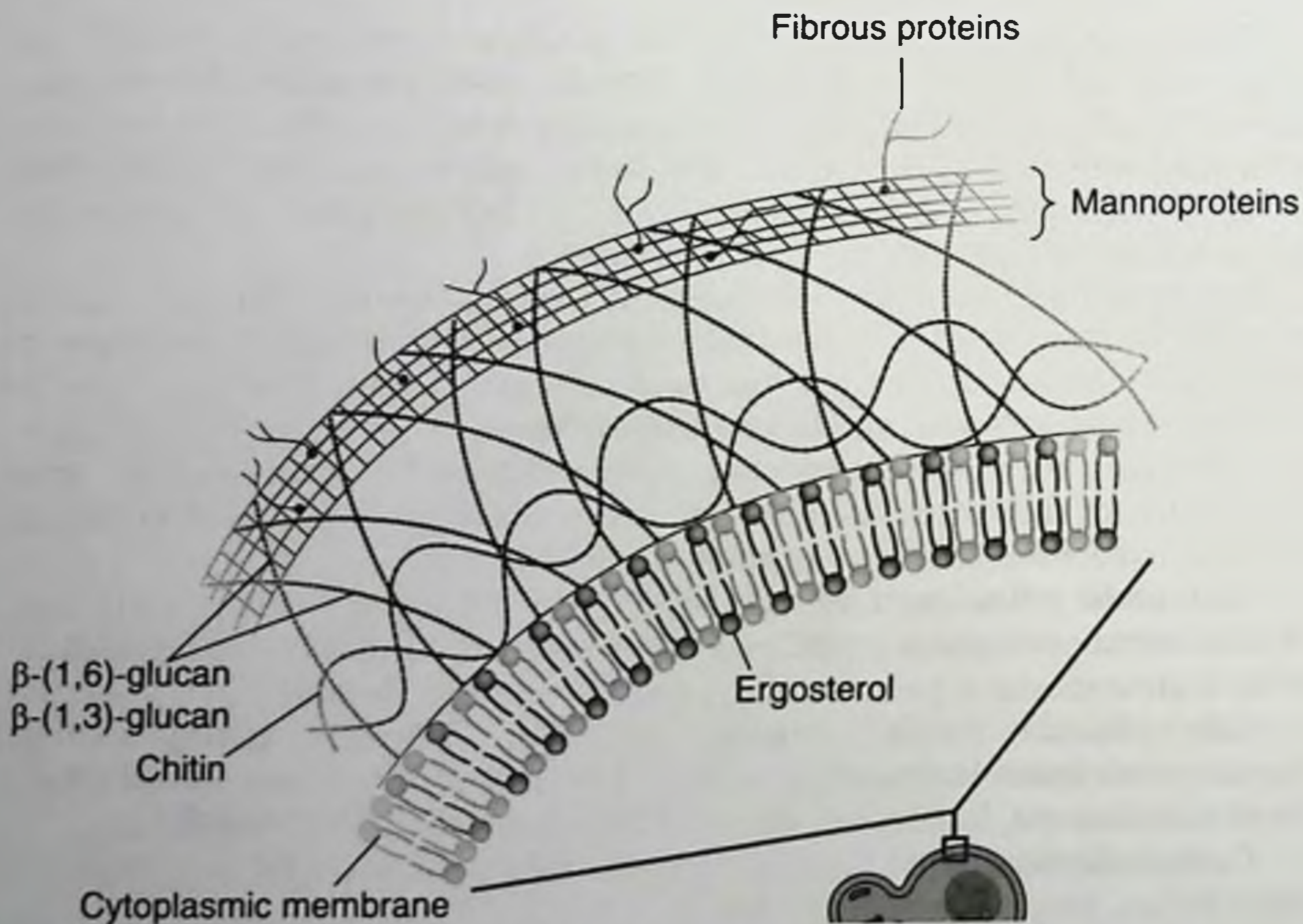


Fig. 22.1. Ultrastructure of fungal cell wall

Cell wall components

1. Mannoproteins β -(1,6)-glucan, β -(1,3)-glucan
2. Chitin

Double layer of cytoplasmic membrane lipids

1. Ergosterol (synthesized from squalene)
2. β -(1,3)-glucan-synthetase (β -glucan synthesis)

Types of fungal diseases

Systemic (deep) fungal infections affect the internal organs and CNS: coccidioidomycosis, cryptococcosis, histoplasmosis, blastomycosis, etc.

Superficial fungal infections (dermatomycoses) affect the skin, nails, hair and are caused by dermatophytes: trichophytosis, microsporia, dermatophytosis, etc.

Candidiasis (caused by *Candida albicans*) more often affects the mucous membranes of the GI tract, bronchi, genitalia.

In rare cases, severe immune deficiency can cause fungal septicemia.

In recent years, diseases caused by pathogenic fungi have been treated with a number of drugs of different origin (natural or synthetic), with different mechanisms of action, therapeutic indications (local or systemic infections), and methods of administration (topical, oral, parenteral).

Classification**By chemical structure****I. Antifungal antibiotics****1. Polyene antibiotics**

- Nystatin*
- Levorin*
- Natamycin (Primacin*, Ecofucin*, Primacin*)
- Mycoheptin*
- Amphotericin B [lipid complex] (Ampholip*)

2. Drugs from other groups

- Griseofulvin*

II. Synthetic drugs**1. Azoles****A. Imidazole derivatives**

- Clotrimazole (Candid*, Candizol*)
- Miconazole (Gynezol*, Daktarin*)
- Ketoconazole (Fungavis*, Nizoral*)

B. Triazole derivatives

- Fluconazole (Diflucan*, Mycosyst*, Flucostat*)
- Itraconazole (Itrazol*, Rumycos*, Irugin*)
- Voriconazole (Vifend*)

2. Nitrophenol derivatives

- Chloronitrophenol (Nitrofungin*)

3. Allylamines (N-methylnaphthalene derivatives)

- Terbinafine (Lamisil[®], Binafin[®], Terbisil[®])
- Naftifine (Exoderil[®], Mycoderil[®])
- 4. Echinocandins.
 - Caspofungin (Cancidas[®], Maxcand[®]), micafungin (Mycamine[®])
- 5. Drugs from other groups
 - Amorolfine (Loceryl[®])
 - Ciclopirox[®]

By therapeutic indication

- I. Drugs used to treat diseases caused by pathogenic fungi
 1. For systemic or deep mycoses (coccidioidomycosis, paracoccidioidomycosis, histoplasmosis, cryptococcosis, blastomycosis)
 - Antibiotics: amphotericin B [liposomal], Mycoheptin[®]
 - Triazole derivatives: Itraconazole[®], Fluconazole[®]
 - Imidazole derivatives: Ketoconazole[®]
 2. For epidermomycoses (dermatomycoses)
 - Antibiotics: Griseofulvin[®]
 - Allylamine derivatives: Terbinafine[®], Naftifine[®]
 - Triazole derivatives: Itraconazole[®], Fluconazole[®]
 - Imidazole derivatives: Ketoconazole[®], Clotrimazole[®], Miconazole[®]
 - Nitrophenol derivatives: Chlornitrophenol[®]
- II. Drugs used to treat diseases caused by opportunistic fungi (e.g., candidiasis)
 - Antibiotics: Nystatin[®], amphotericin B [liposomal]
 - Triazole derivatives: Fluconazole[®], Itraconazole[®]
 - Imidazole derivatives: Miconazole[®], Clotrimazole[®], Ketoconazole[®]
 - Echinocandins: Caspofungin[®], Micafungin[®]

By mechanism of action

- I. Drugs affecting the structure and function of fungal cell membranes
 1. Ergosterol synthesis inhibitors
 - Triazoles: Itraconazole[®], Fluconazole[®]
 - Imidazoles: Ketoconazole[®], Miconazole[®], Clotrimazole[®]
 - Allylamines: Terbinafine[®], Naftifine[®] (Exoderil[®])
 2. Agents binding to ergosterol and forming pores in the cytoplasmic membrane
 - Antibiotics (polyene antibiotics): amphotericin B [liposomal], Nystatin[®]
- II. Inhibitors of fungal cell wall synthesis (β -glucan synthesis block)
 - Echinocandins: Caspofungin[®], Micafungin[®]
- III. Inhibitors of fungal mitosis
 - Griseofulvin[®]
- IV. Inhibitors of fungal DNA synthesis
 - Flucytosine[®]

Antifungal antibiotics

Polyene antibiotics are products of Actinomycetes (ray fungi). They are substances with a complex chemical structure that contain a polyunsaturated macrocyclic lactone ring. Multiple double (diene) bonds in the structure of the polyene molecule

explain both the name of this drug group and its mechanism of action. Depending on the concentration, they can have both fungistatic and fungicidal effects. They are essentially not absorbed in the GI tract and when administered topically. They cross the BBB poorly.

Mechanism of action: Unsaturated double bonds in the antibiotic molecule bind ergosterol (the main component of the fungal cell membrane), since they have an affinity for sterol elements, disrupt the permeability of the fungal cell wall and change its cytoskeleton (forming hydrophilic pores in the shell). These processes result in an "ionic boom": loss of K^+ and other low-molecular-weight compound and death of the fungal cell. Since there is no ergosterol in the biological membranes of the macro-organism, polyene antibiotics have no specific toxicity in humans.

Spectrum of activity:

- ▶ Systemic use (amphotericin B [liposomal], mycoheptin) is effective against *Candida spp.* (resistant strains occur among *C. lusitaniae*), *Aspergillus spp.* (*A. terreus* may be resistant), *Cryptococcus neoformans* (cryptococcosis), mucormycosis pathogens (*Mucor spp.*, *Rhizopus spp.*, etc.), *Sporothrix schenckii* (sporotrichosis), pathogens of endemic mycoses (*Blastomyces dermatitidis*) (blastomycosis), *Histoplasma capsulatum* (histoplasmosis), *Coccidioides immitis* (coccidioidomycosis), *Paracoccidioides brasiliensis* (paracoccidioidomycosis).
- ▶ *Candida spp.* is predominantly affected by nystatin and natamycin.

Specific properties of individual drugs

Nystatin⁺

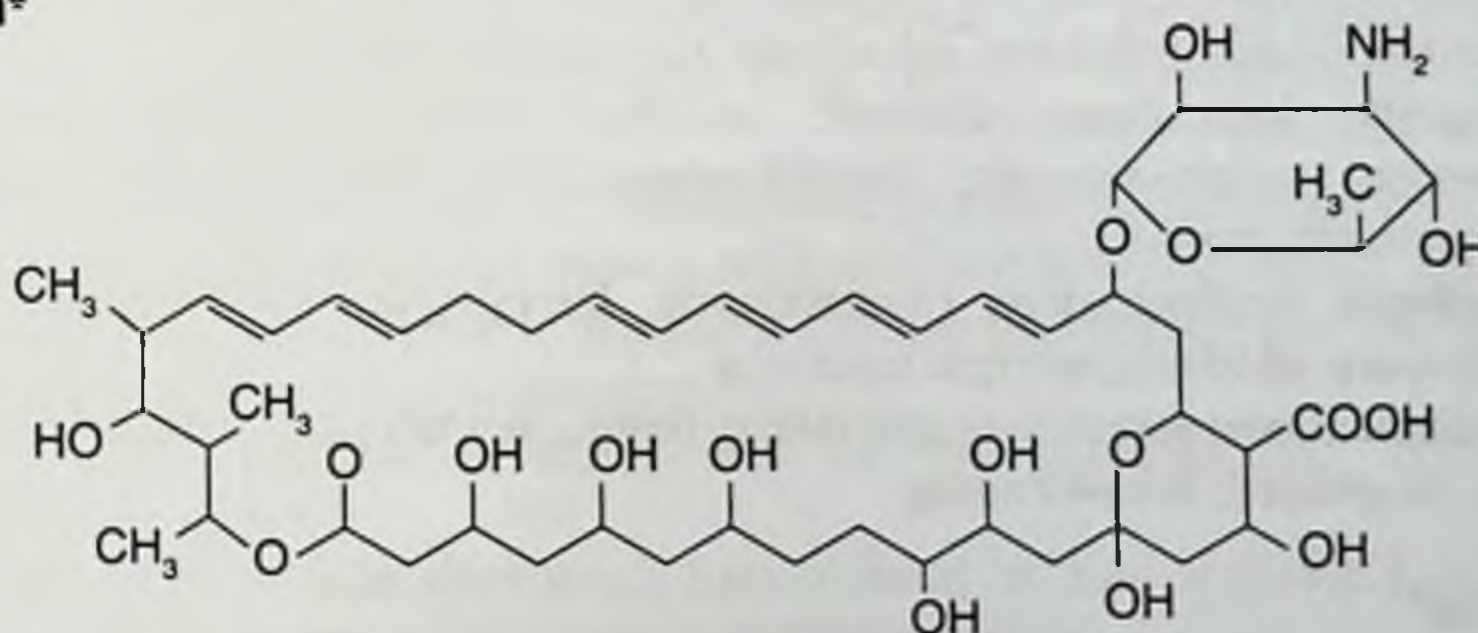


Fig. 22.2. (1S,3R,4R,7R,9R,11R,15S,16R,17R,18S,19E,21E, 25E,27E,29E,31E,33R,35S,36R,37S)-33-[(3-Amino-3,6-dideoxy- β -L-mannopyranosyl)oxy]-1,3,4,7,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo [33.3.1]nonatriaconta-19,21,25,27,29,31-hexaene-36-carboxylic acid

- ▶ Produced by *Streptomyces noursei*. Type of action: fungicidal or fungistatic. Poorly absorbed following oral administration. Does not enter the systemic circulation when used topically. Does not accumulate.
- ▶ Metabolized in the liver. Excreted in bile. For oral, topical administration.

Therapeutic indications: mucosal candidiasis (oral, etc.), genital, cutaneous, gastrointestinal candidiasis

Side effects (oral administration): nausea, vomiting, diarrhea, increased body temperature, allergic reactions

Contraindications: liver failure, gastric and duodenal ulcer, allergic reactions, pregnancy

Amphotericin B [liposomal] (Ampholip⁺)

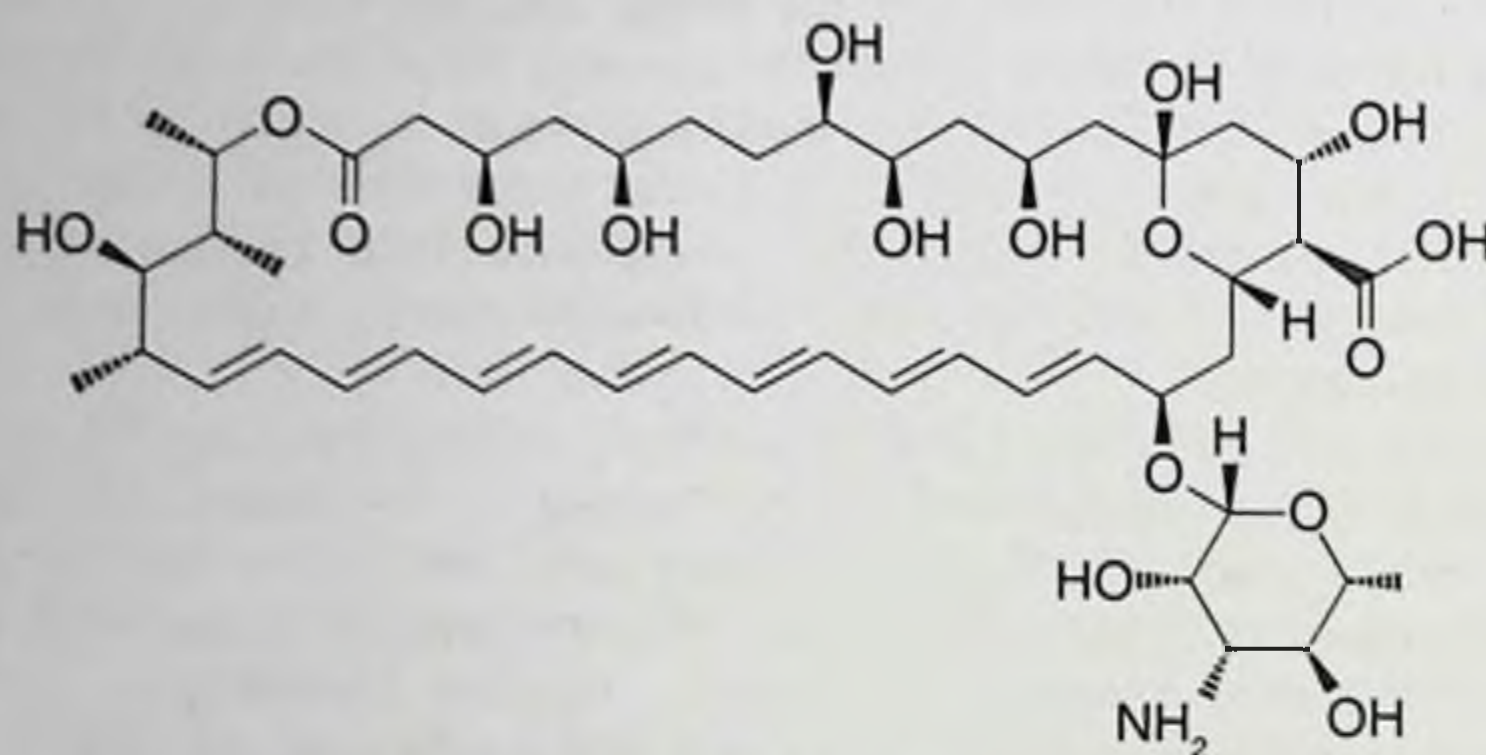


Fig. 22.3. N-(1-Deoxy-D-fructos-1-yl)-N-methyl-, methyl ester, L-aspartate

- ▶ Produced by *Streptomyces nodosum*. Type of action: fungicidal or fungistatic. Essentially not absorbed in the GI tract. Does not cross the BBB, but crosses the placental barrier. Accumulates.
- ▶ Metabolized in the liver. $T_{1/2}$: 15 days. Excreted slowly (in urine). For intravenous, intrathecal administration, inhalation, topical administration.

Therapeutic indications: systemic mycoses (candidamycosis, aspergillosis, histoplasmosis, cryptococcosis, coccidioidomycosis, blastomycosis, pulmonary mycoses (actinomycosis))

Side effects: nephrotoxicity (hypokalemia, hypomagnesemia), hematotoxicity, fever, dyspepsia, phlebitis, allergic reactions

Contraindications: severe liver and kidney failure, hematopoietic disorders, allergic reactions, pregnancy, breastfeeding

Mycoheptin⁺

- ▶ Produced by the actinomycetes *Streptoverticillium mycoheptinicum*. Not completely absorbed in the GI tract.
- ▶ Metabolized in the liver. Excreted in urine. For oral, topical administration.

Therapeutic indications: visceral mycoses (coccidioidomycosis, histoplasmosis, cryptococcosis, aspergillosis, candidiasis, blastomycosis, sporotrichosis, phycomycosis, chromoblastomycosis); interdigital erosion, cheilitis, lesions of skin folds and external genitalia

Side effects: headache, dizziness, nausea, vomiting, diarrhea, nephrotoxicity, allergic reactions

Contraindications: liver and/or kidney failure, gastric and duodenal ulcer, draining wound (ointment), allergic reactions, pregnancy, breastfeeding

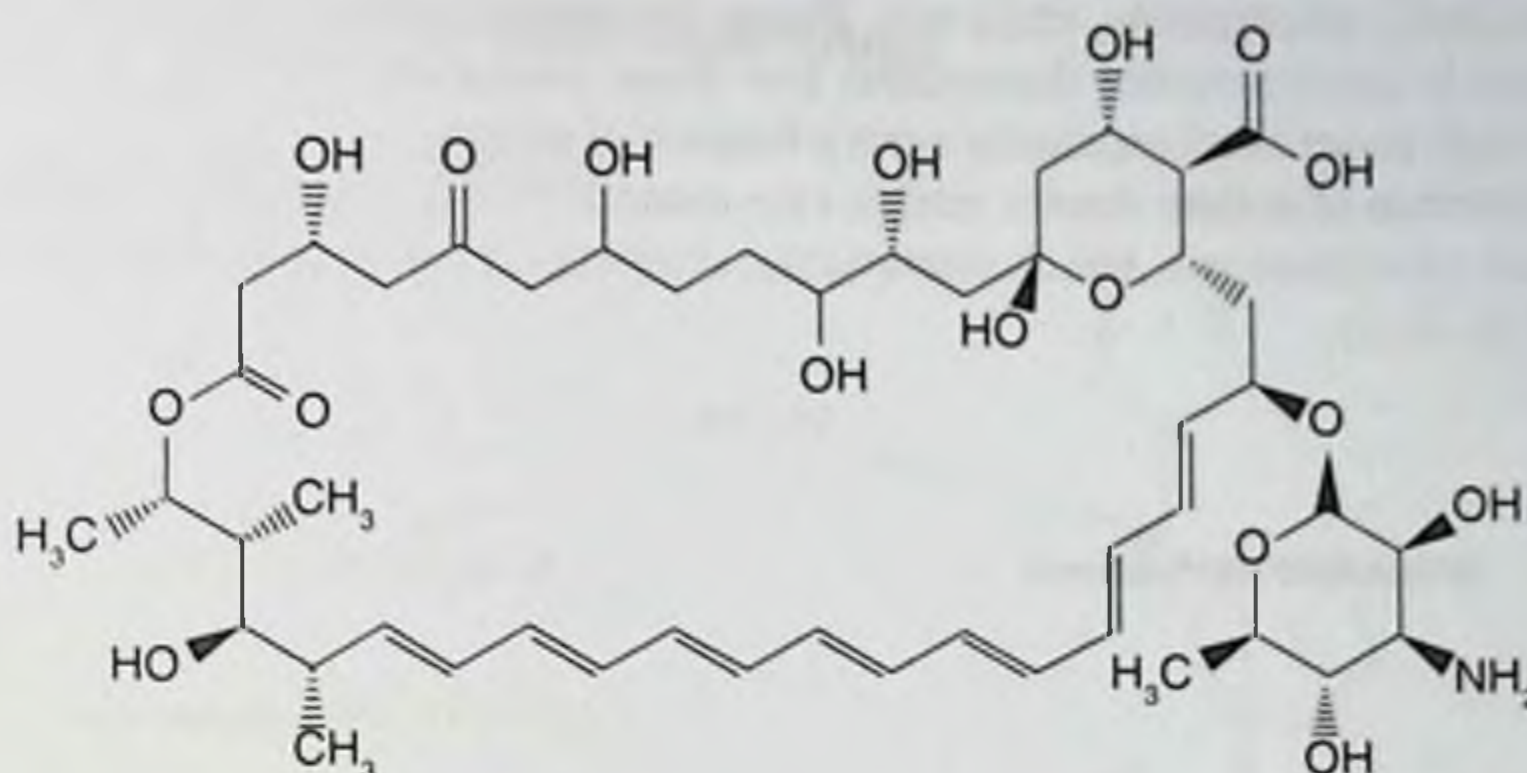


Fig. 22.4. 7-Dihydro-5-dehydrocandidin

Griseofulvin (Fulcin®)

- ▶ Antibiotic produced by *Penicillium nigricans* (griseofulvum). Easily absorbed in the GI tract. Exerts fungistatic action. Accumulates at different concentrations in cells of the skin, hair, and nails.
- ▶ Metabolized in the liver. $T_{1/2}$: 20 hours. Excreted in urine and bile as unchanged drug. For oral, topical administration.

Mechanism of action: affects the microtubule proteins of the fungal cell, resulting in the rupture of spindle-shaped mitotic structures and stopping mitotic cell division in the metaphase; inhibits protein synthesis, disrupts the formation of the cell wall in chitin-containing fungi (fungistatic action).

Spectrum of activity: dermatophytes of the *Trichophyton*, *Microsporum*, *Epidermophyton* genera

Therapeutic indications: dermatophytosis of the scalp, skin, and nails (microsporia, trichophytosis, favus, etc.); tinea pedis and tinea manuum

Side effects: dyspepsia, headache, dizziness, disorientation, leukopenia, allergic reactions

Contraindications: pregnancy, breastfeeding

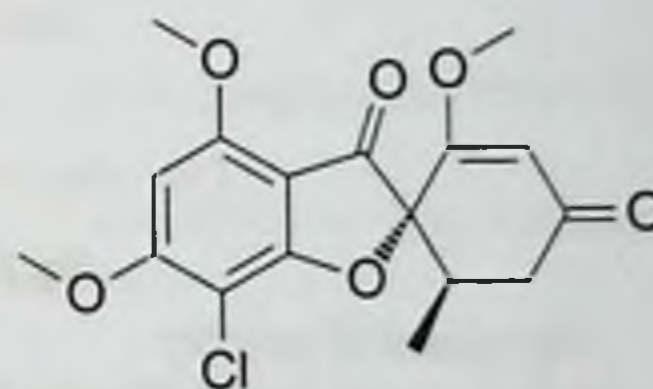


Fig. 22.5. (1'S--trans)-7-Chloro-2',4,6-trimethoxy-6'-methylspiro[benzofuran-2(3H),1'-[2]cyclohexen]-3,4'-dione

Synthetic drugs

Azoles

Azoles (imidazole and triazole derivatives) are the most abundant group of synthetic antifungals. They have a broad spectrum of antifungal activity. Azoles include drugs for systemic (ketoconazole, fluconazole, itraconazole, etc.) and topical

(clotrimazole, miconazole, etc.) use. Fungi are rarely resistant to this drug group. Its action is concentration dependent: low doses predominantly exert a fungistatic action, high doses predominantly exert a fungicidal action.

Mechanism of action: Azoles inhibit 14 α -demethylase (catalyzes the conversion of lanosterol to ergosterol), which disrupts the synthesis of cell membrane ergosterol in fungi (Fig. 22.6).

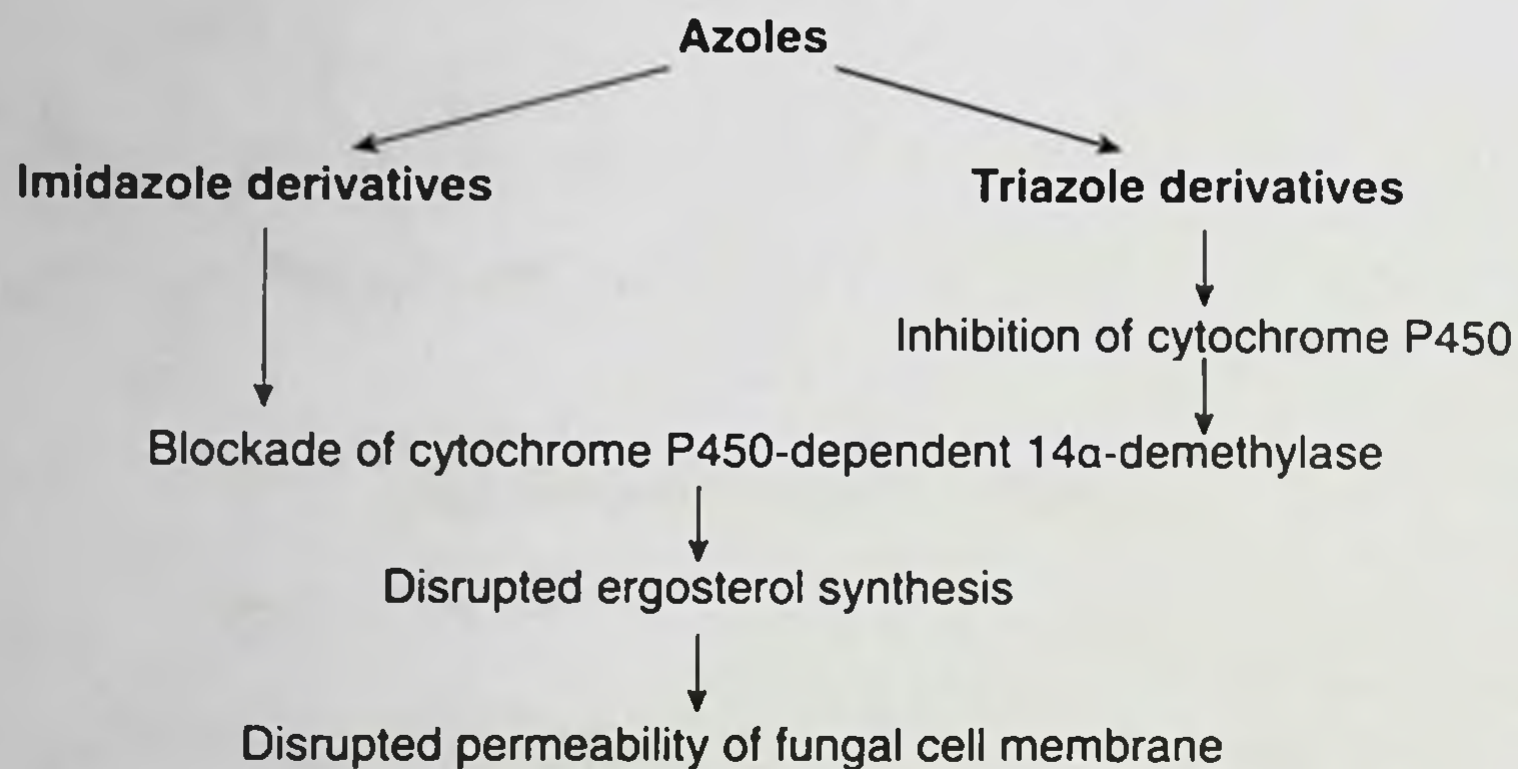


Fig. 22.6. Mechanism of action of azoles

Spectrum of activity

- ▶ Itraconazole is effective against major candidiasis pathogens (*C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. lusitaniae*, etc.), *Aspergillus spp.*, *Fusarium spp.*, *C. neoformans*, dermatomycetes (*Epidermophyton spp.*, *Trichophyton spp.*, *Microsporum spp.*), *S. schenckii*, *P. boydii*, *H. capsulatum*, *B. dermatitidis*, *C. immitis*, *P. brasiliensis*, and other fungi. *C. glabrata* and *C. krusei* often show resistance.
- ▶ Ketoconazole has a similar spectrum of activity to itraconazole but is not effective against *Aspergillus spp.*
- ▶ Fluconazole is most active against the majority of candidiasis pathogens (*C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. lusitaniae*, etc.), *Cryptococcus*, *Coccidioides*, and dermatomycetes. Blastomycetes, *Histoplasma*, *Paracoccidioides*, and *Sporothrix* are less susceptible to it. It is not active against *Aspergillus*.
- ▶ Azoles used for topical administration are predominantly active against *Candida spp.*, dermatomycetes, *M. furfur*. They act against a number of other fungi that cause superficial fungal infections.

Side effects

- ▶ With systemic administration: abdominal pain, loss of appetite, nausea, vomiting, diarrhea; headache, dizziness, somnolence, decreased vision acuity, paresthesia, tremor, seizures; thrombocytopenia, agranulocytosis; increased activity of transaminases, cholestatic jaundice, allergic reactions.
- ▶ With intravaginal administration: pruritus, burning, mucosal hyperemia and edema, vaginal discharge.

Contraindications: allergic reactions, pregnancy, breastfeeding

Specific properties of individual drugs

Ketoconazole (Fungavis⁺, Nizoral⁺)

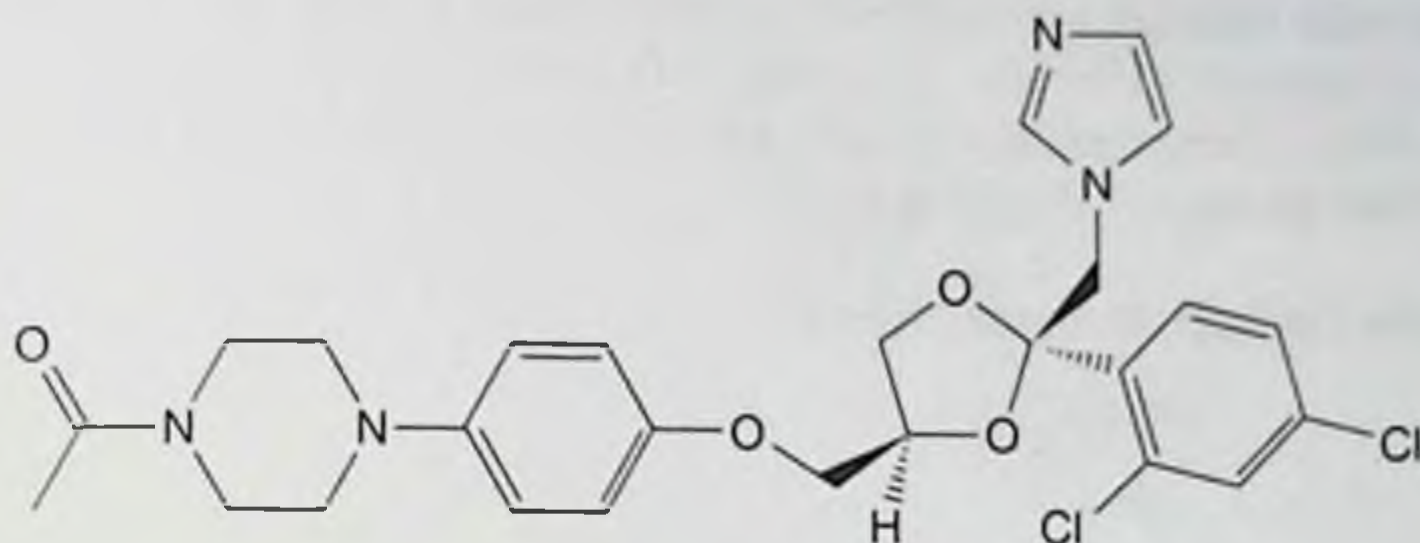


Fig. 22.7. 1-[4-(4-[(2*R*,4*S*)-2-(2,4-Dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl)piperazin-1-yl]ethan-1-one

- ▶ Easily absorbed in the GI tract and distributed in tissues, poorly penetrates the cerebrospinal fluid.
- ▶ Metabolized in the liver to form multiple inactive metabolites. $T_{1/2}$: 8 hours. Excreted in urine and bile. For oral, topical administration.

Therapeutic indications

- ▶ External use: treatment and prophylaxis of fungal lesions of the skin and scalp.
- ▶ Intravaginal administration: treatment of acute and chronic recurrent vaginal candidiasis; prophylaxis of fungal vaginal infections with reduced resistance of the body and during treatment with antibacterial and other drugs interfering with the normal vaginal microflora.
- ▶ For oral administration: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, paracoccidioidomycosis.

Fluconazole (Diflucan⁺, Mycosyst⁺, Flucostat⁺)

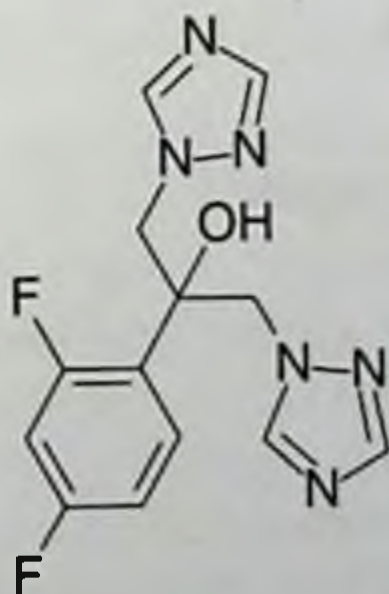


Fig. 22.8. 2-(2,4-Difluorophenyl)-1,3-bis(1*H*-1,2,4-triazol-1-yl)-2-propanol

- ▶ Well absorbed in the GI tract. Distributed in the majority of tissues, organs, and bodily fluids, reaching high concentrations (bioavailability: 90 %). Easily crosses

the BBB (CSF levels can reach 50–90 % of plasma levels) and blood-ocular barrier.

- Metabolized in the liver. $T_{1/2}$: 30 hours. Excreted predominantly in urine as unchanged drug. For oral and intravenous administration.

Therapeutic indications: cryptococcal meningitis, prophylaxis of AIDS-related mycoses, treatment of fungal infections during radiation therapy, treatment with cytostatic drugs, immunosuppressants, antibiotics. Fungal infections of the skin and mucous membranes (GI tract, vagina)

Itraconazole (Itrazol⁺, Rumycos⁺, Irunin⁺)

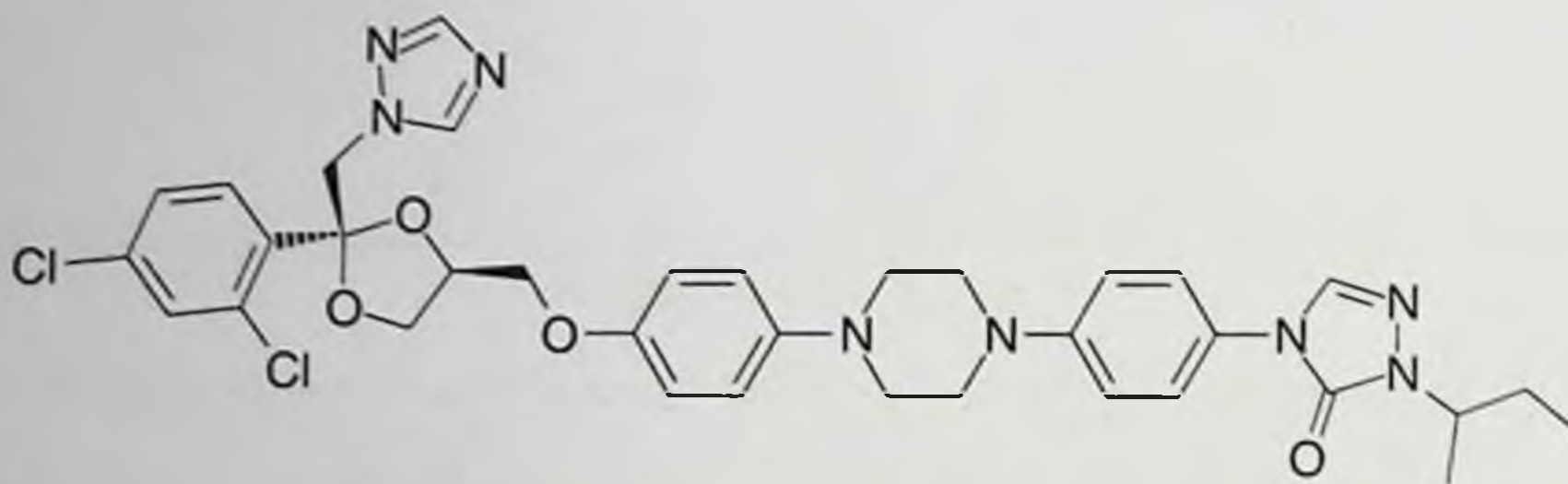


Fig. 22.9. (2''R'',4''S'')-''rel''-4-[4-[4-[4-[[2-(2,4-Dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4,-triazol-3-one

- Easily absorbed in the GI tract. Does not cross the BBB.
- Metabolized in the liver. $T_{1/2}$: 36 hours. Excreted in urine. For oral administration.

Therapeutic indications: treatment and prophylaxis of fungal skin and mucosal infections (vulvovaginal candidiasis; dermatomycoses; tinea versicolor; oral mucosal candidiasis; fungal keratitis); onychomycosis caused by dermatophytes and/or yeasts; systemic mycoses (aspergillosis and candidiasis; cryptococcosis; histoplasmosis; sporotrichosis; paracoccidioidomycosis)

Nitrophenol derivatives

Chloronitrophenol (Nitrofungin⁺)

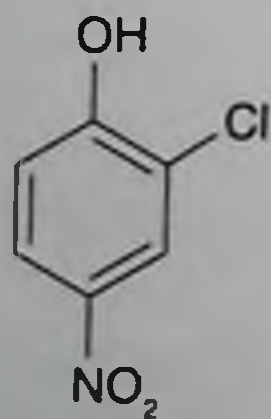


Fig. 22.10. 2-Chloro-4-nitrophenol

For external use.

Spectrum of activity: *Microsporum canis*, *Trichophyton gypseum*, *Candida albicans*; exerts antibacterial action against gram-positive and gram-negative bacteria

Therapeutic indications: fungal skin infections (dermatophytosis caused by *Trichophyton rubrum*, tinea cruris, foot mycoses, trichophytosis, microsporia, candidiasis)

Side effects: local irritation, photodermatitis, allergic reactions

Contraindications: pregnancy, breastfeeding, allergic reactions

Allylamines (N-methylnaphthalene derivatives)

Mechanism of action: Allylamines inhibit squalene epoxidase cells in the endoplasmic reticulum, disrupting the synthesis of ergosterol necessary for formation of the cytoplasmic membrane (Fig. 22.11).

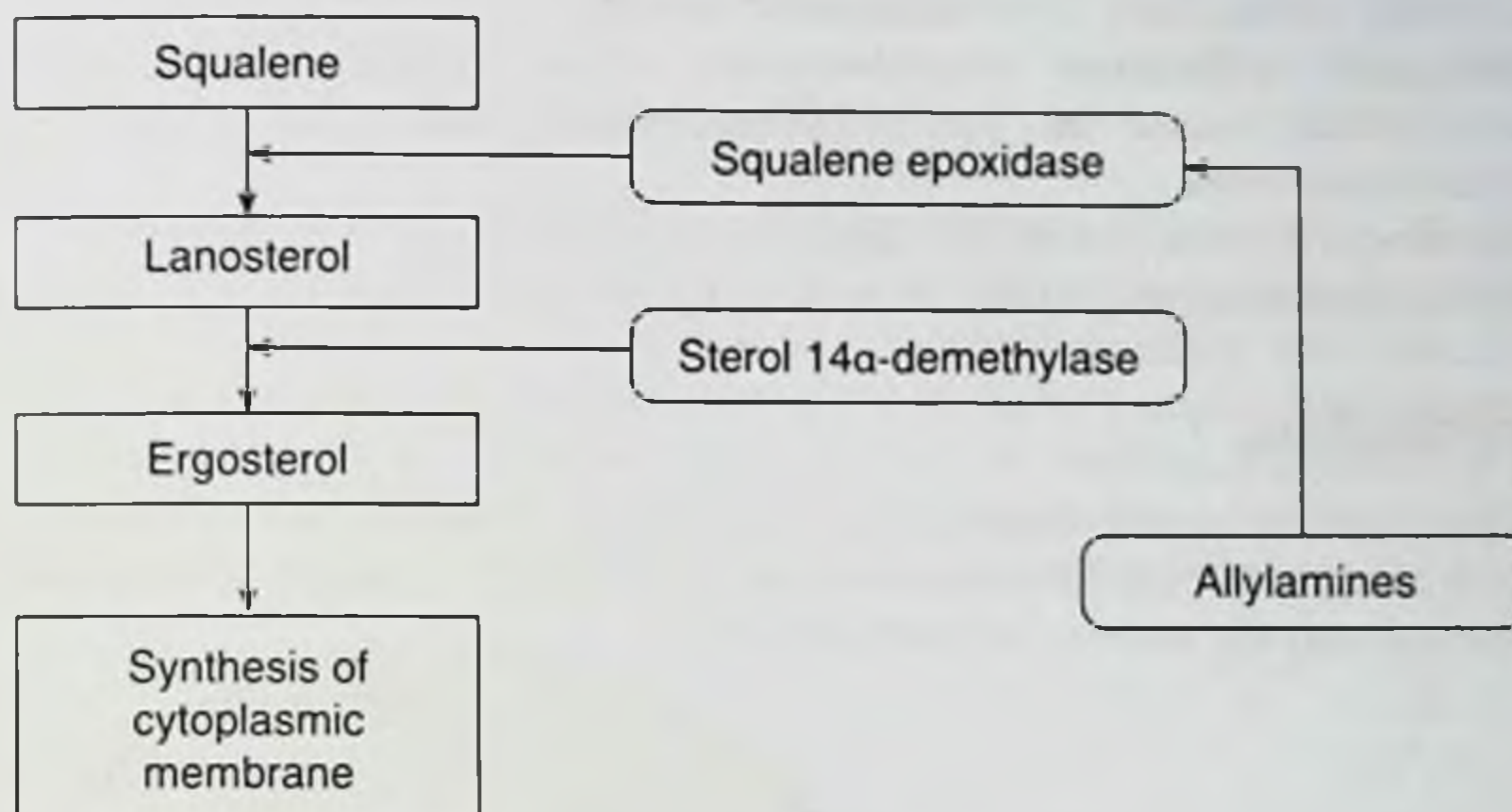


Fig. 22.11. Mechanism of action of allylamines

Terbinafine (Lamisil[®], Binafin[®], Terbisil[®])

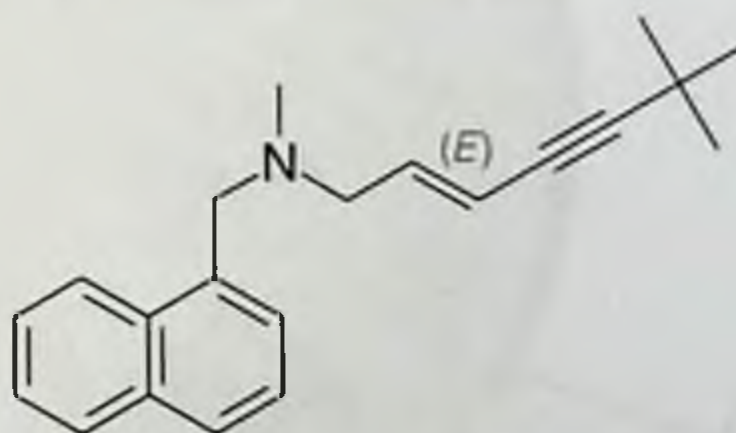


Fig. 22.12. (E)-N-(6,6-Dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine

Depending on the type of yeasts, it exerts fungicidal or fungistatic action. Rapidly absorbed in the GI tract. Crosses the blood-tissue barriers and is distributed in tissues; accumulates in the skin (including sebaceous glands and hair follicles) and subcutaneous tissue at high concentrations. For oral, topical administration.

Spectrum of activity: *Trichophyton* spp. dermatophytes (*Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton verrucosum*, *Trichophyton tonsurans*, *Trichophyton violaceum*), *Microsporum canis*, *Epidermophyton floccosum*, molds (e.g., *Aspergillus*, *Cladosporium*, *Scopulariopsis brevicaulis*), yeasts (*Candida albicans*).

Therapeutic indications: fungal infections of the skin, nails, hair, mucous membranes

Side effects: epigastric pain, dysgeusia, nausea, diarrhea; headache, dizziness, depression; arthralgia, myalgia; skin allergic reactions

Contraindications: liver and/or kidney failure, pregnancy, breastfeeding

Naftifine (Exoderil⁺, Mycoderil⁺)

- ▶ For external use. Easily penetrates the skin, reaching long-lasting antifungal concentrations in its various layers. Exerts fungicidal action against dermatophytes and *Aspergillus*. Exerts fungicidal or fungistatic action against yeasts.
- ▶ Partially metabolized. Excreted in urine and bile.

Therapeutic indications: onychomycosis, tinea versicolor, dermatophytoses, dermatophytosis caused by *Trichophyton rubrum*, trichophytosis, microsporia, cutaneous candidiasis

Side effects: dry and red skin, burning, pruritus at the administration site.

Contraindications: pregnancy, breastfeeding, allergic reactions

Echinocandins

Echinocandins exhibit fungicidal action. They are used to treat systemic fungal infections. Bioavailability following enteral administration is very low; therefore, they are intended only for intravenous administration.

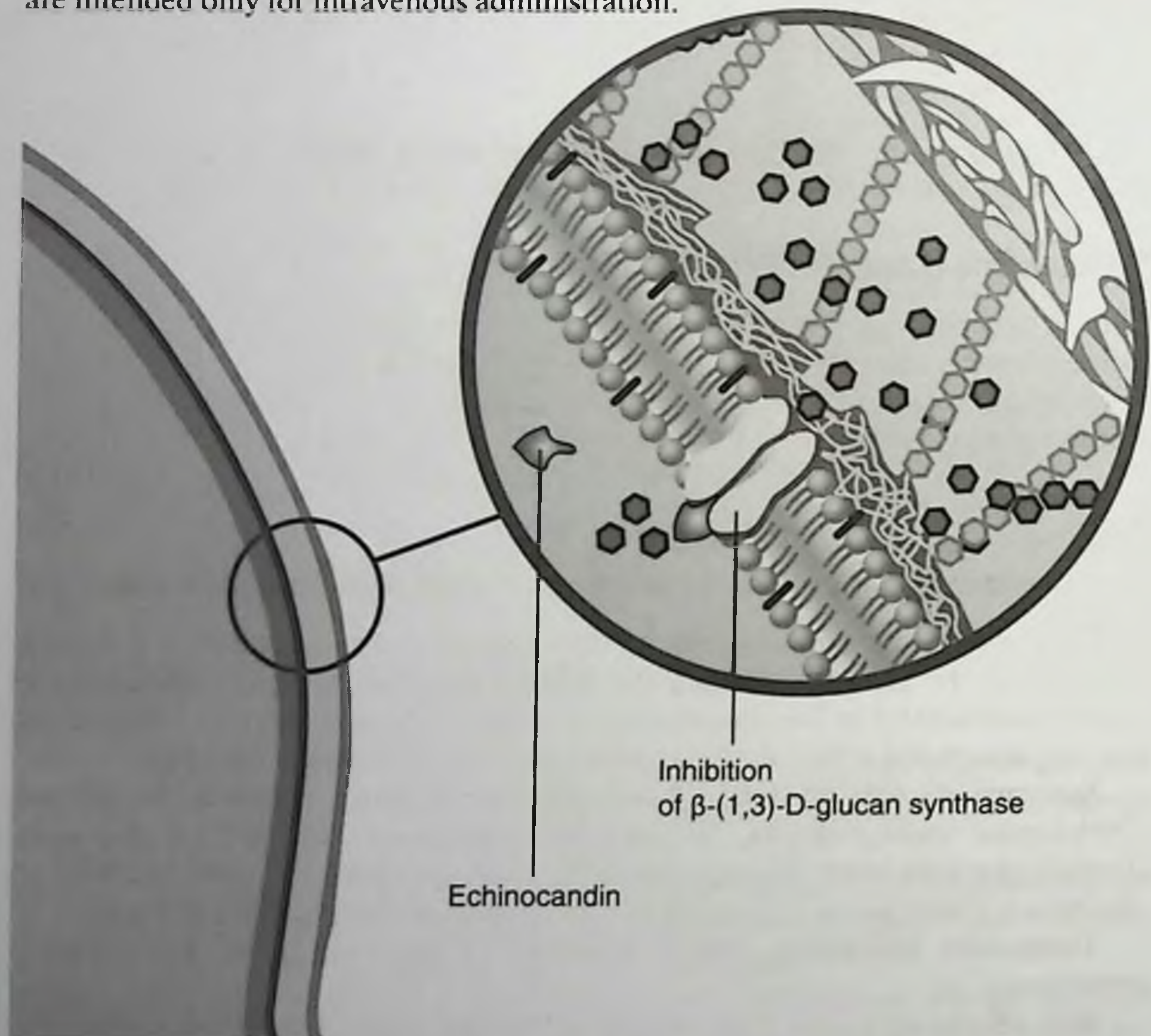


Fig. 22.13. Mechanism of action of echinocandins

Mechanism of action: They inhibit the synthesis of β -(1,3)-D-glucan, the most important component of the fungal cell wall, disrupting its formation (Fig. 22.13).

Spectrum of activity: *Candida spp.*, including strains resistant to azoles (fluconazole, itraconazole) and amphotericin B [liposomal]; *Aspergillus spp.*

Caspofungin (Cancidas⁺, Maxcand⁺)

- ▶ For systemic administration. Semisynthetic lipopeptide compound (echinocandin) synthesized from the product of *Glarea lozoyensis* fermentation.
- ▶ Metabolized in the liver by hydrolysis. Excreted in urine and bile. Plasma concentrations decrease in a multiphasic manner after a single 1 hour intravenous infusion. A short α -phase occurs immediately after infusion, followed by β -phase with $T_{1/2}$ of 9 to 11 hours (plasma concentrations decrease significantly during this period), and an additional γ -phase with $T_{1/2}$ of 40 to 50 hours.

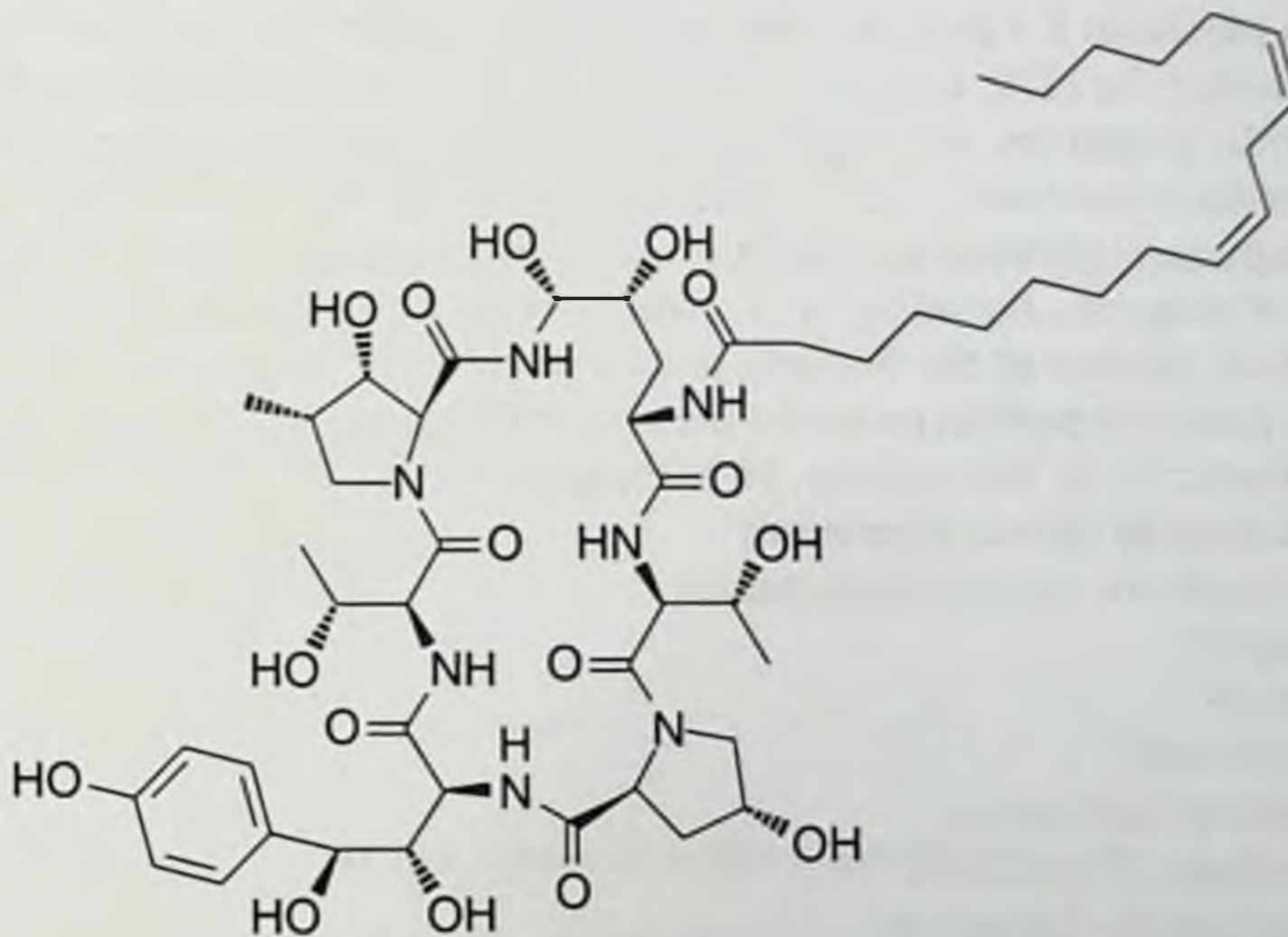


Fig. 22.14. 1-[(4*R*,5*S*)-5-[(2-Aminoethyl)amino]-*N*₂-(10,12-dimethyl-1-oxotetradecyl)-4-hydroxy-L-ornithine]-5-[(3*R*)-3-hydroxy-L-ornithine]pneumocandin B₀ (as an acetate)

Therapeutic indications: empiric therapy in patients with febrile neutropenia when a fungal infection is suspected, invasive candidiasis (including candidemia), invasive aspergillosis, esophageal candidiasis, oropharyngeal candidiasis

Side effects: fever, headache, abdominal pain, vomiting

Contraindications: allergic reactions, pregnancy, breastfeeding

23. ANTISEPTICS AND DISINFECTANTS

Antiseptics are antimicrobial substances that are mainly used externally to treat skin and mucous membranes and to clean wounds.

Disinfectants are chemical substances used to treat surfaces in order to destroy pathogenic microorganisms.

Antiseptics were used even before the role of microorganisms in the development of infections was elucidated. In the 1830s, the Russian pharmacologist A. P. Nelyubin recommended using chlorinated lime to disinfect various items. In the 1840s, the Hungarian physician I. P. Semmelweis suggested that obstetricians use chlorinated lime to disinfect their hands before examining women in labor. In the 1860s, healthcare professionals started using boric acid as an antiseptic in medicine. In 1867, the British physician J. Lister introduced phenol (carbolic acid) as an antiseptic into surgical practice. In 1879, brilliant green was obtained for the first time in Germany. The antiseptic properties of this substance were only discovered in the next century, when it was discovered while staining preparations for microscopy that one of the dyes — brilliant green — destroys microorganisms. In Russia, antiseptics were employed by a number of surgeons, including N. V. Sklifosovsky, C. C. Reyher, S. P. Kolomnin, P. P. Pelekhin (author of the first article on antiseptics in Russia), I. I. Burtsev (first surgeon in Russia to publish on use of the antiseptic method in 1870), L. L. Levshin, N. I. Studensky, N. A. Velyaminov, N. I. Pirogov.

Classification by chemical structure

1. Detergents (or cationic surfactants)

- Cerigel^o
- Roccal^o
- Miramistin⁺

2. Nitrofuran derivatives

- Nitrofurazone (Furacilin⁺).

3. Phenol and its derivatives

- Pure phenol⁺
- Birch tar (Berestin birch tar⁺)
- Ichthammol (Ichthyo⁺)
- Resorcin⁺

4. Dyes

- Brilliant green⁺
- Methylthioninium chloride (Methylene blue⁺)
- Ethacridine lactate^o

5. Halogen-containing compounds

- Chlorhexidine⁺
- Chloramine B⁺
- Iodine alcoholic solution⁺

6. Metal compounds

- Silver nitrate*
 - Copper sulfate*
 - Zinc oxide*
 - Zinc sulfate*
7. Oxidants
- Hydrogen peroxide solution*
 - Potassium permanganate*
8. Aldehydes and alcohols
- Formaldehyde solution, ethanol (Ethyl alcohol*)
9. Acids and alkalis
- Boric acid*
 - Ammonia solution*

A common criterion for evaluating the activity of antiseptics is the so-called **phenol coefficient**: the ratio of the potency of an antiseptic when compared to phenol. A coefficient of 1 means the antiseptic has about the same level of effectiveness as phenol.

Specific properties of individual drugs

Cerigel[®] is a solution for external use that contains cetylpyridinium chloride, polyvinyl butyral, and ethanol.

Cetylpyridinium chloride*

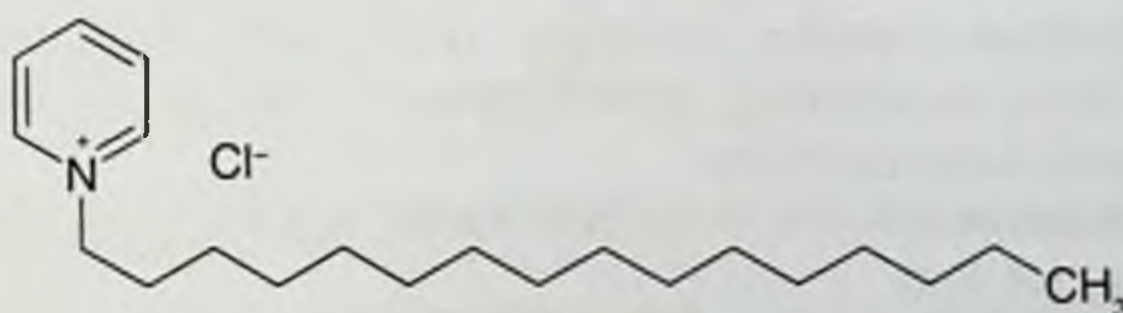


Fig. 23.1. 1-Hexadecylpyridin-1-ium chloride

Quaternary ammonium compound. Acts as a cationic detergent. Exhibits antimicrobial, antifungal, antiviral action.

Mechanism of action: Cetylpyridinium chloride accumulates at the phase boundary (with the microbial cell membrane serving as the medium), disrupts the permeability of microbial cell membranes, and causes the death of microbial cells.

Therapeutic indications: hand disinfection before surgery and medical interventions

Side effects and contraindications: allergic reactions

Miramistin*

Cationic detergent. Exhibits antimicrobial, antifungal, antiviral action. Effective at preventing wound and burn infections. Activates regeneration processes. Stimulates protective reactions at the application site by activating the absorptive and digestive functions of phagocytes, potentiating the activity of the monocyte–macrophage

system. Has a marked hyperosmolar activity, thus relieving wound and perifocal inflammation; it absorbs purulent exudate, facilitating the formation of a dry scab. Does not damage granulation tissue and viable skin cells, does not inhibit marginal epithelialization. Not absorbed through the skin and mucous membranes. Does not cause local irritation or allergic reactions. For topical administration 3–4 times daily.

Mechanism of action: see "Cetylpyridinium chloride"

Miramistin is used in otorhinolaryngology, dentistry, surgery, traumatology, obstetrics, gynecology, burn medicine, dermatology, venereology, and urology for the treatment and prevention of infectious and inflammatory diseases.

Nitrofurantoin (Furacilin[®])

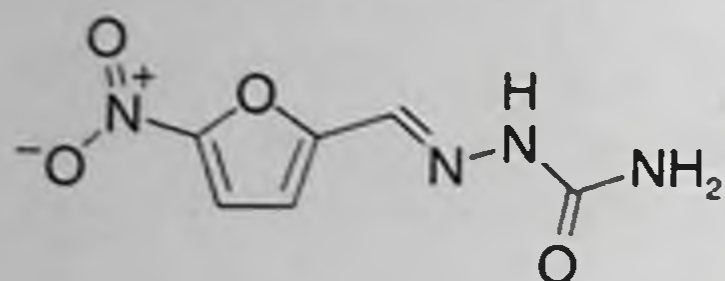


Fig. 23.2. (2E)-2-[(5-Nitro-2-furyl)methylene]hydrazine carboxamide

Nitrofuran derivative. Solution for topical administration. Not absorbed. Exhibits antimicrobial action.

Mechanism of action: See "Synthetic antimicrobials, Nitrofuran derivatives"

Therapeutic indications: treatment of cutaneous and mucosal wounds, cleaning of serous and articular cavities

Side effects: local allergic reactions, dermatitis

Contraindications: allergic dermatosis, hemorrhage

Algipor[®]

Ingredients: sodium alginate, nitrofurantoin (Furacilin[®]). Stimulates regeneration processes, contributes to draining (absorbs wound discharge), accelerates wound cleaning. For topical administration.

Therapeutic indications: 2–3rd degree burns, chronic non-healing wounds, including in cancer patients

Side effects and contraindications: allergic reactions

Birch tar (Berestin birch tar[®])

Liquid for external use. Product derived from distillation of the bark of birch trees. Contains phenol (carbolic acid, the most active aromatic antiseptic) and its derivatives. Exhibits keratoplastic (at low concentrations) or keratolytic (at high concentrations), antiseptic, antiparasitic, drying, anti-inflammatory, local anesthetic, regenerating effects. Used in ointments (e.g., Vishnevsky liniment), pastes and liniments.

Mechanism of action: The action of phenols results in the denaturation of microbial proteins (primarily enzyme proteins).

Therapeutic indications: psoriasis, eczema, neurodermatitis, seborrheic dermatitis

Side effects: burning, folliculitis, allergic reactions

Contraindications: exacerbation of chronic skin disorders, especially with marked exudation; allergic reactions

Ichthammol (Ichthyol⁺)

Antiseptic derived from the distillation of shale oil. Exhibits antibacterial action, exerts anti-inflammatory, local anesthetic, antiseptic, keratoplastic effects. For topical administration.

Mechanism of action: Ichthammol causes denaturation of proteins.

Therapeutic indications: erysipelas, eczema, pyoderma, including furunculosis, stationary and regressive stages of psoriasis; in gynecology: endometritis, salpingitis; in urology: chronic non-specific prostatitis

Side effects and contraindications: allergic reactions

Brilliant green⁺

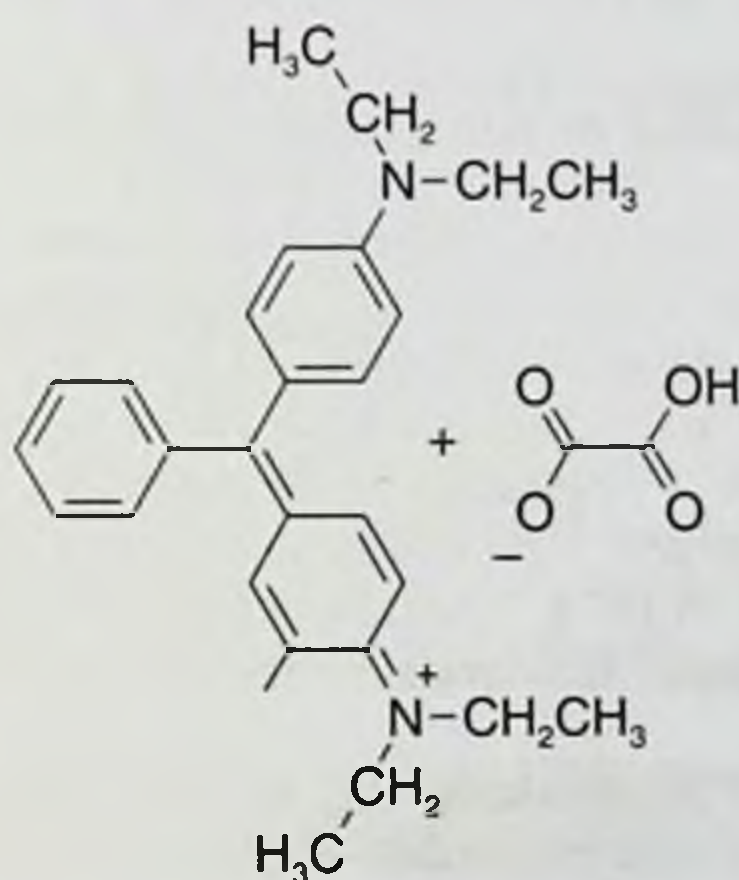


Fig. 23.3. bis-(para-Diethylamine)-triphenyl-hydrocarbinol oxalate

Synthetic aniline based triphenylmethane dye. Used as aqueous or alcohol-based solutions. One of the most highly active and fast-acting antiseptics. Exerts antiseptic, disinfecting, anti-inflammatory action. Exerts antimicrobial action without increasing the interstitial pressure, in contrast with iodine solution. Does not irritate the skin. A 0.05–2.00 % solution of brilliant green is used as a drug product, and a solution in isopropanol or ethanol is used in pencils (works like a marker pen).

Mechanism of action: Dehydrogenation of microbial proteins by dye cations

Therapeutic indications: 1–2 % aqueous and alcohol-based solutions: fresh postoperative and post-traumatic scars, meibomitis (stye), blepharitis, pyoderma, abrasions, cuts, erysipelas, folliculitis

Side effects: burning at the application site, lacrimation in case of contact with the conjunctiva

Contraindications: allergic reactions, dermatitis

Chlorhexidine*

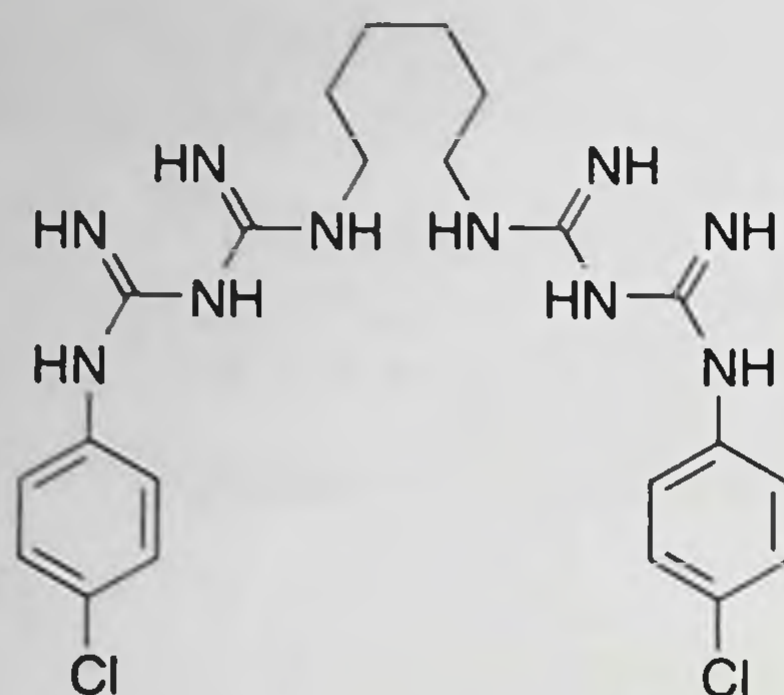


Fig. 23.4. N,N"-bis(4-Chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecanediimidamide (as an acetate, dihydrochloride, or di-D-gluconate)

Biguanide derivative containing chlorine. Has a marked surface activity and exerts antimicrobial action similar to that of quaternary ammonium compounds. Solution for topical and external use. Bacteriostatic action occurs at concentrations of 0.01 % or less, bactericidal action occurs at concentrations exceeding 0.01 % at 22 °C and 1 min exposure. Fungicidal action occurs at a concentration of 0.05 % at 22 °C and 10 min exposure. Virucidal action (against lipophilic viruses) occurs at concentrations of 0.01–1.00 %. Remains active in the presence of blood, pus, various secretions and organic substances. Does not cause damage to glass, plastic, and metal objects.

Mechanism of action: Chlorhexidine interacts with phosphate groups on the cell surface, which results in a shift in osmotic equilibrium, disruption of cell integrity and cell death.

Therapeutic indications: disinfection of hands, surgical site, injection site; wound infections, oral mucosal diseases, prophylaxis of sexually transmitted diseases; surface disinfection for small medical devices (when heat treatment is undesirable)

Side effects: dry and itchy skin, dermatitis, dysgeusia (when treating oral mucosal diseases)

Contraindications: dermatitis, allergic reactions

Iodine alcoholic solution*

Solution for external use 5 %. The main active ingredient is molecular iodine. Exerts antibacterial, locally irritating, cauterizing (at high concentrations) action. Alcohol slows down the excretion of iodine and reduces its irritating effect on tissues. Excreted in urine (predominantly), bile, sweat.

Mechanism of action: Iodine alcoholic solution coagulates proteins to form iodamines.

Therapeutic indications: infectious and inflammatory skin disorders; abrasions, cuts; inflammatory infiltrates; treatment of wound edges, skin prior to injection, puncture, catheterization

Side effects: skin irritation, allergic reactions

Contraindications: allergic reactions

Silver nitrate (AgNO_3)⁺

Heavy metal compound. Exhibits antibacterial, anti-inflammatory, and cauterizing (at high concentrations) action.

Mechanism of action: Binds sulfhydryl and carboxyl groups, which can cause changes in protein conformation, structure, or denaturation. When silver nitrate dissociates, silver ions cause protein precipitation and bactericidal action. Silver albuminate formed as a result of the interaction of silver nitrate with tissue proteins blocks certain enzyme systems, disrupting metabolic processes in the microbial cell. Thus, silver nitrate produces a short-term bactericidal effect and then exerts a long-term bacteriostatic effect.

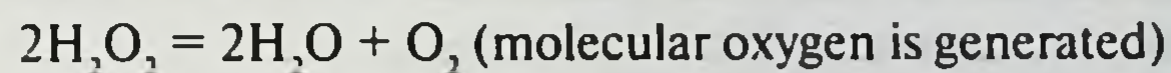
Therapeutic indications: erosions, ulcers, excessive granulation, fissures

Side effects and contraindications: allergic reactions

Hydrogen peroxide solution (H_2O_2)

Oxidizer. Short-acting. Exhibits antiseptic, astringent, anti-inflammatory, cauterizing, deodorizing, bleaching, disinfecting action. The antimicrobial activity of molecular oxygen is significantly lower than that of atomic oxygen. Therefore, H_2O_2 is mainly used for the mechanical debridement of wounds since it produces foam and bubbles. It increases blood coagulation by promoting the conversion of fibrinogen to fibrin.

Mechanism of action: When applied to tissues in the presence of proteins, hydrogen peroxide is cleaved under the influence of catalase with the release of molecular oxygen:



Molecular oxygen destroys oxidizing substrates in microorganisms, which ultimately results in their death.

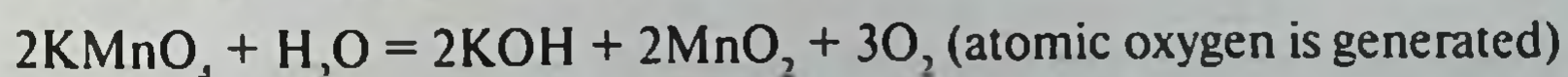
Therapeutic indications: inflammatory diseases of mucous membranes (stomatitis, tonsillitis, gynecological disorders), purulent wounds, capillary bleeding from superficial wounds, nosebleeds

Side effects and contraindications: allergic reactions

Potassium permanganate (KMnO_4)

Oxidizer. Exerts more pronounced but shorter-term antiseptic action than hydrogen peroxide. Exhibits astringent (at low concentrations), irritating, cauterizing, tanning (at high concentrations), deodorizing effects.

The mechanism of action is based on its potent oxidizing properties. In the presence of organic substances, KMnO_4 detaches atomic oxygen, and the oxide forms complex compounds (i.e. albuminates) with proteins:



Atomic oxygen is the strongest antiseptic and deodorizing agent, while manganese dioxide is astringent and cauterizing (with tissue proteins producing dense albuminates).

Therapeutic indications: infected wounds, skin ulcers and burns; infectious inflammatory diseases of the mouth and oropharynx; gynecological and urological diseases; gastric lavage for poisoning caused by alkaloids (morphine, nicotine), hydrogen cyanide, phosphorus

Side effects and contraindications: allergic reactions

Ethanol (Ethyl alcohol*) (C_2H_5OH)

Solution for external use. Exhibits antimicrobial, antiseptic (70 % solution), tanning (90–95 %), locally irritating action.

Mechanism of action: Ethanol coagulates microbial cell proteins.

Therapeutic indications: disinfection of a surgical site and pre-surgical disinfection of the surgeon's hands (70 % solution is used for better penetration into deeper layers of the epidermis); early stage of inflammatory skin disorders (furuncle, whitlow)

Side effects and contraindications: allergic reactions

Boric acid (H_3BO_3)

Alcohol-based solution for topical administration. Lipophilic. Easily penetrates cells. Exhibits anti-inflammatory, astringent, cauterizing (coagulative necrosis with formation of a dry scab) effects.

Mechanism of action: Boric acid coagulates proteins (including enzymes) in the microbial cell, disrupting the permeability of the cell wall.

Therapeutic indications: otitis externa (acute and chronic) without involvement of the eardrum, bacterial or fungal stomatitis (2 % solution), bad breath; as an antiseptic or antipruritic when rubbing healthy skin areas around superficial pyoderma lesions.

Side effects: irritation at the application site

Contraindications: allergic reactions, perforated eardrum; pregnancy, breastfeeding

24. ANTHELMINTICS

Anthelmintics are drugs used to expel parasitic worms (helminths) from the body.

Diseases occurring as a result of getting infected with helminths are called helminthiasis.

These infections can be intestinal or extraintestinal, depending on where the helminths are located in the human body, with roundworms (nematodes) and flatworms, i.e. tapeworms (cestodes) and flukes (trematodes), as the pathogens.

Nematode infections include intestinal infections — ascariasis, enterobiasis, ancylostomiasis, dracunculiasis, necatoriasis, strongyloidiasis — and extraintestinal infections (filariasis) — filariasis due to *Wuchereria bancrofti*, filariasis due to *Brugia malayi*, loiasis, onchocerciasis.

Cestode infections include alveolar hydatid disease, diphyllbothriasis, mesocystoidiasis, taeniarhynchosis, taeniasis, cysticercosis, echinococcosis.

Trematode infections include opisthorchiasis, fascioliasis, cercarial dermatitis, schistosomiasis.

Classification.

- a) anthelmintics used for nematode infections: piperazine adipate (Piperazine[®]), pyrantel (Pyrantel pamoate[®]), mebendazole (Vermox[®]), albendazole (Nemazole[®]), levamisole (Decaris[®])
- b) anthelmintics used for cestode infections: niclosamide (Phenasal[®]), aminoacrichine
- c) anthelmintics used for extraintestinal (tissue) helminthiasis: diethylcarbamazine citrate[®] (ditrazin citrate[®], loskuran[®]), sodium antimonyl tartrate[®] (antimony sodium tartrate[®]), praziquantel (Biltricide[®])

Anthelmintics used for nematode infections

Specific properties of individual drugs

Piperazine adipate (Piperazine[®])

Rapidly absorbed in the GI tract, excreted predominantly in urine. A single dose is completely eliminated within 24 hours. Dehelmintization in ascariasis is 90–100 %. For oral administration.

Mechanism of action: Piperazine adipate has a paralyzing effect on nematodes (*Ascaris lumbricoides*, *Enterobius vermicularis*), disrupting their neuromuscular functions; the resulting muscle paralysis prevents their movement through the intestine and their penetration into the bile ducts. This creates favorable conditions for

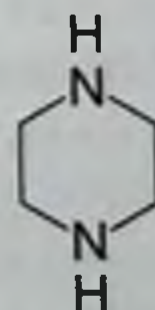


Fig. 24.1. 1,4-Diazacyclohexane

living helminths to be eliminated from the intestine (no risk of absorption of biological toxic degradation products).

Spectrum of activity: *Ascaris lumbricoides*, *Enterobius vermicularis*

Therapeutic indications: ascariasis and enterobiasis

Side effects: dyspepsia, headache

Contraindications: organic CNS lesions, chronic kidney disease, pregnancy, breastfeeding

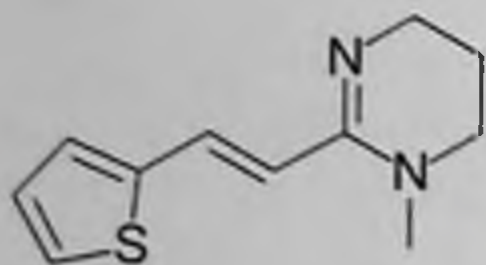


Fig. 24.2. (E)-1,4,5,6-Tetrahydro-1-methyl-2-[2-(2-thienyl)ethenyl]pyrimidine (as an embonate or tartrate)

Pyrantel (Pyrantel pamoate⁺)

Pyrimidine derivative. Poorly absorbed in the GI tract. Partially metabolized in the liver to N-methyl-1,3-propanediamine. About 93 % of the oral dose is excreted in bile as unchanged drug, with 7 % excreted in urine as unchanged drug or its metabolite. For oral administration.

Mechanism of action: Pyrantel disrupts nematode neuromuscular transmission, inhibits cholinesterase, and causes spastic muscle paralysis.

Spectrum of activity: *Ascaris lumbricoides*, *Enterobius vermicularis*, *Ancylostoma*, and other nematodes

Therapeutic indications: ascariasis, enterobiasis, ancylostomiasis, trichuriasis

Side effects: abdominal pain, anorexia, nausea, vomiting, diarrhea, headache, dizziness, somnolence

Contraindications: myasthenia gravis, liver failure, pregnancy, breastfeeding

Mebendazole (Vermox⁺)

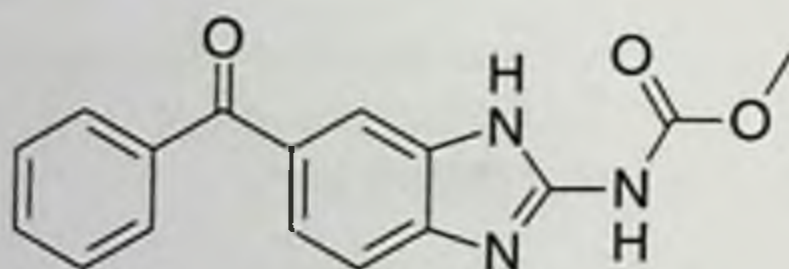


Fig. 24.3. 5-benzoyl-1H-benzimidazol-2-yl carbamic acid methyl ester

Imidazole derivative. Slowly and not completely absorbed in the GI tract. Bioavailability increases when taken with food, especially fatty foods. Maximum blood concentrations are reached in 2–5 hours. Accumulates in the liver, adipose tissue, parasitic cysts. Crosses the placental barrier. Partially metabolized in the liver. More than 90 % is excreted in bile. $T_{1/2}$: 2.5–5.5 hours. For oral administration.

Mechanism of action: Mebendazole causes irreversible disruption of glucose utilization, depletes glycogen stores in helminth tissues, inhibits cellular tubulin synthesis, and inhibits ATP synthesis, which causes degenerative alterations in the tegument and intestinal cells of helminths and results in paralysis and death of the parasite.

Spectrum of activity: *Ascaris lumbricoides*, *Enterobius vermicularis*, *Ancylostoma*, *Trichuris trichiura*, *Trichinella*, and other nematodes; larval stages of certain cestodes (*Echinococcus*, *Echinococcus multilocularis*)

Therapeutic indications: enterobiasis, ascariasis, ancylostomiasis, trichuriasis, trichinosis, echinococcosis, alveolar hydatid disease, polyinvasion

Side effects: abdominal pain, diarrhea, nausea, vomiting, headache, dizziness, neutropenia

Contraindications: non-specific ulcerative colitis, Crohn's disease, pregnancy, breastfeeding

Albendazole (Nemozole[®])

Benzimidazole derivative. Poorly absorbed in the GI tract. Undergoes biotransformation during the first pass through the liver to form the active metabolite albendazole sulfoxide, which produces the systemic anthelmintic action. Maximum blood concentrations are reached in 2–5 hours.

High concentrations are reached in the liver, bile. Excreted in urine. $T_{1/2}$ of the metabolite: 8–12 hours. Induces P450 cytochrome. For oral administration.

Mechanism of action: Albendazole disrupts the activity of the microtubular system of helminth intestinal cells, causing damage to the tubulin protein. This results in biochemical alterations in the cell (inhibition of glucose and fumarate reductase) and suppression of cell division during metaphase, which is associated with inhibition of oviposition and development of helminth larvae. Albendazole blocks the movement of secretory granules and other organelles in the muscle cells of roundworms, causing their death.

Spectrum of activity: *Ascaris lumbricoides*, *Enterobius vermicularis*, *Ancylostoma*, *Strongyloides stercoralis*, *Trichuris trichiura*, *Trichinella*, and other nematodes, *Echinococcus*, *Taenia solium*

Therapeutic indications: ascariasis, ancylostomiasis, strongyloidiasis, trichinosis, trichuriasis, toxocariasis, enterobiasis, echinococcosis, neurocysticercosis, polyinvasion

Side effects: abdominal pain, dyspepsia, headache, dizziness; increased transaminases, alkaline phosphatase activity; bone marrow suppression (neutropenia, thrombocytopenia, leukopenia, granulocytopenia)

Contraindications: retinopathy, pregnancy, breastfeeding

Levamisole (Decaris[®])

Benzimidazole derivative. Levamisole is highly and rapidly absorbed in the GI tract. Peak blood concentrations are reached in 1.5–2.0 hours. Metabolized in the liver to form inactive metabolites, excreted predominantly in urine. $T_{1/2}$: 3–4 hours. Exerts an immunomodulatory effect. For oral administration.

Mechanism of action: Levamisole causes depolarizing neuromuscular paralysis of the muscle membrane of helminths, blocks succinate dehydrogenase, and inhibits fumarate dehydrogenase, disrupting bioenergetic processes in helminths.

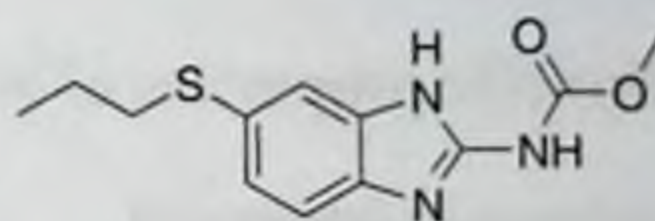


Fig. 24.4. [5-(Propylthio)-1H-benzimidazole-2-yl]carbamic acid methyl ester

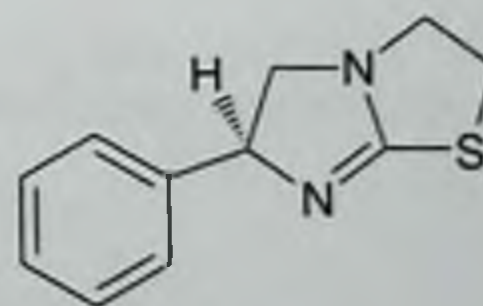


Fig. 24.5. (S)-2,3,5,6-Tetrahydro-5-phenylimidazo[2,1-b]thiazole (as a hydrochloride)

Spectrum of activity: *Ascaris lumbricoides*, *Enterobius vermicularis*

Therapeutic indications: ascariasis (drug of choice), enterobiasis

Side effects: abdominal pain, dyspepsia, leukopenia

Contraindications: agranulocytosis, pregnancy, breastfeeding

Anthelmintics used for cestode infections

Specific properties of individual drugs

Niclosamide (Phenasal[®])

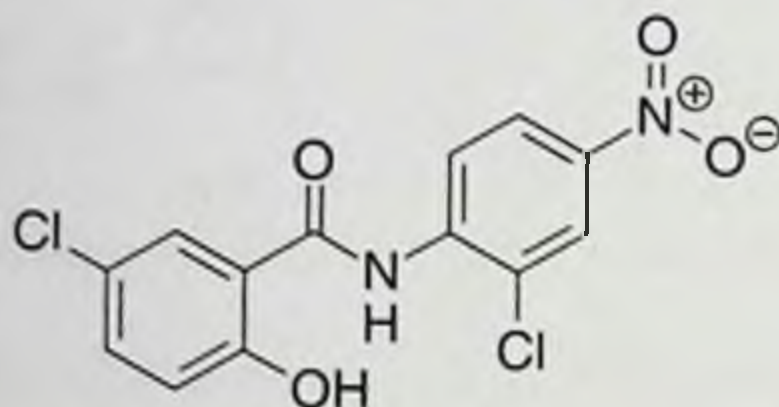


Fig. 24.6. 5-Chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide

Salicylanilide derivative. Essentially not absorbed in the GI tract. Excreted in bile. For oral administration.

Mechanism of action: Niclosamide inhibits oxidative phosphorylation in cestodes, exerts paralytic action, decreases the helminths' resistance to proteolytic enzymes in the GI tract which destroy cestodes.

Spectrum of activity: *Taenia saginata*, *Hymenolepis nana*, *Diphyllobothrium latum*

Therapeutic indications: taeniarhynchosis, diphyllobothriasis, hymenolepiasis

Side effects: abdominal pain, nausea, allergic reactions

Contraindications: gastric and duodenal ulcer, anemia, taeniasis (risk of cysticercosis), pregnancy, breastfeeding

Aminoacrichine[±]

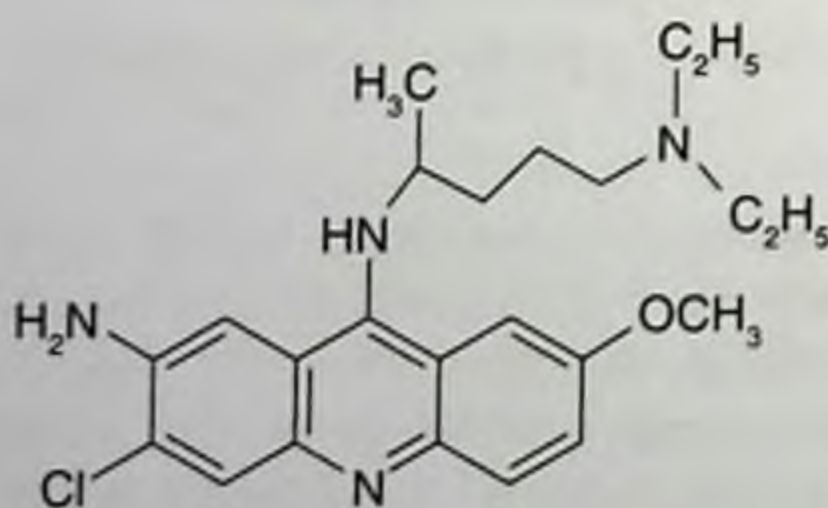


Fig. 24.7. 2-Methoxy-6-chloro-7-amino-9-(1-methyl-4-diethylaminobutylamino)-acridine dihydrochloride

Drug whose efficacy is inferior to that of Phenasal[®].

Mechanism of action: Aminoacrichine causes muscle paralysis in intestinal cestodes, certain trematodes, *Ancylostoma* hookworms.

Therapeutic indications: cestode infections (second-line drug)

Side effects: nausea, vomiting, abdominal pain

Contraindications: taeniasis (risk of cysticercosis), pregnancy, breastfeeding

Anthelmintics used for extraintestinal (tissue) helminthiases

Specific properties of individual drugs

Praziquantel (Biltricide[®])

Isoquinoline derivative. Well absorbed in the GI tract, forms a complex with plasma proteins (80 %). Metabolized in the liver, excreted in urine. $T_{1/2}$: 1.0–2.5 hours. For oral administration.

Mechanism of action: Praziquantel increases the permeability of helminth cell membranes for Ca^{2+} ions, which causes generalized contraction of parasite muscles and inhibits glucose uptake by helminth cells, thus reducing glycogen levels and stimulating the release of lactic acid.

Spectrum of activity: cestodes and trematodes

Therapeutic indications: cestode infections (taeniarhynchosis, taeniasis, diphyllorhynchiasis, hymenolepiasis, cysticercosis); trematode infections (opisthorchiasis, clonorchiasis, paragonimiasis, schistosomiasis)

Side effects: abdominal pain, dyspepsia, headache

Contraindications: cysticercosis of the eye, pregnancy, breastfeeding

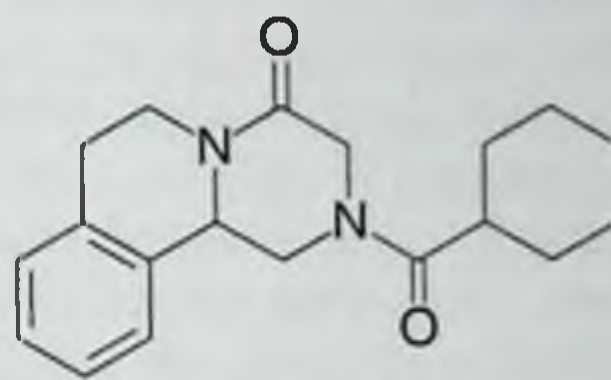


Fig. 24.8. 2-(Cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one

Diethylcarbamazine citrate[®] (Ditrazin citrate[®], Loskuran[®])

Well absorbed in the GI tract. Maximum plasma concentrations are reached in 3 hours. Excreted in urine as metabolites and partially as unchanged drug. For oral administration.

Mechanism of action: Diethylcarbamazine citrate disrupts neuromuscular transmission in helminths and causes their death.

Spectrum of activity: Filariidae

Therapeutic indications: systemic filariasis, ascariasis

Side effects: headache, weakness, nausea, vomiting, allergic reactions

Contraindications: onchocerciasis with eye lesions, pregnancy, breastfeeding

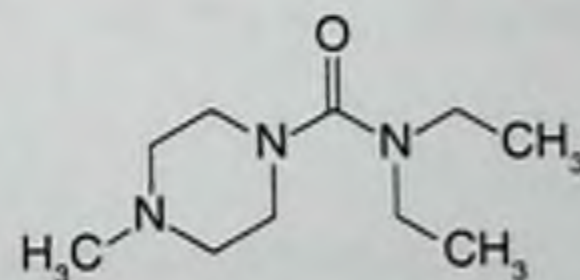


Fig. 24.9. 1-Methyl-4-diethylcarbamoylpiperazine citrate

25. ANTIVIRAL DRUGS

Antiviral drugs directly affect viral replication. They act on a virus-specific target in their replication cycle.

Thiosemicarbazone was the first drug proposed as a specific antiviral drug. Its virucidal action was described by German pathologist and bacteriologist G. Domagk in 1946. The compound 1,4-benzoquinone-guanyl-hydrazinothio-semicarbazone, a derivative of this group, is used under the name "Faringosept" as lozenges for the treatment of upper respiratory tract infections. Later, methisazone was synthesized, which effectively suppressed the replication of pox viruses; the nucleoside idoxuridine suppressing the herpes simplex virus was synthesized in 1959. Idoxuridine was followed by other nucleosides [aciclovir, ribavirin (Ribamidil[®]), etc.] and then by rimantadine in 1965. In 1967, the key role of high-molecular-weight double-stranded RNA in IFN induction was demonstrated and the search began for the most active drugs for clinical use. In the 1980–1990s, it was established that the action of a number of immunostimulants and antiviral drugs [Poludan[®] (polyadenylic acid, polyuridylic acid), umifenovir (Arbidol[®]), etc.] is due to their interferogenic activity. Russian researchers have developed a number of synthetic and natural drugs for systemic and topical use [bromnaphthoquinone (Bonaphton[®]), umifenovir (Arbidol[®]), dioxotetrahydroxytetrahydronaphthalene (Oxolin[®]), deitiforin, tebropfen, tetrahydroxyglucopyranosylxanthene (Alpizarin[®]), etc.].

Classification by stage of viral replication cycle targeted

- ▶ M₂ proton channel inhibitors
 - Rimantadine (Remantadin[®], Orvirem[®])
 - Amantadine (PK-Merz[®], Midantan[®])
- ▶ Maturation inhibitors
 - HIV protease inhibitors: Saquinavir (Invirase[®])
 - DNA or RNA synthesis inhibitors: aciclovir, vidarabine[®], riamilovir (Triazavirin[®])
 - Reverse transcriptase inhibitors: zidovudine
- ▶ Inhibitors of virus release
 - Neuraminidase inhibitors: zanamivir (Relenza[®]), oseltamivir (Tamiflu[®])
- ▶ Antiviral drugs with various mechanisms of action
 - Interferon alfa-2a
 - Interferon alfa-2b
 - Interferon inducers: tilorone (Lavomax[®], Amixin[®]), meglumine acridonacetate (Cycloferon[®]), Poludan[®] (polyadenylic acid, polyuridylic acid)
 - Other: umifenovir (Arbidol[®])

Classification by clinical use

1. Influenza antiviral drugs

- M₂ proton channel inhibitors: rimantadine (Remantadin[®], Orvirem[®])
- Inhibitors of nucleic acid synthesis: vidarabine[®]
- Neuraminidase inhibitors: zanamivir (Relenza[®]), oseltamivir (Tamiflu[®])

2. Herpes antiviral drugs

- Inhibitors of nucleic acid synthesis: aciclovir (Zovirax[®]), valaciclovir (Valtrex[®])
3. Antiretroviral drugs
- Nucleoside/nucleotide reverse transcriptase inhibitors: zidovudine (Azidothymidine[®], Retrovir[®])
 - Protease inhibitors: saquinavir (Interfast[®])
4. Broad spectrum drugs
- Interferons
 - Interferon alfa-2a, interferon alfa-2b, pegylated interferon alfa (2a or 2b)
 - Interferon inducers
 - Tilorone (Lavomax[®], Amixin[®]), meglumine acridonacetate (Cycloferon[®]), Poludan[®] (polyadenylic acid, polyuridylic acid)
 - Other: umifenovir (Arbidol[®])

Specific properties of individual drugs

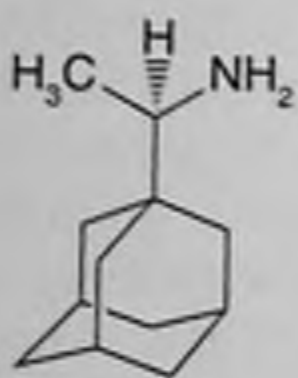


Fig. 25.1. α -Methyl-tricyclo[3.3.1.1^{3,7}]decane-1-methanamine (as a hydrochloride)

Rimantadine (Remantadin[®], Orvirem)

Mechanism of action: The M2 membrane protein that functions as an ion channel is present in the influenza A virus. Rimantadine inhibits the early stage of replication (after viral entry into the cell and prior to initial RNA transcription). It induces production of alpha and gamma interferons. Rimantadine blocks fusion of the virion coat to the endosome membrane, thus preventing transfer of viral genetic material into the cell cytoplasm. It also inhibits the release of viral particles from the cell, i.e., it interrupts viral genome transcription.

- ▶ It is essentially completely absorbed in the GI tract; meals do not affect bioavailability. Maximum blood concentrations are reached in 2–4 hours. High concentrations are reached in the nasal mucus, saliva and tear fluid. Crosses the BBB and placental barrier.
- ▶ Metabolized in the liver. $T_{1/2}$: 1.0–1.5 days, excreted in urine predominantly as inactive metabolites.

Spectrum of activity: influenza A virus

Therapeutic indications: treatment and prophylaxis of illness caused by influenza A virus

Side effects: abdominal pain, loss of appetite, nausea, somnolence, insomnia, headache, dizziness

Contraindications: hypersensitivity, breastfeeding

Vidarabine[®]

Mechanism of action: Phosphorylated in the cell to form a triphosphate derivative, which inhibits viral DNA polymerase, preventing elongation of the DNA chain.

- ▶ Vidarabine is distributed in the aqueous humor of the eye chamber (ensuring corneal integrity if the corneal epithelium is intact), in bodily tissues and fluids; it crosses the BBB and placental barrier. The concentration of arabinosyl hypoxanthine in the cerebrospinal fluid is about 35 %. $T_{1/2}$: 1.5 hours for

vidarabine, 3.3 hours for arabinosyl hypoxanthine. Excreted predominantly in urine. For intravenous, topical administration.

Spectrum of activity: *Herpes simplex*, *Varicella zoster*.

Therapeutic indications: illness caused by type 1 and 2 Herpes simplex; keratitis, keratoconjunctivitis, recurrent genital herpes, encephalitis

Side effects (intravenous administration): dyspepsia (nausea, vomiting, diarrhea), skin rash, hallucinations, psychosis, tremor, hepatic dysfunction, thrombophlebitis

Contraindications: allergic reactions, pregnancy, breastfeeding

Zanamivir (Relenza⁺)

Mechanism of action: This is a highly selective neuraminidase (influenza virus surface enzyme) inhibitor. Replication of the influenza virus is restricted to surface epithelial cells in the respiratory tract. Zanamivir exerts its action in the extracellular space, reducing the replication of both types of influenza viruses (A and B) and preventing viral particles from exiting the cells of the respiratory tract.

- ▶ Bioavailability following inhalation: 15 %.
- ▶ $T_{1/2}$: 2 hours. Excreted in urine. For intranasal and inhaled administration.

Spectrum of activity: influenza A and B viruses

Therapeutic indications: treatment and prophylaxis of infections caused by influenza A and B virus

Side effects: nausea, vomiting, headache, dizziness

Contraindications: allergic reactions

Oseltamivir (Tamiflu⁺)

Its chemical structure and action are similar to those of zanamivir. Oseltamivir in the phosphate form is a prodrug that is converted to the active form — oseltamivir carboxylate — by hydrolysis in the liver. Oseltamivir carboxylate is an anti-influenza neuraminidase inhibitor that affects the release of viral particles.

- ▶ 75 % of the dose enters the bloodstream as a metabolite, with less than 5 % entering it as oseltamivir.
- ▶ Excreted predominantly in urine. $T_{1/2}$ of oseltamivir: 1–3 hours, $T_{1/2}$ of its metabolite: 6–10 hours. For oral administration.

Spectrum of activity: influenza A and B viruses

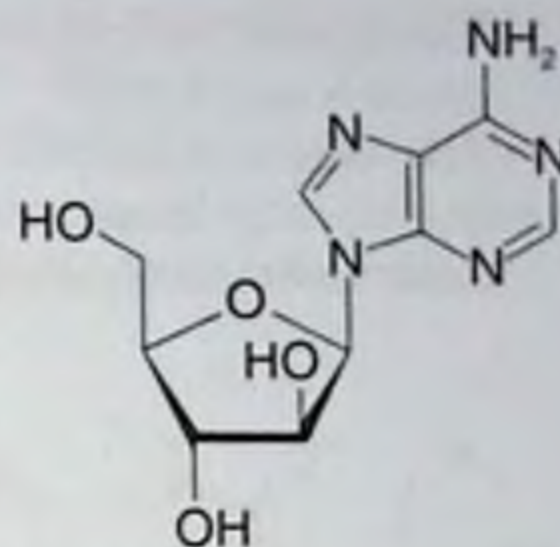


Fig. 25.2. (2R,3S,4S,5R)-2-(6-Amino-9H-purin-9-yl)-5-(hydroxymethyl)oxolane-3,4-diol hydrate

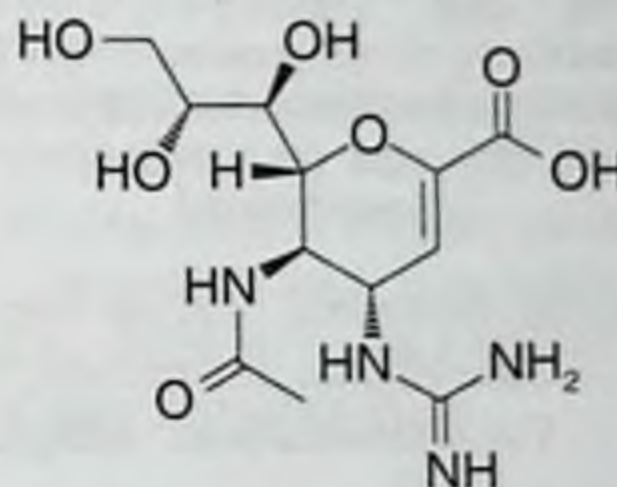


Fig. 25.3. (2R,3R,4S)-4-[(Diaminomethyliden)amino]-3-acetamido-2-[(1R,2R)-1,2,3-trihydroxypropyl]-3,4-dihydro-2H-pyran-6-carboxylic acid

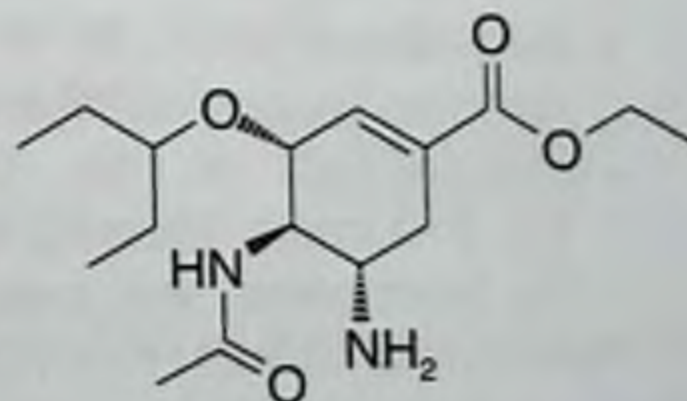


Fig. 25.4. (3R,4R,5S)-4-(Acetylamino)-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid ethyl ester (and as a phosphate)

Therapeutic indications: treatment and prophylaxis of infections caused by influenza A and B virus

Side effects: dyspepsia, headache, dizziness, general weakness, insomnia, nasal congestion, sore throat, cough, allergic reactions

Contraindications: allergic reactions, severe kidney and liver failure

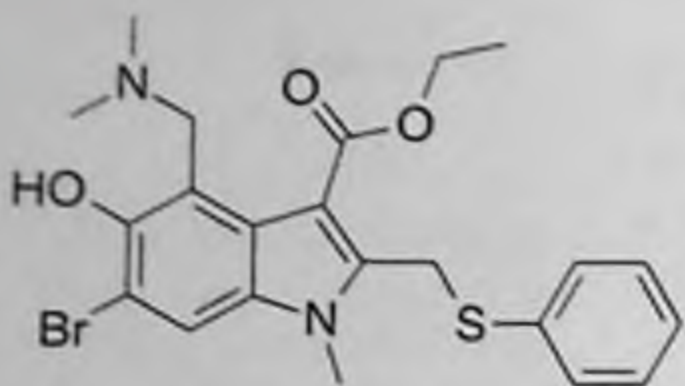


Fig. 25.5. 6-Bromo-5-hydroxy-1-methyl-4-dimethylaminomethyl-2-phenylthiomethylindole-3-carboxylic acid ethyl ester (as a hydrochloride monohydrate)

Umifenovir (Arbidol⁺)

- ▶ Indolecarboxylic acid derivative. Viral neuraminidase inhibitor. Has interferon-inducing activity, stimulates cellular and humoral immunity.
- ▶ Rapidly absorbed in the GI tract. Partially metabolized in the liver. About 40 % is excreted as unchanged drug, predominantly in bile. $T_{1/2}$: 17 hours. For oral administration.

Spectrum of activity: influenza A and B viruses

Therapeutic indications: prophylaxis and treatment of illness caused by influenza A and B virus, treatment of acute respiratory infections

Side effects: allergic reactions (rash, urticaria, etc.)

Contraindications: allergic reactions, pregnancy

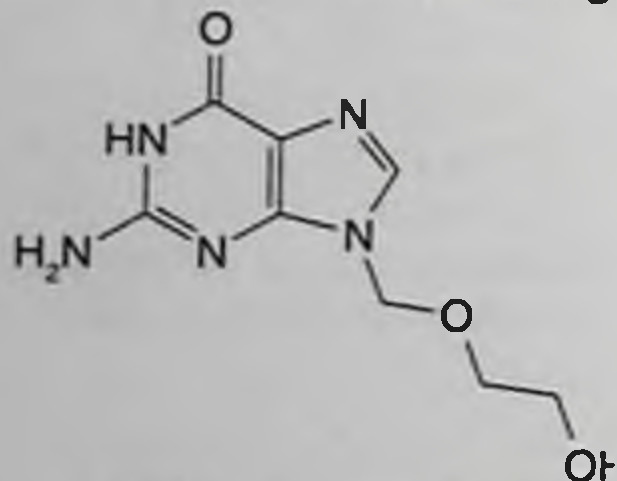


Fig. 25.6. 2-Amino-9-((2-hydroxyethoxy)methyl)-1,9-dihydro-6H-purin-6-one

Aciclovir (Zovirax⁺)

Synthetic purine nucleoside analog.

Mechanism of action: Aciclovir triphosphate — the active metabolite of aciclovir formed in cells affected by the herpes virus after its phosphorylation — has antiviral action. Aciclovir triphosphate interacts with viral DNA polymerase; it is incorporated into the viral DNA chain, blocking further replication of viral DNA without damaging the host cells.

- ▶ Bioavailability: 15–20 %. Well distributed in the body. Crosses the BBB, placental barrier, excreted into breast milk.

- ▶ Metabolized in the liver to form 9-carboxymethoxymethylguanine. $T_{1/2}$: 2–3 hours. Excreted in urine, with 60–90 % excreted as unchanged drug. For intravenous, oral, topical administration.

Spectrum of activity: type 1 and type 2 herpes simplex virus, varicella zoster virus, Epstein–Barr virus, and cytomegalovirus

Therapeutic indications: infections caused by type 1 and type 2 herpes simplex virus (skin and mucosal infections, eye herpes, genital herpes, herpes simplex encephalitis, neonatal herpes); infections caused by *Varicella zoster* (herpes zoster [shingles], chickenpox, pneumonia, encephalitis); prophylaxis of cytomegalovirus infection after kidney transplantation; topical treatment of skin and mucosal infections caused by herpes simplex virus

Side effects: burning after applying to mucous membranes; with intravenous administration: headache, dizziness, nausea, vomiting, diarrhea

Contraindications: allergic reactions, pregnancy, breastfeeding

Valaciclovir (Valtrex[®])

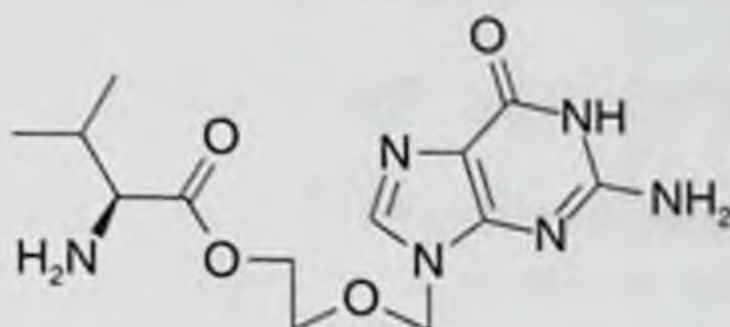


Fig. 25.7. L-Valine 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl ester (as a hydroxide)

- ▶ Bioavailability: 54 %. Rapidly and almost completely converted to aciclovir and L-valine by the liver enzyme, valacyclovir hydrolase.
- ▶ Excreted in urine as aciclovir (> 80 % of the dose) and its metabolites. $T_{1/2}$: about 3 hours. For oral administration.

Spectrum of activity: cytomegalovirus, varicella zoster virus, herpes simplex virus

Therapeutic indications: herpes zoster [shingles], treatment and prophylaxis of herpes infections of the skin and mucosal membranes; prophylaxis of infections caused by cytomegalovirus and diseases following solid organ transplantation

Side effects and contraindications: see "Aciclovir"

Zidovudine (Azidothymidine[®], Retrovir[®])

Nucleoside derivative, thymidine analog.

Mechanism of action: Zidovudine blocks HIV (human immunodeficiency virus) reverse transcriptase and selectively inhibits viral DNA replication. It is metabolized by enzymes to form triphosphates, which exhibit pharmacological activity. Its ability to inhibit HIV reverse transcriptase is hundreds of times greater than its ability to inhibit human DNA polymerase. Zidovudine is active in HIV-infected T cells and macrophages, inhibiting the early stages of the viral life cycle.

- ▶ Well absorbed in the GI tract (bioavailability: 54–74%), crosses the BBB, placental barrier.
- ▶ About 75 % of zidovudine is metabolized in the liver to form azidothymidine glucuronide. $T_{1/2}$: 3 hours. Excreted in urine.

Spectrum of activity: HIV-1 and HIV-2

Therapeutic indications: early and late stages of HIV infection, prophylaxis of transplacental transmission of HIV

Side effects: anemia, neutropenia, thrombocytopenia, pancytopenia, headache, insomnia, myalgia, nausea and vomiting

Contraindications: allergic reactions to zidovudine, severe neutropenia, hypochromic anemia

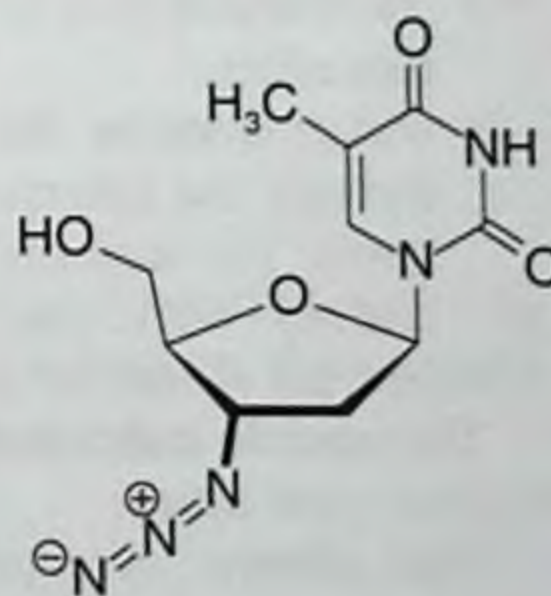


Fig. 25.8. 3'-Azido-3'-deoxythymidine

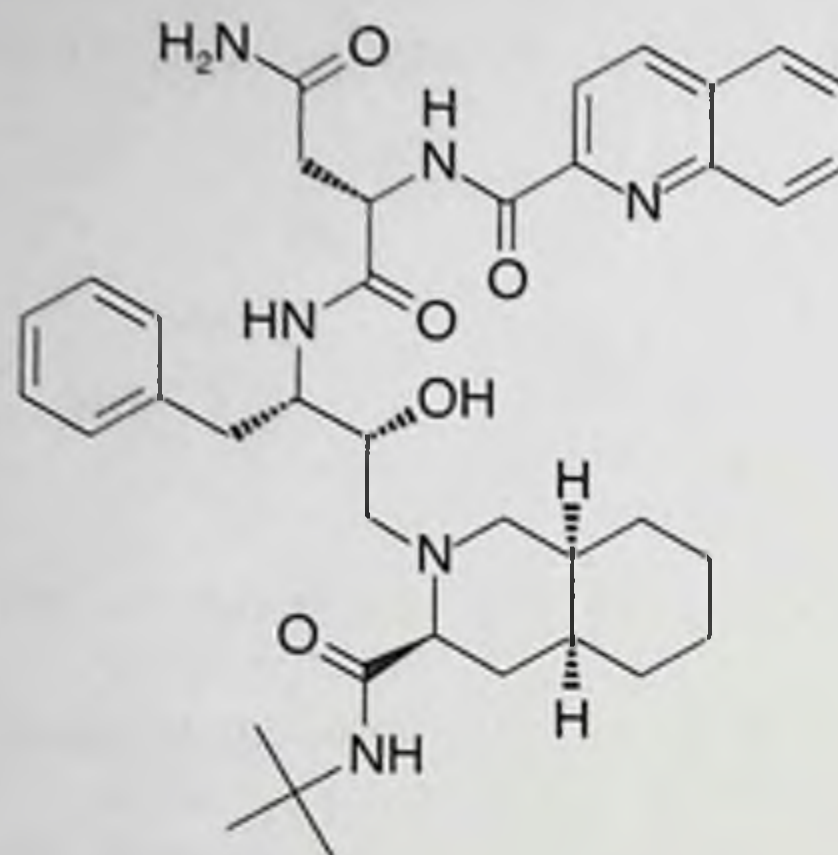
Saquinavir (Invirase®)

Fig. 25.9. (2S)-N-[(2S,3R)-4-[(3S)-3-(Tert-butylcarbamoyl)-decahydroisoquinolin-2-yl]-3-hydroxy-1-phenylbutan-2-yl]-2-(quinolin-2-ylformamido)butanediamide

Mechanism of action: Saquinavir has a direct inhibitory action on viral enzymes without any prior metabolic transformations. It inhibits HIV-1 and HIV-2 protease, the cleavage of viral precursor proteins in infected cells, and the formation of active proteins necessary for the final formation of viral particles that can cause an infection.

- ▶ 30 % is absorbed in the GI tract, but bioavailability is only 4 % due to the first-pass effect.
- ▶ Metabolized in the liver to inactive mono- and dihydroxylated derivatives through the cytochrome P450 system and by the CYP3A4 isoenzyme. $T_{1/2}$: 7 hours. The majority of saquinavir and its metabolites are excreted in bile. For oral administration.

Spectrum of activity: HIV-1 and HIV-2

Therapeutic indications: treatment of HIV infection in combination with other antiretroviral drugs

Side effects: dyspepsia, increased AST and ALT activity, hyperglycemia, peripheral neuropathy, paresthesia, thrombocytopenia, headache

Contraindications: QT prolongation, bradycardia, decompensated chronic heart and liver failure, less than 18 years of age

Interferons

Interferons (IFNs) are biologically active proteins or glycoproteins that are synthesized by the human cells as a protective response to a viral infection or antigenic action.

IFNs are divided into three types based on their structure and biological properties. Recombinant IFN- α s are widely used as antiviral drugs. Depending on the amino acid content, there are interferon alpha-2a and interferon alpha-2b. Pegylated IFNs (with longer $T_{1/2}$, high clinical efficacy, no peak plasma/tissue concentrations, low

toxicity and immunogenicity) are synthesized by adding polyethylene glycol to the IFN molecule.

Classification.

- ▶ Recombinant interferons: interferon alfa-2a, interferon alfa-2b (Altevir[®], Viferon[®], Grippferon[®])
- ▶ Pegylated interferons: peginterferon alfa-2a (40 kDa) (Pegasys[®]), peginterferon alfa-2b (Pegintron[®])

Mechanism of action: Inhibition of viral protein synthesis and viral replication. Recombinant IFN- α s have the same basic properties as natural human IFNs. They exert antiviral action by inducing a state of resistance to viral infections in cells and modulating the immune system response to neutralize viruses or destroy the infected cells.

- ▶ Bioavailability: 80 %, maximum blood concentrations are reached in 3.8 hours on average.
- ▶ They undergo rapid inactivation in the kidneys and to a lesser extent in the liver. $T_{1/2}$: 2–4 hours. For intramuscular, subcutaneous, intravenous administration.

Therapeutic indications for recombinant IFN- α s: chronic hepatitis B and D, acute and chronic hepatitis C

Therapeutic indications for pegylated IFNs: chronic hepatitis B and C

Side effects: influenza-like illness (fever, myalgia); neurological disorders, bone marrow suppression

Contraindications: neutropenia, thrombocytopenia, decompensated cardiovascular disease, pregnancy, autoimmune diseases

Interferon inducers (interferonogens)

IFN inducers stimulate the synthesis of their own IFNs with antiviral action by affecting all parts of the viral process; they increase cellular cytotoxicity, the synthesis of antibodies and interleukins, phagocytic activity.

Tilorone (Lavomax[®], Amixin[®])

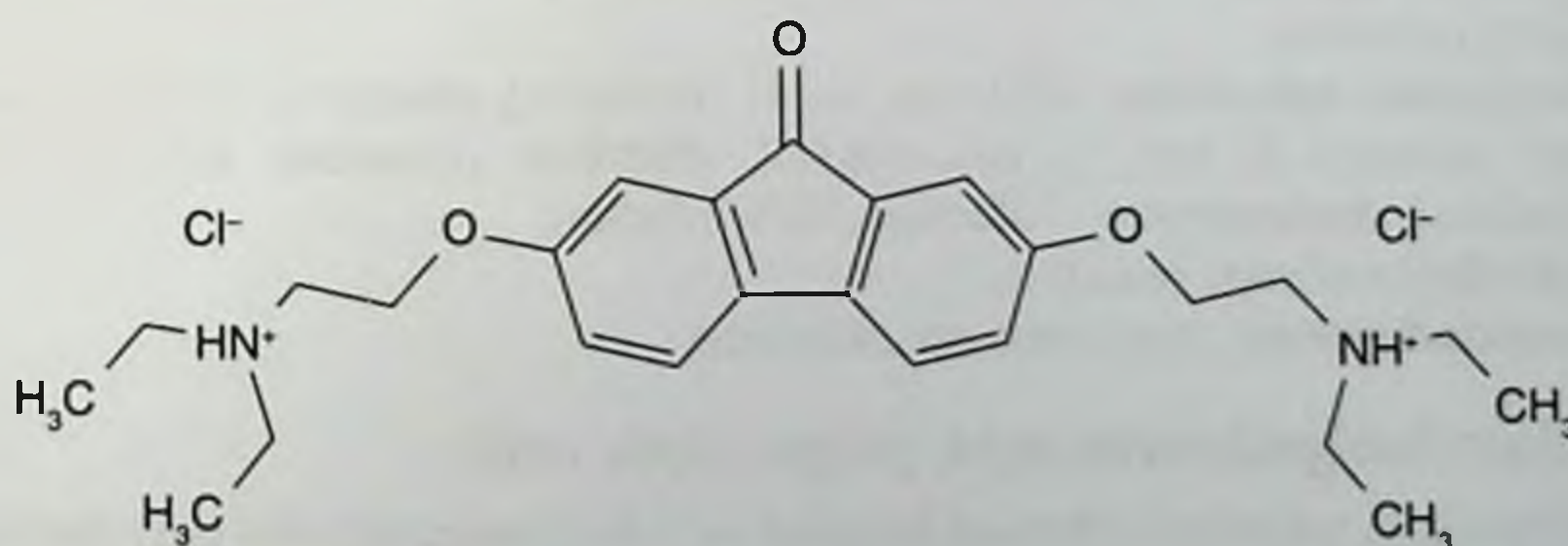


Fig. 25.10. 2,7-bis-[2-(Diethylamino)ethoxy]fluoren-9-one dihydrochloride

Mechanism of action: Inhibition of the translation of virus-specific proteins in infected cells, resulting in suppression of viral replication.

- ▶ Low-molecular-weight synthetic IFN inducer that stimulates the formation of all IFN types in the body. Intestinal epithelial cells, hepatocytes, T cells, neutrophils, and granulocytes are the main producers of IFNs in response to Tilorone administration. Exhibits immunomodulatory and antiviral action. Stimulates bone marrow stem cells, induces a dose-dependent increase in antibody production, decrease in the extent of immunosuppression, restores the T-helper/T-suppressor ratio.
- ▶ Bioavailability: 60 %. Does not undergo biotransformation. Excreted in bile (70 %) and urine. $T_{1/2}$: 48 hours. For oral administration.

Therapeutic indications: influenza and other acute respiratory viral infections, neuroviral infections, herpes and cytomegalovirus infections

Side effects: dyspepsia, short-term chills, allergic reactions

Contraindications: allergic reactions, pregnancy, breastfeeding

Meglumine acridonacetate (Cycloferon[®])

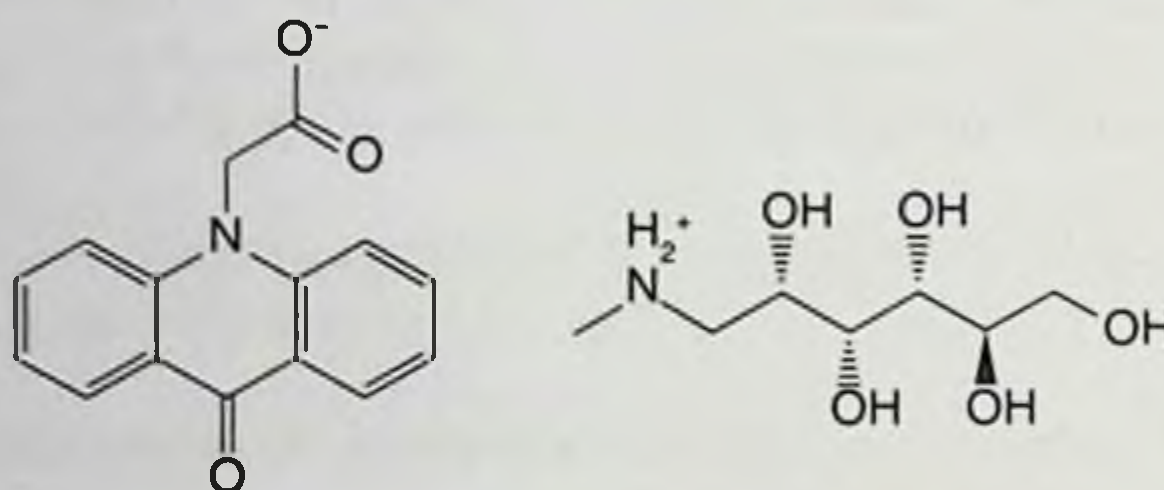


Fig. 25.11. N-Methylglucamine 2-(9-oxoacridine-10(9H)-yl)acetate

Acridonacetic acid derivative. Low-molecular-weight IFN inducer; exhibits antiviral, immunomodulatory, anti-inflammatory activity.

Mechanism of action: Meglumine acridonacetate inhibits viral replication at the early stages of the infection process, penetrates the cytoplasm and nuclear structures, induces the synthesis of “early” interferons. Macrophages, T cells and B cells are the main IFN producers after drug administration.

Maximum plasma concentrations are reached in 2–3 hours. $T_{1/2}$: 4–5 hours. For oral administration.

Therapeutic indications: influenza, acute respiratory disorders, herpes infection, chronic hepatitis B and C, neurological infections (including viral tick-borne encephalitis), acute intestinal infection, HIV infection

Side effects: allergic reactions

Contraindications: pregnancy, breastfeeding

Poludan[®] (polyadenylic acid, polyuridylic acid)

Biosynthetic polyribonucleotide complex of polyriboadenylic and polyribouridylic acids. Exhibits antiviral and immunomodulatory activity. Mainly stimulates the formation of IFN- α s and to a lesser extent the formation of IFN- β s and IFN- γ s in peripheral white blood cells, as well as in tissues and organs containing lymphoid elements. Has a direct antiviral action. For oral, intranasal, subconjunctival administration.

Therapeutic indications: acute respiratory infections, influenza, adenoviral and herpetic eye diseases

Side effects: allergic reactions

Contraindications: hypersensitivity to any of its ingredients

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CHAPTER 10: THE HISTORY OF THE UNITED STATES

10.1 THE EARLY YEARS

10.1.1 The First Americans

The first Americans were Native Americans who lived in the United States for thousands of years before the arrival of European settlers.

10.1.2 The European Colonies

The European colonies were established by settlers from Europe who came to the United States in search of new opportunities and land.

10.1.3 The American Revolution

The American Revolution was a war fought between the thirteen original colonies and Great Britain, resulting in the colonies' independence.

10.1.4 The Early Republic

The early republic was a period of time in the United States' history when the country was still developing and establishing its identity.

10.1.5 The Industrial Revolution

The industrial revolution was a period of time in the United States' history when the country experienced rapid growth and development.

10.1.6 The Civil War

The civil war was a conflict between the northern states and the southern states, fought over the issue of slavery.

10.1.7 The Reconstruction Era

The reconstruction era was a period of time in the United States' history when the country was rebuilding itself after the civil war.

10.1.8 The Progressive Era

The progressive era was a period of time in the United States' history when the country experienced significant social and political reforms.

10.1.9 The Roaring Twenties

The roaring twenties was a period of time in the United States' history when the country experienced a period of economic prosperity and cultural change.

10.1.10 The Great Depression

The great depression was a period of time in the United States' history when the country experienced a severe economic downturn.

10.1.11 World War II

World war II was a global conflict that took place between 1939 and 1945, involving most of the world's nations.

Textbook

PHARMACOLOGY

TRANSLATED FROM RUSSIAN LANGUAGE

Edited by
Galina Zinovyevna Sufianova

Passed for printing: 25.10.2023. Folio: 70x100¹/₁₆.
Coated paper. Offset printing.

Size: 32,75 conventional printed pages. Print run: 1000 pcs. Order № 737.

Print-Service LLC
75B Kharkovskaya St, Tyumen 625023

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ISBN 978-5-600-03764-9



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This textbook was prepared by professors from the Department of Pharmacology at the Federal State Budget Educational Institution of Higher Education (FSBEI HE), Tyumen State Medical University of the Ministry of Health of Russia. It is an integrated and comprehensive guide developed specifically for medical students that complies with all the requirements of the Russian "Federal State Educational Standards" for higher education programs.

This textbook covers a wide range of topics, from the basic principles of pharmacology, pharmacokinetics and pharmacodynamics to an in-depth analysis of different drug classes. Each of these chapters goes into great detail about the development, mechanisms of action, indications and contraindications, adverse reactions, dosing, and use of specific drugs. The text is accompanied by illustrations and diagrams, making it easier to understand complex concepts. This textbook is a reliable and up-to-date source of knowledge that will help students to better understand pharmacology, the principles of drug action and the rationale behind the use of specific drugs.



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