V. V. GODOVAN

PHARMACOLOGY
IN PICTURES AND SCHEMES

In 2 volumes

Volume 1

The ODESSA NATIONAL
MEDICAL UNIVERSITY

V. V. Godovan

PHARMACOLOGY
IN PICTURES AND SCHEMES

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Volume 1

Edited by a fellow of the NAMS of Ukraine,
MD, professor V. I. Kresyun

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У даному пораднику, що складається з двох томів, відображені питання загальної та спеціальної фармакології, стисло викладена історія створення лікарських засобів, подаються сучасні класифікації фармакологічних груп, узагальнені дані про фармакокінетику, фармакодинаміку і фармакотоксикодинаміку ліків, які застосовуються у сучасній медичній практиці. Матеріал висвітлений в інтеграції з іншими медико-біологічними та клінічними дисциплінами. Особливо, унікальне місце у виданні посідає схематичний виклад механізмів дії лікарських засобів та їх ефектів, що розвиваються в результаті цього.

Recommended by Scientific Council of the Odessa State Medical University (Proceedings N1 from 01.09.2008).

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It is dedicated to my Teacher
Valentine Iosiphovich Kresyun
as a token of gratitude for putting much effort to his students and followers…

Author

PREFACE

Every book has its previous history. The decision about creation of this guidance is caused by great interest of doctors, teachers, interns and students to the lectures at the department.

This guidance is an original excursus through the modern pharmacology. Pharmacology became not only a medical science about action of drugs on an organism. It organically integrated with biology, inorganic and organic chemistry, biochemistry, normal and pathological physiology, normal and pathological anatomy, histology microbiology, immunology, all clinical disciplines and pharmacy, a science about the "art of drug making". There was the division of "studies about medications in past centuries": a "chemist branch" (pharmacy) and doctoring (actually pharmacology) were taken separately. Nowadays close interlacing of these sciences is observed because everything in life occurs due to common biological laws. A modern doctor who uses medications with medical and prophylactic aims, should have profound knowledge of pharmacology.

The points we'd like to pay readers' attention are following. At first, as a result of enormous stream of information on numerous original (brand) drugs and thousands of their reproduced copies (generics) with various commercial names the understanding of pharmacology and methods of its cognition changed substantially. A modern doctor, who becomes proficient in pharmacology, should form a general picture of one or the other group of drugs instead of "learning" pharmacological descriptions of separate drugs. Therefore in this book the author concentrated readers' attention on understanding of general conformities to the law of action of every pharmacological group of drugs. It, without doubt, will help a doctor in future to individualize prescribed pharmacotherapy and to orient himself in informative space when new original and generic drugs appear.

A scheme-like presentation of material, such as diagrams, pictures, tables, will help a reader to point out main moments in pharmacokinetics, pharmacodynamics, indications and contraindications to prescription, adverse effects of separate groups of drugs. However, it does not ex-

clude a necessity of deep study of monographic, reference and periodic literature.

Following the main medical principle “Do no make harm”, a doctor should choose a prescribed drug not only according to indications presented in the drug instruction on clinical application or reference books, but the deep understanding of individual features of personality and organism of a patient in comparison with the features of pharmacokinetics, pharmacodynamics and adverse effects of this drug. Taking into account the fact that main demands to modern pharmacotherapy is maximal individualization, efficiency, rationality and, most important, safety, while prescribing drugs a doctor should pay a special attention to possible development of Adverse effects. According to modern requirements to “medicinal safety”, every doctor is obliged (!) to inform a patient about possible negative consequences of administered pharmacotherapy.

These very objects were pursued by the author in the scientific practical guidance, which he offered to the wide circle of readers.

And the last point. Nobody can forget that “only in scillful hands a substance becomes a drug and in clumsy ones — poison”.

A fellow of the NAMS of Ukraine,
Honoured Worker of Science and Technique of Ukraine,
MD, professor
V. I. Kresyun

Part I
INTRODUCTION TO SPECIALITY

Topic 1
GENERAL PHARMACOLOGY

THE DEPARTMENT OF GENERAL AND CLINICAL PHARMACOLOGY OF THE ONMedU

BORISOV
Peter Yakovlevich
(1902–1916)

LAVROV
David Melitonovich
(1921–1928)

TSYGANOV
Sergey Vasilyevich
(1928–1958)

MAXIMOVICH
Yaroslav Borisovich
(1960–1985)

KRESYUN Valentine Iosiphovich
a fellow of the NAMS of Ukraine,
Honoured Science and Technology
Worker of Ukraine, MD, professor.
He has been the head of the Department
since 1985

THE DEPARTMENT OF GENERAL AND CLINICAL PHARMACOLOGY OF THE ONMedU

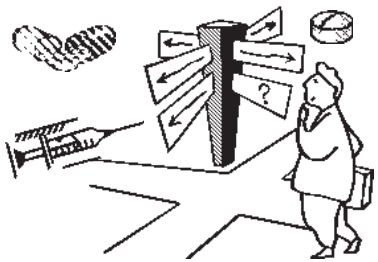
- The course of general and particular pharmacology (the 3rd year of the medical and medical-prophylactic faculties the 2nd–3rd years of the stomatologic faculty, the 3rd–4th years of the pharmaceutical faculty)
- The course of clinical pharmacology (the 4th year of the stomatologic faculty, the 5th year of the medical, pediatric and medical-prophylactic faculties

- The course on clinical farmacy and pharmacotherapy (the 4th–5th years of the pharmaceutical faculty)
- The elective course “The pharmacological supervision system in the world and Ukraine” (the 6th year of the medical faculty)
- The cycle classes on clinical pharmacology for doctors-interns, residents, pharmacists, pre-certificate cycles.

FARMACOLOGY

Drug (Pharmacon)

Pharmacology
is a medical-biological science about interrelation of drugs with living organisms

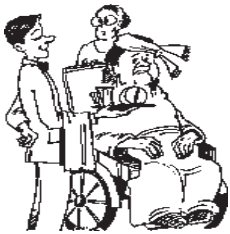


Pharmacy
is a science about drugs structure, properties, making and bringing to the patient

PHARMACOLOGY

Directions

- Theoretical
- Experimental
- Clinical
- *Special:* pediatric, geriatric, radiation, immune pharmacology, psychopharmacology, pharmacogenetics, chronopharmacology, etc.



Types of pharmacotherapy

- Ethiotropic
- Pathogenetic
- Symptomatic
- Prophylactic
- Preventive
- Substitutive
- Stimulating
- Adaptative
- Inhibitory

PHARMACOLOGY

- **Medical prescription** is a part studying order and rules of drug prescription
- **Pharmacokinetics** is a part studying the way of a drug from the moment of introduction to excretion from an organism
- **Pharmacodynamics** is a part, studying all those changes which take place as a result of interconnection of a drug with an organism
- **Pharmacotoxicodynamics** is a part studying the adverse effects of drugs

DRUG NOMENCLATURE

- **International Nonproprietary Name (INN)**, established by official organs of health protection and used in a national and international pharmacopoeia (storage of standards and regulations which standardize quality of drugs), reference books and list of medications
- **Trade (firm or commercial) names**

- **Brand or innovative (original) drug** is a new active substance which has not been used before, or already known pharmacological product with its new indication to application, in the other dose or method of prescription
- **Generic drug** is a brand copy, produced by pharmaceutical firms by the second license, that is the firms did not develop it themselves and did not have the first license to their production

DRUG CLASSIFICATION PRINCIPLES

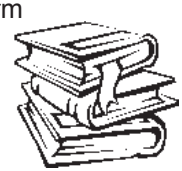
- **Chemical structure** (glycosides, alkaloids, steroids, antibiotics, etc.)
- **Pharmacological action** (cholinergic antagonists, anticoagulants, diuretics, etc.)
- **Therapeutic administration** (hypotensive, antianginal, antimicrobial, etc.)

Recommeded by the World Health Maintenance Organization Anatomical-Therapeutic and Chemical (ATC) classification

is the system of division of medicines into the groups depending on their action on a certain anatomic organ or system, and also on their chemical, pharmacological and therapeutic properties

TERMINOLOGY

- **Crude drug** is the products of herbal, animal, mineral, bacterial, mycotic and synthetic origin from which the drug substance is obtained
- **Drug substance (DS)** is an individual compound or biological substance used as a medication
- **Medicinal agent (MA, drug)** is an agent including one or a few DS and allowed for clinical application by the organ of country authorized by the State Expert Center of the Ministry of Health of Ukraine
- **Medicinal drug** is the DS as a certain medicinal form
- **Drug form** is the form of DS which is suitable for practical application with the purpose to get medical or prophylactic influence



DRUG DOSAGE FORMS

According to indication:

- **dosed**
- **undosed**

According to consistency:

- **hard** (powders, capsules, pills, dragees, powders, etc.)
- **liquid** (extracts, infusions, decoctions, drops, solutions, suspension, emulsions, etc.)
- **soft** (suppositories, plasters, ointments, liniments, etc.)

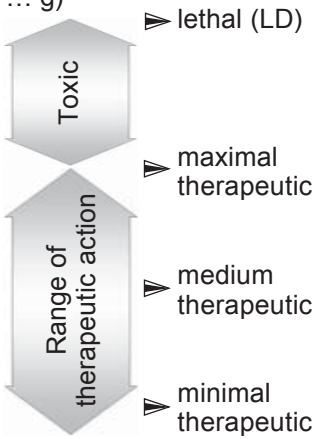
According to making:

- **master**
- **officinal**

DOSE

(from Greek ***dosis — reception, portion) is amount of drug substance expressed in units:***

- weight (… 0.001, 0.01, 0.1, 1.0, 10.0 … g)
- volume (… 0.1, 1, 10 … ml)
- biological (CU, U, IU)



Types of doses:

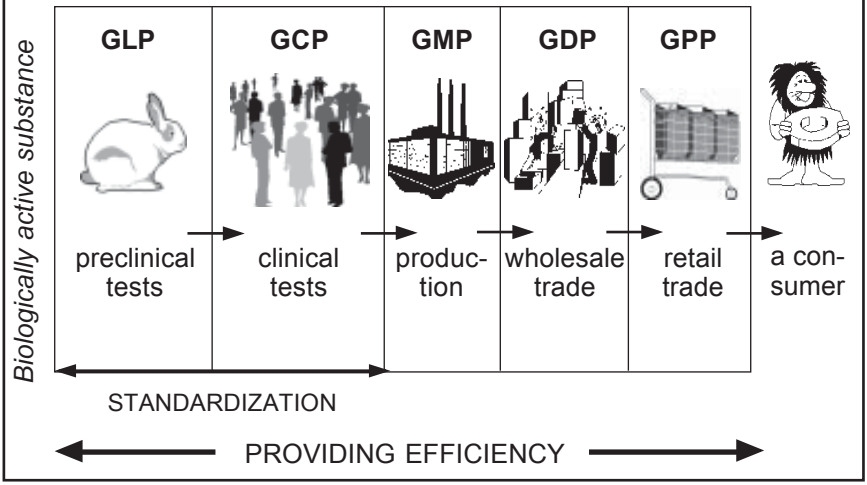
- ♦ **single** *(dosis pro dosi)*: minimum therapeutic acting, medium therapeutic, maximal single, loading, maintaining
- ♦ **daily** *(dosis pro die)*
- ♦ **course** *(dosis pro cursus)*
- ♦ **effective** (ED_{50})

I. PRESCRIPTION

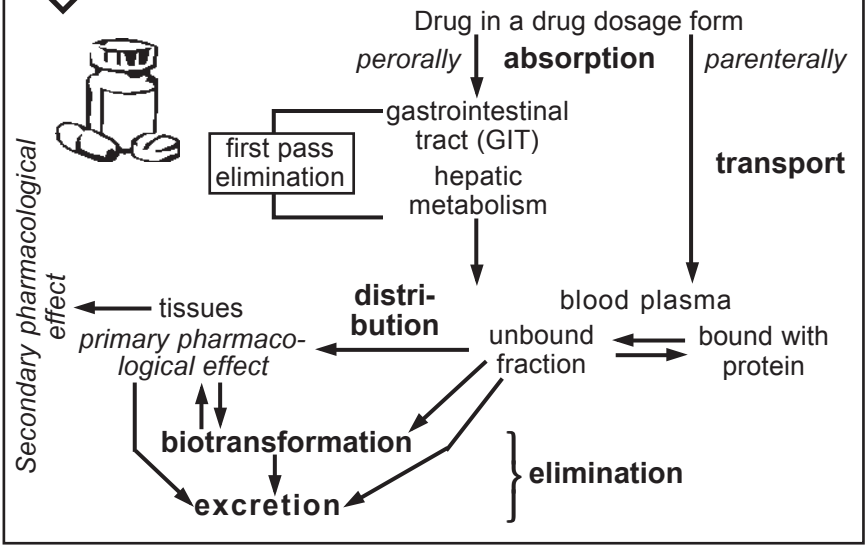
(from Lat. ***recipere — to take) is a wrritten order of a doctor to the pharmacist about production, delivery of a medicinal drug to a certain person with indicating the method of application***

I. Inscriptio		Policlinic N 1 Odessa Odessa, Mizikevich street, 15, tel. 733-33-33 Date — September, 10, 2010 Patient — Ivanov I. I., 56 years old Doctor — Bezymyanny S. S.
II. Praepositio	Rp.:	Pyridoxini hydrochloridi 0.002
III. Designatio materiarum		Acidi nicotinici 0.025 Sacchari 0.3
IV. Subscriptio		M. f. pulvis. D. t. d. N. 12
V. Signatura		S. For a powder 4 times a day
VI. Nomen medici		*Signature* *Seal*

MODERN WORLD STANDARDS OF PROVIDING EFFICIENCY AND QUALITY OF DRUGS



II. PHARMACOKINETICS



DRUG INTRODUCTION WAYS

Enteral

- **Peroral** *(per os)*
- **Sublingual, buccal**
- **Rectal** *(per rectum)*
- **Through a probe**

Parenteral

- **Injection:** subcutaneous (s.c.), intracutaneous (i.c.), intramuscular (i.m.), intravenous (i.v.), intra-arterial, intraosseous, etc.
- **Application** (cutaneous)
- **Inhalation**
- **Intracavitary**

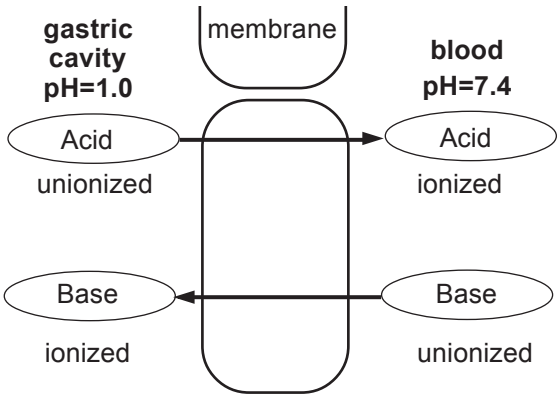
Bioavailability is the amount of drug which reaches the systemic blood flow in per cent of the introduced dose (i.v. — 100%)

Bioequivalency is a degree of therapeutic effect expression when the MA reaches equivalent concentrations in the blood

ABSORPTION OF DRUGS

Barriers

mucosa of the stomach, intestine, skin, capillary wall, hematoencephalic, placental, etc.



- physical and chemical properties of drug:
  - ✓ degree of ionization
  - ✓ pH of the medium
  - ✓ lipidotropic capacity, etc.
- absorbing surface area
- organ vascularization

DRUG TRANSPORT

External space

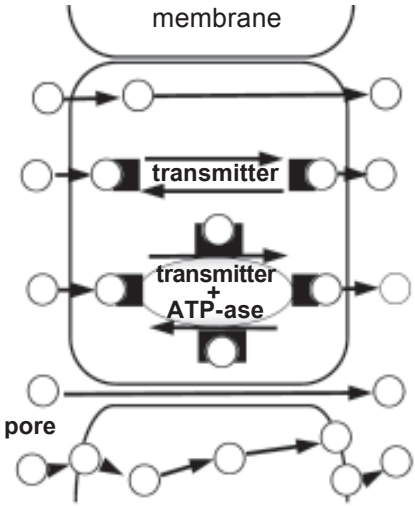
Passive diffusion

Facilitated diffusion

Active transport

Filtration

Pinocytosis



Internal space

Fick's law of diffusion:

$$\frac{dC}{dt} = -D \cdot A \cdot \Delta C,$$

where

$\frac{dC}{dt}$ is speed of diffusion;

D — Fick's coefficient;

A — membrane area;

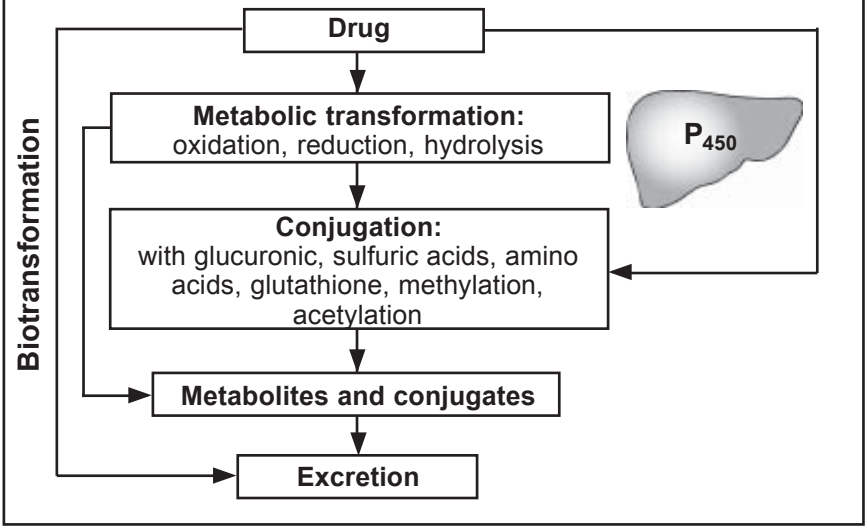
ΔC — concentration gradient

DRUG DISTRIBUTION

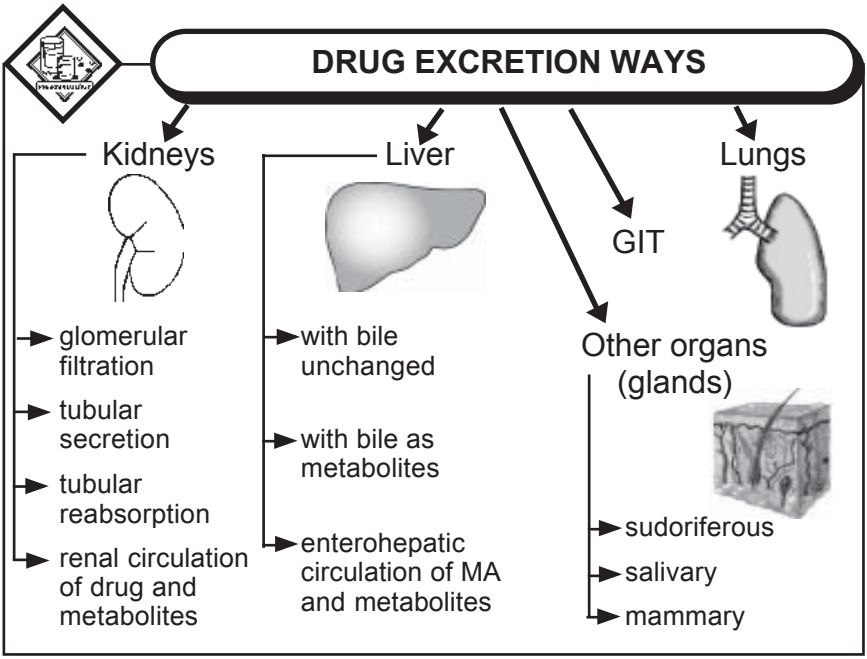
- **Binding with blood proteins:**
  - ✓ *nonspecific* (albumins, to lesser degree — α-, β-globulins)
  - ✓ *specific* (cyanocobalamin — transcobalamin, ions of iron — transferrin, copper — ceruloplasmin, etc.)
- **Reginal blood flow:** for the first time to well vascularized organs and tissues, then to bad ones
- **Physical and chemical properties of drugs** (polarity, coefficient of distribution in the system lipid/water, etc.)
- **Volume of distribution (V_d)** is hypothetical volume of liquids of organism necessary for the even distribution in concentration equal to concentration in blood plasma

$$V_d \text{ (in plasma)} = 0.05 \text{ l/kg}$$

ELIMINATION



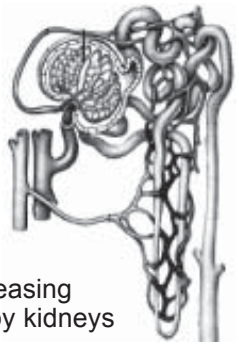
DRUG EXCRETION WAYS



DRUG EXCRETION

Renal excretion depends on:

- extent of drug binding with plasma proteins
- speed of glomerular filtration
- tubular secretion
- tubular reabsorption
- pH of urine, ionizations, etc.



General clearence (Cl_t, ml/min, l/hr) is a conditional volume of blood plasma releasing from drug for a unit of time

Renal clearence (Cl_R) is a conditional volume releasing from drug for a unit of time owing to its excretion by kidneys

$$Cl_R = \frac{\text{C in urine (mcg/ml)} \cdot \text{V of urination (ml/min)}}{\text{C in plasma (mcg/ml)}}$$

THE BASIC PHARMACOKINETIC PARAMETERS

- **The absorption rate constant** (K_{01}, h^{-1}, min^{-1}) is the speed of of drug delivery from the place of introduction to the systemic blood flow
- **The period of half-absorption** ($T_{1/2a}$, hrs, min) is time necessary for absorption from the place of introduction to the systemic blood flow 50% of introduced dose
- **Time of reaching the maximal concentration** (T_{max}, h, min) is time of achievement of maximal concentration of drug in the blood
- **Half-life** ($T_{1/2}$, hrs, min) is a period during which 50% if introduce dose excrete
- **The elimination rate constant** (K_{el}, h^{-1}, min^{-1}) is speed of disappearance (elimination) of the drug from an organism
- **The excretion rate constant** (K_{ex}, h^{-1}, min^{-1}) is speed of the MA excretion with excrete (urine, bile, saliva, sweat, milk, etc.)

III. PHARMACODYNAMICS

Drug action types

- Local and resorptive: direct and indirect (reflex)
- Specific and unspecific
- Selective and nonselective
- Reversible and irreversible
- Main and side (concomitant)
- Desirable and unwanted (adverse)

DRUG ACTION MECHANISMS

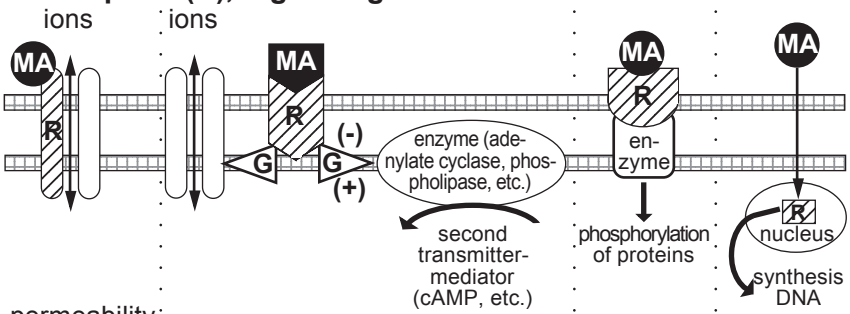
Interaction with biosubstrate

- **Physical and physical and chemical** (rarely; drugs excreted unchanged)
- **Chemical** — formation:
  - ✓coordinting covalent bonds
  - ✓stable complexes (for example, chelate, antidotes)
  - ✓ionic (electrostatic) bonds
  - ✓dipole interconnection
  - ✓van-der-Waals
  - ✓hydrofobic

DRUGS ACTION MECHANISMS

Influence on:

- **receptors (R), regulating:**



DRUG ACTION MECHANISMS

Some types and subtypes of receptors

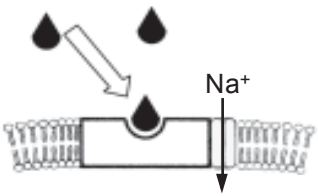
- ✓ Cholinergic: muscarinic (M_1, M_2, M_3, M_4, M_5); nicotine (N_M, N_N)
- ✓ Adrenergic: alfa- ($\alpha_{1A}, \alpha_{1B}, \alpha_{1C}, \alpha_{2A}, \alpha_{2B}, \alpha_{2C}$); beta- ($\beta_1, \beta_2, \beta_3$)
- ✓ Dopamine: D_1, D_2, D_3, D_4, D_5
- ✓ Serotonin: $5\text{-HT}_{1\text{-}7}$
- ✓ GABA: $GABA_A$, $GABA_B$, $GABA_C$
- ✓ Histamine: H_1, H_2, H_3
- ✓ Bradykinin: B_1, B_2
- ✓ Angiotensive: AT_1, AT_2
- ✓ Purinergic: P_1 (adenosin — A_1, A_{2A}, A_{2B}, A_3), P_{2X}, P_{2Y}, P_{2Z}, P_{2U}, P_{2T}
- ✓ Opioid: μ, κ, δ, ε, σ
- ✓ Excitant amino acids (ionotropic): NMDA, AMPA, cainatic
- ✓ Leukotrienic: LTB_4, LTD_4, LTC_4
- ✓ Prostanoid: DP, FP, IP, TP, EP_1, EP_2, EP_3
- ✓ Neuropeptide Y: Y_1, Y_2
- ✓ Cholecyctokinin: CCK_A, CCK_V

DRUG ACTION MECHANISMS

Having affinity to the receptor, drug manifest:

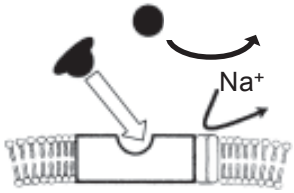
- **agonism** (complete, partial)
- **antagonism** (competitive, noncompetitive)
- **agonism-antagonism**

drug agonist bioligand of an organism



effect similar to the effect of bioligand — *mimetic action*

drug antagonist bioligand of an organism

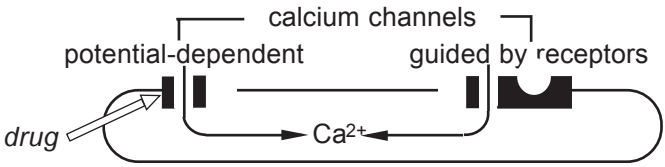


absence of effect — *blocking (lytic) action*

DRUGS ACTION MECHANISMS

Influence on:

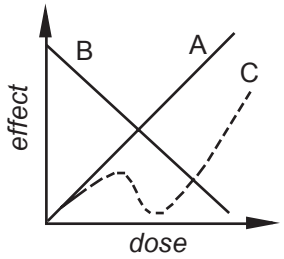
- **ionic channels** (Ca^{2+}, Na^{+}, K^{+}, etc.) — activators and blockers



- **enzymes** (MAO, AC, cAMP, COG, etc.) — inhibitors
- **transporting systems** (proteins-carriers carrying out, for example, noradrenaline neuronal capture) — activators and inhibitors
- **permeability of membranes**
- **nucleic acids and protein synthesis**
- **genes**

THE FACTORS ON WHICH PHARMACOLOGICAL EFFECT DEPENDS

- **Physical and chemical properties of a drug, its quality** (substandard and falsified drugs), **dose** (A — directly proportional, B — inversely proportional, C — stochastic)
- **Condition of a patient** (age, body weight, sex, pregnancy, lactation, the degree of severity of basic and concomitant diseases, allergic status, ethnic and genetic factors)
- **External relative to a patient factors** (climate, ecology, working conditions, daily and seasonal rhythms, therapy conducted by a doctor, polypharmacy, etc.)



REPEATED DRUG INTRODUCTION

✓ **Sensitization** (idiosyncrasy)

✓ **Cumulation** (material and functional)

✓ **Tolerance** (addiction, resistance), **tachyphylaxia**

✓ **Drug dependence** (psychic, physical), **abstinence syndrome** (withdrawal)

✓ **Rebound** (ricochet) **syndrome**

DRUG INTERACTION

Polymedication is simultaneous prescribing of a great number of drugs

➢ **Pharmaceutical** (with i.v. introductions or application of two substances in the same drug)

➢ **Pharmacological**

- ***Pharmacokinetic***
  - ✓ at the absorption stage
  - ✓ owing to displacement from bond with proteins
  - ✓ at the stage of distributing in tissues
  - ✓ during metabolism (inductors, inhibitors of microsomal oxidation)
  - ✓ at the stage of excretion

DRUG INTERACTION

- ***Pharmacodynamic***
  - ♦ **Synergism:**
    - ✓ summing (addition): A1/2 + B1/2 = 1
    - ✓ potentiating (supraaddition): A1/2 + B1/2 > 1
  - ♦ **Antagonism** (antodotism): A1/2 + B1/2 < 1
    - ✓ physical
    - ✓ chemical
    - ✓ physiological (functional): competitive, noncompetitive, independent
  - ♦ **Synergic antagonism**

IV. PHARMACOTOXICODYNAMICS

Drugs safety is absence of serious and unforeseen side reactions/actions at clinical tests or medical application of drugs

Side effect (SE) is any adverse reaction conditioned by pharmacological properties of drug and observed exclusively in therapeutic doses

Side reaction (SR) is an adverse for health, dangerous reaction provided the connection between the reaction and drugs application can not be eliminated

Side phenomenon is an unfavorable clinical manifestation with drugs application which is not proved to be connected with the drug prescribing (a symptom, disease coincided in time with drugs usage)

TYPES OF ADVERSE EFFECT

- **Toxic:** as a rule, at cellular, organ and system levels
- **Allergic reactions:** immediate and slow types
- **Idiosyncrasy:** genetically conditioned perverted reaction of an organism to the medicine (for example, insufficiency, absence of enzymes participating in the drugs metabolism)
- **Mutagenic:** an ability to influence the genetic level, causing mutations in a few generations
- **Blastomogenic:** an ability to cause new formations both benign and malignant *(carcinogenic)*
- **Teratogenic:** an ability to cause deformities in an embryo (in the first trimester of pregnancy)
- **Embryo- and fetotoxic:** an ability of toxical influence on an embryo and fetus accordingly, causing disturbances of normal activity up to death

DRUGS KNOWN FOR THEIR ADVERSE EFFECT

Drug	Date	Side effect	Result
Streptocide	1937	Damage of the liver	Solvent is replaced
Talydomide	1961	Phocomelia	Forbidden
Levomycetin	1966	Blood dyscrasia	Limited usage
Clyochinol	1975	Myopathic neurology	Forbidden
Benoxaprofen	1982	Damage of the liver	the same
Zomepyrak	1983	Anaphylaxis	«
Indoprofen	1984	Abdominal bleeding, perforations	«
Osmozin	1984	the same	«
Butadione	1984	Blood dyscrasia	Limited usage
Aspirin	1986	Reynaud's syndrome (children)	the same
Spyronolactone	1988	Carcinoma in animals	«
Methipranolol	1990	Anterior uveitis	Forbidden
Terodilin	1991	Cardiac arrhythmias	the same

DRUG RESPONSE CLASSIFICATION

1. Dose-dependent (type A) — organotoxic

- Related to pharmacological activity
- With drug overdose
- With drug interaction

2. Dose-independent (type B) — unprognosticated

- Immunological reactions (allergy, disturbances of immunobiological properties)
- Pseudoallergic reactions
- Pharmacogenetic idiosyncrasy

DRUG RESPONSE CLASSIFICATION

3. With prolong usage

- Adaptive changes
- With cessation of drug “rebound”, “withdrawal”, abstinence syndromes
- Organotoxic action

4. Postponed action

- Blastomogenic (including carcinogenic)
- Connected with reproductive function and fetus (decreased fertility, mutagenicity, teratogenicity, embryo- and fetotoxicity)
- Drugs in breast milk

PHARMACOLOGICAL SURVEILLANCE

PHARMACOLOGICAL SURVEILLANCE is the state system of collection, scientific estimation of information about side effects of drug when they are medically used with the purpose of accept proper regulatory resolutions

Part II

DRUGS AFFECTING THE PERIPHERAL PART OF THE NERVOUS SYSTEM

DRUGS AFFECTING EFFERENT INNERVATION

Topic 2

CHOLINOTROPIC DRUGS

HISTORY OF CREATION

1920 H. DALE discovered muscarine- and nicotine-like influence of acetylcholine; described adrenergic and cholinergic fibres

1921 O. LOEWI proved experimentally mediator mechanism of impulse transmission

1924 A. F. SAMOYLOV made a conjecture about the role of chemical mechanism of CNS inhibition

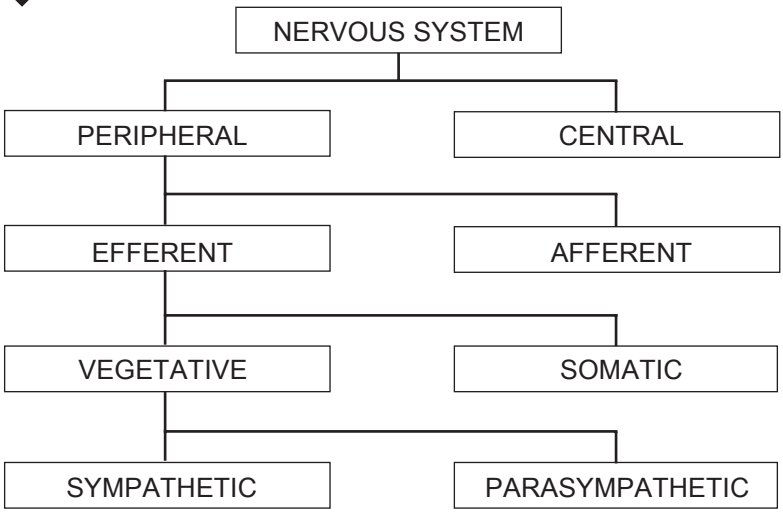
1930 V. V. ZAKUSOV offered the synaptic theory of drug substances action on the CNS

1946 S. V. ANICHKOV discovered N-cholinergic receptors in the sinocarotid zone

1946 U. EULER determined the mediator role of noradrenaline

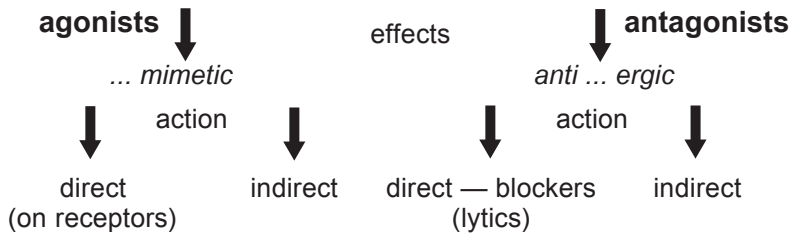
V. V. Zakusov

STRUCTURE OF NERVOUS SYSTEM

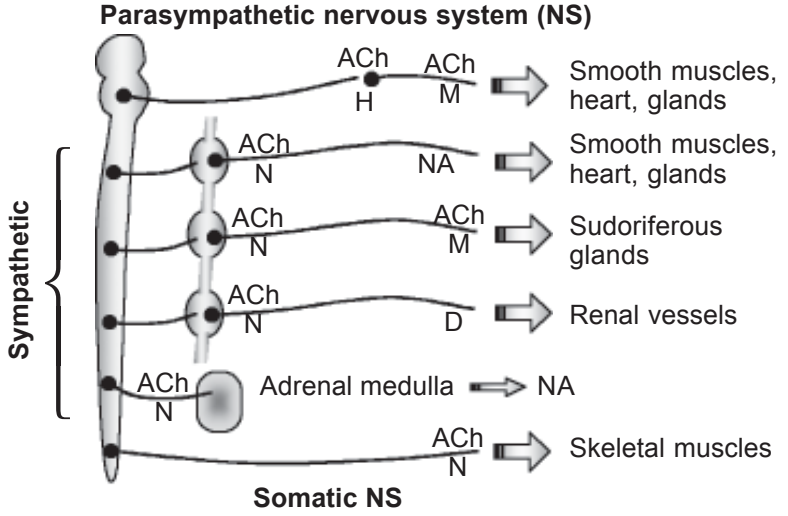


SUBSTANCES AFFECTING MEDIATOR PROCESSES

- Cholinergic (cholinotropic)
- Adrenergic (adrenotropic)
- Dopaminergic (dopaminotropic)
- Serotoninergic
- GABA-ergic
- Histaminotropic, etc.



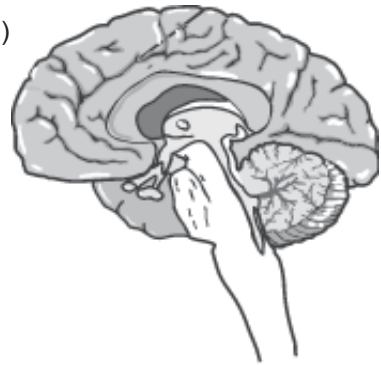
NEURONAL TRANSMISSION SCHEME



N-CHOLINERGIC RECEPTORS LOCALIZATION

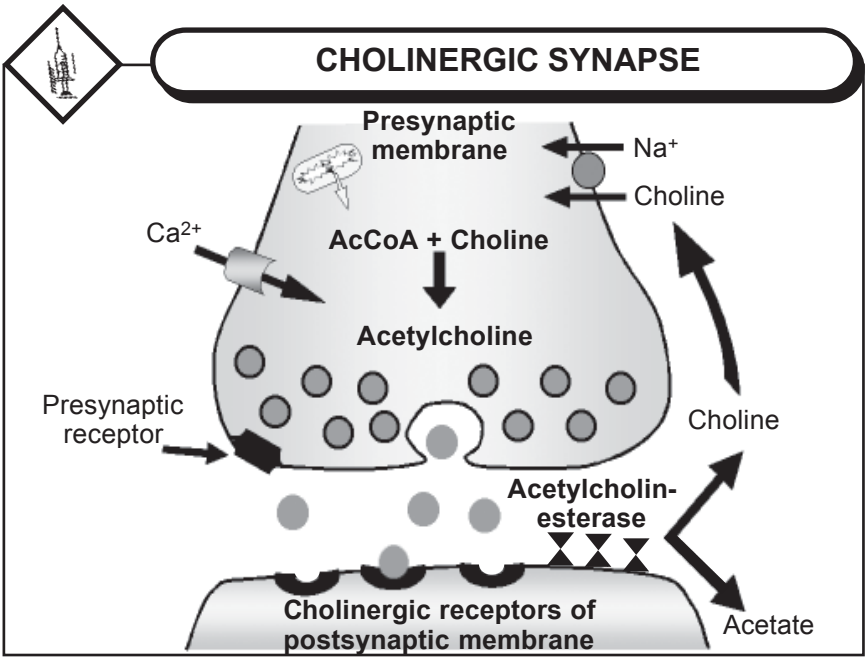
Neuronal type

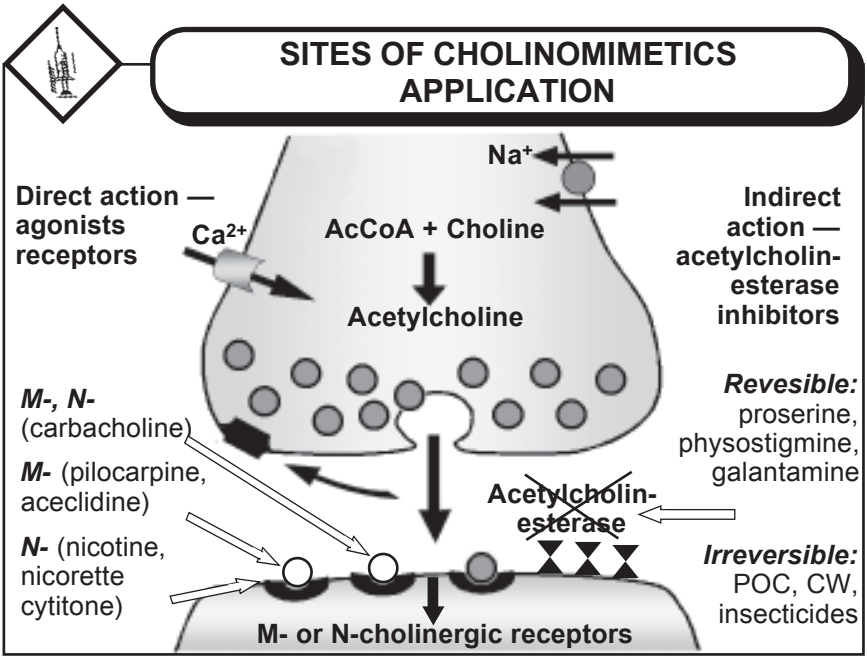
- CNS (cortex of cerebral hemispheres, neurohypophysis, oblong brain, Renshaw cells of the spinal cord)
- Vegetative ganglia
- Cerebral layer of the adrenal glands
- Carotid sinus



Muscular type

- Skeletal muscles


CHOLINERGIC SYNAPSE
Presynaptic membrane
Na+
Choline
Ca2+
AcCoA + Choline
Acetylcholine
Presynaptic receptor
Choline
Acetylcholin-esterase
Cholinergic receptors of postsynaptic membrane
Acetate


SITES OF CHOLINOMIMETICS APPLICATION
Na+
Direct action — agonists receptors
Ca2+
AcCoA + Choline
Indirect action — acetylcholin-esterase inhibitors
Acetylcholine
M-, N- (carbacholine)
M- (pilocarpine, aceclidine)
N- (nicotine, nicorette cytitone)
Revesible: proserine, physostigmine, galantamine
Acetylcholin-esterase
Irreversible: POC, CW, insecticides
M- or N-cholinergic receptors

CHOLINOMIMETICS CLASSIFICATION

M-	N-	M-, N-	
		direct action	indirect action (anticholinesterasa)
Pilocarpine Aceclidine	Cytitone Lobelin Nicorette	Acetylcholine Carbacholine	*Reversible:* proserine (neostigmine), physostigmine, galantamine, pyridostigmine *Irreversible:* poisons organophosphorous compounds (OPC), chemical weapon (CW), insecticides

PHARMACODYNAMICS OF M-CHOLINOMIMETICS

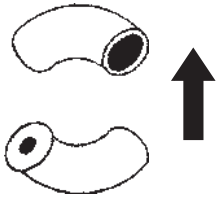
Heart — "–" ino, "–" chrono-, "–" dromotropic effects

Vessels — delation

Bronchi — spasm

GIT — motor activity — rise, sphincters — relaxation, secretion — strengthening

Urinary bladder — detrusor — rise, sphincters — relaxation



PHARMACODYNAMICS OF M-CHOLINOMIMETICS

Glands (sweat, lacrimal, salivary, bronchial increase of secretion)

Eyes miosis, spasm of accommodation, intraocular pressure decrease acetylcholinesterase

CNS hyperkinesia

M-CHOLINOMIMETICS APPLICATION

Indications

- Glaucoma *(pilocarpine)*
- Intestinal atony (paralytic ileus) *(aceclidine)*
- Atony of urinary bladder *(aceclidine)*

Contraindications

- Bronchial asthma, obstructive bronchitis
- Gastric ulcer
- Intestinal obstruction
- Heart rhythm disorders
- Hypotensions
- Hyperkinesia (epilepsy, etc.)

ANTICHOLINESTERASE DRUGS

Proserine, physostigmine, galantamine, pyridostigmine

Pharmacodynamics

- **M-cholinomimetic effects**
  +
- **Neuromuscular transmission** — strengthening

Indications

- Glaucoma *(physostigmine)*
- Atony of urinary bladder, atony and paralytic ileus *(proserine)*
- Myasthenia, paralyses, pareses, poliomyelitis, postrehabilitation period after traumas *(galantamine, proserine)*
- Decurarization *(galantamine, proserine)*

MUSCARINE ACUTE POISONING

Clinical course

- CNS excitation (hallucinations, delirium)
- Bradycardia, atrio-ventrical (AV-) block, hypotension
- Bronchospasm, bronchorrhea
- Vomiting, increased painful intestinal peristalsis (tenesmus), diarrhea
- Perspiration, hypersalivation
- Miosis, spasm of accommodation, lacrimation

Death comes from paralysis of the respiratory center!

The first aid

Intravenous introduction of antidote — **Atropine sulfate** (10–15 mg!)

ACUTE POISONING WITH ORGANOPHOSPHOROUS COMPOUNDS

Clinical course

- Bronchial spasm, paralysis of the respiratory center
- Bradicardia, AV-block, hypotension
- Vomiting, painful hyperperistalsis of intestine (tenesmus), diarrhea
- Hyperhydrosis, hypersalivation
- Miosis, spasm of accommodation, lacrimation
- Enuresis
- Tonoclonic spasms

The first aid

- **Cholinesterase reactivators** — alloxim, dipiroxim, isonitrosin
- Introduction of **atropine sulfate**

SITES OF CHOLINERGIC ANTAGONISTS APPLICATION

Direct action — reversible antagonists of receptors

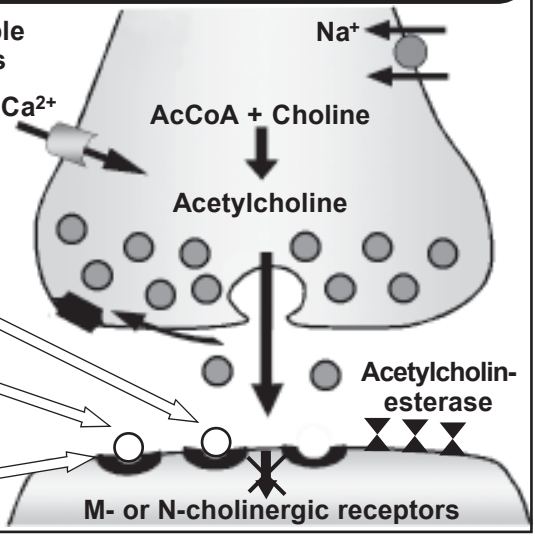
M-, N-
(arfonade)

M-
(atropine, drugs of belladonna, scopolamine, platyphyllin, etc.)

M_1-
(pirenzepine)

central *M-*
(cyclodole)

N-
(ganglionic blockers, myorelaxants)



M-CHOLINERGIC ANTAGONISTS

- **Herbal** — *alkaloids, tertiary amines* (atropine and drugs of belladonna, scopolamine, platyphyllin)
- **Synthetic** — *quaternary* (metacin, ipratropium, etc.), *tertiary amines* (pirenzepine)

Pharmacokinetics

Absorption: tertiary amines are well absorbed in the GIT, quaternary ones — 10–30% from dose

Distribution: the tertiary ones penetrate well through the blood brain barrier (BBB), especially scopolamine!

Excretion: by kidneys (atropine about 60% unchanged)

Duration of action: $T_{1/2}$ atropine about 2 hrs, but effects approximately about 72 hrs and more

PHARMACODYNAMICS OF M-CHOLINERGIC ANTAGONISTS

Along with suppression of parasympathetic, enhancement of sympathetic innervation of

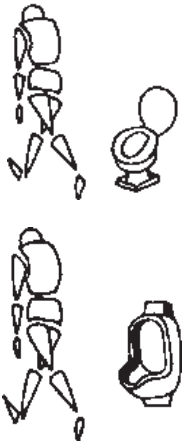
CNS (tertiary amines + central) *in therapeutic* doses — sedative, *in toxic* ones — excitation, hallucinations, agitation, convulsions;
↓ tremor, vestibular disorders

Heart in medium doses
"+" chronotropic (especially in young patients), improvement of AV-conduction;
↑ myocardial need in O_2

Vessels in toxic doses — vasodilatation

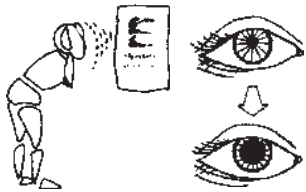
PHARMACODYNAMICS OF M-CHOLINERGIC ANTAGONISTS

GIT	motor activity — reduction, sphincters — contraction, secretion — reduction
Urinary bladder	detrusor — reduction, sphincters — contraction
Bronchi	dilatation, increase of viscous secrete formation
Hollow organs	spasmolytic effect



PHARMACODYNAMICS OF M-CHOLINERGIC ANTAGONISTS

Eyes mydriasis, accommodation paralysis *(cycloplegia, longsightedness),* ↑ intraocular pressure, photophobia, ↑ secretion



atropine (till 12 days) > scopolamine (during 3–5 days) > homatropine (15–20 hrs) > platyphyllin (5–6 hrs, without cycloplegia) > tropicamide (2–6 hrs)

Glands (sweat, lacrimal, salivary, gastrointestinal, bronchial) ↓ secretion, ↓ temperatures of the body (children of younger age!)

Also have a weak local anesthetic and analgesic effect

M-CHOLINERGIC ANTAGONISTS APPLICATION

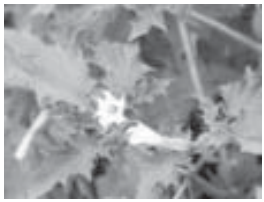
- Premedication
- Vagus cardiac hyperactivity
- Bronchial asthma, obstructive bronchitis *(ipratropium, metacine)*
- In ophthalmology with the diagnostic *(platyphyllin, homatropine)* and medical purpose *(atropine, etc.)*
- Gastric ulcer of stomach, hyperacid gastrites *(pirenzepine)*
- Spasms of smooth muscles *(platyphyllin)*
- Diarrhea *(drugs of belladonna, atropine)*
- Prophylaxis of motion sickness *(aeron, the drugs containing scopolamine)*
- Parkinsonism, hyperkinesias (central M-cholinergic antagonists — *cyclodole*)
- Antidote in case of muscarin, anticholinesterase substances *(atropine)* poisoning

ATROPINE ACUTE POISONING

Clinical course

- Adults — 100 mg, children — 10 mg (2–3 berries of belladonna)
- CNS (hallucinations, agitation, delirium) excitation, after that depression
- Tachycardia (skipped pulse)
- Mydriasis
- Dry, hot and red skin and mucous
- Hyperthermia (especially children of younger age). **The dose of 2 mg atropine can be lethal!**

Deadly nightshade (belladonna)



Thorne apple (datura)

The first aid

✓ Symptomatic

✓ Intravenously **physostigmine** (1–4 mg for adults; 0,5–1 mg for children!)

GANGLIONIC BLOCKERS

✓ **Short-term** (15–20 min) — hygronium, arfonad (trimetaphan)

✓ **Medium** (1–6 hrs) — benzohexonium, pentamine, pachycarpine hydroiodide (alkaloid of thick-fruited pagoda tree)

✓ **Long-term** (6–12 hrs) — pirilen

Pharmacokinetics

- **Absorption:** quaternary amines (benzohexonium, pentamine, hygronium) are badly absorbed in GIT ⇒ i.v., i.m. introduction; tertiary amines (pirilen, pachicarpine) well ⇒ + peroral introduction
- **Distribution:** the tertiary ones penetrate well through BBB ⇒ central effects (psychic disorders, tremor, etc.); quaternary amines do not penetrate through BBB
- **Excretion:** mainly by kidneys

GANGLIONIC BLOCKERS

Pharmacodynamics

Blockade of vegetative ganglia N-cholinergic receptors, that is "pharmacological" denervation

Vessels: acute hypotension, especially standing (orthostatic collapse!) because of:

- ***deprivation of venotonic innervation*** ⇒ venous dilatation ⇒ depositing blood in the venous system ⇒ ↓ venous return to the heart and preloading; redistribution of blood in accordance with the gravitation-factors ⇒ **unloading the lesser circulation** (↓ arterial blood pressure (ABP) in the pulmonary vessels), ↓ filling of cerebral vessels and pressure of cerebrospinal fluid
- ***deprivation of arteriotonic innervation*** ⇒ arterial dilatation ⇒ ↓ ABP in all segments of arterial bed ⇒ ↑ perfusion of organs, ↓ blood flow, ↑ O_2 extraction by tissues; ↓ postloading ⇒ **off-loading of the left ventricle and general loading on heart**
- ***deprivation of the central stimulating of the heart*** ⇒ ↓ stroke volume, minute blood volume, cardiac reflexes ⇒ **off-loading of the left ventricle and general loading on the heart**

GANGLIONIC BLOCKERS

Pharmacodynamics

Heart	↓ contractility, moderate tachycardia
GIT	motor activity — ↓, sphincters — contraction, secretion of salivary and gastric glands — ↓
Urogenital system	delay of urination, ↓ erection, ejaculation
Uterus	contractile activity stimulation (pachycarpine)
Eyes	mydriasis, paralysis of accommodation (cycloplegia, longsightedness), ↑ intraocular pressure
CNS	*tertiary* — sedation, tremor, psychical disorders

Practically all these effects did not find the clinical application (simultaneous uncontrolled cardiovascular dysfunction) and are considered as negative!

GANGLIONIC BLOCKERS

Indications

- Hypertensive crisis
- Managed (moment-to-moment) hypotonia during surgery
- Left ventricle failure
- In case of obstetric aid *(pachycarpine)*

Intensity of effects depends on the initial activity of the sympathetic and parasympathetic systems ⇒ depending on the purposes of application, reaction of patient doses are strictly individual! (initial doses — are minimal)

Overdosage

- ♦ Acute hypotonia (the accumulation of blood in the lower part of the body results in cerebral hypoxia)
- ♦ Rapid, thready pulse
- ♦ Pupils which are not reactive to light
- ♦ Dry warm skin
- ♦ Loss of consciousness

MYORELAXANTS

Drugs relaxing the skeletal muscles

- **Peripheral** (curare-type)
- **Central** (for treatment of spasticity): tranquilizers (diazepam), baclofen, etc.

Myorelaxants of peripheral action — the drugs relaxing the skeletal muscles due to depression of neuromuscular transmission at the level of postsynaptic membrane of the end plate

Classification

- **Nondepolarizing (competitive) action** — tubocurarine, diplacine, atracurium, pipecuronium bromide (arduan), pancuronium bromide, vecuronium bromide, etc.
- **Depolarizing action** — dithyline (succinylcholine, succametonium chloride, listenone)
- **Mixed action** — dioxonium

PHARMACOKINETICS OF MYORELAXANTS

Absorption: all of them — quaternary amines ⇒ are badly absorbed in the GIT ⇒ *only i.v. introduction*

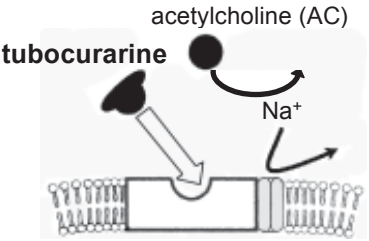
Distribution: nondepolarizing — the rapid phase of distribution, the slow phase of excretion; majority do not penetrate through BBB ⇒ have no central effects; atracurium metabolite penetrates well
⇒ with ↑ concentrations of seizure

PHARMACOKINETICS OF MYORELAXANTS

Drug	Elimination	Duration of action, min	Relative force
Isolinoline derivatives: tubocurarin atracurium	Kidneys (40%) Spontaneous (non-enzimatic and enzimatic hydrolysis of ether bonds)	> 35 20–35	1 1.5
Steroid derivatives: vecuronium	Liver (75–90%), Kidneys	20–35	6
Other: dithyline	Rapidly metabolised with pseudocholin esterase of plasma, liver (100%)	5–10	The other mechanism

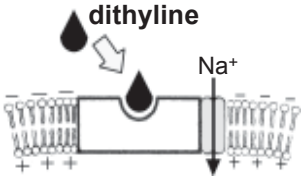
PHARMACODYNAMICS OF MYORELAXANTS

Nondepolarizing: blockade (mainly, by concurrent to Ach-type) of N-cholinoceptors of postsynaptic membrane of synapses of muscles ⇒ removal of block by the anticholinesterase drugs (↑ AC content)



Depolarizing: excite H-cholino-receptors (like Ach), causing steady depolarization of postsynaptic membrane ⇒ ↓ block of pseudocholinesterase

Phase I — depolarizing (muscular twitchings)



Phase II — desensitizing (myoparalytic effect)

N-cholinoceptors of skeletal muscles

PHARMACODYNAMICS OF MYORELAXANTS

Skeletal muscles:

- *nondepolarising:* in 1–2–5 min myasthenia, after that paralysis of muscles in a sequence: muscles of the eyes, jaws, extremities, trunk, diaphragm (breathing arrest); renewal in the reverse sequence
- *depolarizing:* within 1 min at first phase I — transitor fasciculations (muscular twitches), especially of the chest, stomach, then the phase II — relaxation of muscles of the neck, extremities, face, throat, diaphragm

Adverse effects

- **CVS:** *tubocurarine, atracurium* — ↓ ABP (ganglioblock, ↑ release of histamine); *pancuronium* — ↑ heart rate (HR) (vagolytic, simpathomimetic action); *dithyline* — arrhythmias (cholinomimetic action); in low doses and repeated introduction in 5 min — "-" ino-, chronotropic effects; in high — "+" ino-, chronotropic effects

MYORELAXANTS

Adverse effects

- **Bronchi:** *tubocurarine* — bronchial spasm
- **Electrolyte balance:** *dithyline* — hiperkaliemia
- **Eyes:** *dithyline* — ↑ intraocular pressure
- **GIT:** *dithyline* — ↑ intragastric pressure ⇒ vomiting, possibility of aspiration
- **Muscular pains in the postoperative period:** *dithyline* (in 20% of people)
- **Long-term block (> 2 hrs instead of 2–10 min) and apnoea:** *dithyline* in people with genetic insufficiency of cholinesterase
- **Interactions:** potentiation of action — by gaseous drugs for anaesthesia, antibiotics-aminoglycosides, by the low doses of locally anesthetics (high doses weaken block)

MYORELAXANTS DISTINCTIONS

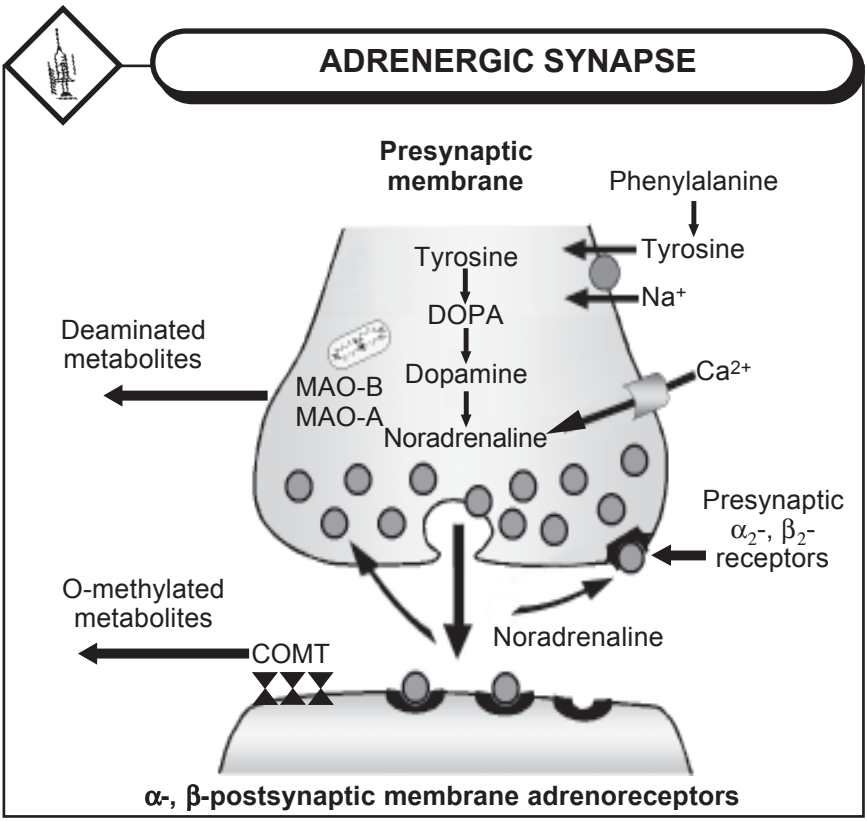
Indices	Concurrent	Depolarizing
Block mechanism	Competition with Ach	Steady membrane depolarization
Interaction with Ach	↓ Block	↑ Block
Removal of block (decurarization)	Anticholinesterase drugs (proserin)	Blood transfusion (pseudocholinesterase)
Loss of K^+ by the muscle	No	Present
Fibrillations	No	Marked (phase I)
Penetration to the muscular tissue	Does not penetrate	Penetrates deeply
Anaesthesia influence	Strengthens	Does not influence

MYORELAXANTS APPLICATION

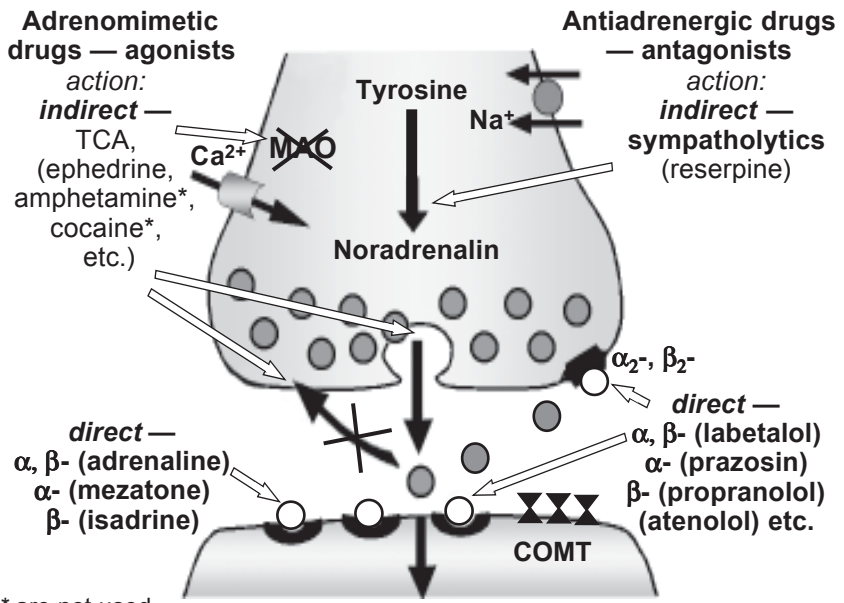
- Relaxation of the muscles of larynx and throat with intubation for the inhalation anaesthesia and APV (artificial pulmonary ventilation) *(dithyline)*
- Setting dislocations, reposition of bone fragments in case of fractures *(dithyline)*
- Operations on the abdominal and chest organs under anaesthesia with artificial ventilation of lungs (AVL)
- Convulsions in case of poisoning by substances which depress the respiratory center, in case of meningitis, cranocerebral traumas for transition to AVL
- Stupor, electroconvulsive therapy
- Spasticity with Parkinson disease, encephalitis and other dysfunctions of the pyramidal and extrapyramidal system *(central myorelaxants)*

Topic 3

ADRENOTROPIC DRUGS



POINTS OF ADRENOTROPIC DRUGS APPLICATION



BASIC EFFECTS OF ADRENORECEPTORS

ADRENORECEPTORS

α_1
- vasoconstriction
- mydriasis
- ↓ intestine
- urinary bladder, urethra, prostatic contraction

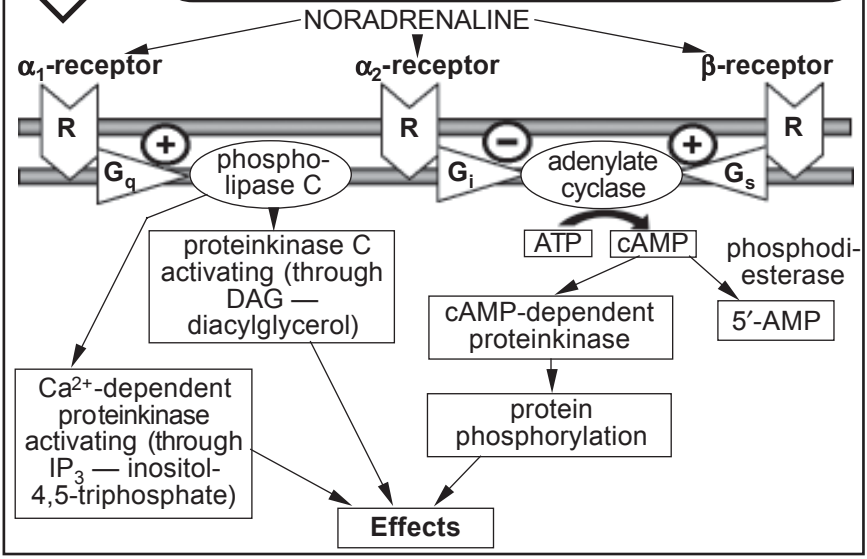
α_2
- ↓ release of NA
- ↓ insulin
- ↓ lipolysis
- ↑ thrombocyte aggregation

β_1
- ↑ heart rate and conductivity of heart

β_2
- vasodilatation
- ↓ tonus of bronchial tubes, uterus
- ↑ glycogenolysis

↑ lipolysis — **β_3**

WAYS OF CONJUGATION WITH EFFECTORS

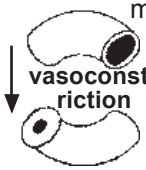


CLASSIFICATION OF ADRENOMIMETICS

- **α-, β-adrenomimetics:**
  - ✓ *direct action* — adrenaline
  - ✓ *indirect action* — ephedrine, dopamine
- **α-adrenomimetics:**
  mesatone (phenylephrine), naphthizin (naphazoline), noradrenaline, and central α_2- (clonidine, methyldopa, guanfacine)
- **β-adrenomimetics:**
  - ✓ *nonselective (β_1 + β_2)* — isadrine (isoprotenasol), orciprenaline (astmopent, alupent)
  - ✓ *selective (β_1)* — dobutamine
  - ✓ *selective (β_2):* short-acting (3–8 hrs) — salbutamol, phenoterol; long-acting (10–12 hrs) — clenobuterol, formoterol

PHARMACODYNAMICS OF ADRENOMIMETICS

Vessels of the skin (α) > kidneys (D_1, α) > intestine (α) > skeletal muscles (β_2, α) > lungs (β_2) > brain (α_2) > heart (β_1)



precapillars > arteries > venules > veins

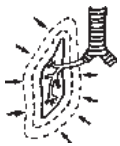
* small doses ↓, greater — ↑

Index	Adrenalin (α, β)	Mesaton (α)	Isadrin (β)
Vascular tone:			
skin (α)	↑↑	↑↑	0
skeletal muscles (β_2, α)	↓ or ↑*	↑	↓
kidneys (D_1, α)	↑	↑	↓
internal organs (α)	↓ or ↑*	↑↑	↓
common peripheral resistance	↓ or ↑*	↑↑↑	↓↓
Arterial pressure:			
systolic	↑↑	↑↑	0 or ↑
diastolic	↓ or ↑*	↑↑	↓↓
pulse	↑↑	0	↑↑

PHARMACODYNAMICS OF ADRENOMIMETICS

Heart "+" chrono-, inotropic,
↑ myocardial need in O_2

Index	Adrenaline (α, β)	Mesatone (α)	Isadrine (β)
Contractility	↑↑↑	0 or ↑	↑↑↑
HR	↓ or ↑	↓↓	↑↑↑
Stroke volume	↑	0, ↓, ↑	↑
Cardiac output	↑	↓	↑↑



Breathing (β_2, vessels of the respiratory passages — α_1)
Bronchodilatation, anti-edematic **(decongestive)**

PHARMACODYNAMICS OF ADRENOMIMETICS

Eye mydriasis,
α-agonists — ↑ outflux of fluid,
↓ intraocular pressure,
β-agonists — ↑ production

GIT motor activity — reduction,
sphincters — contraction

Urogenital system

uterus (α- and β_2-) — relaxation
(tocolytic action)

urinary bladder (β_2-) — relaxation

urethral sphincter and prostate (α-) — contraction

Exocrine glands *Apocrine sweat glands* (α-) — ↑ secretion

PHARMACODYNAMICS OF ADRENOMIMETICS

Metabolism ↑ glycogenolysis, ↑ blood glucose,
β_3 — fatty cells ⇒ ↑ lipolysis

Endocrine function modulates secretion of thyroxin, parathyroid hormone, calcitonin, gastrin, insulin and renin

CNS badly and unpenetrable through BBB (catecholamines, etc.) — nervousness, "feeling of inevitable catastrophe" (large doses)

well penetrable through BBB (indirect action — ephedrine, amphetamines, cocaine, etc.) — psychostimulation, insomnia, etc.

PHARMACOKINETICS OF ADRENOMIMETICS

- **Absorption in GIT:** catecholamines (adrenaline, noradrenaline, dopamine, isadrine) are badly absorbed in contrast to phenylalkilamines (ephedrine, amphetamine, tyramine, etc.)
- **Introduction:** adrenaline — s.c., i.m., i.v.; *noradrenaline, dopamine — only i.v.* (subcutaneous — bad absorption because of acute ↓ of vessels up to the ischemic necrosis); majority of other ones depending on purpose — per oral, s.c., i.m., i.v., inhalation, transdermal
- **Distribution:** catecholamines badly penetrate through BBB; indirect mimetics (ephedrine, amphetamine, inhibitors of MAO, etc.)
- **Biotransformation:** catecholamines are quickly metabolized by MAO and COMT + rapid neuronal capture ⇒ short action (5–30 min); synthetic ones are metabolized by other enzymes or with participation of only one ⇒ more long-acting
- **Excretion:** mainly by kidneys

REPRESENTATIVES OF ADRENOMIMETICS

Adrenaline (epinephrine) — α = β

- ♦ Cardiostimulator (+ chrono-, inotropic effect, acute ↑ consumption of oxygen by myocardium). In case of i.v. introduction bradycardia can occur!
- ♦ Vasoconstrictor but delates the vessels which contain β-receptors (skeletal muscles, heart, cerebrum, liver, lungs)
- ♦ ↑ SAP, ↓ or ↑ DAP and general peripheral resistance *(depending on the ways and dose introduction the two latter effects change!)*
- ♦ In case of α-adrenoblockers introduction "perversion" (adrenaline reversal) of effects on vessels — ↓ ABP
- ♦ Bronchodilatator, tocolytic
- ♦ Functional antagonist of insulin
- ♦ ↓ intraocular pressure, mydriatic

REPRESENTATIVES OF ADRENOMIMETICS

Noradrenaline — $\alpha_1 = \alpha_2 > \beta_1 > \beta_2$

- Vasoconstrictor (↑ SAP, ↑ DAP, ↑ peripheral resistance)
- "+" inotropic effect
- Only i.v. introduction!

Mesatone (phenylephrine) — α

- Vasoconstrictor (↑ SAP, ↑ DAP)
- Mydriatic
- Antiedematous (decongestive)
- Is not inactivated by COMT ⇒ action is longer!

Isadrine — $\beta_1 = \beta_2$

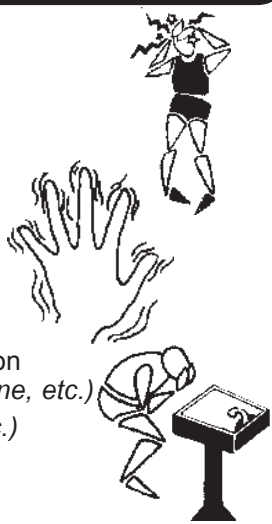
- Vasodilatator (↑ cardiac output, no influence or a little ↑ SAP + ↓ DAP, peripheral resistance)
- "+" chrono-, ino-, dromotropic effects
- Bronchodilatator, ↓ tone of GIT, uterus, ↑ CNS

INDICATIONS TO ADRENOMIMETICS APPLICATION

- Heart arrest — *adrenaline*
- Acute hypotensions (shock, collapse) — *dopamine, mesatone, noradrenaline*
- Cardiogenic shock — *isadrine, dobutamine*
- Anaphylactic shock — *adrenaline*
- Hypoglycemia and insulin overdose — *adrenaline*
- Lowering of the regional blood flow (operations, local anaesthesia) — *adrenaline, mesatone*
- Bronchial asthma — *β-adrenomimetics (salbutamol, astmopent)*
- Threat of preterm labour (miscarriage) — *phenoterol, hexoprenaline*
- Rhinitis — *naphthizin, galazoline*
- Ophthalmology (glaucoma, diagnostics) — *mesatone, adrenaline, etc.*

ADVERSE EFFECTS OF ADRENOMIMETICS

- ✓ ↑ ABP (strokes, pulmonary edema)
- ✓ Arrhythmias, angina prectoris, myocardial infarction
- ✓ Development of necrosis in case of subcutaneous introduction *(noradrenaline)*
- ✓ Dryness in to the nose *(α-adrenomimetics)*
- ✓ Dryness in the mouth *(β-adrenomimetics)*
- ✓ Irritation of conjunctiva, mydriasis
- ✓ Tolerance (down-regulation) of receptors
- ✓ Tachyphylaxis as a result of rapid exhaustion `of noradrenaline presynaptic pool *(ephedrine, etc.)*
- ✓ Excitation, insomnia, tremor *(ephedrine, etc.)*
- ✓ Psychical and physical dependence *(ephedrine, amphetamines)*



CLASSIFICATION OF ANTIADRENERGIC DRUGS

- ♦ **α-, β-adrenergic blockers:** labetalol, carvedilol, proxodolol
- ♦ **α-adrenergic blockers:**
  - ✓ *nonselective (post α_1 + pre α_2)* — dihydroergotamine, aminasin, nicergoline (sermion), phentolamine, piroxane
  - ✓ *selective (α_1)* — prazosin, doxazosin (cardura), terazosin, tamsulosin (omnic)
- ♦ **β-adrenergic blockers:**
  - ✓ *nonselective (β_1 + β_2)* — propranolol (anapriline), nadolol, thymolol
  - ✓ *selective (β_1)* — atenolol, metoprolol, bisoprolol, acebutolol, celiprolol
- ♦ **Sympatholytics** — reserpine, octadin

α-ADRENERGIC BLOCKERS

Dihydroergotamine, phentolamine, pirroxane, prazosin, doxazosin, etc.

Pharmacodynamics

Vessels	acute hypotension (orthostatic collapse!), improvement of intraorgan circulation of blood
Heart	reflex tachycardia
GIT	motor activity — ↑, sphincters — ↓, secretion — ↑
Eyes	miosis
Glands	↓ sweating, nasal stuffiness
Urogenital system	relaxation of sphincters and muscles, ↑ erection

α-ADRENERGIC BLOCKERS

Indications

- Hypertensic crisis — *aminasin*
- Arterial hypertension — α_1-blockers *(prazosin, etc.)*
- Cerebral stroke — *nicergolin*
- Diseases of peripheral vessels (endarteritis, Raynaud's disease)
- Retention of urination benign prostatic hyperplasia (BPH) sexual dysfunctions — *doxazosin, terazosin*
- Migraine — *dihydroergotamine, etc.*
- Excessive local vasoconstriction with α-adrenomimetics

β-ADRENERGIC BLOCKERS

1964 James BLACK developed the first adrenegic blocker (propranolol) and histamine blocker (cimetidine) a Nobel Prize winner (1988)

Classification

- **Nonselective ($\beta_1 + \beta_2$):** propranolol (anapriline, obsidan, inderal), nadolol, timolol
- **Selective (β_1):** atenolol, metoprolol, bisoprolol, acebutolol, celiprolol
- **With the intrinsic sympathomimetic activity:** oxprenolol, pindolol

β-ADRENERGIC BLOCKERS

Pharmacodynamics

Vessels ↓ ABP in people suffering from hypertension (!) (DAP stabilization in 2 weeks)

Heart
- "–" chrono-, ino-, dromotropic effects
- ↓ myocardial need in O_2
- cardioprotective:

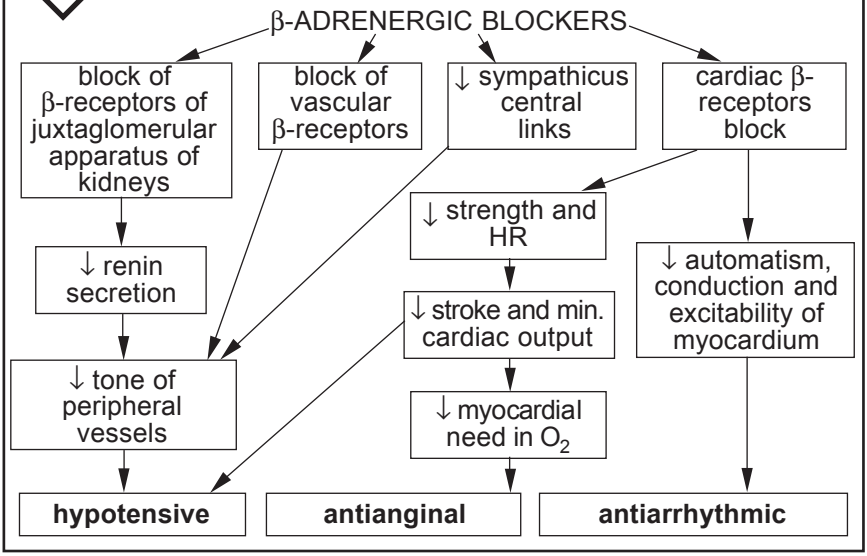
✓ ↓ lipolysis from ↓ time of oxidization of free fatty acids (FFA) ⇒ stabilization of cellular and lysosomal membranes

✓ antioxidant properties

✓ facilitates dissociation of oxyhemoglobin

✓ release prostacycline from the vascular endothelium ⇒ antiaggregate action

β-ADRENERGIC BLOCKERS



β-ADRENERGIC BLOCKERS

Pharmacodynamics

Breathing bronchial spasm (especially nonselective)

CNS penetrable through BBB *(anaprilin, metoprolol, etc.)* — stress-protective action

Eye ↓ intraocular pressure

Metabolism ↓ sugar of blood,
↑ cholesterol,
↓ lypolisis,
↓ renin production

✓ Some of them *(anaprilin, metoprolol, etc.)* have local anaesthetic activity (potassium channels blocking)

✓ Some *(pindolol, oxeprenolol, etc.)* have intrinsic sympathomimetic activity

β-ADRENERGIC BLOCKERS

Pharmacokinetics

- **Absorption:** well absorbed, peak of concentration in 1–3 hrs
- **Bioavailability:** "first pass elimination"
- **Distribution:** even, lipophilic (anaprilin, metoprolol, etc.) well penetrate through BBB
- **Excretion:** with urine (different $T_{1/2}$)

Classification according to duration of action:

➢ **long-acting** ($T_{1/2}$ — 6–24 hrs):
nadolol, timolol, atenolol, bisoprolol, betaxolol

➢ **middle time** of action ($T_{1/2}$ — 3–6 hrs):
anaprilin, pindolol, metoprolol

➢ **short-acting** ($T_{1/2}$ — 1–4 hrs):
oxprenolol, acebutolol

β-ADRENERGIC BLOCKERS

Indications

- ♦ Arterial hypertension, especially accompanied with hypersympathicotonia
- ♦ Ischemic heart disease (IHD) in case of predominance of nervous-metabolic factor in pathogenesis
- ♦ Tachyarrhythmias, especially in case of predominance of sympathetic status
- ♦ Dissecting aneurism of aorta
- ♦ Bleeding from esophageal varicose veins
- ♦ Glaucoma — *timolol*
- ♦ Hyperthyroidism — *propranolol*
- ♦ Neurological disorders (migraine, alcoholic abstinence) — *propranolol*

β-ADRENERGIC BLOCKERS

Adverse effects

- **CVS:** arrhythmogenic action (disturbance of AV-conduction, bradycardia, etc.), heart failure (HF), hypotension, oedemas (↓ renin)
- Bronchial spasm
- Spasm of coronal and peripheral vessels ("intermittent claudication")
- Hypoglycemia
- Thyroidal dysfunction (↓ triiodothyronine)
- Atherogenic action
- ↓ thrombocyte aggregation
- ↑ intestinal peristalsis
- Contraction of pregnant uterus
- Desensitization of receptors
- "Rebound" syndrome with ↑ myocardial ischemia

β-ADRENERGIC BLOCKERS

Peculiarities of drugs which have intrinsic sympathomimetic activity

Oxprenolol, pindolol, etc.

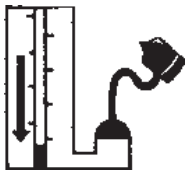
- Less pronounced ↓ HR and strength of contraction, cardiac output at rest and during sleep
- To lesser extent narrow the coronal, peripheral arteries and bronchial tubes
- Less ↓ ABP
- Moderate cardioprotective action
- Do not deteriorate the atherosclerosis course
- Cause the rebound syndrome more seldom

SYMPATHOLYTICS

Antiadrenergic drugs of indirect action
(↓ synthesis, depositing and release of catecholamines in the synaptic chain)

Reserpine (alkaloid of rauwolfia, the sum of alkaloids — raunatine), octadine (guanetidine), metidopa

Pharmacodynamics

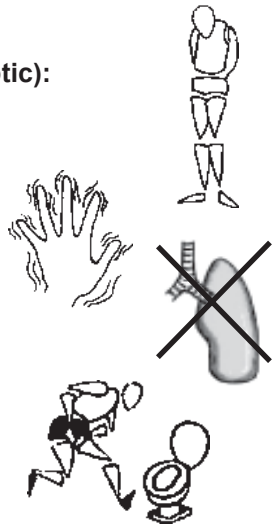


Vessels	slowly developing (reserpine in 5–14 days!), moderate and steady (1–3 month after intake!) hypotension
Heart	↓ HR, cardiac output
CNS	penetrate well through BBB ⇒ psychosedative (methyldopa) and neuroleptic (reserpine) action
GIT	motor activity, tone, secretion — ↑

SYMPATHOLYTICS

Adverse effects

- **CNS (especially reserpine as a neuroleptic):** somnolence, myasthenia, depressions, extrapyramidal disorders
- **Vagotonic action:**
  - ✓ CVS — bradycardia, oedemas
  - ✓ bronchial spasm
  - ✓ swelling of the mucous and parotid glands, hyperhydrosis
  - ✓ diarrhea, exacerbation of peptic ulcer
- **Allergic reactions** urticaria-like



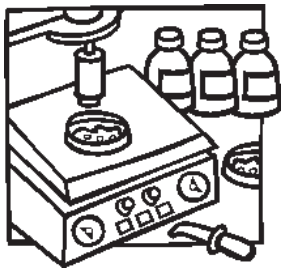
DRUGS AFFECTING AFFERENT INNERVATION

Topic 4

DRUGS WHICH IRRITATE AND PROTECT RECEPTORS

DRUGS WHICH IRRITATE RECEPTORS

- **Irritants of distractive action**
- **Emetics**
- **Expectorants**
- **Bitters**
- **Laxatives**
- **Biligenic**



IRRITANT DRUGS

- **Herbal origin** — menthol and on its menthol-based drugs (validol, ointments “Menovasin”, “Efcamion”), seeds of mustard (mustard plasters), terpentine purified oil (turpentine), etc.
- **Synthetic** — solution of ammonia, finalgon, methylsalicylate, etc.

Pharmacodynamics

nonspecifically exciting (depolarising) the sensitive nerve endings of skin and mucous, render the action:

✓ local

✓ reflex

✓ neurohumoral

PHARMACODYNAMICS OF IRRITANTS

- **Local action:** excitation of endings + local output autacoids (histamine, serotonin, bradykinin, prostaglandin) ⇒ irritation (pain, hyperemia, oedema)
  +
- **Reflex** ⇒
  - ✓ *vasodilatating* with the improvement of organ trophism
  - ✓ *“allowing”:* ↑ functions of segmentary located organs
  - ✓ *“distracting”:* ↓ painful sensations
- **Neurohumoral:** local ↑ autacoids ⇒ their general action on CNS + influence of stream of ascending afferent impulses ⇒ ↑ enkephalins and endorphins in CNS, ↓ mediators of pain (P substance, somatostatin, etc.), ↑ production of releasing-hormones of hypothalamus, adrenocorticotropic hormone (ACTH), thyrotropic hormone ⇒ *antiinflammatory* action

APPLICATION OF IRRITANTS

Menthol — irritates cold receptors ⇒ local anesthesizing, sedative, antiemetic, reflex change of vascular tone ⇒ arthralgias, myalgias, diseases of upper respiratory ways, migraine; *validol* — neuroses, hysterias, motion sickness, angina pectoris attack of middle severity

Solution of ammonia — exciting the sensitive endings of nerves of the upper respiratory ways, reflexly stimulates the respiratory center ⇒ *inhalation* — syncope, alcoholic intoxication, *locally* — antiseptic

Mustard seeds — diseases of respiratory organs, angina pectoris, neuralgias, myalgias

Terpentine purified oil (turpentine): *locally* — myosis, arthrites, neuralgias, *inhalations* — bronchitis

EMETICS

- **Central action** — apomorphine
- **Reflex** — drugs of termopsis, ipecacuanha, copper sulfate, sodium chloride, etc.

Apomorphine hydrochloride

Pharmacodynamics

Direct dopaminomimetic ⇒ ↑ trigger zone of vomiting center; desulfiram-like action

Indications: acute poisonings (in case of difficulty of gastric lavage), medical treatment of chronic alcoholism

Contraindications: burns of stomach by acids and alkalines, peptic ulcer, pulmonary bleedings, atherosclerosis, organic deffects of the heart and CNS, elderly age

In case of poisonings by the substances which depress the vomiting center is uneffective!

EXPECTORANTS

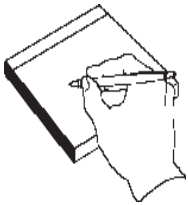
Classification

- **Secretomotor (stimulating expectoration):**
  - ✓ *reflex action* — herb of thermopsis, root of milkwort, etc.
  - ✓ *direct action* — herb of thyme, root of marsh mallow, rhizome of Jacob's ladder, leaf of plantain, mucaltin, pertussin, terpinhydrate, breast tea, potassium iodide, etc.

- **Mucolytic (bronchosecretolytic):** acetylcystein (ACC), bromhexine, ambroxol (lasolvan)

EXPECTORANTS

Pharmacodynamics



Secretomotor drugs

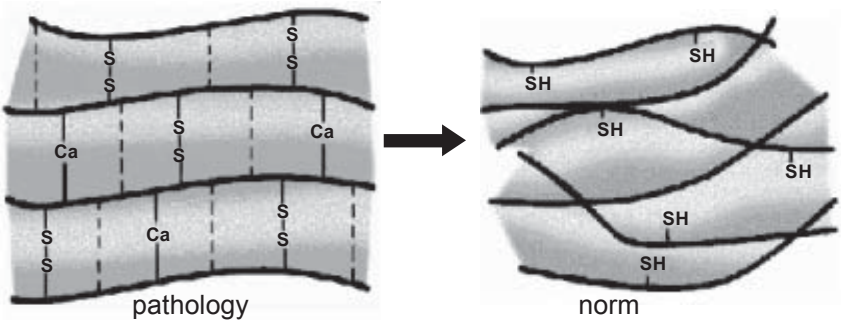
- **Reflex action:** irritating receptors of the stomach, reflexly ↑ secretion of bronchial glands, activity of ciliated epithelium, bronchial muscles contraction
- **Direct action:** excreting with the bronchial glands, ↑ water flow, accelerate liquefaction of sputum, render the coating action on the mucous membranes

EXPECTORANTS

Pharmacodynamics

Mucolytic drugs

Acetylcystein: donator of sulfhydryl groups, breaks the disulfide bonds of mucopolysaccharides and mucus viscosity



pathology norm

Ambroxol: ↑ surfactant contents, immunoglobulin A and G, ↓ viscosity of mucus and its adhesion to the surface of bronchial tubes

EXPECTORANTS

Indications

Bronchitis, pneumonia, sanation of the bronchial tree in pre- and postoperative periods, mucoviscidosis, poisoning with paracetamol *(ACC)*

Adverse effects

Nausea, vomiting, allergy, arterial hypotension and bronchial spasm in case of i.v. introduction *(ACC)*

Contraindications

- **Secretomotor** — diseases with susceptibility to pulmonary bleeding, organic defeats of CNS and CVS, peptic ulcer
- **Mucolytic** — the first trimester of pregnancy, individual hipersensitization

PULMONARY SURFACTANTS

Curosurf, exosurf, beractant

Pharmacodynamics

As superficially active substances temporarilly substitute a natural surfactant (antiatelectatic factor) in case of its formation failure, restore adequate breathing (oxigenation)

Indications

Respiratory distress-syndrome, associated with surfactant deficiency in new-born and prematurely born children

They are used only in the hospital!

BITTERS

✓ **True:** root of dandelion, herb of centaury

✓ **Aromatic:** infusion of capsicum, wormwood, rhizome of sweet flag, appetizing tea, juice of plantain leaves, plantaglucide

Pharmacodynamics

Irritate taste receptors of mucous membranes of mouth cavity, reflexly ↑ excitability of hunger center, secretion of gastric juice and appetite, ↑ digestion

Indications

Hypoacidic, chronic atrophic gastritis, anorexia nervosa, after surgical interventions

CLASSIFICATION OF LAXATIVES

According to localization

- **Enhancement of motor function along the whole length of the intestine:**
  - *salt* — sodium and magnesium sulfate
  - *polyatomic alcohols* — xylitol, lactulose
  - *increasing intestine content volume* ("bulk-laxatives") — laminaria, bran, agar, forlax, flax-seed, etc.
  - *favours softening of stool* (softening) — vaseline, almond, sesame, sunflower oil
- **Enhancement of mainly the small intestine motility** — castor (ricine) oil
- **Enhancement of mainly the large intestine motility:** *herbal* (anthraglycosides) — rind of buckthorn, leaves of senna, cafiol, regulax; *synthetic* — bisacodil, phenolftalein (purgen), guttalax

CLASSIFICATION OF LAXATIVES

According to effect

- **Aperients *(aperitiva)*:**
  - *"bulk-laxatives" drugs* — laminaria (lamineride), agar-agar
  - *softening* — almond, olive, sunflower, sesame, vaseline oil
- **Laxatives *(purgantia, laxantia):***
  - *herbal* — drug of rhubarb, buckthorne, senna, castor oil
  - *synthetic* — phenolftalein, isafenine, bisacodil, guttalax
- **Evacuents *(drastica):***
  - salt (sodium and magnesium sulfates), Karlovy Vary and Morshin salts

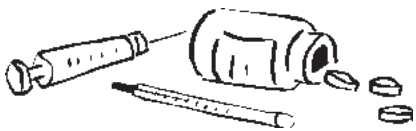
CLASSIFICATION OF LAXATIVES

According to mechanism of action

- Causing *chemical irritation of receptors* of mucous membrane: phytodrugs containing anthraglycosides (rind of buckthorn, garden-stuffs of buckthorn, leaves of senna), castor oil; synthetic (isafenine), etc.
- Causing *mechanical irritation* of receptors of mucous membrane (softening of content and increase of its volume): osmotic (salt laxatives), laminaria, etc.
- Assisting in softening the stool: vaseline, almond, olive oil

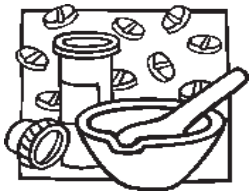
APPLICATION OF LAXATIVES

- Poisoning *(salt — magnesium sulfate)*
- Chronic conspiration *(herbal and synthetic laxatives)*
- Preparation of patient to the operation, X-ray exam, colonoscopy, etc. *(herbal and synthetic laxatives)*
- Cracks of the anus, hemorrhoids *(drugs of senna, buckthorn, vaseline oil)*
- Application of antihelminthic drugs of “first generations”
- Constipations caused by hyperacid conditions



CLASSIFICATION OF BILIGENIC DRUGS

- **Stimulating bile production (cholesecretics):**
  - containing *bilious acids and bile* — cholenzyme, allochol, liobil
  - *herbal origin* — fruits of wild rose (cholosas), flowers of immortelle
  - *synthetic* — oxafenamide, ciqualone
- **Stimulating bile exrection (cholekinetics):**
  - *cholecystokinetics* — magnesium sulfate, xylit
  - *spasmolytics* — atropine, papaverine, no-spa, dibasol, aminophylline



PHARMACODYNAMICS OF BILIGENIC DRUGS

Choleretics

- ↑ bile production by hepatocytes, its flow and entering the gall-bladder prevent gall-stones formation, ↑ secretory and motive activity of GIT

Cholekinetics

- *Cholecystokinetics* — cause cholecystokinin secretion, contraction of gall-bladder and relaxation of sphincters with the output of bile in to duodenum
- *Spasmolytics* — lower tone of biliary tracts, duct sphincters, gall-bladder

APPLICATION OF BILIGENIC DRUGS

Choleretics

Chronic cholecystitis, cholangitis, hepatitis, cirrhosis of liver, chronic constipation, dyskinesis of biliary tracts

Cholekinetics

Cholecystokinetics — atony of the gall-bladder at dyskinesis, chronic cholangitis and cholecystitis, hypoacid states

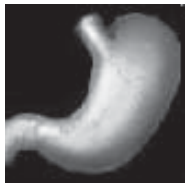
Spasmolytics — hepatic colic with cholelithiasis, acute cholecystitis, attack of chronic cholecystitis, cholangiohepatitis

ADVERSE EFFECTS OF BILIGENIC DRUGS

Choleretics

Diarrhea, allergic reactions

Contraindications — acute hepatitis, cholangitis, cholecystitis, jaundice, pancreatitis, peptic ulcer, gastroduodenitis at the acute stage



Cholekinetics

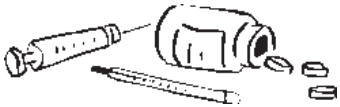
Cholecystokinetics — diarrhea, allergy

Contraindications — cholelithiasis, acute hepatitis, cholangitis, cholecystitis, hyperacid gastritis, peptic ulcer

Spasmolytics — constipation, hypotension

DRUGS PROTECTING RECEPTORS

- Local anaesthetics (LA)
- Astringents
- Coating substances
- Antacids
- Adsorbent drugs



LOCAL ANAESTHETICS

Substances which block reversibly peripheral nervous impulses transmission at the site of direct application; cause the loss of pain sensitivity, in large concentrations — sensory block at the site of introduction

Types of local anaesthesia

- **Terminal** (surface, application, superficial)
- **Infiltration**
- **Regional** and its varieties (conductive, epidural, spinal, intraosseous)

HISTORY OF DISCOVERY

1859 A. NIEMANN separated alkaloid cocaine from the bush *Erythroxylon coca*

1879 V. C. ANREP defined local anesthetic properties of cocaine

1882–1884 the first operations with the use of cocaine (I. N. CATSAUROV, C. COLLER, A. I. LUKASHEVICH) have been executed

V. C. Anrep

1905 A. EINHORN synthesized novocaine

1943 N. LEFGREN synthesized lidocaine

DEMANDS TO LOCAL ANESTHETIC DRUGS

- High selectivity
- Wide spectrum of therapeutic action
- Long-acting
- Sterility
- Low toxicity (especially on CNS and CVS)

CLASSIFICATIONS OF LOCAL ANESTHETICS

According to chemical structure

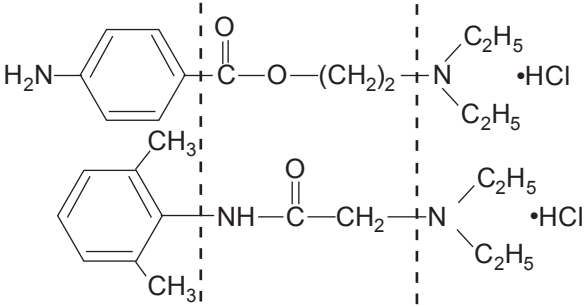
- **Complex ethers** (esters) — novocaine (procaine), dicaine (tetracaine), benzocaine (anesthezin), cocaine
- **Amides** — trimecaine, lidocaine (xicaine), mepivacaine, ultracaine, bupivacaine, piromecaine
- **Other chemical groups** — pramoxin, etc.

According to duration of action

- **Short** (up to 30–50 min) — novocaine
- **Middle** (up to 45–90 min) — lidocaine, trimecaine, mepivacaine, ultracaine
- **Long** (90 min and more) — bupivacaine, dicaine, etidocaine

CHEMICAL STRUCTURE AND PROPERTIES

Lipophilic group | *Intermediate chain (ether or amide group)* | *Hydrophilic group*

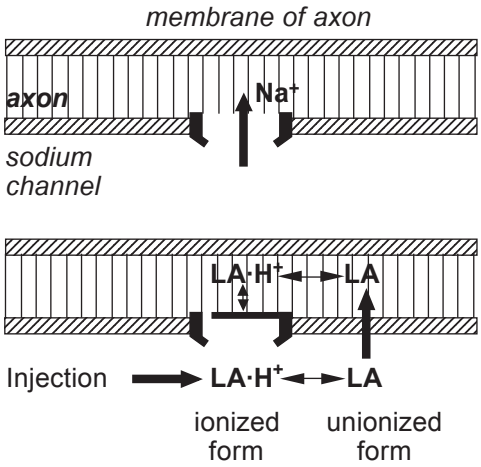


Ethers: novocaine (unstable — spontaneous hydrolysis, in case of heating)

Amides: lidocaine (stable, insensitive to heat)

- Weak bases, badly water-soluble
- Made as **hydrochloride** salts, water-soluble and well penetrable to the tissues

PHARMACODYNAMICS OF LOCAL ANESTHETICS (LA)



- ✓ In the organism are hydrolysed **(in alkaline medium!)**
- ✓ The unionized (lipophilic) bases penetrate well through the membrane and again deionized
- ✓ The ionized forms binding with receptors on the internal side of the membrane **block sodium channels**
- ✓ Potential of action does not generate

PHARMACODYNAMICS OF LOCAL ANESTHETICS

Type of fibres	Type of sensitivity	Diameter, mcm	Myeli-zation	Blockade
Type A				
α	Motor	15–20	Complete	+
β	Tactile	5–12	Complete	++
γ	Contractile	3–6	Complete	++
δ	Pain, temperature	2–5	Complete	+++
Type B	Preganglionic vegetative	< 3	Weak	++++
Type C	Pain (post-ganglionic)	0.3–1.2	–	++++

PHARMACODYNAMICS OF LOCAL ANESTHETICS

Blockade of nerve fibres depends on:

✓ *size:* thin ones are easier blocked than large ones

✓ *myelinization:* nonmyelinic are more liable than myelinic (3 successive ganglia)

✓ *location in the nerve tract*

Sequence of blockade:

thin fibres of C and B type, then A type fibres

Clinically: at first loss of pain, then olfactory, taste, temperature, and then tactile sensitivity and depression of motor functions

PHARMACOKINETICS OF LOCAL ANESTHETICS

Absorption

- Injection or application introduction
- The ↑ concentration, volume, blood supply, the better penetration
- Binding with proteins: novocaine — 6%, ultracaine — 95%

Distribution

- Well vascularized → badly

Metabolism

Hydrolized:

- *ether* — rapidly in blood and tissues with pseudocholinesterase ($T_{1/2}$ < 5 min)
- *amide* — in the liver with participation of microsomal enzymes

Excretion

- Mainly by kidneys

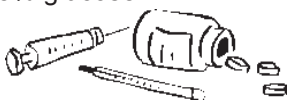
ACTIVITY AND EFFECT RATE OF LOCAL ANAESTHETICS

Activity and effect rate of local anaesthetics depend on:

- **chemical structure and properties:**
  - degree of dissociation
  - lipid-solubility
  - pH solution
  - pH at the site of injection
- **concentration**
- **volume of solution**
- **site of introduction**
- **blood supply and presence of vasoconstrictor**

INDICATIONS TO LOCAL ANAESTHETICS

- **Infiltration anaesthesia** — novocaine, trimecaine, lidocaine, mepivacaine, ultracaine *in low concentrations* (0.25–0.5%)
- **Regional anaestesia**
  - *Block anaesthesia* — novocaine, trimecaine, lidocaine, mepivacain, ultracaine, bupivacaine, etc., but in *higher concentrations* (1–4%) *and less amount*
  - *Epidural anaesthesia* — lidocaine (1.5–2%), bupivacaine (0.5%) + vasoconstrictors
  - *Subarachnoid (spinal) anaesthesia* — they often use hyperbaric (more high density, than cerebrospinal fluid) solutions of local anaesthetics, adding 5% glucose



INDICATIONS TO APPLICATION OF LOCAL ANAESTHETICS

- **Terminal anaesthesia** — dicaine (0.25–1%), anaesthesin, piromecaine, lidocaine, trimecaine in concentrations 1–5%
  - endoscopic and other clinical-laboratory researches
  - in urology and proctology
  - in ophthalmology
  - diseases of the skin accompanied with itch, wounds, ulcers, burns
  - GIT diseases (ulcers, gastrites, diarrhea)
- **Arrhythmias** — lidocaine (2–10%)

ADVERSE EFFECTS OF LOCAL ANAESTHETICS

- **CNS** — stimulating (cocaine) and inhibiting (majority): nystagmus, trembling, tonicoclonic convulsions with subsequent death
- **CVS** — "–" dromo- and bathmotropic effects; except for cocaine, "–" inotropic effect, hypotension
- **Blood** — methemoglobinemia (prilocaine in doses < 10 mg/kg)
- **Allergic reactions of slow and immediate type (up to the anaphylactic shock!)** — ether anaesthetics
- **Tachyphylaxis** — epidural and spinal anaesthesia
- **On tissue of nerve at the site of introduction** — remaining block; dicaine — ↑ intraocular pressure, corneal oedema

ASTRINGENTS

- ✓ **Organic** — oak rind, tannin, whortleberry, sage, knot-grass, greater celandine, fruits of walnut
- ✓ **Inorganic** — salts of metals (lead, bismuth, copper, zinc, silver)

Pharmacodynamics

Coagulate the proteins on the mucous membrane surface, forming a film which protects the nerve endings

Organic — form insoluble albuminates, make an effect only on the superficial layer of proteins

ASTRINGENTS

Pharmacodynamics

Inorganic — form albuminates which are capable to dissociate, render the *astringent, irritating, cauterizing, bactericidal* action

Schmiedeberg row

Al, Pb, … Fe, Cu, Zn, Ag, … Hg

Albuminates dense ⟶ Albuminates loose

astringent ⟶ irritating ⟶ cauterizing

Depending on concentration the effect ↑

keratoplastic ⟶ *keratolytic*

INDICATIONS TO ASTRINGENTS

- **Inflammatory diseases of GIT** — extracts, decoctions, rinses, enemas *(sage, camomile, oak rind)*
- **Acute laryngitis, tracheitis, bronchitis** — *sage, camomile, leaf of eucalyptus*
- **Conjunctivitis, urethrits** — *zinc and copper sulfate*
- **Burns, ulcers, traumas of skin and soft tissues** — organic *(sage, camomile, oak rind)*
- **Acute poisoning by alkaloids, salts of heavy metals** — *tannin* (0.5%)

COATING DRUGS

Starch, flax seeds, salop tubers, marsh root mallow, aluminium salt

Pharmacodynamics

Form a coat protecting the nerve endings from irritation on the surface of damaged mucous

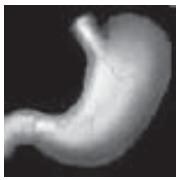
Indications

Symptomatic treatment!

- Inflammatory diseases of the intestine, liver and pancreas
- Poisoning
- Trophic ulcers, purulent wounds

ANTACIDS

- ✓ **Absorbing** — sodium hydrocarbonate, calcium carbonate, magnesium oxide
- ✓ **Unabsorbing** — aluminum-containing (phosphalugel), aluminum-magnesium-containing (almagel-neo, maalox, etc.)
- ✓ **Combined** — Bi-containing (vicair, vicalin)



Pharmacodynamics

- ♦ **Antacid action:** selected (!) HCl neutralization, at ↑ pH up to 3.5 the free ions of hydrogen bind by 99% ⇒ arrest of retrodiffusion and damage of gastric mucous by HCl

ANTACIDS

Pharmacodynamics

- **Adsorbing action (Al-containing):** adsorption of pepsin, biliary acids, toxins, bacteria ⇒ ↓ proteolytic activity of gastric juice and damaging action of aggression factors, depression (not eradiction) of *Helicobacter pylori*
- **Cytoprotective:** ↑ prostaglandins, bind the growth factors and ↑ their binding to the ulcer surface, ↑ proliferation and differentiation of cells ↑ angiogenesis and regeneration of tissues in the zone of defeat ⇒ ↑ closing of deffect; ↑ formation of mucus and fucoglycoproteids ⇒ ↑ mucous resistance
- **Coating and/or astringent (Bi-containing):** ↓ contact of aggressive factors of gastric medium with the wall of the organ and is accompanied with ↑ defense and resistance of the mucous
- **Weak antiinflammatory (Bi- and Mg-containing)**

ANTACIDS

Indications

- **Additional treatment** of acid-dependent diseases of GIT (peptic ulcer, reflux-gastritis, functional dyspepsia, etc.), pancreatitis, hepatitis, irritable intestine syndrome and **symptomatic treatment** of heartburn (at ↑ basal secretion — an hour before the meal; at ↑ stimulated secretion — in an hour after the meal, repetition in 3 hrs and for the night)
- **Acidosis** and all associated extreme conditions — *sodium hydrocarbonate* (i.v.)

ANTACIDS

Adverse action

- **Nausea, vomiting, meteorism**
- **Absorbing** — phenomenon of “acid ricochet”, hypernatremia, oedemas, alkalosis, hypocaliemia, myasthenia
- **Agents of aluminium** — constipation, hypophosphatemia, hypercalcemia; in case of long-term application of high doses — osteopathy, encephalopathy, nephropathy
- **Agents of magnesium** — diarrhea, myasthenia, hypophosphatemia, hypercalciemia, risk of nephrolithiasis, sedation
- **Agents of bismuth** — diarrhea, depositing in mucous and bones, paresthesia, memory impairment

ADSORBENTS

Activated carbon, carbolong, argil, enterosorbents — enterosgel, polysorb

Pharmacodynamics

Adsorb the substances on their surface

Indications

- Acute poisoning
- Meteorism
- Diarrhea
- Anticholesterolemic
- Obesity, diabetes mellitus

FILM-FORMING DRUGS

Medical glue, oblecol, furoplast, lifuzol

Pharmacodynamics

With application on the wound or ulcer they form a dense polymeric elastic protective layer

Indications

- For treatment of scratches, burns, postoperative wounds, trophic ulcers
- In combination with wound-healing, antimicrobial, anaesthetic drugs

Part III

DRUGS AFFECTING THE CENTRAL NERVOUS SYSTEM

Topic 5

ANAESTHETIC DRUGS. ALCOHOLS

SUBSTANCES AFFECTING CNS

- **Depressing functions of CNS:**
  - general anaesthetic drugs
  - hypnotics
  - anticonvulsants
  - non-narcotic analgesics
  - *psychotropic* drugs (narcotic analgesics, psychodysleptics, neuroleptics, tranquilizers, psychosedatives)
- **Stimulating functions of CNS:**
  - *psychotropic* (psychostimulants, antidepressants)
  - nootrops, adaptogens
  - analeptics

CREATION OF GENERAL ANAESTHETIC DRUGS

1842 C. LONG applied ether general anaesthesia for the first time

1846 October, 16 V. MORTON showed in public the anaesthetic action of ether anaesthesia (birthday of general anaesthesia)

C. Long

CREATION OF GENERAL ANAESTHETIC DRUGS

1847 February, 1 F. I. INOZEMTSEV applied ether anaesthesia for the first time in Russia

F. I. Inozemtsev

1847 N. I. PIROGOFF applied ether anaesthesia on the battle-field for the first time

1847 D. SIMPSON discovered anaesthetic action of chloroform

N. I. Pirogoff

After 100 years the first fluorine-containing anaesthetic — halothane — is used

DEMANDS TO GENERAL ANAESTHETIC DRUGS

- High anaesthetic and analgesic activity
- Wide spectrum of therapeutic action
- Good ability of anaesthesia management
- Absence of the excitation stage and low toxicity (especially breathing, CVS, liver, kidneys)
- Good storage qualities, non-inflammability, explosion-proof

CLASSIFICATION OF GENERAL ANAESTHETIC DRUGS

- For **inhalation** narcosis (general anaesthesia):
  - fluid volatile substances — *halothane, enflurane, isoflurane*
  - gaseous — *nitrous oxide*
- For **noninhalation** narcosis (general anaesthesia):
  - barbiturates — *thiopental, hexenal*
  - nonbarbiturates — *ketamine (kalipsol), propanidid (sombrevin), midasolam, sodium oxybutyrate, etc.*

GENERAL ANAESTHETIC DRUGS

Substances causing a reversible loss of consciousness, all types of sensitivity, decline of muscular tone and reflex activity with saving vitally important functions of an organism

Stages of anaesthesia

- Analgesia
- Excitation
- Surgical narcosis
  - 1st level (III_1) — superficial
  - 2nd level (III_2) — mild
  - 3rd level (III_3) — deep
  - 4th level (III_4) — extremely deep
- Recovery from anaesthesia (agony)

STAGES OF ANAESTHESIA

Symptoms	Analgesia	Excitation	Surgical stage			Paralysis
			I	II	III	
Eye symptoms pupils	⊙	◉	⊙	⊙	⊙	◉
mobility of eyes	++++	++++	++	are fixed		
corneal reflex	++++	++++	+	–	–	–
light response	++++	++++	++	+	–	–
palpebral fissure	Norm	Closed	Half-open			Open
Reflexes (pharyngeal, abdominal)	+++	++++	++	–	–	–
Breathing	Deep	Deep arrhythmic	Deep rhythmic	Depression	Depression	Superficial infrequent
Pulse	Accelar.	Rapid	N	N	Rapid	Thready
ABP	N	Increased	N	N	Decreased	Falls
Tone of muscles	+++	++++	++	+	–	–

MECHANISM OF ANAESTHETIC DRUGS ACTION

- ↑ threshold impulsation of cells
- ↑ permiability of membranes ⇒ change of permeability of ionic channels
- ↓ activity of enzymes ⇒ ↓ cell breathing intensity

Overton–Meyer theory (lipid)

Anaesthetic activity (K) the higher, the greater lipid-solubility

anaesthetic concentration × molecular volume of phase × lipid-solubility = K

Anaesthetic activity evaluation

Minimum alveolar concentration (MAC) — is concentration of an anaesthetic preventing a motive response in 50% of patients with pressure of 1 absolute atmosphere

DRUGS FOR INHALATION NARCOSIS

Halothane, enflurane, isoflurane, nitrous oxide

Advantages

- Broad spectrum of therapeutic action
- Good capacity of anaesthesia management

Disadvantages

- Application in operating-room
- Irritating action on mucous membranes of the respiratory tract and organotoxicity
- Inconvenient technical characteristics (explosiveness, inflammability, etc.)

DRUGS FOR INHALATION NARCOSIS

Drugs	Activity	Speed of recovery from anaesthesia	Myorelaxation	Influence on the systems
Halothane	High	Intermediate	Strong	↓ ABP, HR, breathing
Enflurane	High	High	Very strong	Mild hypotension, ↓ breathing
Isoflurane	High	High	Strong	Mild hypotension, ↑ HR, ↓ breathing
Nitrous oxide	Low	Very high	Does not cause	–

DRUGS FOR NONINHALATION NARCOSIS

- **Short-acting** (up to 15 min) — ketamine (calipsol), propanidide
- **Middle-acting** (20–30 min) — barbiturates (thiopental sodium, hexenal)
- **Long-acting** (60 min and more) — sodium of oxybutyrate

Advantages

- High activity
- Is used outside an operating room and at any conditions
- No irritation of mucous membranes, rarely vomiting

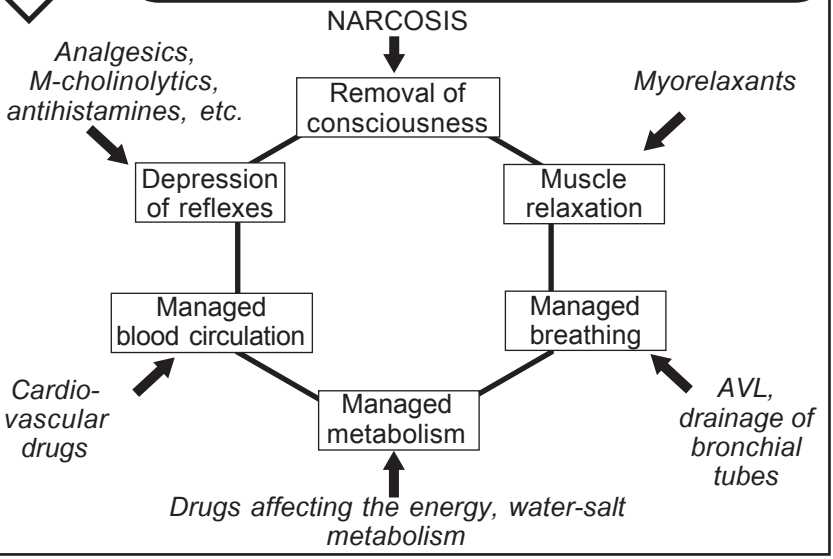
Disadvantages

- Bad capacity of anaesthesia management
- Narrow spectrum of therapeutic action

COMPLICATIONS OF NARCOSIS

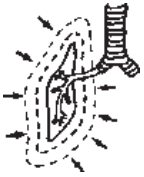
- **Breathing** — reflex arrest of breathing, ***inhalation drugs*** — atelectasis, postanaesthetic pneumonia, laryngo-, bronchial spasm, bronchitis
- **CVS** — arrhythmias (fibrillations), heart arrest
- **GIT** — nausea, vomiting
- **Hepatotoxicity** (halothane), **nephrotoxicity**
- **Blood** — methemoglobinemia (nitrous oxide)
- **Hyperthermia of anaeathesia**
- **Allergic reactions**
- **Reproductive function** (nitrous oxide)
- **Carcinogenic** (personnel)

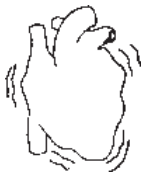
ELEMENTS OF MODERN NARCOSIS



PREMEDICATION

- Removal of alarm and fear — benzodiazepines *(diazepam, lorazepam)*
- Decrease of glands secretion and removal of negative reflexes *n. vagus* — M-cholinoblockers *(atropine, platyphyllin)*
- Analgesics — narcotic analgesics *(morphine, fentanil)*
- Antiemetics (antivomiting drugs) — neuroleptics *(aminazin)*





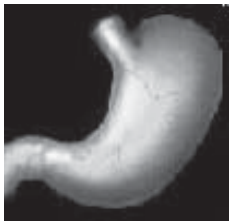
APPLICATION OF ETHANOL

- Disinfectant (70–90%)
- Antiseptic (70%)
- Rubbing, hot compresses (30–40%), ↑ appetite (8–12% *per os*)
- Because of caloriegenity (100 g – 770 kcal), for the parenteral nutrion at cachexia (50–70 g per a day)
- Pulmonary oedema, as foam-remover (by vapour)
- Sepsis (33% solution i.v.)
- Antidote in case of poisoning by methanol, ethylene glycol (30% solution 50–100 ml per os, every 2 hrs by 50 ml and i.v. drop by drop introduction 100–400 ml 5% solution up to 1 ml/(kg/per day))
- In pharmacia as a solvent, preservant, extragent, etc.

PHARMACOKINETICS OF ALCOHOL

Absorption:
20% — in the stomach; 80% — in the thin intestine

- ↓ absorption:
  - ✓ high concentrations of alcohol
  - ✓ sugar and tannic substances
  - ✓ fat, carbohydrates
- ↑ absorption: carbon dioxide



Distribution:

- High lipophility — easily penetrates through BBB, placenta, etc.
- High concentrations — the brain (cortex, limbic system and cerebellum), heart, lungs, liver, reproductive organs

Excretion:
kidneys, lungs, intestine, exocrine glands

ALCOHOL BIOTRANSFORMATION

Takes place with the speed of 10 ml/hr

The first stage — oxidization up to acetaldehyde with participation of:
I. Alcoholdehydrogenase (70–80% of alcohol)

$$C_2H_5OH + NAD \rightarrow CH_2CHO + NAD{\cdot}H + H^+$$

II. Cytochrome R-450 microsomal ethanoloxidizing system (10–20% alcohol)

$$C_2H_5OH + NADP{\cdot}H + H^+ + O_2 \rightarrow CH_2CHO + NADP^+ + 2H_2O$$

III. Catalase (10–20% of alcohol)

$$C_2H_5OH + H_2O_2 \rightarrow CH_2CHO + 2H_2O$$

The second stage — oxidization of acetaldehyde in the acetic acid with participation of alcoholdehydrogenase

$$CH_2CHO + NAD^+ + H_2O \rightarrow CH_2COOH + NAD{\cdot}H + H^+$$

PHARMACODYNAMICS OF ALCOHOL

Local action

Astringent — skin epithelium proteins dehydratation

Irritating — influence on the sensitive nerve endings

Bactericidal — dehydratation and denaturation of bacteria proteins

Reflex influencing (result of local irritating effect)

Is characterized by:

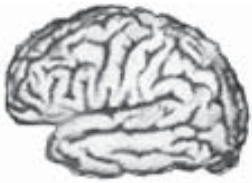
- segmental reflexes
- distracting analgesic action

PHARMACODYNAMICS OF ALCOHOL

Resorptive action

♦ **CNS** — depressive (depreming)

- **mild alcohol intoxication (0.005–0.015 g/l)** emotional disturbances, worsening of a working ability, movement coordination impairment as a result of inhibition of the cortex and release of subcortex from its influence
- **middle degree of intoxication (0.015–0.025 g/l)** scrambled speech, staggaring gait, diplopia caused by cortex dysfunction, basal ganglia, spinal cord
- **severe intoxication (0.025–0.035 g/l)** soporous condition, convulsions, hypothermia, depression of breathing, cardiac activity, ABP fall



MEDIATORY MECHANISM OF ALCOHOL ACTION

Damaging factors — alcohol itself and its metabolite acetaldehyde

Intoxication → alcoholdehydrogenase is engaged in oxidization of acetaldehyde and less inactivates biogenic aldehydes (products of deamination of noradrenaline, dopamine, serotonine)

The latter ones condense with monoamines, forming hallucinogens (morphine-like substances):

acetaldehyde + dopamine → salsolinole

acetaldehyde + serotonin → garmaline

Perversion of effects of catecholamine (CA) exchange — formation of "false mediators" (tetrahydroisochinolines) → liberation of endorphins → stimulation of opiat receptors

Acetaldehyde → accumulation in the blood of fat acids, glycerin, pyruvic and milk acids → metabolic acidosis

PHARMACODYNAMICS OF ALCOHOL

- **Circulation of blood** — capillarotoxicity, increase of thrombocyte aggregation, disturbance of microcirculation (thromboses and hemorrhages)
- **Brain, heart** — microstrokes and microinfarctions, disturbances of metabolism (hypoxia, ↑ lipolysis, etc.), disturbances of the neurohumoral regulation (diencephalic syndrome)
- **GIT** — in the low concentrations ↑ secretion, in high — ↓, hyperacid gastritis as well
- **Liver** — fatty degeneration ⇒ hepatitis
- **Pancreas** — pancreatitis, fibrosis, atrophy
- **Immunosupression**
- **Sexual dysfunction, teratogenicity**

ACUTE ALCOHOL POISONING

3–4 g/l — pronounced intoxication

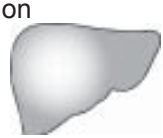
5–8 g/l — LETHAL concentration!

- **Prevention of further alcohol absorption** (gastric lavage, adsorbents, salt laxatives)
- **Maintenance of vital functions** (AVL, cardiotonics)
- **Acceleration of alcohol metabolism and excretion** (fructose — i.v., forced diuresis)
- **Removal of metabolic disorders** (sodium hydrocarbonate, inozin, glucose, etc.)

CHRONIC ALCOHOL POISONING

PSYCHIC and PHYSICAL dependence!

- **Nervous system** — polyneurites, alcoholic encephalopathia, delirium, degradation of personality
- **Internal organs** — chronic gastritis, fatty degeneration of the heart, livers, kidneys, cirrhosis of the liver, impotence



Treatment

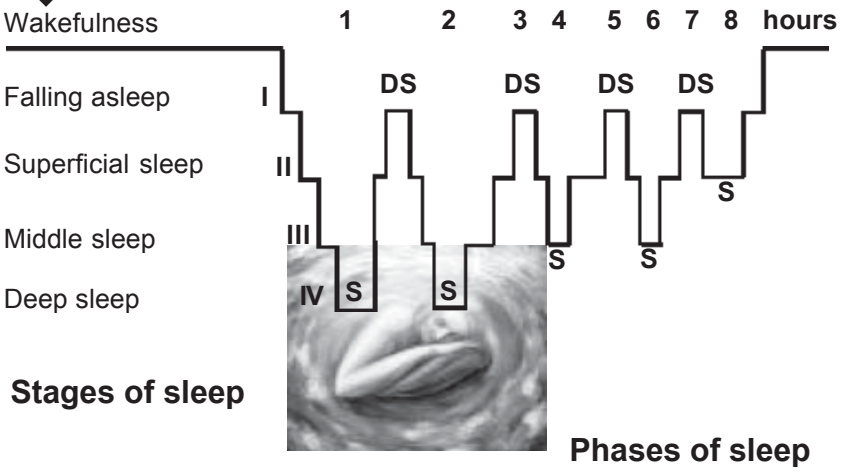
Suppression of appetence to alcohol!

Teturam (disulfiram, antabus, esperal) — with taking alcohol inhibits oxidation of acetaldehyde ⇒ a complex of grave symptoms (vomiting, arrhythmias, fear of death, etc.) ⇒ disgust to alcohol

Topic 6

HYPNOTIC AND ANTICONVULSANT DRUGS

PHYSIOLOGICAL SLEEP STRUCTURE



- **Synchronized (S) or slow sleep (75%) non-REM-phase (non-rapid eye movement)**
  EEG — slow correct high-voltage activity muscular twitching, *n. vagus* predominance

- **Desynchronized (DS) or fast sleep (25%) REM-phase (rapid eye movement)**
  EEG — rapid wrong low-valtage activity, presence of dreams, rapid eye movement, rise of sympathetic innervation

TYPES OF INSOMNIA

- **Emotional (juvenile)** — a process of falling asleep is broken (neurasthenia, overstrain)
- **Senile** — short sleep (2–5 hrs), after which a patient can not fall asleep (sclerosis of cerebral vessels)
- **Pathological** — phases and stages of sleep are broken (pain, neurosis, etc.)

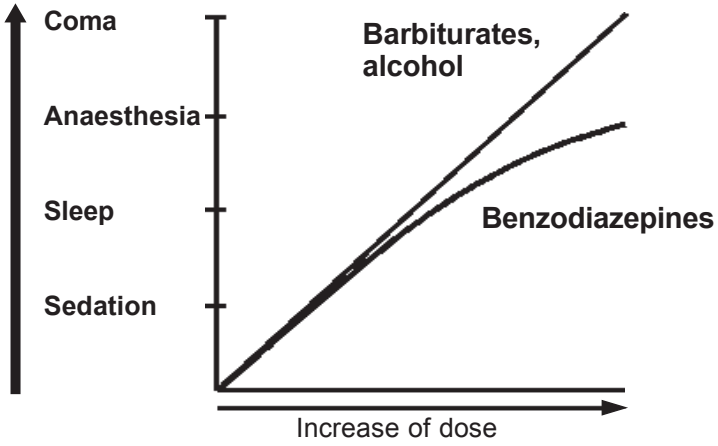
DEMANDS TO HYPNOTIC DRUGS

- An ability to fast provoking physiological-like sleep without disturbing its structure and night awaikening
- Preserving wakefulness all the day long (absence of cumulating and aftereffect)
- Absence of tolerance and drug dependence
- Low organotoxicity, including absence of negative influence on the moving activity, memory, somatic and reproductive functions
- Absence of adverse interaction with other drugs
- Absence of unpleasant odour, taste and irritating influence

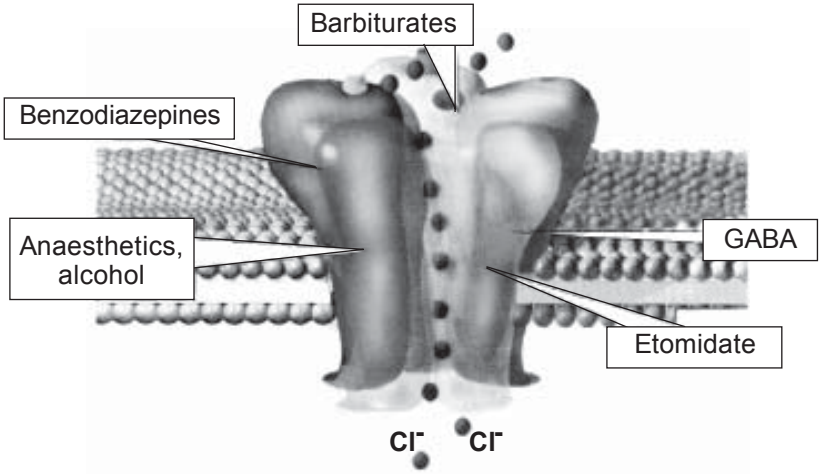
CLASSIFICATION OF HYPNOTIC DRUGS

- **Derivatives of benzodiazepine (tranquilizers):** *nitrazepam, phenazepam, flunitrazepam, alprazolam, triazolam*
- **Derivatives of barbituric acids (barbiturates):** *phenobarbital (luminal), relanorm (cyclobarbital+diazepam)*
- **Derivatives of different chemical groups:**
  - ✓ *cyclopirrilones — zopiclone (imovan)*
  - ✓ *imidazopiridins — zolpidem*
  - ✓ *pyrazolopirimidins — zaleplone (andante)*
  - ✓ *ethanolamines — doxylamine (donormil)*
  - ✓ *tiazoles — clomethiazole (hemineurin)*
  - ✓ *aliphatics — chloralhydrate, bromisoval*

DOSE-EFFECT DEPENDENCE FOR HYPNOTIC AND SEDATIVE DRUGS



MODEL OF COMPLEX $GABA_A$-RECEPTOR-CHLORIONIC CHANNEL



BARBITURATES

Classification

- **long-acting (6–10 hrs)** — phenobarbital
- **middle-acting (4–6 hrs)** — cyclobarbital
- **ultrashort-acting (30–40 min)** — thiopental, hexenal

Mechanism of action

- **GABA-mimetic action:**
  - interaction with barbituric receptors of $GABA_A$-receptor-chlorionic channel ⇒
  - affinity of GABA to $GABA_A$-receptors and the term of opening of chloride channels ⇒
    ↑ *inhibition influence of GABA in the CNS*
- ↓ liberation of excitatory neurotransmitters (glutaminic, asparginic acids)
- ↓ system of wakefulness — reticular formation of the mesencephalone (sleep coming)
- ↓ hypnogenic zone of the hindbrain (fast sleep)

PHARMACODYNAMICS OF BARBITURATES

Influence on sleep structure

- ↓ process of falling asleep
- ↑ general term of sleep
- Substantially change sleep structure
  - — ↑ duration of slow sleep, causing deficit of fast sleep
  - — ↑ II and III stage due to reduction of I and IV stages of
- ↓ frequency and completeness of awakenings

	sedative	→	**hypnotic**	→	**anaesthesia**
doses	small		middle		large

Cause also anticonvulsive, myorelaxant action

PHARMACOKINETICS OF BARBITURATES

Introduction: peroral, absorption in the stomach (weak acids)

Bioavailability: depends on diseases of the liver

Binding with proteins: 5–75%

Distribution: well penetrate through BBB, placenta!

Biotransformation: *strong inductors* of enzymes of microsomal oxidation of liver!

Excretion: by kidneys, partially with bile. The speed of inactivation depends on the structure of drug and functional state of the liver: $T_{1/2}$ cyclobarbital — 18 and 48 hrs in different people, phenobarbital — 4–5 days

Cumulation is pronounced!

ADVERSE EFFECTS OF BARBITURATS

- **Afteraction syndrome (hangover)** (apathy, drowsiness, weakness)
- **Somatic and neurological disturbances** (apnoea, ↓ ABP during sleep, depressions, disturbances of co-ordintion, neurotrophic injury of joints, allergic reactions)
- **Tolerance**
- **Accelerated metabolism of other drugs**
- **Rebound syndrome**
- **Drug dependence** (physical and psychical)

ACUTE POISONING BY BARBITURATES

- **CNS** (depression of respiratory and vasomotor centers, coma)
- **System of respiratory organs** (bronchorrhea, pulmonary edema)
- **CVS** (heart failure, collapse)
- **Acid-base disturbance** (acidosis)
- **The urinary system** (anuria)
- **Other diagnostic symptoms** (miosis, then mydriasis, areflexia, hypothermia)

Death from paralysis of the respiratory center!

EMERGENCY IN CASE OF POISONING BY BARBITURATES

- **Prevention of further absorption and acceleration of excretion** (gastric lavage, adsorbents, salt laxatives, forced diuresis)
- **Maintenance of basic vital function** (i.v. introduction of sodium hydrocarbonate, adrenomimetics, dopamine, etc.)
- **If necessary — AVL, hemosorption, hemodialysis**

TRANQUILIZERS (ANXIOLYTICS)*

Tranquillium — rest; anxious — warried, frightened atharactics (atharaxia — "coolness")

— depriming psychotropic drugs, separately removing emotional unstableness, anxiety, fear (phobia), tension

According to chemical structure:

- Derivatives of 1,4-benzodiazepine (typical) — clordiazepoxide, diazepam (sibazon, seduxen), phenazepam, lorazepam, flurazepam, alprazolam, triazolam, etc.
- Derivatives of different chemical groups (atypical) — mebikar, grandaxin, amizil, litonit, phenibut

* full characteristics of the group is in the Topic 9

SPECTRUM OF TRANQUILIZERS' PHARMACOLOGIC EFFECTS

- ♦ Anxiolytic (antianxious + stress-protective + antiphobic)
- ♦ Sedative
- ♦ Hypnotic (hypnotic)
- ♦ Myorelaxant
- ♦ Anticonvulsant
- ♦ Vegetostabilizing
- ♦ Amnestic (anterograde amnesia — it is impossible to remember the events taking place while the drug acting)
- ♦ ↑ the effect of the drugs which depress the CNS

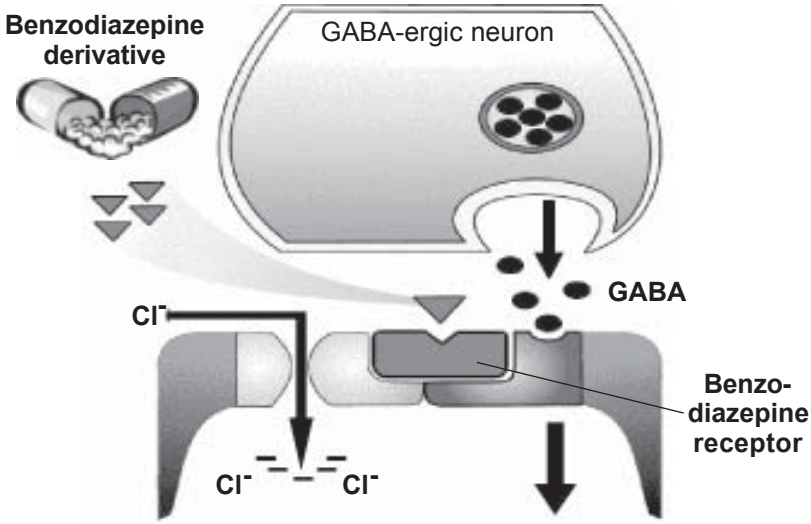
According to spectrum of the sedative-hypnotic action:

- Sedative ("large", night) — nitrazepam, flurazepam, diazepam, phenazepam, etc.
- Day ("small"), having stress-protecting activity with activating component — mezapam, gidazepam, buspiron, mebicar

MECHANISM OF BENZODIAZEPINES ACTION

- ♦ Benzodiazepine as an agonist of benzodiazepine (BZ-) receptors of the $GABA_A$-receptor-chlorionic channel causes its stimulation ⇒
- ♦ ↑ sensitivity of GABA to GABA-receptors and ↑ the rate of chlorine channels opening ⇒ hyperpolarization of the membrane
- ♦ ⇒ ↑ inhibition influence of GABA in CNS
- ♦ ↓ activity of the cerebral structures with maximal excitement (limbic system, cerebral cortex, hypothalamus, reticular formation, etc.)
- ♦ ⇒ ↓ effect on *emotional sphere* (anxiolytic, sedative-hypnotic, amnestic) + *motor and vegetative systems* (anticonvulsive, myorelaxant, vegetostabilizing)

MECHANISM OF BENZODIAZEPINES ACTION



TRANQUILIZERS AS HYPNOTICS

Nitrazepam, diazepam, phenazepam, flunitrazepam, triazolam, alprozolam

Influence on sleep structure

- ↓ a process of falling asleep
- ↑ general term of sleep
- ↓ fast phase of sleep
- In the part of slow sleep the II (non-deep) stage prevails due to reduction of the I, III and IV stages
- ↓ frequency and completeness of awakenings

Advantages over barbiturates

- Less pronounced suppression of fast phase of sleep
- Sleep is more superficial than with intake of barbiturates, ↓ probability of apnoea and other complications

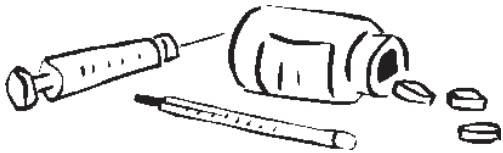
PHARMACOKINETICS OF BENZODIAZEPINES

- ***Absorption:*** in the duodenum (weak bases); time of absorption with per oral and i/m intake is almost the same! (peak of concentration is in 0.5–4 hrs)
- **Binding with proteins:** 60–95%
- **Distribution:** penetrates well through BBB, placenta!
- **Biotransformation** in the liver:
  - — short-acting (triazolam): conjugation with glucuronides formation;
  - — long-acting (diazepam): at first they undergo the microsomal oxidization of the liver (N-dealcylizing and hydroxilizing) with formation of active metabolites (diazepam → nordiazepam → oxazepam), then conjugation → glucuronides
- **Excretion:** as glucuronides by kidneys
  $T_{1/2}$: triazolam — 1.5–3 hrs, diazepam — about 40 hrs

CLASSIFICATION OF BENZODIAZEPINES

According to the term of action

- **Short-acting ($T_{1/2}$ up to 6 hrs):** triazolam
- **Intermediate-acting ($T_{1/2}$ = 6–24 hrs):** lorazepam, nozepam (oxazepam), flunitrazepam, etc.
- **Long-acting ($T_{1/2}$ = over 24 hrs):** nitrazepam, fenazepam, diazepam, flurazepam, etc.



COMPARATIVE CHARACTERISTICS OF HYPNOTIC DRUGS

Drug	Ways of introduction	Additional application	Duration, hrs
Nitrazepam	Per os	Neurosis, alcoholic abstinence	6–8
Zolpidem	Per os	—	2–3
Zopiclon	Per os	—	4–5
Phenobarbital	Per os	Prophylaxis of seizures, epilepsy	6–8
Chloralhydrate (rarely)	Per os, rectal (coating)	Seizures	8–10

APPLICATION OF HYPNOTIC DRUGS

- ✓ Insomnias
- ✓ Neuroses and psychopathies
- ✓ The abstinence syndrome
- ✓ Symptomatic therapy of seizures, epilepsy
- ✓ Premedication
- ✓ Postoperative period
- ✓ For potentiating effects of analgesics and other substances which depress CNS

CONTRAINDICATIONS TO HYPNOTIC DRUGS

- Dysfunction of the liver and the kidneys
- Respiratory insufficiency, sleep apnea syndrome
- Myasthenia
- During the pregnancy, lactation
- Children and teenagers younger than 18 years old
- Persons the working activity of which is connected with heightened attention and high speed of reaction (drivers, pilots, etc.)
- Drug addiction
- Alcoholism

FUNDAMENTALS OF HYPNOTIC DRUGS PHARMACOLOGY

- Hypnotic drugs cause sleep cycles disturbances by way of ↓ of the REM-phase, as well as the delta-sleep
- Stoppage of the hypnotic drugs intake leads to ↑ REM-phase (rebound phenomenon). During REM-phase vegetative and hormonal phases of an organism ↑ ⇒ risk of stroke and myocardial infarction ↑
- With regular intake of hypnotic drugs periods of falling asleep and night awakening ↑ ⇒ the general duration of insomnias ↑, which is more than that one in patients who don't take hypnotic drugs
- As a rule, the affect of hypnotic drugs ↓ in 2 weeks ⇒ patients increase the dose for themselves, intake additional medicines or stimulate the affect of hypnotic drugs by alcohol addiction, which sharply ↑ the risk of severe complications

FUNDAMENTALS OF HYPNOTIC DRUGS PHARMACOLOGY

- Drug dependence appears in case of prolonged intake of hypnotic drugs
- Some hypnotic drugs (barbiturates) excrete from an organism fast. With repeated intake their cumulation takes place. The risk of intoxication ↑ with the age ⇒ barbiturates are contraindicated after 60 years old
- A majority of hypnotic drugs have aftereffect, or hangover (fatigue, feeling jaded, working ability ↓, etc.)
- Drivers should be especially careful with hypnotic drugs
- Alcohol ↑ hypnotic drugs effect ⇒ simultaneous intake of these medicines and alcohol is contraindicated

BASIC PRINCIPLES OF HYPNOTIC DRUGS

Pharmacotherapy

- **Emotional** — *psychosedatives, benzodiazepines of short action*
- **Geriatric** — *benzodiazepines of middle and short action, ZZZ-preparations (zopiklon, zolpidem, zaleplon)*
- **Pathological** — *therapy of the basic disease*

✓ Duration of treatment course is no more than 3 weeks (optimally 10–14 days)

✓ The presence of pauses in the medical treatment is necessary (“medicinal vacations”)

✓ The patients of elderly age are appointed a half dose

✓ With apnoe in sleep *ZZZ-preparations* are better

CLASSIFICATION OF ANTICONVULSANT DRUGS

- **For reduction of seizures** — barbiturates (phenobarbital, hexenal), benzodiazepines (diazepam, phenazepam), chloralhydrate, sodium oxybutyrate, lidocaine, magnesium sulfate, nitrous oxide, myorelaxants
- **Antiepileptic** — valproats (sodium valproat), benzodiazepines (clonazepam, diazepam), barbiturates, suximides (etosuximide), carbamazepine, diphenine (phenytoin), trimetine
- **Antiparkinsonic** — central M-cholinolytics (cyclodol, tropacin), dopaminomimetics (levodopa, nacom, sinemet, bromocriptine)
- **For treatment of spasticity** — benzodiazepines (diazepam, fenazepam), GABA-ergic (fenibut, baclofen), dantrolen, midocalm

BASIC MECHANISMS OF ANTICONVULSANT DRUGS

- **Facilitation of the GABA-dependent** (inhibitor) **transmission** — barbiturates, benzodiazepines, valproats
- **Depression of excitant** (usually glutamatergic) **transmission**
- **Modification of ionic currents —** magnesium sulfate, lidocaine, suximides, difenine, carbamazepine

EPILEPSY

Group of chronic convulsive pathology with sudden attacks (fits) with the loss or disorder of consciousness accompanied with convulsions and spontaneous hyper reactivity

Generalized attacks		Partial (focal) seizures
large	small	
Tonicoclonic seizures with the sudden loss of consciousness up to 10–15 min *(grand mal)*	**Absans** — sudden short-termloss of consciousness *(petit mal)* **Akinetic** — sharp short-term decrease of muscular tone **Myoclonic** — small rhythmic twitches of muscles **Hypertensive** — short-term tonic tension of muscles **Infantile spasms** — epileptic syndrome	*Simple* — forms: motive sensitive psychic vegetative-visceral *Complex (mixed)* *Secondary generalized*

Epileptic status — prolonged attacks or those following in sequence with small intervals

GENERAL PRINCIPLES OF EPILEPCY TREATMENT

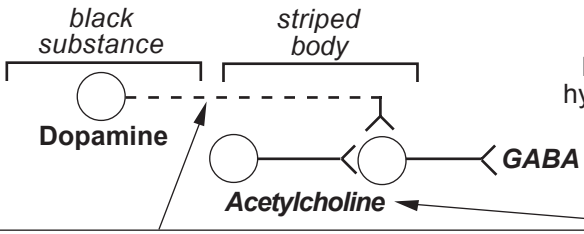
- In-time diagnosis and early (strictly) individual (!) pharmacotherapy, especially in children
- If possible monotherapy
- Strict following the dosages and rhythm of drugs introduction (combination); transition from one to another takes place step by step
- Uninterrapted treatment continues for 3–4 years after disappearence of clinical signs of epilepsy; then during 1–2 years long gradual withdrawal

COMPARATIVE EFFICIENCY OF ANTIEPILEPTIC DRUGS

Drug	Generalized attacks		Parttial attacks
	large	small	
Sodium valproat	+++	+++	++
Clonazepam	+++	+++	++
Phenobarbital	+++	+	++
Phenytoin	+++	–	+++
Carbamazepine	+++	–	+++
Etosuximide	–	+++	–

With epileptic status — i.v. introduction of diazepam (10–30 mg), phenytoin (13–18 mg/kg), phenobarbital (500 mg), lidocaine, etc.

ANTIPARKINSONIC DRUGS



Parkinsonism — hypokinesia, rigidity, tremor

Making better a dopaminergic transmission ***(dopaminomimetics)***		**Central M-cholinergic antagonists**
indirect (↑ synthesis, dopamine reuptake inhibitors inhibitors, MAO-B, etc.)	*direct* (agonists of D-receptors)	
Levodopa *and combined with periph. inhibitor of dopa-decarboxylase* (nacom, sinemet), midantan, selegidin	Bromocriptine, apomorphine	Cyclodol, norakin, tropacin

Topic 7

NON-NARCOTIC ANALGESICS, NONSTEROID ANTI-INFLAMMATORY DRUGS (NSAIDs), ANTIPYRETICS

GENERAL CHARACTERISTICS OF NON-NARCOTIC ANALGESICS

Synthetic substances rendering moderate analgesic effect mainly at the expense of blocking of formation and action on pain endings of tissue "algogenic" substances which form in case of inflammation, ischemia, trauma, and not causing euphoria and drug dependence

There are three types of activity:

- **Anti-inflammatory** ⇒ *nonsteroidal antiinflammatory drugs* (NSAIDs)
- **Analgesic** ⇒ *non-narcotic analgesics*
- **Antipyretic** ⇒ *antipyretics*

About 20% of population of the planet intake NSAIDs regularly

HISTORY OF CREATION

2500–3500 years ago curative properties of white willow *(Salix alba)* rind were well known in the ancient Egypt and Rome

1828 I. BUCHNER obtained yellow crystals with bitter taste from Salix alba and called them salicyl

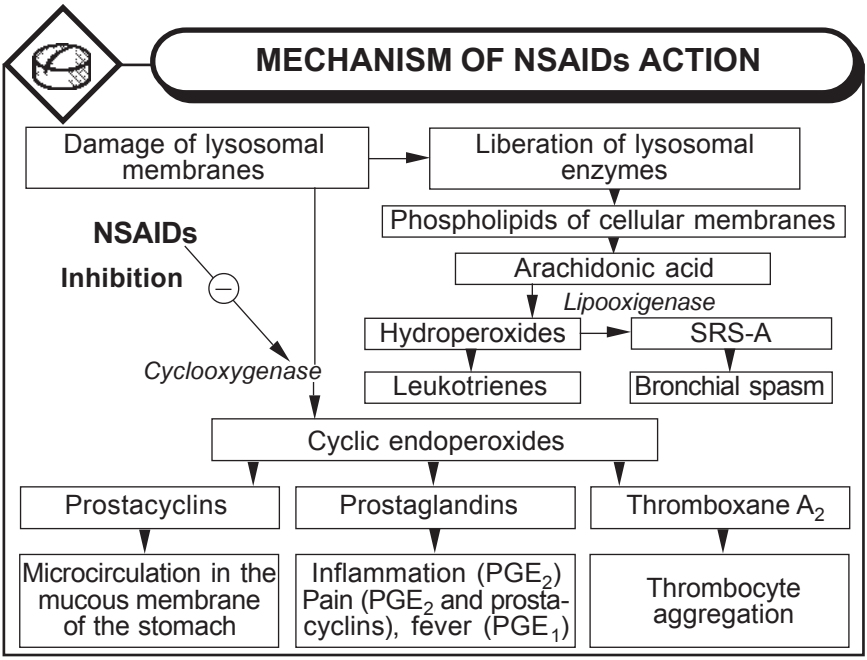
1835 K. LOVIG separated salicylic acid from Maedow sweet blossoms *(Spiraea ulmaria)*

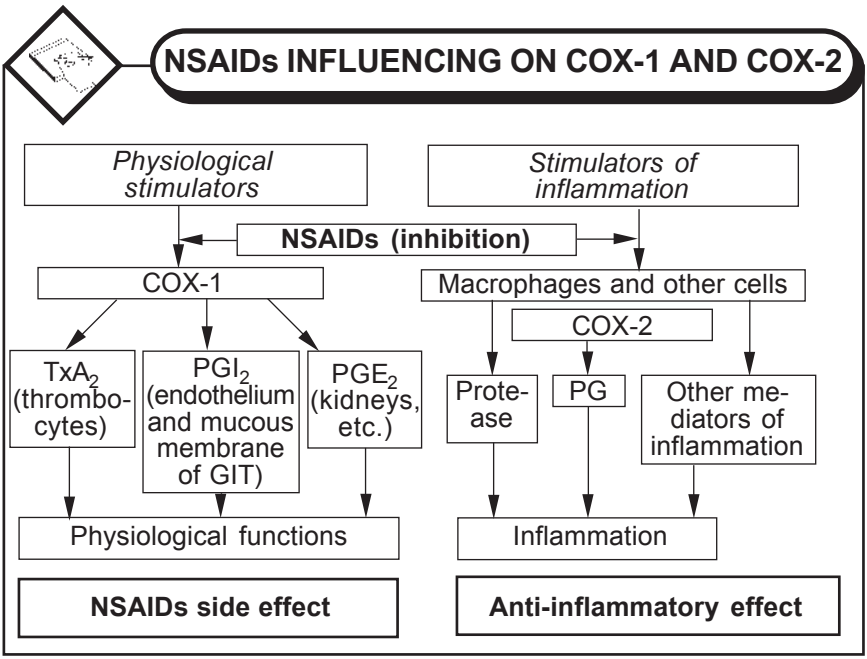
1897 F. HOFFMAN and A EICHENGREEN obtained salicylic acid by acetylating In the "Bayer" firm laboratory, called it aspirin

1982 J. VANE became a Nobel Prize Winner for the discovery of aspirin influence on prostaglandin synthesis

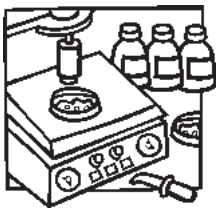
NSAIDs CLASSIFICATION

- **Derivatives of salicylic acid** — acetylsalicylic acid (ASA — aspirin), methylsalicylate
- **Derivatives of pyrazolon** — analgin, metamizole, butadion (phenylbutazone)
- **Derivatives of aniline** — paracetamol (acetaminofen, panadol, tailenol)
- **Derivatives of phenylpropion, phenylacetic and anthranil acids** — ibuprofen, sodium-diclofenac (voltaren, orthofen), cetoprofen, naproxen, flugalin, mefenamic acid, etc.
- **Derivatives of indolacetic acid** — indolmethacin, etodolac, clinoril
- **Derivatives of oxicams** — piroxicam, meloxicam, etc.
- **Derivatives of different classes** — cetorolac (cetanov), nimesulid, celecoxib, etc.
- **Combined drugs** — arthrotec, ambene, dolaren, baralgin, tempalgin, coldrex, pentalgin, solpadein, citramon, etc.


MECHANISM OF NSAIDs ACTION
Damage of lysosomal membranes
Liberation of lysosomal enzymes
Phospholipids of cellular membranes
NSAIDs
Inhibition
Arachidonic acid
Lipooxigenase
Hydroperoxides
SRS-A
Cyclooxygenase
Leukotrienes
Bronchial spasm
Cyclic endoperoxides
Prostacyclins
Prostaglandins
Thromboxane A2
Microcirculation in the mucous membrane of the stomach
Inflammation (PGE2) Pain (PGE2 and prostacyclins), fever (PGE1)
Thrombocyte aggregation


NSAIDs INFLUENCING ON COX-1 AND COX-2
Physiological stimulators
Stimulators of inflammation
NSAIDs (inhibition)
COX-1
Macrophages and other cells
COX-2
TxA2 (thrombocytes)
PGI2 (endothelium and mucous membrane of GIT)
PGE2 (kidneys, etc.)
Protease
PG
Other mediators of inflammation
Physiological functions
Inflammation
NSAIDs side effect
Anti-inflammatory effect

NSAIDs CLASSIFICATION ACCORDING TO CYCLOOXYGENASE INHIBITION SELECTIVITY (COX-1 AND COX-2)

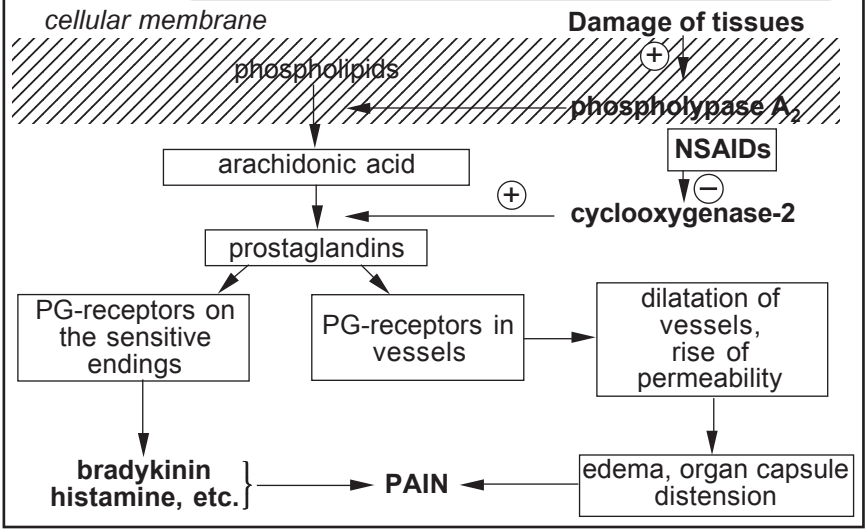


- **Inhibitors COX-1 and COX-2** — majority of modern NSAIDs
- **Selective inhibitors COX-1** — acetylsalicylic acid (in low doses)
- **Selective inhibitors COX-2** — nimesulid (mesulid), meloxicam (movalis)
- **Highly active inhibitors COX-2** — celecoxib

NSAIDs ANTI-INFLAMMATORY ACTION MECHANISM

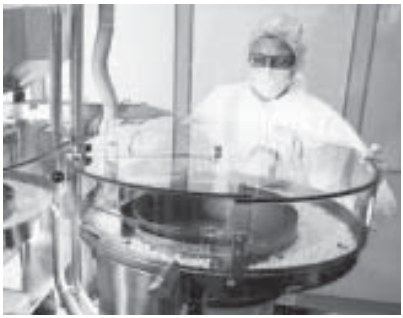
- **Depression of prostaglandin synthesis** (cyclooxygenase inhibition)
- **Adhesion inhibition** (disturbance of cell migration to the focus of inflammation)
- **Stabilization of lysosomes** ⇒ ↓ release of hydrolytic enzymes (proteases, lipases, phosphotases)
- **Antialterative action** (↑ stability of collagen and its ripening)
- **Antagonism with mediators of inflammation** (↓ synthesis of histamine, serotonin, bradykinin)
- **Inflammation bioenergetics limitation** (ATP synthesis disorder, disjoining of oxidization and phosphorylation, ATP-ase inhibition)
- **Immunotropic action** (↓ specific reaction on antigens, T-lymphocytes proliferation, interleukine synthesis)

MECHANISM OF NSAIDs ANALGESIC ACTION



NSAIDs COMPARATIVE ANALGESIC ACTIVITY

Ketorolac > piroxicam > diclofenac sodium > naproxen > indomethacin > butadion > mefenamic acid > analgin > ibuprofen > paracetamol > acetylsalicylic acid

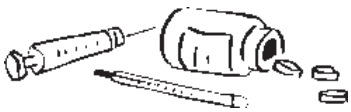


COMPARATIVE CHARACTERISTICS OF ANALGESICS

Effect	Analgesic	
	narcotic	non-narcotic
Analgesic	Pain of any genesis	Pain associated with inflammation
Anti-inflammatory	–	+
Antipyretic	–	+
Hypnotic	+	–
Euphoria	+	–
Dependence	+	–
Tolerance	+	–
Respiratory depression	+	–

ANTIPYRETIC ACTION OF NSAIDs

Hyperthermia genesis: increased formation of PGE_2 in the zone of hypothalamus → deranged cAMP accumulation → disbalance of Na^+ and Ca^{2+} proportion → ↑ thermoregulation center function → ↑ thermoproduction → ↑ the body temperature



NSAIDs → PGE_2 synthesis reduction → renewal of thermoregulation center function → increase of heat emission by way of dilatation of the skin vessels and enhancement of perspiration

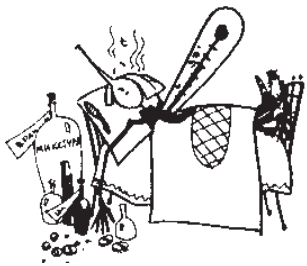
PHARMACOLOGICAL EFFECTS OF MODERN NSAIDs

NSAIDs	Anti-inflammatory	Analgesic	Antipyretic	Chondroprotector
Meloxicam				
Nimesulid				
Celecoxib				
Ibuprofen*				
Diclofenac				
ASA (aspirin)				

* A series of NSAIDs (ibuprofen, indomethacin etc.) have uricosuric effect (excretion of uric acid)

NSAIDs APPLICATION

- **Diseases of connective tissue or joints** (reumatoid arthritis, osteoarthritis, radiculitis, myocarditis, glomerulonephritis, etc.), **gout** (indomethacin, naproxen, etc.)
- **Post-operative pains of medium intensity**
- **Acute inflammatory diseases of traumatic or catarrhal character** (injuries, raptures of ligaments, dislocations, myosites, neuralgias, etc.)
- **Headache, toothache**
- **Spasms of bile and urinary tracts** (in combination with spasmolytics)
- **Hyperthermia** in case of infectious diseases, infusion therapy
- **Prophylaxis and treatment of thromboses** — ASA (325 mg 1 time per a week)



SALICYLATES DOSAGE

mg/dl blood	Effect	Complications
	Intoxication	
160	*lethal*	Renal and respiratory failure
	severe	Collapse, coma
	medium	Fever, acidosis, dehydratation
80	*weak*	Central hyperventilation
50		Ringing in the ear
	Anti-inflammatory (up to 4 g a day)	
20	Uricosuric	Ulcerogenity, hypersensitivity, hemostatic disorder
10	Analgesic	
	Antipyretic	
0	Antiaggregate	

ANTIPYRETICS APPLICATION MANAGEMENT

- There shouldn't be appointed for the «course» introduction, as well as to children intaking antibacterial drugs (masking of infection, "false well-being")
- To initially healthy children at the body temperature **not below 39.0–39.5 °C**
- To children of the risk group (with chronic diseases of the heart, metabolism disorders, neurological pathology, febrile cramps in anamnesis and during first 2 months of life) **at t = 38.0–38.5 °C**
- It is necessary to take into account its safety, presence of child's medicinal forms and fractional dosages

PHARMACOKINETICS OF NSAIDs

Absorption: majority — weak acids ⇒ absorption in the stomach; at ↑ of pH about 3.5 ↓ of ulcerogenicity, but also efficiency;

Introduction: peroral, rectal, i.m., i.v., transdermal; presistemic metabolism is possible!

Binding with proteins: 50–99%, ASA displaces from the bond triiodothyronine, thyroxin, urinary acid, difenin, penicillins, other NSAIDs

Distribution: good, including through BBB (especially with acidosis!)

Biotransformation: a considerable part of ASA conjugates with the glyucoronic acid, glycine, oxidizes to nonactive metabolites; some (ketorolac) eliminate unchanged

Excretion: mainly by kidneys; urine alkalinization ↑ excretion. $T_{1/2}$ ASA in daily dose 0.6 g — 4–5 hrs, in dose 4 g — about 15 hrs!

ULCEROGENIC ACTION OF NSAIDs

The death rate in the USA caused by NSAIDs-induced gastrointestinal bleedings ranges from 5 to 10% (0.22% a year):

- the same as with AIDS
- higher than with melanoma, bronchial asthma, cervical cancer, lymphogranulomatosis
- takes the 15th place among the most frequent causes of death

Direct expenditures on the medical treatment of only gastroenterologic complications — $ 2 milliard

ULCEROGENIC ACTION OF NSAIDs

- ♦ Dispeptic disorders — in 30–40% of patients
- ♦ Erosions and duodenal and gastric ulcer — 10–20%
- ♦ Bleeding and perforations — 2–5%

Specific syndrome — NSAIDs-gastroduodenopathy

- ♦ More frequent in women
- ♦ Localization — anthral and prepiloric parts of the stomach (erythema of the mucous membrane, erosions, ulcers, hemorrhages)
- ♦ Asymptomatic (60% patients, especially elderly ones)
- ♦ The first weeks of administration are most dangerous
- ♦ In case of intake during 6 months — there are pathological changes in 68% cases

ULCEROGENIC ACTION OF NSAIDs

Ulcerogenic risk:

Tolmetin > ketoprofen > piroxicam > indomethacin > naproxen > aspirin > diklofenac > metamizol > ibuprofen

Tolerance improvement measures:

- ✓ Simultaneous administration of the drugs protecting the mucous membrane of GIT: artrotec (diklofenac + misoprostol), inhibitors of proton pump, H_2-histamine blocking agents (?), cytoprotectors (sucralfat)
- ✓ Change of NSAIDs administration management: decrease of the dose; transition to parenteral (?), rectal (?) or local application; administration of intestine-soluble medicinal forms; use of prodrugs (sulindac)
- ✓ Application of selective inhibitors COX-2 (meloxicam, nabumeton, nimesulid, celecoxib)

NEPHROTOXICITY OF NSAIDs

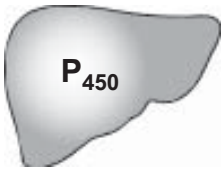
NSAIDs-associated nephrotoxicity (5–10%)

- **Renal failure:**
  - blockade of synthesis of PGE_2 and prostacycline in the kidneys ⇒ vasoconstriction and ↓ renal blood flow ⇒ ↓ glomerular filtration and diuresis
  - ⇒ water-electrolyte exchange disorder: retention of water, hypernatriemia, hyperkaliemia, hypercreatininemia, edemas, ↑ ABP (indomethacin, phenylbutazone, COX-2 inhibitors)

- **Direct influence on renal parenchyma:**
  - acute papillar necrosis (ibuprofen, naproxen)
  - acute interstitial nephritis ⇒ "analgesic nephropathy" (phenylbutazone, indomethacin, metamizol, ibuprofen, paracetamol, and also combinations with it, ASA, caffeine

HEPATOTOXICITY OF NSAIDs

- In spite of the NSAIDs chemical structure, it develops by the following types:
  - **immunoallergic** (butadion, piroxicam, naproxen, etc.)
  - **toxic** (paracetamol, butadion, sulindac, diklofenac, etc.)
  - **mixed**



- Prevails in elderly women
- Unpredictable and sometimes clinically asymptomatic
- With NSAIDs repeated intake it appears suddenly and has more severe course
- Does not depend on COX-selectivity (!)
- A regular estimation of liver function tests is necessary

HEPATOTOXICITY OF NSAIDs

Drugs	Type of defeat	Mechanism of defeat	Relative rate	Lethality
Aspirin	Hepatocellular	Toxic	Dose-dependence	Yes
Butadion	Hepatocellular, cholestatic	Toxic, hypersensitivity	3	Yes
Indomethacin	Hepatocellular	Unknown	2	Yes
Ibuprofen	The same	The same	1	Yes
Ketoprofen	Exchange of enzymes	«	1	No
Piroxicam	Hepatocellular	Hypersensitivity	1	Yes
Diclofenac	The same	Unknown	3	Yes

Paracetamol is a direct toxin (at daily dose > 6 g)
Selective COX-2 inhibitors are also hepatotoxic

NSAIDs ADVERSE EFFECTS CONCERNING BLOOD

- **Anaemia** (hypochromic microcytic anaemia, hemolytic anaemia, hypo- and aplastic anaemias, posthemorrhagic in case of the prolong occult bleeding) — *pyrazolones, indomethacin, ASA*
- **Thrombocytopenia** (cytostatic reaction of allergic origin) up to thrombocytopenic purpura
- **Leukopenias** up to agranulocytosis — *pyrazolones*
- **Pancytopenia** (rarely)
- **Coagulopathy** with bleeding: ↓ aggregation of thrombocytes (antiagregate) and formation of protrombin in the liver (moderate anticoagulant) — *ASA, indomethacin*
- **Methemoglobinemia** — *paracetamol*
- **Acute intravascular hemolysis** with subsequent renal failure (deficit of glucoso-6-phosphatdehydrogenase) — *ASA*

OTHER ADVERSE EFFECS OF NSAIDs

- **CNS:** headache, dizziness, fatigue, hyposomnia, hallucinations, mental confusion, seizures (*ASA, cetorolac*, etc. — 1–6%), "salicylic intoxication", temporal hearing loss (*indomethacin* up to 10%)
- **Allergy and reactions of individual sensitiveness (12–15%):**
  - urticaria, allergic interstitial nephritis, the Lyell's and Stevens — Johnson's syndrome (more frequent pyrazolones during first 1–3 weeks), Quincke's oedema, anaphylactic shock (0.5%)
  - "aspirin asthma", rhinitis, conjunctivitis, Widal syndrome (rhinitis, pollinosis of the nasal mucous membrane, urticaria, bronchial asthma) — *ASA*
  - alopecia — *ibuprofen*
  - morbidity rate: *diclofenac* > *naproxen* > *piroxicam* > *ibuprofen* > *indomethacin* > *ketoprofen*

OTHER ADVERSE EFFECS OF NSAIDs

- **Cardiovascular toxicity:** ↑ ABP, HR — *celecoxib*, myocardiodystrophy — *butadion*
- **Concerning eyes:** keratoleukoma, change of visual fields; toxic amblyopia, neuritis of the visual nerve *(ibuprofen)*, retino- and keratopathy because of deposition in the retina and cornea *(indomethacin)*
- **Degeneration of cartilaginous tissue**
- **Teratogenicity** (*ASA* — cleft palate of the fetus (8–14 by 100 observations)); **fetotoxicity** (*indomethacin* — premature closing of arterial channel with hyperplasia of vessels and hypertension in the pulmonary circulation); **prolongation of pregnancy and births** (*indomethacin*, etc.)
- **Mutagenicity** (↑ chromosomal abberations in lymphocytes — *ASA*, *butadion*) and carcinogenicity *(amidopirin)*
- **Rey syndrome in children** (severe encephalopathy with hepatic insufficiency and lethality more than 50%) — *ASA*

COMPARATIVE TOXICITY OF NSAIDs

Drug	Adverse effects			
	GIT	Liver	Kidneys	Blood
Butadion	++	+++	+++	+++
Indomethacin	+++	+++	+++	+++
Sulindac	+	+	–	–
Orthofen	+	+	–	+
Ibuprofen	+	–	+	+
ASA	+++	+++	–	+
Ketoprofen	+	–	+	+
Piroxicam	+	–	+	+
Meloxicam	–	–	–	–
Paracetamol	–	+++	+++	+
Ketorolac	++	++	++	–

RISK FACTORS OF NSAIDs ADVERSE EFFECTS DEVELOPMENT

Proved

- Age of patient (over 65 years)
- Presence of GIT pathology in anamnesis
- Concomitant diseases and their treatment (arterial hypertension (AH), cardiac, renal, hepatic insufficiency + angiotensin-converting enzyme (ACE) inhibitors, diuretics)
- The NSAIDs administration in high doses or simultaneous usage of a few NSAIDs
- Prolonged (> 3 month) NSAIDs administration
- Simultaneous application of anticoagulants, glucocorticoids, immunosupressants

Probable

- Presence of rheumatoid arthritis
- Helicobacter pylori infection (?)
- Female gender
- Smoking, alcohol addiction

EVALUATION OF BENEFIT / RISK WITH NSAIDs ADMINISTRATION

- Is determined in every case with the choice of drug with the optimum efficiency and duration of action (with pain syndrome — long-acting, for prolonged treatment — short-acting)
- Taking into account probability of GIT complications
- It is necessary to reveal other factors of risk and possible drug interaction
- When choosing analgesic, an alternative drugs should be considered
- It is necessary to inform a patient about adverse effects of the administered NSAIDs

RULES OF NSAIDs ADMINISTRATION

- **Individualization of drug choice:** the analgesic effect (first hours) precedes the antianflammatory one (in 10–14 days of regular intake and with naproxen or oxicams administration still later — on the 2nd–4th week)
- **Dosage** (descending and ascending methods)
- **Time of intake:**
  - after the meal; in order to get rapid analgesic or antipyretic effect they prescribe 30 min before the meal or in 2 hrs after the meal, washing down with 1/2–1 glass of water; after intake it is better not to lie down during 15 min for prophylaxis of esophagitis development
  - according to maximal pronounced symptoms: with morning constraint it is expedient more early administration of quickly absorbed NSAIDs (naproxen-sodium, diclofenac-potassium, “sparkling” aspirin, ketoprofen) or prescription of long-acting drugs for the night

PSYCHOTROPIC DRUGS

Topic 8

PSYCHODYSLEPTICS. NARCOTIC ANALGESICS

CLASSIFICATION OF PSYCHOTROPIC DRUGS

- **Psychodisleptics:** psychosomimetics, hallucinogens — LSD*, mescalin*, psilocibin*, heroin*, marihuana*; narcotic analgesics (morphine and other chemical groups), central M-choliniblockers
- **Neuroleptics:** derivatives of phenothiasin, butirofenone, etc.
- **Tranquilizers (anxiolytics):** derivatives of benzodiazepine, etc.
- **Psychosedatives:** bromides, valeriana, motherwort, etc.
- **Antidepressants:** MAO inhibitors; tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), etc.
- **Psychostimulators:** sidnocarb, caffeine, amphetamine*, cocaine*

* They are not used in medical practice

HISTORY

V century B.C. the first records of the hypnotic poppy

III century B.C. PARACELS described the opium action

1803 F. SERTURNER selected the main alkaloid of opium in the crystalline form and called it “morphine”

1915 nalorphine is synthesized

1942 its antagonism to morphine is defined

F. Serturner

NARCOTIC ANALGESICS

The drugs capable with resorptive action to depress the intracentral conducting of pain, and in repeated administration to cause psychic and physical dependence (drug addiction)

Sources

Opium (from Gr. *opos* — juice) — dried-up milk juice of poppy hypnotic *(Papaver somniferum)*

Alkaloids of opium

- ***Derivatives of fenantren:*** *morphine, codeine, tebaine*
- ***Derivatives of isoquinoline:*** *papaverin, narceine, narcotin*

ALKALOIDS

Alkali-like substances of herbal origin containing nitrogen

- Solid, colourless, bitter, optically active
- Alkaloids-bases — badly soluble in water, well — in organic solvents
- Salts of alkaloids — soluble in water and badly soluble in organic solvents

Reactions of neutralization

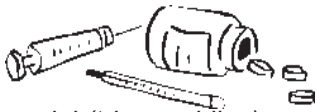
✓ **Tannin, iodides, heavy metals** → sediment

✓ **Potassium permanganate** → universal oxidant

✓ **Solution of alkaloid salts is incompatible with alkalines** → sediment

CLASSIFICATION OF NARCOTIC ANALGESICS ACCORDING TO CHEMICAL STRUCTURE

♦ ***Derivatives of fenantren:***
- alkaloids of opium — *morphine, codeine, omnopon*
- synthetic analogs — *ethilmorphine, buprenorphine, nalbuphine, nalorphine, naloxone, naltrexone*



♦ ***Benzomorphans*** — *pentazocine*

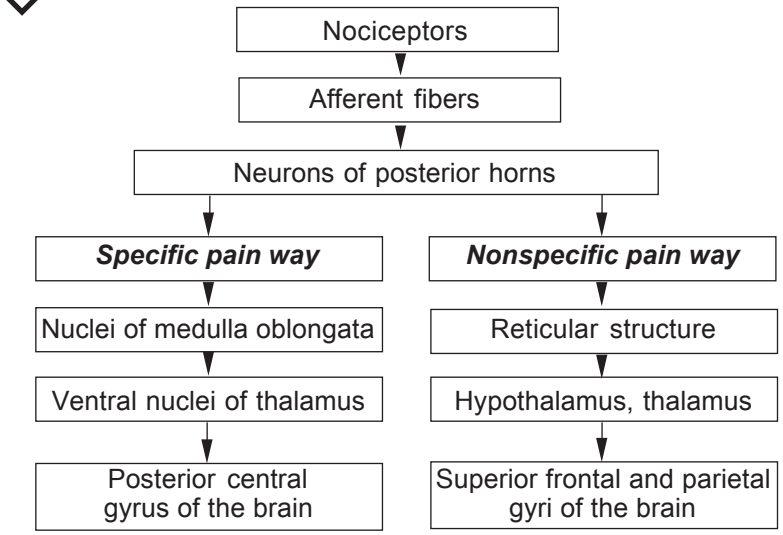
♦ ***Morphinans*** — *butorfanol*

♦ ***Derivatives of phenylpepiridin*** — *promedol (trimeperidine), fentanyl, prosidol, dipidolor, loperamide (imodium)*

♦ ***Derivatives of heptanone*** — *metadone, palfium*

♦ ***Different chemical groups*** — *tramadol, etc.*

NOCICEPTIVE SYSTEM



FUNCTIONS OF OPIOID RECEPTORS

Opiate receptors (μ, κ, δ, ε, σ) — lipoprotein zones with the high affinity to endogenous peptides (enkephalins, endorphins) and narcotic analgesics in the membranes of the neurons, conducting pain impulses

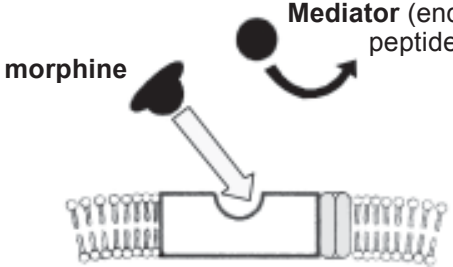
Function	Receptors	Agonist influence
Analgesia: spinal	μ_1, κ_3, δ_1, δ_2	↑
supraspinal	μ_2, κ_1, δ_2	↑
Psychotomimetic	κ	↑
Sedative	μ_1, κ	↑
Breathing	μ_2	↓
GIT	μ_2, κ	Constipation
Diuresis	κ_1	↑
Pupils	μ_2	Miosis
Secretion of hormones: prolactin, somatotropin	μ_1, μ_2	↑

FUNCTIONS OF OPIOID RECEPTORS

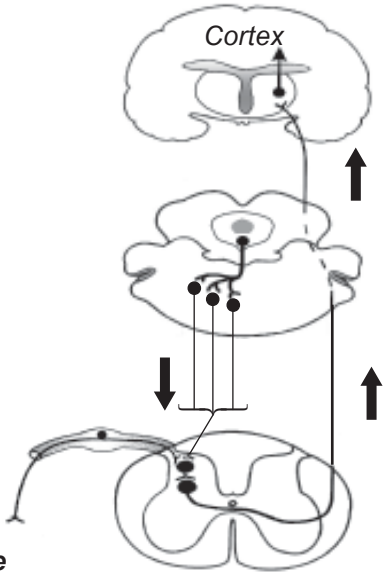
Properties	μ (mu)	κ (cappa)	δ (delta)
Activating	Analgesia, dependence, euphoria, vegetative reactions	Analgesia, sedation, miosis	Emotions, convulsive reactions, vegetative reactions
Activators: — endogenous peptides — narcotic analgesics	 β-Endorphins, metenkephalin Morphine, fentanyl, promedol, etc.	 Dinorphine, neoendorphin Pentazocine, buprenorphine, etc.	 Leuenkephalin —

CLASSIFICATION ON AFFINITY TO OPIOID RECEPTORS

- **Agonists:**
  - strong — *morphine, promedol, fentanyl, metadone, prosidol*
  - weak — *codeine, omnopon*
- ***Agonists-antagonists:*** *buprenorphine, nalbuphine, nalorphine, butorfanol, pentazocine, tramadol, tilidin*
- ***Antagonists:*** *naloxone, naltrexone*



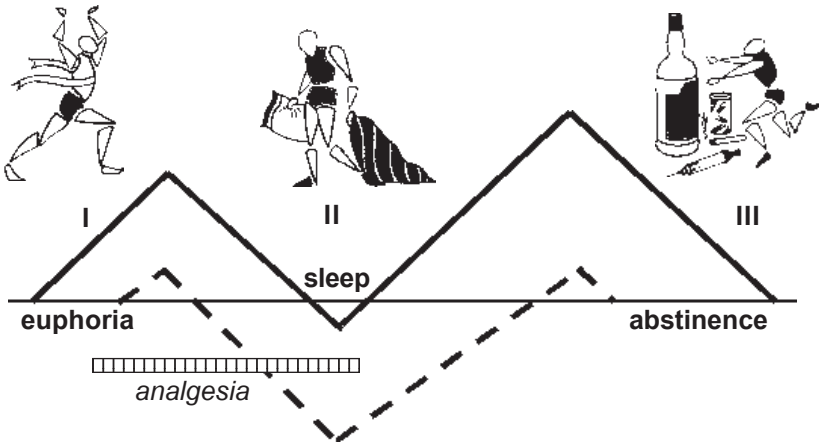
SITES OF MORPHINE ACTION



ANALGESIC ACTION OF NARCOTIC ANALGESICS

- Insignificant rise of pain threshold *and low efficiency in case of suprathreshold irritations* (cut of the skin)
- Depression of suprathreshold pain irritations summation at all levels of pain conducting
- Prevailing *efficiency at chronic visceral pains*
- Presence *of antianxious and euphoric action,* suppressing expectation of pain, smoothing of appreciation and estimation of pain sensations

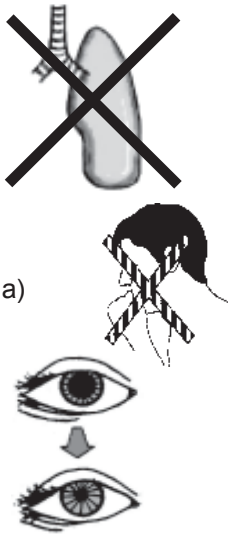
PHASES OF MORPHINE ACTION



PHARMACODYNAMICS OF MORPHINE

CNS

- **Cortex of cerebral hemispheres:** "mosaic" action (euphoria, sedation, sensitive, superficial sleep)
- **Medulla oblongata:**
  - *respiratory center* — ↓ (reduction of respiratory rate and depth, decline of sensitiveness to CO_2)
  - *coughing center* — ↓
  - *center of thermoregulations* — ↓ (hypothermia)
  - *center of vagus nerve* — ↑ (bradycardia, bronchial spasm, etc.)
  - *vomiting center* — ↑ or ↓
  - *vasomotor center* — in the therapeutic doses does not influence; in toxic — ↓
- **Mesencephalon:** ↑ center of III pair (miosis)
- **Spinal cord:** ↑ spinal tendon reflexes



PHARMACODYNAMICS OF MORPHINE

CVS: insignificant with tendency to ↓ ABP, bradycardia; ↑ intracranial pressure

Breathing: bronchial spasm

GIT: ↑ tone, spasm of sphincters of the stomach, intestine, Oddi, but ↓ peristalsis ⇒ prolongation of food evacuation from stomach (8–12 hrs), "locking" and spasmogenic effects (colics)

Urinary bladder: ↓ urination (spasm of sphincter + ↑ ADH secretion), but ↑ tone ⇒ colics; **uterus:** ↓ tonus

Metabolism: hyperglycemia, ↓ oxidizing phosphorylation, ACTH, corticosteroids, gonadotropins, ↑ prolactin, somatotropic hormone (STH)

PHARMACOKINETICS OF NARCOTIC ANALGESICS

Introduction: the majority are well absorbed from the mucous cavity of the mouth, nose, GIT

Bioavailability: subjected to presistemic metabolism ⇒ s.c., i.m., i.v., transdermal (fentanyl), peroral (codeine)

Binding with proteins: 20–96%

Distribution: at first they penetrate well to the lungs, liver, kidneys, spleen, then to the skeletal muscles (reservoir), fatty tissue, BBB, placenta!

Biotransformation: a considerable part metabolizes in the polar nonactive compounds, ethers (heroin), hydrolyze up to morphine and other compounds, a part of them (morphine and other ones) conjugate with the glucoronic acid transforming into active metabolites!

Excretion: by kidneys, partly with bile. $T_{1/2}$ of morphine — 4–6 hrs!

COMPARATIVE CHARACTERISTICS OF NARCOTIC ANALGESICS

Indices	Morphine	Promedol	Fentanyl	Pentazocine	Tramadol
Dose, mg	**10**	20–40	0.1	30	50–100
Duration of action, hrs	4–5	3–4	0.5	2–3	3–5
Euphoria	+++	++	+	+	+
Respiratory depression	+++	++	++++	+	+
Hemodynamics	↓ HR	Unchanged	↓ ABP, ↓ HR	↑ ABP, ↑ HR	↓ ABP, ↑ HR
Spasmogenic action	++++	++	+++	+	+
Nausea, vomiting, %	35–40	2–35	Rarely	2–6	5
Abstinence	+++	+++	++	++	+

NARCOTIC ANALGESICS APPLICATION

- Severe traumas and burns *(morphine, promedol, fentanyl, etc.)*
- Myocardial infarction and pre-infarction condition *(fentanyl, etc.)*
- Pulmonary edema *(morphine, promedol)*
- Renal and hepatic colic, acute pancreatitis *(pentazocine, promedol, fentanyl, omnopon, etc.)*
- Inoperable tumours *(morphine, dipidolor, promedol, etc.)*
- Premedication in postoperative period *(morphine, pentazocine, promedol, fentanyl)*
- *Neuroleptanalgesia, ataralgesia (fentanyl)*
- Epidural and cerebrospinal analgesia *(morphine)*
- Labor pain releif *(pentazocine, promedol)*

ADVERSE EFFECTS OF NARCOTIC ANALGESICS

- **Anxiety, tremor, hyperactivity** (with dysphoria)
- **Respiratory depression**
- **Nausea, vomiting, constipation, urine retention**
- **Postural hypotension** (with hypovolemia), ↑ **intracranial pressure**
- **Itching in the zone of nasal wings, urticaria** (with parenteral introduction)
- **Tolerance, including a cross one:** begins after the 1st dose; manifests itself in 10 days of intake 10 mg 5 times a day — ↑ dose 10–35 times as much and more; quicklier develops to analgesic, euphoric effects, ↓ breathing (in a drug addict in case of intake of 2 g of morphine every 2–3 hrs ↓ breathing does not take place); then to hypotensive, antidiuretic, emetic effects; **but not to** miotic, constipation, convulsive ones
- **Psychical and physical dependence** — drug addiction

DRUG ADDICTION — CHRONIC POISONING

- **Psychical dependence:** euphoria, indifference to surrounding, inhibition of thinking result in uncontrolled drug addiction
- **Physical dependence:** a concomitant of tolerance; the main purpose is a removal of syndrome of abstinence (deprivation)
- **Abstinence syndrome:** after the drug withdrawal
  1. *Acute phase (7–10 days):*
     - in 8–10 hrs — lacrimation, yawning, rhinorrhea, perspiration
     - in 36–48 hrs — uneasy sleep, weakness, chill, gooseflesh, nausea, vomiting, muscular pains, involuntary motions, shortness of breath, hyperthermia, hypertension, diarrhea
  2. *Prolonged phase (26–30 weeks)* — hypotension, bradycardia, hypothermia, mydriasis, ↓ breathing
- **As the disease progresses:** change of psyche (irritability, flaccidity, loss of sence of duty and own dignity), loss of appetite, disturbance of skin sensitiveness, sweating and other vegetative disorders

CONTRAINDICATIONS TO NARCOTIC ANALGESICS APPLICATION

- To children under 1 year old (morphine — up to 3 years old)
- Pregnancy, period of lactation
- Craniocerebral traumas, strokes (provocation of cerebral edema)
- Respiratory depression
- Cachexy
- Acute diseases of abdominal organs (before establishment of diagnosis)
- Chronic pain syndromes, excluding tumours

ACUTE POISONING BY NARCOTIC SUBSTANCES

- Mental confusion, coma
- Miosis, replacing with mydriasis
- Hypothermia
- Hypotension
- Hypopnoe, infrequent respiration (2–4 per a minute), turning into Cheyne—Stokes respiration
- Urine retention
- Preserving of **spinal tendon reflexes** (in contrast to barbiturates!)
- Acidosis

The death comes from paralysis of the respiratory center!

HELP IN CASE OF ACUTE POISONING BY NARCOTIC SUBSTANCES

- **Recovery of respiration (AVL)**
- **Antidote therapy:**
  - physiological antagonists:
    - ✓ concurrent — naloxone (0.001–0.004)
    - ✓ non-concurrent — atropine sulfate
  - physical — adsorbents
  - chemical — potassium permanganate
  - gastric lavage
  - acceleration of excretion from an organism (hydratation and dehydratation therapy)
  - hemosorption
- **Symptomatic therapy:**
  - myotropic spasmolytics
  - alkaline solutions
  - cardiotonics
  - heating
  - catheterization of the urinary bladder

Topic 9

NEUROLEPTICS. TRANQUILIZERS. PSYCHOSEDATIVES

NEUROLEPTICS (ANTIPSYCHOTICS)

(*neuron* — nerve; *lepticos* — capable to perceive) — psychotropic drugs which depress the CNS and remove delirium, hallucinations and other signs of psychosis without impairment of consciousness

Five signs (according to J. Delay and P. Deniker)

- Reduce some psychoses (antipsychotic action)
- Removal of psychomotor excitation of different genesis
- Mainly influence the subcortical cerebral structures
- Psychodysleptic action without hypnotic influencing is possible
- Cause typical neurological and neurovegetative reactions *(3 "H": hypodynamia, hypothermia, hypotension)*

HISTORY OF NEUROLEPTICS CREATION

1950 A derivative of phenothiazine is synthesized in Paris — aminazine

1952 J. DELAY and P. DENIKER showed its efficiency

1957 They initiated the term “neuroleptics” (“taking nerve”), signs of neuroleptics are defined

1958 The first antipsychotic neuroleptic — haloperidol

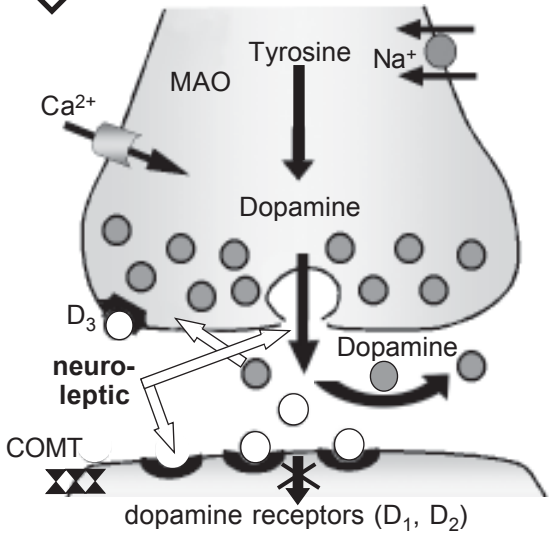
1966 A founder of the benzamide group — sulpiride — is synthesized

1968 The first atypical neuroleptic — clozapine (absence of extrapyramidal disorders)

CLASSIFICATION OF NEUROLEPTICS

- **Derivatives of phenothiazine** (typical neuroleptics):
  - ✓ *alifatic* — aminazine (chlorpromazine), levomepromazin
  - ✓ *piperazine* — etaperazine, triftazine
  - ✓ *piperidin* — neuleptil
- **Derivatives of butirophenone** — haloperidol, trifluperidol, droperidol
- **Derivatives of benzamide** — sulpiride (eglonil), metoclopramide (cerucal)
- **Derivatives of diphenylbutilpiperidine** — flushpirilen, pimozide
- **Derivatives of different chemical classes** — reserpine, chlorprotixen, azaleptine

MECHANISM OF NEUROLEPTICS ACTION



Main dopaminergic ways
Mesolimbic and mesocortical systems *(antipsychotic action, depression)*
Hypothalamus-hypophysis *(hypothermia, ↑ of prolactin)*
Extrapyramidal system *(manifestations parkinsonism)*
Trigger zone of the vomiting center (antiemetic effect)

SPECTRUM OF PSYCHOTROPIC ACTION OF NEUROLEPTICS

Aminasine — $\alpha > 5\text{-}HT_2 \geq D_2 > D_1$

Haloperidol — $D_2 > D_1 = D_4 > \alpha_1 > 5\text{-}HT_2$

antipsychotic

Sedatives:
droperidol >
aminasine >
levomepromazine >
chlorprotixen >
closapine > neuleptil

Antipsychotics:
haloperidol >
pimozide >
flushpirilen >
triftazine >
etaperazine > sulpiride

neuroleptic

H_1- **M-** **α-** **$D_{1,2,3,4,5}$-** **$5HT_2$-**

PHARMACODYNAMICS OF NEUROLEPTICS

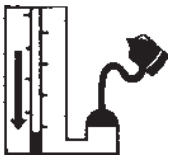
Neuroleptic (sedative)	Antipsychotic
• Apathy, general inhibition of thinking, drowsiness	• Removal of persistant changes of personality and asocial behaviour
• Decrease of motives, initiative, "paralysis" of the will, loss of interest to surrounding	• Removal of hallucinosis, delirium
• Removal of motor excitation, sharp motor lethargy	• Enhancement of motives and initiative, interest to surrounding
• Develops quickly	• Develops in 1–2 weeks
• Vegetative disturbances (collaptoid reactions, etc.), especially at the beginning of therapy	• Extrapyramidal disorders (increasing during the therapy course)

PHARMACODYNAMICS OF NEUROLEPTICS

CNS

- **Antivomiting** (anti-emetic) **and antihiccup effects** (blockade of D_2-receptors of the trigger zone of the vomiting center)
- **Hypothermia** ($\downarrow$ the center of heat release because of blockade of α-adreno- and serotonin receptors of hypothalamus + dilatation of the skin vessels)
- **Hypodynamia** (muscular tone as a result of activating influence of reticular formation and spinal cord through α-adrenoblockade)
- **Disorders in the motor sphere with systematic intake:** parkinsonism, acute dystonia, tardive dyskinesia, cataleptogenicity, etc. (extrapyramidal system D_2-receptors blockade)
- **Potentiation of anaesthesia and analgesia,** especially with sedatives (blockade of α-adrenoreceptors of the reticular structure and $\downarrow$ activating influence on the cerebral cortex)

PHARMACODYNAMICS OF NEUROLEPTICS



Vegetative reactions

- Acute hypotension, ↑ HR
- ↓ tone of hollow organs, motility and GIT secretion
- Disturbance of accommodation, dry mouth

Endocrine and other disorders

- ↑ prolactin, ↓ gonadotropins, estrogens, gestagens
- In women — amenorea, ↑ libido; in men — ↓ libido, gynecomastia, impotence
- ↓ STH, ACTH, ADH, oxytocin
- ↑ melanostimulating hormone
- ↑ appetite and body weight
- Antiallergic and antipruritic action (H_1-receptors blockade)

PHARMACOKINETICS OF NEUROLEPTICS

Introduction: with per oral administration absorption is unpredictable (first pass metabolism, change of GIT motility because of cholinolytic action; partial biotransformation in the intestine), bioavailability — 30–60%; at i.m. — ↑ 10–40 times as much, but also is unpredictable (precipitation in the muscle)

Binding with proteins: 90–95%

Distribution: accumulate in tissues of the brain, lungs and other well vasculirized organs; penetrate well through the BBB, placenta!

Biotransformation: takes place by various ways (oxidization, conjugation) not only in the liver, but also in the lungs, brain, kidneys and intestine with formation of active and nonactive metabolites. The age, smoking, sex, body weight and other are determined by metabolism rate and V of distribution

Excretion: with the kidneys and bile mainly as **nonactive metabolites**; $T_{1/2}$: at majority — 20–40 hrs ⇒ **prolonged forms** are created — flushpirilen, pimozide, fluorphenazine-decanoate (4–20 days)

APPLICATION OF NEUROLEPTICS

- **Schizophrenia**
- **Attack (relapse) of endogenous psychoses with delirium, hallucinations, aggressiveness**
- **Acute psychical disorders** (traumas, infections, postoperative period, psychologic traumatic situations)
- **Delirium, abstinence syndrome** — *haloperidol, sedative neuroleptics*
- **Neuroleptanalgesia** — *haloperidol, droperidol* in combination with opioids *(fentanyl)* and premedication
- **Vomiting of the central origin, hiccup** (radiation disease, chemotherapy of oncologic patients) — *pimozide, haloperidol, aminazine, chlorprotixen, etaperazine*

APPLICATION OF NEUROLEPTICS

- **Shock** (traumatic and burn) — *droperidol, aminazine*
- **Hypertensive crisis** — *levomepromazine, droperidol, tizercin, aminazine*
- **Hyperthermia** (resistant to NSAIDs) — *aminazine*
- **Vegetoneuroses** (ischemic heart disease (IHD), peptic ulcer, climax) — *sulpiride (antidepressive action), thioridazine, clorprotixen*
- **Neurodermatoses** (pruritis) — *aminazine, levomepromazine, chlorprotixen*
- **Migraine** — *sulpiride*
- **In gastroenterology** — *metoclopramide*

ADVERSE EFFECTS OF NEUROLEPTICS

- "Behavioral" affects like "pseudodepressions" (flaccidity, lack of initiative, indifference, etc.)
- As a result of dopamine blockade

  Extrapyramidal disorders (neuroleptic syndrome):

  ✓ *at the early stages:* **parkinsonism** (rigidity, tremor), akatisia (uncontrolled motor anxiety), **acute dystonia** (spasm of muscules of the tongue, face, spine)

  ✓ *at the late stages* (in months and years), **tardive dyskenesis** (winking, spasm of eyelids, prolapse of the tongue, choreoatetosis as usual in women)

- **Malignant neuroleptic syndrome** (malignant hyperthermias) — rigidity of muscles, high temperature, arrhythmia, coma

ADVERSE EFFECTS OF NEUROLEPTICS

- **Collaptoid reactions** (α-adrenoblockade)
- **M-cholinolytic action** (dry mouth, mydriasis, difficulty of urination, constipation, etc.)
- **Change of endocrine function:**

  ✓ **"castration effect"** (dopamine blockade $\Rightarrow \uparrow$ prolactin, $\downarrow$ gonadotropic hormones, their action on the sexual glands $\Rightarrow$ in women galactorrhea, amenorrhea, in men — gynecomastia, $\downarrow$ libido, importance)

  ✓ $\downarrow$ **secretion of STH, ACTH, TTH, oxytocyn,** $\uparrow$ **melanostimulating hormone**

- **Hepatotoxicity** (cholestatic hepatites)
- **Cardiotoxicity**
- **Allergic reactions** (rush, hemolysis, agranulocytosis)
- **Corneal and lenticular opacity** (20–30%)
- **Teratogenic, embryo-, phetotoxic action**

CONTRAINDICATIONS FOR NEUROLEPTICS

- Parkinson disease and medicinal parkinsonism
- Severe depression
- Epilepsy
- Pronounced cerebral sclerosis
- Glaucoma
- Benign prostate hyperplasia
- Porphyria
- Agranulocytosis
- Hypotension
- Pregnancy and breast feeding
- A working activity requiring exactness of psychical and motor reactions

A PERFECT NEUROLEPTIC

- ♦ A broad spectrum of biochemical and clinical action
- ♦ Efficiency with different variants and stages of schizophrenia
- ♦ Rapid relief of psychomotor excitation with maintenance of normal wakefulness of patients
- ♦ Long-term application without development of tolerance
- ♦ Administration 1 time a day or rarer (for long-acting drugs)
- ♦ Good tolerance (absence of extrapyramidal and other somatoneurologic effects)
- ♦ Minimal number of drug interactions

TRANQUILIZERS (ANXIOLYTICS)

tranquillium — rest; anxious — warried, frightened
ataractics (ataraxia — coolness)

— depriming psychotropic drugs, selectively removing emotional instability, anxiety, fear (phobia), tension

HISTORY OF CREATION

1954 a new tranquilizer meprobamate was introduced in the USA

1957 Swiss scientists synthesized the first tranquilizer from a series of derivatives of 1,4-benzodiazepine — chlordiazepoxide (elenium)

1963 Diazepam (valium) was applied

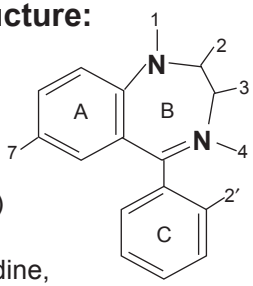
CLASSIFICATIONS OF TRANQUILIZERS

Historically:

- **I generation:** meprobamate, hydroxizine (atharax), amizil, (benactizine), mebicar, benzoclidine (oxilidine), etc.
- **II generation:** benzodiazepine derivatives (chlordiazepoxide, diazepam, etc.)
- **III generation:** buspirone, etc.

According to chemical structure:

- **Benzodiazepine derivatives (typical)** — *1,4-benzodiazepine* — chlordiazepoxide, diazepam, phenazepam, lorazepam, flunitrazepam, alprazolam, etc.; *1,5-benzodiazepine* (clobazam) *2,3-benzodiazepine* (tophyzopam/grandaxin/)
- **Of different chemical groups (atypical)** — buspirone, mebicar, amizyl, trioxaxine, oxalidine, meprobamate, etc.



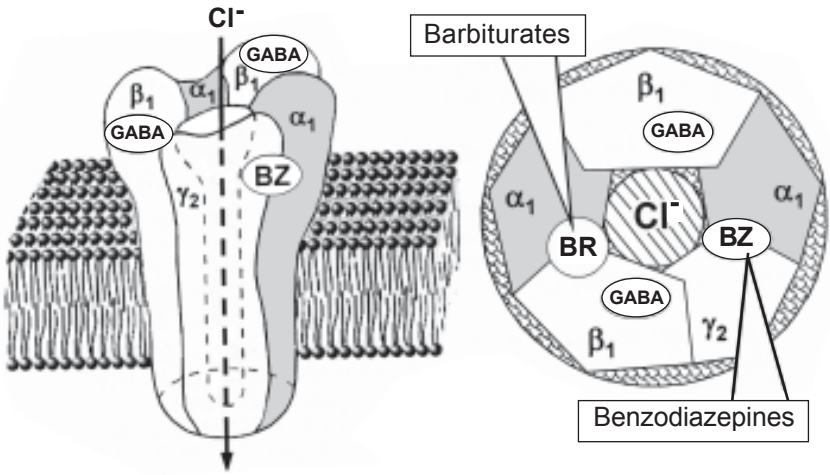
CLASSIFICATIONS OF TRANQUILIZERS

According to mechanism of action:

- **Direct agonists of benzodiazepine receptors* of the $GABA_A$-receptor-chlorionic channal** — derivatives of benzodiazepine (diazepam, oxazepam, lorazepam, etc.)
- **Direct agonists of serotonine receptors** — buspirone and others
- **Different mechanism of action** — amizyl, meprobamate, mebicar, trioxazine, oxilydin, etc.

* — some subtypes of benzodiazepine receptors (BZ_1, BZ_2, BZ_3, or ω_1, ω_2, ω_3) are known. Endogenic ligands: peptides, purins, nicotinamide, hypoxanthine, β-carbolines, diazepam binding inhibitor (DBI), etc. A majority of benzodiazepines are nonselective

MODEL OF THE COMPLEX $GABA_A$-RECEPTOR-CHLORIONIC CHANNEL



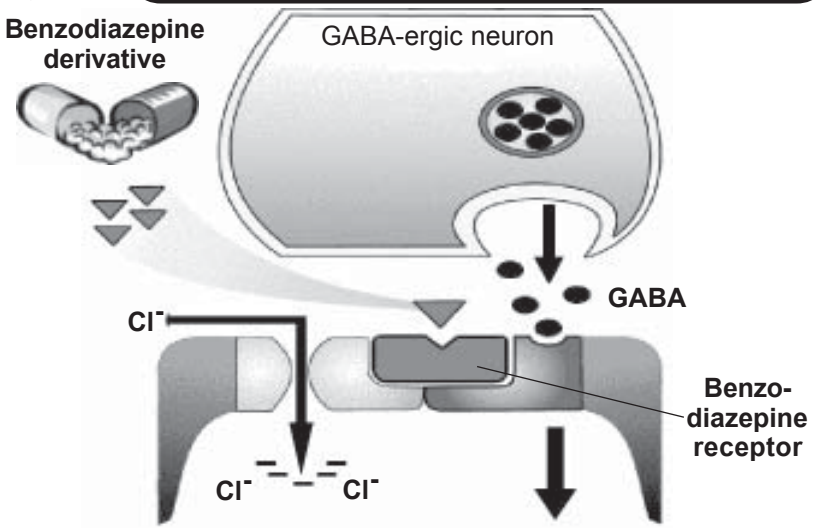
SPECTRUM OF TRANQUILIZERS' PHARMACOLOGICAL EFFECTS

- **Anxiolytic** (reduction of anxiety + stress-protective + antiphobic)
- **Sedative**
- **Hypnotic**
- **Myorelaxant**
- **Anticonvulsant**
- **Vegetostabilizing**
- **Amnestic** (*anterograde amnesia* — impossibility to remember the events taking place during the drug action)
- **Activate action of hypnotics, narcotic analgesics, alcohol**

According to spectrum of action:

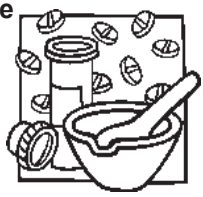
- **Sedative** ("large", night) — nitrazepam, flurazepam, diazepam, phenazepam, etc.
- **Daily** ("small"), having stress-protective activity with an activating component — mezapam, gidazepam, buspirone, mebicar

MECHANISM OF BENZODIAZEPINES ACTION



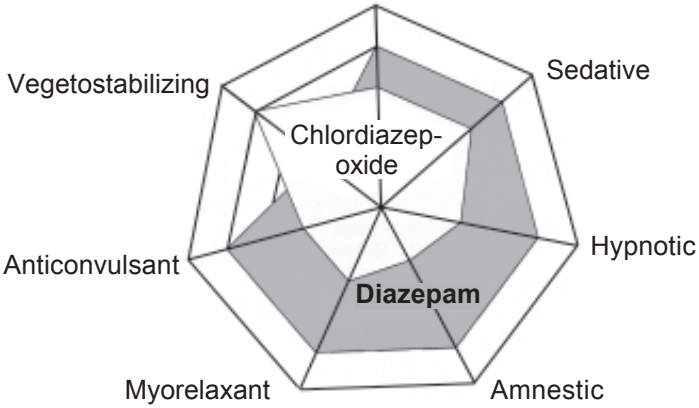
PHARMACODYNAMICS OF BENZODIAZEPINES

- Benzodiazepine → stimulation of BZ-receptor of the complex $GABA_A$-receptor-chlorionic channel ⇒
- ↑ sensitivity of GABA-receptors to GABA ⇒
- ↑ the rate of chlorine channels opening, which ↑ the entering current of Cl^- ⇒
- Hyperpolarization of the neuron postsynaptic membrane ⇒
- GABA-transmission ⇒ inhibition process development in definite departments of the CNS (limbic system, cerebral cortex, hypothalamus, thalamus, reticular formation, spinal cord, etc.)
- ⇒ Suppressing effect on the **emotional sphere** (anxiolytic, sedative-hypnotic, amnestic), **motor and vegetative systems** (myorelaxation, relief of seizures, vegetostabilization)



SPECTRUM OF BENZODIAZEPINES' PHARMACOLOGICAL EFFECTS

Anxiolytic *(reduction of anxiety + stress-protective + antiphobic)*



PECULIARITIES OF BENZODIAZEPINES' CLINICAL ACTION

- **With pronounced anxiolytic effect** — *phenazepam, diazepam, lorazepam, alprazolam,* etc.; **moderate** — *chlordiazepoxide, gidazepam, oxazepam,* etc.; **"daily"** (anxioselectivity with activating component) — *medazepam, tophizopam, gidazepam,* etc.
- **With pronounced hypno-sidative effect** — *nitrazepam, flunitrazepam, phenazepam, diazepam, lorazepam, chlordeazepoxide, oxazepam, triazolam, midazolam,* etc.
- **With pronounced anticonvulsant effect** — *clonazepam, diazepam, phenazepam, lorazepam, nitrozepam*
- **With pronounced myorelaxant effect** — *diazepam, chlordeazepoxide, lorazepam,* etc.

PHARMACOKINETICS OF BENZODIAZEPINES

Absorption: in the duodenum; time of absorption with per oral and i.m. administration almost identical (peak of concentration comes in 0.5–4 hrs)

Binding with proteins: 60–95%

Distribution: well penetrate through the BBB, placenta!

Biotransformation in the liver:

1) short-acting (lorazepam): conjugation with glucuronides formation;
2) long-acting (diazepam): at first undergo microsomal oxidization in the liver (N-dealkylation and hydroxilation) with active metabolites formation (diazepam → nordiazepam → oxazepam), then conjugation → glucuronides

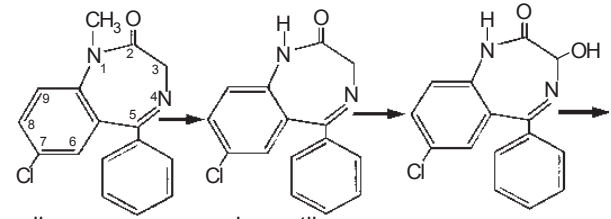
Excretion: as glucuronides by the kidneys

$T_{1/2}$: flurazepam — 2–3 hrs, clonazepam — up to 60 hrs

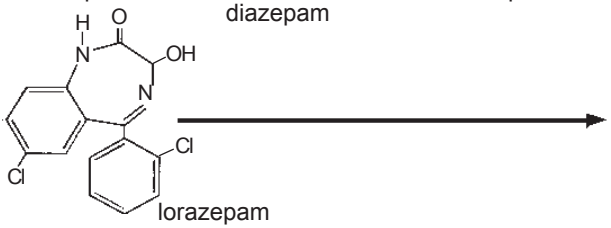
THE MAIN WAYS OF BENZODIAZEPINE ELIMINATION

Phase I — microsomal oxidization (N-dealkylation, aliphatic hydroxylation)

Phase II — conjugation



diazepam — desmetil-diazepam — oxazepam



lorazepam

Glucoro-nides

Excretion with urine + other metabolites through the intestine

PHARMACOKINETICS OF BENZODIAZEPINES

$T_{1/2}$ depends on:

- Age (in newborns — 31, infants — 8–14, adults 24–72, elderliers — 100 hrs)
- Concomitant diseases of the liver, kidneys, etc.

According to duration of action

- **Short-acting ($T_{1/2}$ to 6 hrs):** triazolam, medazolam
- **Medium-acting:** lorazepam, nozepam (oxazepam), flunitrazepam, etc.
- **Long-acting ($T_{1/2}$ over 24 hrs):** nitrazepam, phenazepam, diazepam, flurazepam (prodrug, $T_{1/2} \approx 100$ hrs), etc.

APPLICATION OF TRANQUILIZERS

- **All the kinds of fobic disorders** (neuroses, psychopathy, neurosis-like and psychotic conditions accompanied with alertness, fear, emotional strain, etc.) phenazepam, alprazolam, lorazepam
- **Anxiety with a background of depressive conditions of various genesis** — with antidepressants alprazolam, lorazepam, oxazepam
- **Endogenic psychiatric diseases (schizophrenia)** — diazepam, phenazepam, etc.
- **Acute conditions (psychomotor agitation, alcohol abstinence, delirium)** — i.v. diazepam, phenazepam, etc.
- **In somatic diseases therapy** (IHD, hypertension, peptic ulcer and duodenal ulcer, cholecystitis, bronchial asthma, etc.)

APPLICATION OF TRANQUILIZERS

- **Sleep disorders** — nitrazepam, phenazepam
- **Epilepsy, epileptic status, seizures of various genesis, tetanus** — clonazepam, diazepam, etc.
- **Neurologic disorders accompanied with muscular hypertonus** — diazepam, lorazepam
- **For premedication and anesthesia** (atharalgesia — diazepam + phentanyl), during the postoperative period — flunitrazepam, midazolam, diazepam, etc.
- **Labours** (tranquilizing effect + an ability to accelerate cervical dilatation), climax
- **Acute reactive stress conditions in healthy people in extreme situations** (but not with everyday stress)

ADVERSE EFFECTS OF TRANQUILIZERS

- **"behavioral" reactions:** ↓ apprehensive and psychomotor processes, disturbance of orientation, anterograde amnesia
- **aftereffect (hangover),** especially in elderly people (dose-dependent hypersedation, dyscoordination of movement)
- **"paradoxal" reactions:** movement anxiety, nightmares, ↑ aggressiveness, inadequate conduction (in children, elderly and mentally ill patients)
- **tolerance**
- **drug dependence** (psychic and/or physical) neuroses-like. The risk of arising with administration for more than 6 months, especially high doses

ADVERSE EFFECTS OF TRANQUILIZERS

- **Rebound syndrome**
- **↓ myocardial contractility, hypotension** (*diazepam, lorazepam* with parenteral introduction in elderly people)
- **Moderate depressive influence on the respiratory center** (in pulmonary patients)
- **Dry mouth, dyspepsia, ↑ appetite, ↑ intraocular pressure, impotence; seldom allergy, hematologic changes** (leukopenia, agranulocytosis)
- **Teratogenic, embryo- and fetotoxic action**

CLASSIFICATION OF PSYCHOSEDATIVES

- **Herbal origin:** valeriana, common motherwort, passiphlora, Baical scullcup
- **Bromides:** potassium and sodium bromide
- **Combined:** Quater mixture (extract of valerian + extract of mint + sodium bromide + magnesium sulfate + amidopirin + caffeine), Ivanov — Smolensky mixture (extract of valerian + sodium bromide + amidopirin + barbital-sodium), valocordin, corvalol (ethyl ether of bromine isovaleric acid + phenobarbital + oil of peppermint + ethanol), valocormide (extract of valeriana, lily of the valley, belladonna, sodium bromide, mentol), novopassit, etc.

HERBAL PSYCHOSEDATIVES

Valeriana *(Valeriana officinalis)* — the root and rhizome contain 0.5–2% of essential oil (borneolic ether of isovaleric acid), borneol (similar to camphor), borneolic ethers of formic, acetic, oil acids, alkaloids of valerin and chatinin, glycoside valeride, tannic substances, saponins, etc.

Valeriana

Five-laciniate motherwort *(Leonurus quinquelobatus),* siberian *(L. sibiricus),* cardiac *(L. cardiaca)* — the herb contains flavonoid glycoside, essential oil, saponins, during flowering alkaloids (stachidrin); in siberian motherwort alkaloid leonurin

Five-laciniate motherwort

PHARMACODYNAMICS OF HERBAL PSYCHOSEDATIVES

- ↓ excitability of reticular structure, medulla oblongata and hypothalamus
- ↑ threshold of neuronal excitability
- ↓ emotional and motive excitation
- ↓ threshold of convulsive activity (especially in children)
- Adrenolytic activity (↓ ABP, "-" ino-, chronotropic effects)
- ↓ afferent impulsation to the cerebral cortex
- Spasmolytic action (↓ vessels of the heart and brain, ↓ tone of smooth muscles of the intestine)
- Intensification of action of hypnotic drugs

HERBAL PSYCHOSEDATIVES

Indications

- **Insomnia** (caused by vegetative disorders)
- **Emotional overexcitation**
- **Neurotic disorders**
- **Angina pectoris with background of neurotic disorders**
- **Arrhythmias** (extrasystole, paroxysmal tachycardia)
- **Initial stage of hypertension**
- **Climacteric disorders**
- **Intestinal colic** (especially in children)

BROMIDES

Pharmacodynamics

- **Facilitate** all types of the internal (conditional) inhibition
- **Restore** the mosaic of excitative and inhibition processes
- **Concentrate** the irradiating (spreading) excitation
- ↑ inhibition processes in the cortex
- **Facilitate** differentiation, restore conditional-reflex activity
- ↓ excitability of motive neurons of the **cortex** and prevent from exhaustion (for example, at epilepsy)
- **Prevent** or **remove** dysrhythmia of the **brain**, render an antiepileptic effect
- According to I. P. Pavlov: "strengthen assimilation processes in the neurons of **cortex**"
- The effects depend on the nervous activity type and its functional condition

BROMIDES

Pharmacokinetics

Absorption: well absorbed in the GIT; strong irritating effect on the mucous ⇒ as solutions, mixtures with starch; therapeutic effect comes in 2–3 days
Distribution: extracellularly; concentration in the brain is 3–4 times less than in the blood
Excretion: by the kidneys, and also by the glands (sweat, lacrimal, bronchial, salivary, mammary)
$T_{1/2}$: 12 days, signs in a month; **strong cumulation**!

Indications

- Vegetative disorders (on the ground of mental instability of nervous processes)
- Emotional excitation
- Neurasthenia, neuroses, hysterias
- Spontaneous tachycardia
- Convulsive states, in large doses at epilepsy

BROMIDES

Adverse effects

- General weakness, fatigue, indifference to surrounding, weakening of memory, drowsiness
- Irritating action on gastric mucous, anorexia, constipation
- Excessive sweating
- Sexual dysfunction (↓ libido, potentia)
- Cumulation ⇒ acute and chronic poisoning (bromism): sleep, apathy, hallucinations, delirium, tremor of eyelids, tongue, hands, speech disorder, conjunctivitis, rhinitis, bronchitis, acne-like rash (acne bromica)

Bromism treatment

- Withdrawal of drug
- Antidote — sodium chloride (5–10 g on 3–4 l of liquid)
- Diuretics (aminophyllin, ammonium chloride)
- Hemodialysis
- Symptomatic treatment

Topic 10

ANTIDEPRESSANTS. NORMOTIMICS. PSYCHOSTIMULATORS. ACTOPROTECTORS. NOOTROPS. ADAPTOGENS. ANALEPTICS

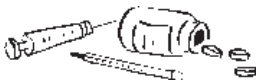
ANTIDEPRESSANTS (THYMOLEPTICS, THYMOANALEPTICS)

(from Gr. thymos — soul, ana — movement upwards, lepticos — able to apprehend)

— psychotropic drugs which relieve depression, "correct" a pathologically changed mood, return interest to the life, activity and optimism

Types of depressions

- **Endogenous** — in case of psychical diseases (schizophrenia, psychosis)
- **Exogenous** (reactive) — in case of severe psychical trauma, incurable disease, fatigue



PATHOGENESIS OF DEPRESSIONS

In the centers of the limbic system ↓ content of monoamines — serotonin, norepinephrine and dopamine

Serotonin — neurotransmitter of "well-being"

- ↑ mood (thymoleptic effect itself)
- Control after the impulsive drive
- Sexual practices
- ↑ level of aggressiveness
- Facilitation of falling asleep
- Regulation of sleep cycles
- ↓ appetite
- ↓ sensitivity to pain

HISTORY OF ANTIDEPRESSANTS

1951 The onset of history of antidepressants. The given properties are revealed in hydrazide of isonicotinic acid derivative — iproniazide

N. KLINE used this "side" effect for the treatment of depression

1957 R. KUHN applied a term "thymoanaleptic" action while studing imipramine — a derivative of trycyclic compounds

1960 J. AXELROD revealed a mechanism of antidepressive action of imipramine (the Nobel Prize)

At the same time the first home-produced antidepressant azafen (laboratory of M. N. Shchukina, Moscow) was obtained, then — pirazidol (M. D. Mashkovsky)

R. Kuhn

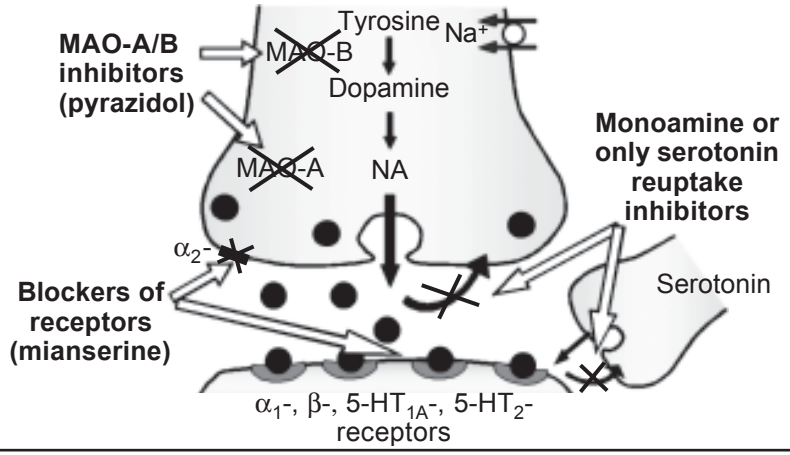
M. D. Mashkovsky

CLASSIFICATION OF ANTIDEPRESSANTS

- **Inhibitors of monoaminooxidase (MAO):** *irreversible* — nialamide; *reversible* — pirazidol, moclobemide, etc.
- **Inhibitors of neuronal reuptake of monoamines:**
  - **nonselective action:** *tricyclic (TCA, typical)* — imipramine (imizine), amitriptyline, clomipramine; *fourcyclic (atypical)* — maprotiline
  - ***selective (elective) serotonin reuptake inhibitors (SSRI):*** fluoxetine (prozac), fluvoxamine, paroxetine, etc.
- **With the receptor mechanism of action:** nefazodone, mirtasapine, mianserine (blockers of presynaptic α_2-, depressing serotonin release, and *postsynaptic 5-HT-receptors*, *modulating a serotoninergic transmission*), etc.
- **Reuptake activators (!):** thianeptine

MECHANISM OF ANTIDEPRESSANT ACTION

Potentiation and regulation of monoaminergic transmission in the CNS



SELECTIVITY OF ANTIDEPRESSANTS

Along with reuptake inhibition, a series of drugs block central and peripheral M-, α- and H_1-histamine receptors

Groups	Reuptake inhibition			Postsynaptic receptors blockade		
	NA	S	DA	M-	H_1-	α-
Typical (TCA):						
— imipramine	+++	+++	+	+++	++	++
— amitriptyline	+++	+++	+	+++	++	+++
Atypical (tetracyclic):						
— maprotyline	++++	+	+	+	+	++
SSRI	–	++++	–	–	–	–

MAO inhibitors do not have cholinolytic activity!

PHARMACODYNAMICS OF ANTIDEPRESSANTS

Sedative, antianxious ← **Thymoleptic** → **Thymeretic (stimulant)**

+ ↓ negative emotions, fears

an ability ↑ mood (in 10–15 days)

+ ↑ psychomotorics (in 5–7 days)

clomipramine

amitriptyline

fluoxetine

MAO inhibitors

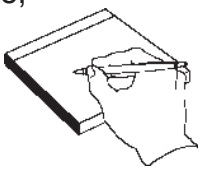
M-, N_1-, α-receptors blockade

↑ serotoninergic transmission

↑ noradrenergic transmission

CLINICAL CLASSIFICATION OF ANTIDEPRESSANTS

- **Thymeretics (with the stimulant action)** — majority of MAO inhibitors (nialamide, moclobemide), imipramine, fluoxetine, sidnofen, etc.
- **Sedatics (with the sedative action)** — amitriptyline, fluoracizine, fluvoxamine, mianserine
- **"Balanced" action (bipolar, modulating)** — pyrazidol, clomipramine, majority of SSRI (paroxetine)



PHARMACODYNAMICS OF ANTIDEPRESSANTS

- **Anaesthetic and potentiate analgesing action** *(mainly TCA)*
- **Hypothermia** *(TCA)*
- **Antivomiting** *(TCA)*
- **Nootropic** *(pyrazidol)*
- **Anxiolytic** (drugs with the receptor mechanism of action — *nafazodone*)
- **Hypotensive** *(TCA, nialamide)*

PHARMACOKINETICS OF ANTIDEPRESSANTS

Introduction: TCA are absorbed in GIT incompletely, undergo presystemic metabolism, MAO inhibitors and SSRI — well-absorbed

Bioavailability: 30–90% (depending on group)

Binding with proteins: 73–98%

Distribution: well penetrate the tissues

Biotransformation *(generalized for TCA, 4-cyclic and electoral inhibitors):*

1) hydroxilation and conjugation to glucuronoids;

2) dimethylation up to active metabolites formation

MAO inhibitors: acetylation, distinction by genotype! The liver cytochrom R-450 function inhibitors. Slowing down with age, liver diseases!

Excretion: by kidneys, partly with bile

INDICATIONS TO ANTIDEPRESSANTS

- Depressions in mentally ill patients
- Reactive and post-traumatic depressions, after neuroinfections, poisonings (PhOC, mercury, lead, etc.)
- Neurotic reactions with elements of depression, asthenia, night-time enuresis, nervous anorexia or bulimia, insomnia, narcolepsy, etc.
- A series of psychosomatic diseases (irritable colon syndrome, peptic ulcer, bronchial asthma, neurodermatites, etc.)
- Chronic pain syndromes
- Vegetodiencephalic crises
- Syndrome of chronic fatigue, etc.

ADVERSE EFFECTS OF ANTIDEPRESSANTS

- **CVS:**
  - TCA — orthostatic hypotension (blockade of α-adrenoreceptors), arrhythmias, ↓ conductivity, sudden death
  - thymeretics — TCA and especially MAO inhibitors — adrenomimetic reactions, "cheese" syndrome (↑ HR, ABP, arrhythmias)

- **CNS:** psychic excitation (insomnia, delirium, hallucinations, etc.) — more frequent timeretics; depression (with alcohol, sedatics)
- **Rebound syndrome** — suicides, especially in teenagers

ADVERSE EFFECTS OF ANTIDEPRESSANTS

- **Toxic-allergic** (hepatitis, bone marrow supression, allergy, etc.)

- **Cholinolytic** (dry mouth, mydriasis, sedation, constipation, difficulty of urination, etc.) — TCA
- **Antihistamine** (sedation, ↑ weight) — TCA

- **Other** (sexual dysfunction, ↓ appetite, weight, tremor, etc.) — SSRI

PRINCIPLES OF ANTIDEPRESSANTS RATIONAL ADMINISTRATION

- **Correct choice depending on the form and clinical course of the process:**
  - at asthenodepressive syndrome — **thymeretics** or balanced action drugs
  - at the anxious-depressive syndrome — **sedatics** from TCA and SSRI
- **Correct choice of doses and treatment regimen:**
  - presence of a "therapeutic window" in TCA ⇒ gradual ↑ of dose, beginning from minimal
  - administration of thymeretics — in the morning, sedatics — in the evening
  - gradual ↑ of the effect (with severe endogenous — in 1.5 months)

PRINCIPLES OF ANTIDEPRESSANTS RATIONAL ADMINISTRATION

- **Combined treatment**
  - TCA + MAO inhibitors or their rapid change are forbidden! (sympathico-adrenal crises, death); turn from TCA to MAO inhibitors — 3–7 days; from MAO inhibitors to TCA — 2–3 weeks
  - SSRI + MAO inhibitors — "serotonin" crises (hyperthermia, seizures, coma, death)
  - Are *inhibitors of microsomal* oxidization of the liver ⇒ slow down biotransformation of other drugs
  - Undesirable simultaneous administration of TCA with beta-adrenal blockers, antacids, H_1-histamonoblockers, contraceptives, depressing CNS, alcohol, etc.; MAO inhibitors and thymeretics — with adrenomimetics, products containing thyramine (cheese, etc.)

NORMOTIMICS

Drugs of lithium — lithium oxybutyrate, lithium carbonate (lithionite-durel, micalit)

- Prevent the arising of both mania and depressions with manic-depressive and schizophrenic psychoses, render the medical action at manias
- Li ions partly substitute Na^+ and K^+ in cells; as the Ca^{2+} and Mg^{2+} antagonists ↓ activity of dependent enzymes, ↓ hyperfunction of the monoaminergic systems and excitability of neurons

Adverse effects

- Tremor of extremities, drowsiness, headaches
- Diarrhea (may be very severe)
- Polyuria, thirst, electrolyte balance impairment (loss of Na^+, K^+, Mg^{2+}, water) and renal function
- Thyroid dysfunction

PSYCHOSTIMULATORS

(or psychomotor stimulators) — psychotropic drugs which have agitation effect, quickly mobilize functional and energy reserves of an organism, at first CNS, stimulating mental and physical working-ability of ill and healthy people (with fatigue)

Classification

- ♦ **Phenylalkylamines** — amphetamines (phenamine)
- ♦ **Sidnonimins** — sydnocarb
- ♦ **Derivatives of purinea** (xanthins) — caffeine, sodium caffeine-benzoates

HISTORY OF PSYCHOSTIMULATORS

Caffeine (tea, coffee, cacao, cola, etc.)

Cocaine (leaves of coca)

Nicotine (tobacco)

1819 F. RUNGE selected caffeine

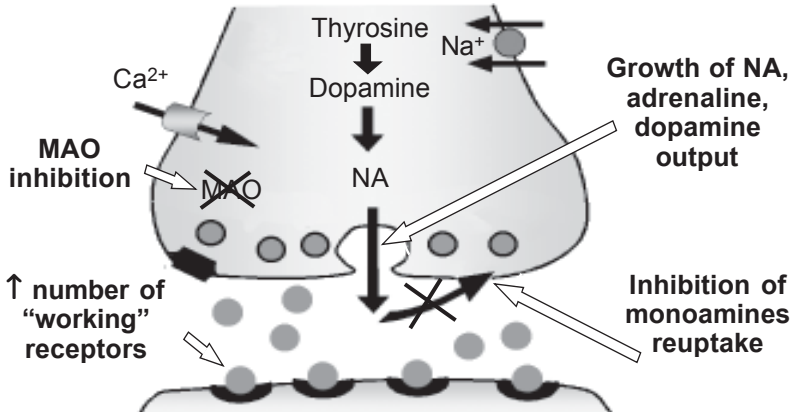
1887 L. EDELEANO synthesized an analogue of alkaloid catinone of coca leaves (Catha edulis) — amphetamine

"Excessive information looks like excessive meal — both result in indigestion"

V. Levi "Following the thought"

MECHANISM OF PHENYLALKYLAMINES ACTION

Significant activation of adrenergic transmission at all the levels: from CNS to the cellular metabolism



PHARMACODYNAMICS OF PHENYLALKYLAMINES

♦ **CNS:**

- ***neurophysiologic processes:***
  - ✓ ↑ *wakefulness of the brain* — ↓ fatigue, put off a necessity in sleep for 10–12 hrs, ↑ perception, vision, hearing, touch (activating of reticular formation (RF), thalamus)
  - ✓ ↑ *emotional-motivation reaction* — burst of energy, initiative, ↑ mood (↑ limbic system, hypothalamus)
  - ✓ *revival of motions* — ↑ motive activity, lack of loading control (↑ RF)
- ***psychophysiologic processes:***
  - ✓ ↑ attention, short-term (!) memory, ↑ stereotype work, but a creative one suffers ("leap of ideas", errors)

PHARMACODYNAMICS OF PHENYLALKYLAMINES

♦ **CNS:**

- ↓ the hunger center, ↑ the hypothalamus saturation center ⇒ anorexinogenic effect
- ↑ the respiratory center

♦ **Metabolism:**

- mobilization of ATP resources and creatine phosphate in the CNS, the heart, the liver, the skeletal muscles
- ↑ glycogenolysis and lipolysis, delivery and utilization of glucose and fatty acids ⇒
- in the blood ↑ glucose, piruvate, lactate, metabolic acidosis
- disjoining of phosphorylation and oxidization, ↑ necessity of organs in O_2, macroergs synthesis inhibition
- uneconomical energy expenditure, ↑ the body temperature, rapid exhaustion

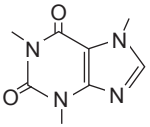
PHARMACODYNAMICS OF PHENYLALKYLAMINES

- **CVS:**
  - "+" ino-, chrono-, batmo-, dromotropic effects ⇒ tachyarrhythmia
  - ↑ ABP, stroke and minute volume
- **Features:**
  - the degree of activating is proportional to the dose
  - under complicated conditions (highland, high temperature of environment), with deep fatigue, prolonged stress, "strained work of the adrenergic system" the application is dangerous (rapid exhaustion of monoamine depot, heart failure)
  - a rebound phenomenon, psychic and physical dependence
  - ⇒ ***these drugs are for a single administration, in the first half of the day (break is no less than 4 days)***
  - in 10–15% of people there is paradoxical reaction (alarm, malice, depression, drowsiness, etc.)

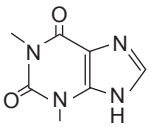
XANTHINE DERIVATIVES

(oxidized purines, analogues of urinary acid)

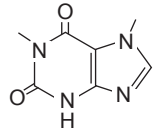
- **Alkaloids:** caffeine (1,3,7-trimethylxanthine), theobromine (3,7-dimethylxanthine), theophylline (1,3-dimethylxanthine)
- **Half-synthetic:** aminophylline (euphylline — theophylline + ethylenediamine!), diprophylline, pentoxiphylline (trental, agapurine), etc.



caffeine



theophylline



theobromine

Sources of obtaining

- **Caffeine:** tea (about 5%), coffee (2–2.5%), cola nut (2%), etc., and by the synthetic way from the urinary acid
- **Theobromine:** seeds of a chocolate tree (2%)
- **Theophylline:** tea (refer to Topic 16)

CAFFEINE

Mechanism of action

- Concurrent antagonist of adenosine receptors A_1 (purine P_1) $\Rightarrow \uparrow$ cAMP synthesis
- Inhibits phosphodiesterase (in large doses), that $\downarrow$ cAMP inactivation
- In the end $\uparrow$ intracellular level of cAMP in the CNS, the heart, the smooth and skeletal muscles, fatty tissue

Pharmacodynamics

- **CNS** — $\uparrow$ excretion of neuromediators in synapses:
  - *dopaminergic* — psychostimulation
  - *cholinergic of the cortex* — $\uparrow$ intellect
  - *cholinergic of medulla oblongata* — $\uparrow$ respiratory center
  - *adrenergic of the hypothalamus and medulla oblongata* — $\uparrow$ vasomotor center

CAFFEINE

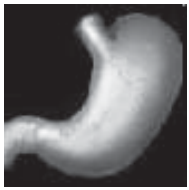
Pharmacodynamics

- **Heart:**
  - direct cardiostimulating effect — "+" inotropic effect, $\uparrow$ organ need in O_2, in the large doses arrhythmia
  - tachy- ($\uparrow$ sinus node automatism) or bradycardia ($\uparrow$ the vagus nerve center)

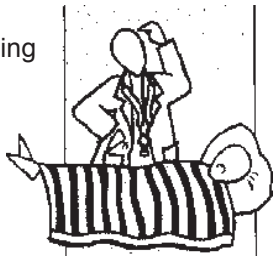
- **Vessels:**
  - narrowing of skin vessels, mucous membranes, abdominal organs (influence of the vasomotor center)
  - delation of coronal vessels, lung vessels, skeletal muscles (managed with cAMP participation)
  - $\uparrow$ ABP with mild hypotension (in the norm changes a little)
  - cerebral blood flow in healthy people caffeine can worsen with spasms, migraine — normalizes (spasmolytic action)

CAFFEINE

Pharmacodynamics



- **GIT** — gastric secretion stimulation
- **Kidneys** — ↑ diuresis (moderately)
- **Smooth muscles** — relaxation of bronchial muscles and bile-excreting ways
- **Metabolism** — ↑ lipolysis, glycogenolysis, basic metabolism by 10–25%
- **With drug abuse** — myocarditis, worsening of blood circulation in the extremities, deterioration of IHD clinical course, insomnia, tremor, psychical dependence (caffeinism)



INDICATIONS TO PSYCHOSTIMULATORS

- Temporal ↑ mental work — *sydnocarb (2–3 days)*, *caffeine*
- Single ↑ of exercise tolerance under extraordinary conditions — *sydnocarb (2–3 days ones a day) + rest*
- Neuroses with asthenia phenomena, prolonged depressions, enuresis — *sydnocarb (2–3 weeks)*
- Narcolepsy — *sydnocarb, caffeine*
- For weakening of the action of substances which depress the CNS — *sydnocarb, caffeine*
- Central origin hypotension (traumas, intoxications, infectious diseases) — *caffeine*
- Migraine — *caffeine*
- As an analeptic — *caffeine*

ACTOPROTECTORS (bemitil)

(lat. astus — motion) **— stimulating a working ability and promoting resistance of organism under complicated conditions (acute oxygen starvation, cooling, hyperthermia, etc.) due to the rise of conjugation of oxidation and phosphorylation, fall of oxygen demand, weakening of catecholamines exhaustion with loading**

Indications

- Asthenia, neuroses
- Traumas, infections, intoxications
- Hypoxia, stress, etc.
- Extreme working conditions
- Sport medicine

NOOTROPICS

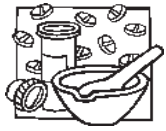
(psychometabolic stimulators) ***— render a selective mnemotropic action*** *(from Gr. mneme — memory, tropos — direction)* ***improving higher integrative functions of the brain — an ability to study, memory, operator activity***

Classification

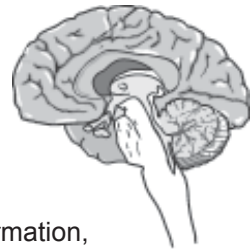
- **Pyrrolidone derivatives** — piracetam (nootropil) and its analogues (aniracetam, etc.)
- **GABA-ergic** — aminalone, picamilone, fenibut, sodium oxybutyrate
- **Derivatives of different groups** — *membranoprotectors* (piriditol, acefen); *glutamatergic* (memantin, glycine); *neuropeptides* (semans, ebiratide)

MECHANISM OF NOOTROPICS ACTION

- ↑ **bioenergetics of the brain:**
  - ↑ ATP and cAMP synthesis, glucose utilization, glycolysis, aerobic breathing, activity of adenylate cyclase
  - antihypoxic action (GABA-ergic nootropics)
- ↑ **synthesis and secretion of mediators:** dopamine, noradrenaline, acetylcholine, inhibit MAO ↑ formation of neuromediators (blockade of potassium channels, facilitation of membranes depolarization)
- ↑ **synthesis of protein and membrane phospholipids** due to ↑ regeneration of neurons, synthesis of informative neuropeptides, metabolism of phospholipid membranes, ↓ catabolism in the brain



MECHANISM OF NOOTROPICS ACTION



- ↑ **cerebral blood flow and hemorrheology:**
  - dilatation of cerebral vessels
  - improvement of blood flow (zone of ischemia), prevent from brain edema development
  - ↓ aggregation of thrombocytes, thrombi formation, ↑ microcirculation
- **Antioxidant action:** ↓ LPO (lipid peroxidation), protection from phospholipids cellular membranes destruction ⇒ facilitation of memory traits fixation
- ↑ **mnemotropic effects of memory neuropeptides** due to agonism with receptors for memory neuropeptides (ACTH fragments, vasopressin, P substances) ⇒ ↑ consolidation process (transmission of information to long-term memory)

PHARMACODYNAMICS OF NOOTROPICS

Only with long administration!

- ↑ **concentration of attention, ability of studying, long-term memory** (with asthenias, chronic fatigue, in children with the defects of development, but not in healthy people!)
- ↓ **perception of stress, renewal of interest to life, optimism, vitality** in people with neurotic states, after the stress situations (*stress-protective* ("day-time") — piracetam, picamilon + anticonvulsant — phenibut + *moderate psychostimulating* — acefen, etc.)
- **Cerebroprotective,** ↑ **restorative processes in the damaged brain** (rehabilitation after the cranial-cerebral traumas, strokes, intoxications with alcohol and other neurotropic substances, convulsive status, other cerebrovascular disturbances)
- ↑ **general tonus and functional activity in elder age groups**

ADAPTOGENS

Natural drugs rendering unspecific general restorative action on the CNS function, endocrine regulation, metabolic processes and promoting adaptation of an organism to unfavorable conditions

Schizandra (Schizandra)

Eleuterococcus (Eleuterococcum)

Ginseng (Radix Ginseng)

Leuzea (Leuzea)

ADAPTOGENS

Prolong administration!

- ↑ volume and limit of physical work, ↓ fatigue, ↑ tolerance
- ↑ mental work indicators (short- and long-term memory, attention, an ability to study, especially in fatigue)
- Activate the cerebral cortex, RF
- Psychostimulating effect due to the new formation of energy (↑ glycolysis, oxidization of lipids, etc.)
- ↑ synthesis of glycogen in the liver and skeletal muscles
- ↑ synthesis of DNA, RNA, protein, membrane phospholipids, processes of regeneration
- ↑ secretory function of adrenal cortex, thyroid

INDICATIONS FOR ADAPTOGENS

- **Asthenia** — schizandra, leuzea, eleuterococcus, ginseng
- **Moderate hypotension** — mountain angelica, devil's club, eleuterococcus, ginseng
- **For elderly people to rise the vital tone and a working ability** — schizandra, leuzea, eleuterococcus, ginseng
- **For the rise of immunological reactivity of an organism at the period of epidemics** — ginseng, eleuterococcus, rose-root

Rose-root
(Rhodiola r.)

- **For healthy people to rise a working ability and accelerate adaptation to mental and physical loading** — ginseng, eleuterococcus, rose-root

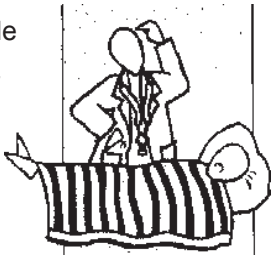
ANALEPTICS (reviving)

(from Gr. ana — movement upwards, lepticos — capable to perceive)

— tone up respiratory and vasomotor centers of medulla oblongata

Classification

- **With the prior influence on the vital centers (respiratory and vasomotor centers)** — caffeine, bemegride, ethimizole
- **With the mixed mechanism of action** — camphor, sulfocamphocain, cordiamine



PHARMACODYNAMICS OF ANALEPTICS

- ↑ depolarization of neurons at the expause of ↑ permeability of the Na^+ and Ca^{2+}-channels
- ↑ lability of nervecentres
- ↓ latent period of reflexes
- ↑ expense of macroergs, O_2 consumption
- antagonism with inhibiting mediators of the CNS (bemegride — GABA, caffeine — adenosine)

- **activate depressed respiratory center** (for a short term, repetition — seizures!):
  - ✓ ↑ sensitivity to CO_2, H^+, reflexes from the carotid glomerules, hemoreceptors of the vessels, lungs
  - ✓ accelerate and deepen breathing, ↑ minute volume of breathing
- **activate vasomotor center:** ↑ tone of arterioles and venules, venous return to the heart, secondary ↑ cardiac output (except for caffeine and camphor)

INDICATIONS TO ANALEPTICS

- Asphyxia of new-borns — *ethimizole*
- Collaptoid states of central genesis — *caffeine, cordiamine*
- Transient disorders of cerebral circulation (faints) — *sulfocamphocaine, caffeine*
- Chronic hypoventilation with CO_2 retention at respiratory diseases — *sulfocamphocaine, camphor*
- "Convulsive" therapy — *bemegride*
- Poisoning of moderate severity with hypnotics, barbiturates and other depressants of the CNS (causing antinarcotic awakening action) — *bemegride, camphor, cardiamine*

Part IV
DRUGS AFFECTING THE CARDIOVASCULAR SYSTEM

Topic 11
CARDIOTONIC DRUGS. CARDIAC GLYCOSIDES. NONGLYCOSIDE CARDIOTONICS

CARDIAC GLYCOSIDES

(from Gr. glikis — sweet) ***herbal substances consisting of 2 parts: nitrogen-free (aglycone) and saccharine (glycone), which have cardiotonic and cardiotrofic action used for heart failure treatment***

Foxglove
(Digitalis)

Pheasant's eye
(Adonis vernalis)

Lily of the valley
(Convallaria)

HISTORY OF CARDIAC GLYCOSIDES CREATION

1785 W. WITHERING introduced digitalis into the clinical practice

1865 E. V. PELIKAN examined strofant action on the frog's heart

1880 In the S. P. BOTKIN's Clinic and I. P. PAVLOV's Laboratory there were examined in detail and introduced into clinical practice the other medical plants containing cardiac glycosides (CG) — Adonis (N. A. Bubnov), Lily of the valley (I. P. Bogoyavlensky), Helleborus (N. Ya. Tchistovich)

W. Withering

S. P. Botkin

CLASSIFICATION OF CARDIAC GLYCOSIDES

- **Long-acting with significant cumulative properties the drugs of:**
  - *Digitalis purpurea* — digitoxin, cordigit (leaves)
  - *Digitalis fernigine* — digalen-neo
- **Intermidiate-acting and average cumulative effect the drugs of:**
  - *Digitalis lanata* — digoxin, celanide, lantozide, medilazide
  - *Adonis vernalis* — adoniside (herbal) extract
  - *Erysimum diffusum* — cardiovalen (complex: "+" adoniside)
- **Rapid and short-term action with a slight cumulation the drugs of:**
  - *Strophanthus* — strophanthine K (Combe)
  - *Convallaria majalis* — corglycone, extract of lily of the valley
  - *Seillamarina* — meproscillarine

STRUCTURE OF CARDIAC GLYCOSIDES

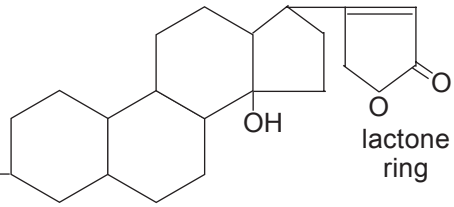
Glycone — O — **Aglycone**

n=1 — monozide
n=2 — diozide
n=3 — triozide
n=4 — tetrozide

n — quantity of molecules

activity

steroid alcohol (the agents of cyclopentanoperhydro-phenanthrene)



saccharine part — O

Pharmacokinetic properties and biological activity on the whole

Cardiotonic properties

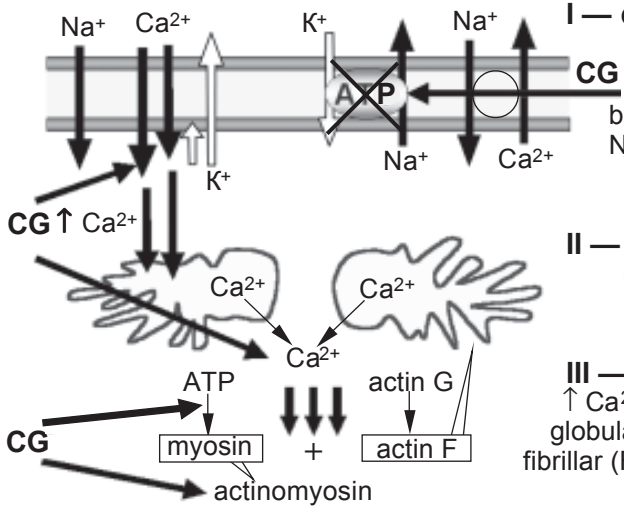
PHARMACODYNAMICS OF CARDIAC GLYCOSIDES

Cardiac effects

- **"+" inotropic** (systolic) — enhancement and shortening of a systole
- **"+" tonotropic** — ↓ myocardial tone
- **"–" chronotropic** (diastolic) — ↓ heart rate
- **"–" dromotropic** — ↓ conduction
- **"+" bathmotropic** — ↑ excitability

P. S. These effects characterize the **therapeutic phase**, but, as a rule, last two effects are most marked at overdosage **(toxic phase)** and are considered as adverse, excepting application of "–" dromotropic at supraventricular tachyarrhythmia

MECHANISM OF CARDIOTONIC ACTION OF CARDIAC GLYCOSIDES



I — excitation of membrane

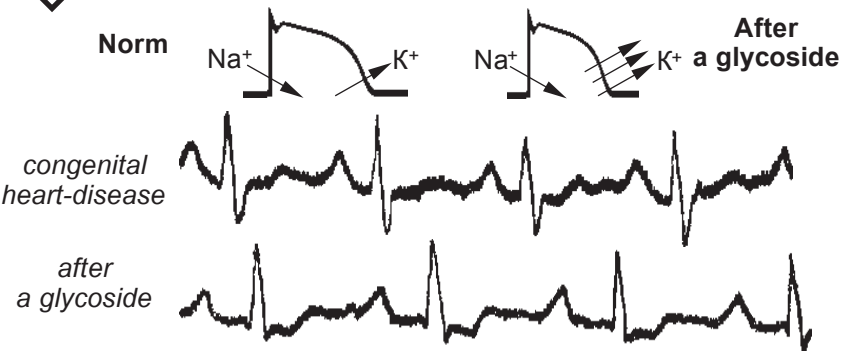
block of SH-groups Na^+, ATP-ase, Na^+, K^+-pump, ↑ Ca, Na^+, ↓ K^+

II — coupling of excitation with contraction

III — contraction

↑ Ca^{2+}, transition of globular (G) actin into fibrillar (F), ATP-activity of myosin

CHANGES OF ECG



In therapeutic doses:

- ↓ wave T (early sign — ↑ tissue metabolism), ↓ ST below the isoelectric line, ↓ QRST, ↑ R (signs of *"+" inotropic*);
- ↑ PP intervals *("–" chronotropic)*
- ↓ PQ *("–" dromotropic)*

PHARMACODYNAMICS OF CARDIAC GLYCOSIDES

Mechanism of "+" inotropic effect means that

- ♦ **Ca^{2+}** — synergist CG
- ♦ **K^+ and SH-groups donators (unithiol, etc.)** — CG antagonists

- **"+" tonotropic** — ↓ sizes of dilated heart
- **"–" chronotropic (diastole):**
  - ✓ ↑ vagus influencing reflexly from baroreceptors of the sinocarotid zone and myocardium — "vagal factor"
  - ✓ ↓ reflex tachycardia due to the direct antiadrenergic influencing — "extravagal factor"
- **Cardiotrophic:** renewal of energy, lipid balance, ↓ need in O_2, stabilization of lysosomes, ↓ tissue hypoxia

PHARMACODYNAMICS OF CARDIAC GLYCOSIDES

Noncardiac effects

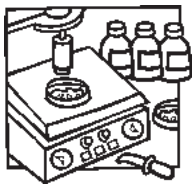
- ♦ **↑ Hemo- and lymphodynamics:**
  - ↑ stroke and minute volume of blood
  - ABP ↓↑ (normalization)
  - ↓ venous pressure (unloading of the venous part of systemic circulation)
  - ↓ diastolic pressure in the ventricles, tension of ventricle walls, ↑ subendocardiac blood flow
  - ↓ pressure in the vessels of pulmonary circulation (normalization of gas exchange — disappearance of cyanosys, dyspnea,tissue hypoxia, metabolic acidosis)
  - ↑ general and cerebral circulation of blood
  - ↑ lymphatic circulation of the heart

P. S. Depending on the dose — a 2-phase action: therapeutic doses — delatation of blood and lymphatic vessels (strophanthine) or indifference (foxglove); toxic and high doses — their narrowing

PHARMACODYNAMICS OF CARDIAC GLYCOSIDES

Noncardiac effects

- **Kidneys** — diuretic effect due to:
  - ↑ kidney blood flow and glomerular filtration
  - ↓ reabsorption of water, Na^+ and Cl^-:
    - ✓ ↓ activity of Na^+, K^+-ATP-ase of tubular epithelium and blockade of SH-groups of other enzymes of energy providing of Na^+ and Cl^- reabsorption processes
    - ✓ ↓ synthesis and activity of aldosterone and antidiuretic hormone
- **Clotting of blood** — ↓ clotting of blood (corglycone) ↑ clotting of blood (foxglove, strophanthine)
- **CNS** — sedation (drugs of lily of the valley, adonis)

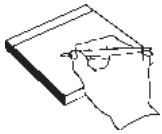


PHARMACOKINETICS OF CARDIAC GLYCOSIDES

Indices	Group of digitalis	Group of strophant
Absorption in GIT	70–96% (nonpolar lipophilic), it is possible inactivation by microphlora — 10%	3–8% (polar water-soluble)
Way of introduction	Enteral, i. v. (30–50 min)	i. v.! (in 2–5 min)
Binding with proteins	Stable (20–97%)	Weak (10–20%)
Distribution	Even, slow penetration to the myocardium	Even, rapid penetration to the myocardium
Coefficient of elimination	7–20%, enterohepatic way!	40%
$T_{1/2}$	Digoxin — 40 hrs digitoxin — 168 hrs	20–25 hrs
Cumulation	Pronounced!	Weak

INDICATIONS FOR CARDIAC GLYCOSIDES

- **Acute heart failure** (corglycone, strophanthine K, digoxin i.v., dilution only on ***sodium chloride solution***!)
- **Chronic heart failure:** decompensated cardiac valve abnormalities, cardiosclerosis, overload of myocardium with arterial hypertension (AH), etc. (for per oral administration, see further the management of prescription)
- **Prophylaxis of heart failure**
- **Supraventricular (!) tachycardic disturbance of heart rhythm and conduction:** paroxysmal tachycardia, atrial fibrillation, atrial flutter
- **Complete AV-block which is not caused by CG intoxication**



MANAGEMENT OF CARDIAC GLYCOSIDES DOSAGE

Principles of digitalization

- **Phase of saturation** (introduction of optimum saturating or complete individual dose, i.e. a dose administered parenterally or per os, which results in achievement of optimum therapeutic effect in a concrete patient):
  ✓ *rapid* (during a day 100% of a complete dose)
  ✓ *middle* (3–4 days; during the 1st day — 1/2 of the total dose)
  ✓ *slow* (5–7 days; during the 1st day — 1/4 of the total dose)
- **Phase of maintenance therapy** (for years): maintaining dose = total dose x coefficient of elimination (%) / 100%

Digitalization therapeutic level indices

- The replacement of tachycardia by normocardia
- Transition of tachysystolic form of atrial fibrillation into bradysystolic, disappearance of pulse deficit
- ↓ clinical signs of circulation insufficiency (dyspnea, cyanosis, oedemas, ↑ daily diuresis), ↓ size of the liver

PECULIARITIES OF CARDIAC GLYCOSIDES APPLICATION

Contraindications

- CG intoxication
- CG individual intolerance
- Pathological conditions when "+" inotropic effect is undesirable: (dissecting aortic aneurysm, hypertrophic obstructive myocardiopathy, etc.)

Factors that predispose to CG intoxication

✓ Little wideness of therapeutic action
✓ CG intolerance because of severe myocardial defeat
✓ Hypokaliemia
✓ Hypercalcemia
✓ Hypomagnesemia
✓ Renal and hepatic insufficiency
✓ Simultaneous application of some MA
✓ Elderly and geriatric age

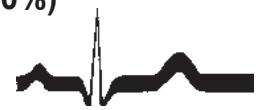
INTERACTION OF CARDIAC GLYCOSIDES

Indices	Interactive component	Result
Absorption in GIT	Adsorbents, laxatives	↓
	Anticholinergic	↑
(+) inotropic	Insulin, Ca^{2+}	↑
	Anaprilin, verapamil, reserpine	↓
(-) dromotropic	Anaprilin, novocainamide, reserpine, quinidin	↑
Renal excretion	Hypotensive	↓
Metabolism	Phenobarbital, butadion, phenytoin	↑
Tolerance	Glucocorticoids, salicylates; O_2	↑
Toxicity	Phenytoin, halothane	↓
Arrhythmo-genicity	Phenytoin, lidocaine, propranolol	↓
	Adrenergic, CNS stimulators, saluretics	↑

INTOXICATION BY CARDIAC GLYCOSIDES

- **"-" dromotropic** — depression of AV-conduction (↓ PQ, QRS remove):
  - ↑ the K^+ deficit in the cell
  - ↓ Na^+ entrance in the cell
  - ↑ *n. vagus* tone
  - excessive SH-group inactivation
- **"+" bathmotropic** — change of excitability and automatism ⇒ heterotopic foci (about 20 types of arrhythmias, especially ventricular ones)

Cardiac symptoms (50–90%)



✓ Onset — bradycardia with extrasystole
✓ Replaced by tachycardia with acute ↑ ABP
✓ Then tachyarrhythmia, *more frequent ventricular one,* ***down to ventricular fibrillation and death****!*

INTOXICATION BY CARDIAC GLYCOSIDES

Extracardiac symptoms

- **On the part of GIT (75–90%):** anorexia, vomiting (↑ dopamine in the trigger zone of vomiting center), intestinal spasm, diarrhea (↑ *n. vagus* tone), intestinal necrosis (spasm of vessels of mesentery) — ***as a rule, arise up first before cardiac symptoms****!*
- **Neurological (30–90%):** xanthopsia (vision of objects in yellow-green colors — 95%), headache, hyposomnia, pain along trigeminal and facial nerve, neurites, paresthesia; depression, disturbances of speech, loss of consciousness
- **The other ones (seldom)** — bronchial spasm, allergy, thrombocytopenia, gynecomastia, local-irritative action

TREATMENT OF INTOXICATION WITH CARDIAC GLYCOSIDES

- At the beginning — **decrease of dose**; with marked — **withdrawal of drugs** and application of charcoal (50–100 g) or cholestiramine (4–8 g)
- **Drugs containing potassium** (panangin, polarizing mixture — solution of potassium chloride in 5% solution of glucose with insulin and ascorbic acid)
- **Donators of SH-groups** (unithiol, methionine, acetylcysteine)
- **Chelators** (EDTA, sodium citrate)
- **Antiarrhythmic** (lidocaine, propranolol, phenytoin, verapamil)
- **Antianginal agents**
- **Ascorbic, pantothenic acids**
- With severe poisoning — **digibind** (antibodies to foxglove)

NONGLYCOSIDE CARDIOTONICS

Classification

- **Adrenomimetics sympathomimetics*** — dopamine, dobutamine, etc.
- **Phosphodiesterase inhibitors*** — amrinone, milrinone
- **Metabolic drugs** — glucagon, riboxine, neotone, glutaminic acid, etc.
- **Various** — sulmazole, vesnarinone, levosimendan

*Indications

- Cardiogenic shock *(dopamine, dobutamine)*
- Severe chronic heart failure (HF) of III–IV classes unresponsive to glycoside therapy *(dobutamine, milrinone, etc.)*

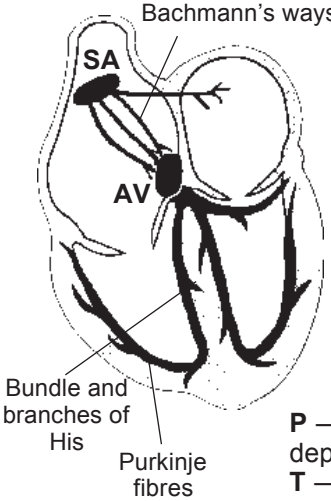
CHARACTERISTICS OF NONGLYCOSIDE CARDIOTONICS

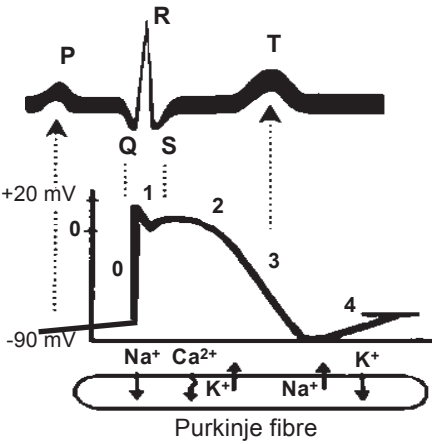
Drug	Mechanism of action	Effects	Adverse effects
Dopamine	Agonist of α-, β_1-, D-receptors	"+" ino-, chrono-, ↑ diuresis, coronal blood flow	↑ HR, ↑ ABP, tremor
Dobutamine	Agonist of β_1-receptors	(+) ino-, chrono-	↑ HR, arrhythmias, ↑ ABP, etc.
Amrinone	Blockade of phosphodiesterase	"+" ino-, vasodilating	↑ ABP, ↑ HR, ↑ the body temperature, arrhythmia, thrombocytopenia, etc.
Milrinone	The same	The same	↓ ABP, arrhythmia, hypokaliemia

Topic 12

ANTIARRHYTHMIC DRUGS

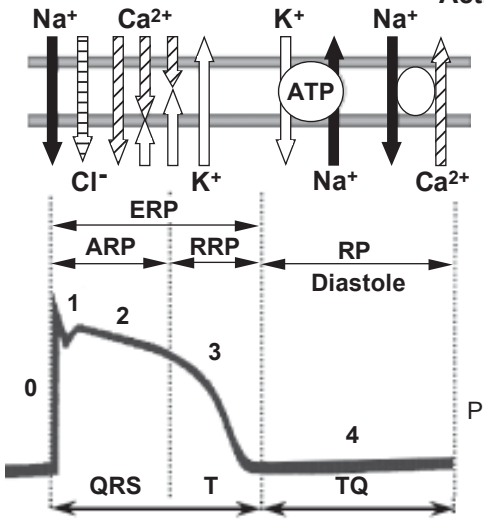
CARDIAC CONDUCTION SYSTEM





P — atrial depolarization; **QRS** — ventricular depolarization (intraventricular conduction); **T** — ventricular repolarization; **PR** — time of conduction from atria to ventricles; **QT** — duration of action potential in ventricles

ELECTROPHYSIOLOGY OF THE HEART



Action potential phases (AP):

0 — rapid depolarization (Na^+ rapid entrance)
1 — initial rapid repolarization (Cl^- entrance)
2 — plateau (Ca^{2+} entrance)
3 — eventual rapid repolarization (K^+ exit)
4 — diastolic depolarization (Na^+, K^+-pump)

P. S. ARP and RRP — absolute and relative refractory period accordingly; PR — potential of rest

ARRHYTHMIAS

Processes of myocardial depolarization, anomalous:

- according to the site of impulse arising (any nonsinus rhythm)
- their rate (< or > 60–90 per min)
- regularity (irregular)
- character of conduction

Types

- Tachyarrhythmias
- Bradyarrhythmias
- Subventricular
- Ventricular

Pathogenesis:

- **Aberrations in impulse generation** — *automaticity* of SA-node, abnormal automaticity (ectopic foci), early and late depolarizations
- **Defect in conduction** — simple physiological refractivity, its lengthening, ↓ potential of rest, fading impulse conduction, reentry, disturbance of intercellular electrotonic interaction, etc.

CLASSIFICATION OF ARRHYTHMIAS

I. Impulse generation abnormality

A. SA-node automaticity disturbance of (nomotopic arrhythmias): *sinus tachycardia; sinus bradycardia; sinus arrhythmia;* sick sinus syndrome

B. Ectopic (heterotopic) rhythms, conditioned by predominance of ectopic centers automaticity: slow (replacing) escape rates; accelerated ectopic rates (nonparoxysmal tachycardia), supraventricular pacemaker migration

C. Ectopic (heterotopic) rhythms, conditioned predominantly by reentry mechanism:

- ✓ *extrasystole* (atrial, from AV-node, ventricular)
- ✓ *paroxysmal tachycardia* (atrial, from AV-node, ventricular)
- ✓ atrial flutter
- ✓ atrial fibrillation
- ✓ flutter and fibrillation of ventricles

II. Conduction abnormalities: blocks (complete and incomplete) — sinoatrial; interatrial; *atrioventricular of I, II, III degrees*; intraventricular; ventricular asystole; preexcitation syndromes: Wolff — Parkinson — White's (WPW); of shortened interval P-Q(R) (CLC)

III. Combined rhythm disturbances

P.S. The types most often observed in the clinical practice are italicized

ARRHYTHMIAS

Approaches to pharmacotherapy:

- **Etiotropic** — removal:
  - neurogenic and endocrine disturbances *(depressing CNS, antithyroid)*
  - inflammatory phenomena in myocardium *(NAID, glucocorticoids)*
  - acute or chronic oxygen deficiency of myocardium *(angioprotectors, coronarodilating, etc.)*
- **Pathogenetic** — removal of disturbances:
  - Electrolyte metabolism in the phases of cardiac cycle and accompanied changes of automaticity and excitability *(membranostabilizing, Ca^{2+}- and K^{+}-channels, drugs of potassium)*
  - nervous regulation of cardiac activity (conduction) at tachyarrhythmias *(beta-adrenoblockers), bradyarrhythmias (M-cholinergic antagonists, beta-adrenomimetics)*

SITES OF ANTIARRHYTHMIC DRUGS APPLICATION

I. Effect on the heart

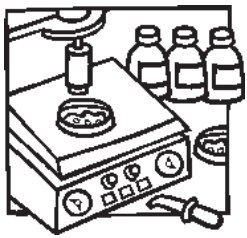
- *Refractery* period (↑ resistance)
- *Automaticity* (↓ diastole, depolarization, ↑ threshold of excitation)
- *Conduction* (↑ P-R ↑ R-R)
- *Excitability* (↓)
- *Contraction* (↓)

II. Effect on efferent innervation

- *With tachycardic arrhythmias* (↓ sympathetic and ↑ cholinergic innervation)
- *With bradycardic arrhythmias* (↓ cholinergic and ↑ sympathetic innervation)

REQUIERMENTS TO ANTIARRHYTHMIC DRUGS

- ♦ Efficiency at different types of arrhythmias
- ♦ Absence of negative influence on cardiac contraction, coronary blood flow and hemodynamics (especially with myocardial infarction, heart failure)
- ♦ Wide spectrum of therapeutic action **(!)**
- ♦ Possibility of long-term application (for years)
- ♦ Long antiarrhythmical effect (not less than 12–24 hrs)



CLASSIFICATION OF ANTIARRHYTHMIC DRUGS

With tachycardic arrhythmia:

- *I class* — **sodium channel blockers (membrane-stabilizing):**
  - IA — lengthening an effective refractery period (ERP): quinidine, novocainamide, dizopyramide, etc.
  - IB — shortening ERP: lidocaine, mexiletine, phenytoin, etc.
  - IC — different effect on ERP: propafenone
- *II class* — **β-adrenergic blockers:** propranolol, atenolol, metoprolol, etc.
- *III class* — **potassium channel blockers:** amiodaron, sotalol, brethilium
- *IV class* — **calcium channel blockers:** verapamil, gallopamil, diltiazem
- *V class* — **normalizing electrolyte metabolism:** panangin, potassium chloride, etc.

SODIUM CHANNEL BLOCKERS (membrane-stabilizing)

Sub-groups

IA — *quinidine, novocainamide, dizopyramide, etmozine, etc.*

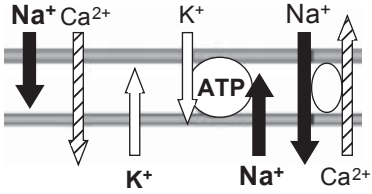
IB — *lidocaine, mexiletine, phenytoin, etc.*

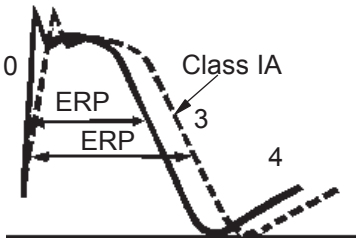
IC — *propafenone, etacizine, etc.*

Subgroups	↓ speed of rapid depolarization	Duration of action potential
IA	++	↑
IB	+	↓
IC	+++	–

IA SUBGROUP (quinidine-like)

✓ **Block Na^+-channels** and slow depolarization (phase 0 — excitability, phase 4 — automaticity)





✓ **Block K^+-channels** and slow up repolarization (phase 3)

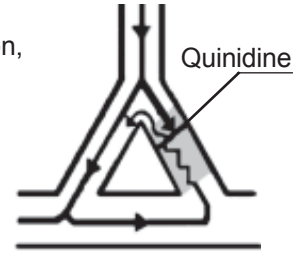
✓ ⇒ ↑ **AP and** ↑ **ERP**

- ↓ **automaticity, excitability and conduction**
- **vagolytic action on SA and AV-nodes**

IA SUBGROUP (quinidine-like)

♦ **On SA-node:** ↓ automaticity, ↑ vagolytic action ⇒ *slight tachycardia*

♦ **On AV-node:** ↓ automaticity and conduction, ↑ vagolytic action ⇒ *at supraventricular tachyarrhythmias*



♦ **On Purkinje's fibres:**

- ↓ automaticity and excitability ⇒ *at tachyarrhythmias and extrasystoles*
- ↑ ERP ⇒ *at tachyarrhythmias because of excitation circulating along the closed chains*
- ↓ conduction ⇒ *at arrhythmias according to reentry-type (transition of one-direction block in a complete one)*

IA SUBGROUP

Quinidine

- **"-" inotropic action**
- **Peripheral vessels dilatation** (α-adrenolytic action)
- **↓ ABP** (↓ cardiac output, systemic peripheral vascular resistance)

Indications

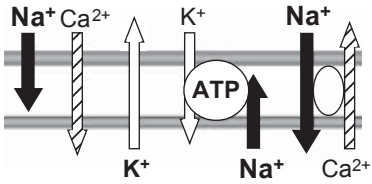
- Atrial fibrillation
- Ventricular and subventricular paroxysmal tachycardia
- Atrial and ventricular extrasystoles

Adverse effects

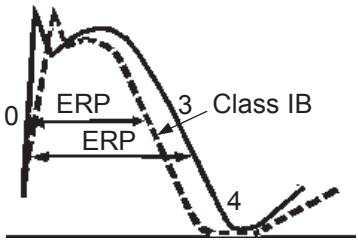
- ↓ contraction power, ↓ ABP, disturbance of AV-conduction, arrhythmogenic action (ventricular tachycardias — *dorsades de points*)
- Hearing and visual impairment, dyspepsia, hepatotoxicity, allergic reactions, SLE-syndrome, etc.

IB SUBGROUP (lidocaine)

✓ **Block Na^+-channels** and slow up depolarization (phase 0 — excitability, phase 4 — automaticity)



✓ ↑ **permeability for K^+** and ⇒ accelerate repolarization (phase 3)



✓ ⇒ ↓ **AP and ERP**

- **↓ automaticity, excitability and conduction (less than IA group)**
- **on AV-node a weak depressive action**

IB SUBGROUP

Indications:

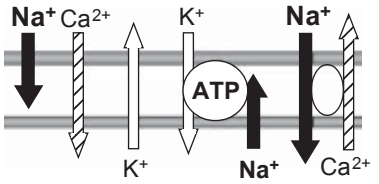
- Ventricular tachyarrhythmia and extrasystole, in particular at myocardial infarction *(lidocaine — 2% solution i.v. droply, 10% solution i.m.; mexiletin — i.v., per oral)*, cardioversions
- Arrhythmias caused by cardiac glycosides *(phenytoin, lidocaine)*

Adverse effects

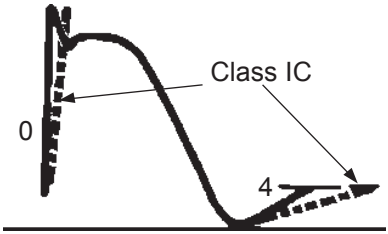
- **Arrhythmogenic action** (AV-conduction abnormality, etc.)
- **Neurological** (paresthesia, tremor, hearing impairment, seizures)

IC SUBGROUP (propafenone)

✓**Block Na^+-channels** and considerably slow up rapid depolarization (phase 0 — excitability, phase 4 — automaticity)



- **↓ automaticity, excitability and conduction**
- **↓ AV-conduction**
- **Marked arrhythmogenicity (10–15%)**



Indications

Ventricular and, to lesser degree, atrial tachyarrhythmias and extrasystoles at uneffectiveness of other AAD

II CLASS — BETA-ADRENOBLOCKERS

- **Nonselective ($\beta_1 + \beta_2$):** propranolol (anaprilin), nadolol, thymolol
- **Selective (β_1):** atenolol, metoprolol, bisoprolol, acebutolol, celiprolol
- **With inner sympathomimetic activity:** oxprenolol, pindolol

Action on the heart

- ↓ automaticity of SA-node
- ↓ automaticity and conduction of AV-node
- ↓ automaticity of Purkinje's fibres
- "–" ino- and chronotropic effects
- ↓ myocardium demand in oxygen

Indications

- Supraventricular tachyarrhythmias and extrasystoles
- Ventricular extrasystoles associated with the rise of automaticity

III CLASS — POTASSIUM CHANNEL BLOCKERS (amiodarone)

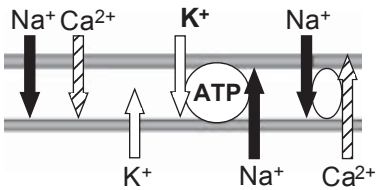
✓ **Block K^+-channels** and ↓ repolarization (phase 3)

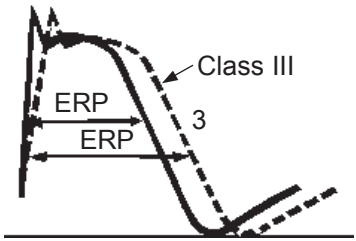
✓ **⇒ ↑ AP and ↑ ERP**

✓ **Block Na^+- and Ca^{2+}-channels**

✓ **β-adrenolytic action**

By action they can be referred to IA, II, and IV classes





- **"–" ino-, chronotropic effects**
- **↓ AV-conduction**

III CLASS — POTASSIUM CHANNEL BLOCKERS (amiodarone)

Indications

- ♦ Different forms of tachyarrhythmias and extrasystole, including arrhythmias resistant to other AAD
- ♦ IHD: angina pectoris

Adverse effects

- **Arrhythmogenic action** (AV-conduction abnormality, ↓ HR, etc.), **hypotension**
- **With prolong administration (cumulates, $T_{1/2}$ up to 100 days!):**
  - ✓ neurological (tremor, ataxia, paresthesia)
  - ✓ hypo-, hyperfunction of the thyroid gland
  - ✓ pulmonary fibrosis
  - ✓ dysfunction of the liver, constipation
  - ✓ yellow-brown deposits in the cornea, visual impairment
  - ✓ photodermatitis (grey-blue discoloration), photosensibilization, etc.

IV CLASS — CALCIUM CHANNEL BLOCKERS

General characteristics of the group

Calcium channel blockers (CCB), or calcium channel antagonists — the drugs which decrease calcium ions entering the cell mainly through the L-type potential-dependent ("slow") calcium channels

HISTORY OF CREATION

1961 Doctor F. DENGEL synthesized verapamil while trying to make a synthetic analogue of papaverine

1967 A. FLEKENSHTEIN determined mechanism of its action and proposed the term "calcium antagonists"

1966 and 1971 Nifedipine and diltiazem (correspondingly) were synnthesized

CLASSIFICATION OF CALCIUM CHANNEL BLOCKERS

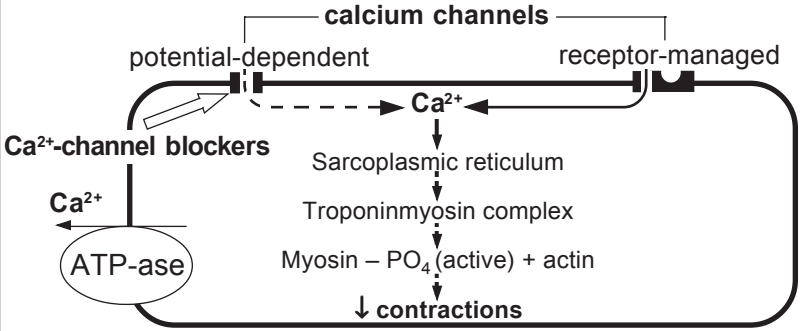
- **I type (cardiotropic)** — *phenylalkylamine derivatives*: I generation — verapamil (finoptine), II generation — gallopamil, etc.
- **II type (vasotropic):**
  - ✓ **General action:** *dihydropyridine (DCCB) derivatives:* I generation nifedipine (fenihidine, corinfar), II generation — nifedipine-GITS, amlodipine, nimodipine, isradipine, nicardipine, etc.
  - ✓ **Cerebrovasotropic** — *diphenylpiperaxine derivatives:* I generation — cinnarizine (stugerone), II generation — flunarizine (nomigrein), as well as some dihydropyridine derivatives (nimodipine)
- **III type (mixed)** — *benzothiazine derivatives:* I generation — diltiazem, II generation — clentiazem

TYPES OF CALCIUM CHANNELS

Type	Localization	Function	Blockers
L_m	Cardiomiocytes, smooth muscles	Contraction	Verapamil diltiazem nifedipine
L_n	Neurons	?	ω-Conotaxin
T_m	SA- and AV-nodes	Depolarization of membrane	Mibefradil
T_n	Cerebral neurons	?	Cinnarizine, flunarizine
N	Neurons	Mediator secretion	Amiloride
P	Purkinje's cells of the cerebellum	?	A-aperta
R	Vascular endothelium	NO and endo-thelin-1 secretion	Isradipine

MECHANISM OF CALCIUM CHANNEL BLOCKERS ACTION

↓ Ca^{2+}-entering the cell mainly through the L-type potential-dependent ("slow") channels (the cardiac muscle, smooth muscle of vessels, bronchi, GIT, uterus as well as thrombocytes) by the way of binding with them and influence on their modulation (↑ and/or ↓ duration of various state phase), but not at the expense of these channels block or antagonism to Ca^{2+} (!)



PHARMACODYNAMICS OF CALCIUM CHANNEL BLOCKERS

Are distignished by:

- Chemical structure
- The sites of channels binding
- Tissue specificity

Choosing of DCCB nifedipine, amplodipine to vessels is 10 times, phebodipine — 100 times, nisoldipine — 1000 times greater than to myocardium, as verapamil and diltiazem's

Nimodipine has selectivity to cerebral arteries, nisoldipine — to coronary ones, felodipine — to both cerebral and coronary arteries

⇒ Differences in main effects on the CVS:

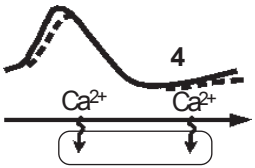
- vasotropic (DCCB): marked vasodilatation, weak influence in myocardial contraction and absence of influence on conduction **⇒ hypotensive, antianginal**
- cardiotropic (verapamil) and mixed (diltiazem): pronounced influence on myocardial contraction and conduction, moderate vasodilatation **⇒ antianginal, antiarrhythmic, hypotensive**

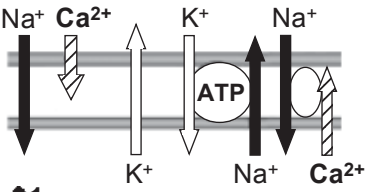
PHARMACODYNAMICS OF CALCIUM CHANNEL BLOCKERS

- **Vessels** (influence is more pronounced in DCCB) — relaxation (mainly arterial) ⇒
  - ↓ Systemic peripheral vascular resistence (SPVR) ⇒ ABP ⇒ **hypotensive action**
  - as a result of ↓ SPVR ↓ loading on the heart myocardial need in O_2 + ↓ coronarospasm ⇒ O_2 delivery to the myocardium + ↑ coronary blood flow in the ischemized sites ⇒ **antianginal**
  - ↓ cerebral vagospasm and consequences of the stroke (nimodipine, cinnarizine) ⇒ **cerebroprotection**
- **Heart** (verapamil, diltiazem):
  - "**–**" ino- and chronotropic effects, ↓ cardiac output ⇒ ↓ myocardial need in oxygen ⇒ **antianginal action** (in DCCB the given effects smooth over because of marked ↓ SPVR with ↑ HR in I generation drugs)
  - ↓ SA-node automaticity, ↓ ectopic foci in the atria, ↓ conduction in AV-node ⇒ "**–**" bathmo- and dromotropic effect ⇒ **antiarrhythmic action**
  - **Cardioprotective action** ⇒ regression of the left ventricle hypertrophy

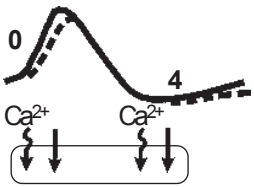
IV class — CALCIUM CHANNEL BLOCKERS (verapamil, diltiazem)

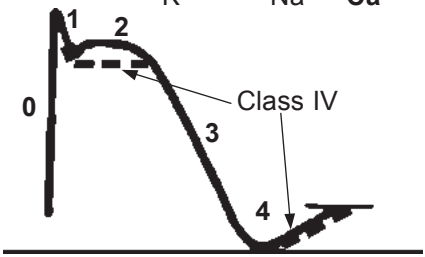
✓↓ **CA-node automaticity** (phase 4)





✓↓ **conduction** (phase 0) **and automaticity** (phase 4) **of AV-node**





blocking the **Ca^{2+}-channels of Purkinje's fibres**, ↓ a little their automaticity

PHARMACODYNAMICS OF CALCIUM CHANNEL BLOCKERS

- **Kidneys**
  - ↓ renal vasoconstriction ↑ renal blood flow ⇒ **nephroprotective** effect
  - ↑ glomerular filtration rate + ↓ sodium reabsorption ⇒ **diuretic** effect (contribution to hypotensive effect)
- **Smooth muscle of the inner organs:** relaxation ⇒
  - ↓ bronchial spasm ⇒ **broncholytic** effect
  - ↓ GIT tone ⇒ **spasmolytic** effect
  - ↓ uterine tone ⇒ **tocolytic** effect
- **Blood:** ↓ thrombocyte aggregation and thromboxane formation ⇒ antiaggregation action
- **Metabolism:**
  - ↓ atherosclerosis progression (↑ endothelial function) ⇒ **antiatherogenic** action
  - ↓ lipid peroxidation (LP), which prevents free radicals formation

PECULIARITIES OF CALCIUM CHANNEL BLOCKERS

The I generation drugs — disadvantages

- A number of adverse effects (reflex neurohumoral activation: nifedipine — ↑ HR)
- A short duration of action ⇒ intake **3–4 times** a day
- Sharp leaps of concentration in blood ⇒ fluctuation of ABP (an ABP curve looks like “teeth of a saw”) ⇒ ↑ risk of myocardial infarction, stroke

⇒ The II generation drugs — advantages

- Includes prolong drug forms of I generation (with slow-release, two-phase (rapid-retard) release, therapeutic systems of 24-hour action — slow-release system) and new chemical structure drugs
- More ↑ vasoselectivity and safety
- Improved pharmacokinetics: smooth ↑ of drug concentration in plasma (there are no picks), more postponed onset of action and time of maximal effect arising, more prolong $T_{1/2}$ and more duration of action (intake 1–2 times a day)

PHARMACOKINETICS OF CALCIUM CHANNEL BLOCKERS

Absorption: lipophylic, with *per os* administration the onset of the action in 20–30 min, but the II generation drugs (amlodipine, felodipine) get to the blood slowly (the onset of the action in 2–12 hrs); at i.v. — in 1–3 min; sublingually (nifedipine, amlodipine) — about 15 min

Bioavailability: marked "first-pass elimination" (5–80%), careful with hepatic diseases

Binding with proteins: 70–98%, careful with hypoproteinemia, with drugs having great affinity with blood proteins (diazepam, cardiac glycosides, indirect coagulants, etc.)

Distribution: even, permeable through barriers!: Css retard-form, amplodipine in plasma — in 6–7 days, a maximal antihypertensive effect — in 4–8 weeks

Biotransformation: in the liver with P450 participation; form nonactive metabolites, except for verapamil and diazepam

Excretion: mainly by kidneys, $T_{1/2}$ of the I generation verapamil — 4–6 hrs; II generation ≈ 12–24 hrs; amlodipine — 30–50 hrs; cumulation is possible (verapamil and diltiazem)

PHARMACOKINETICS OF CALCIUM CHANNEL BLOCKERS

Classification according to duration of action

- **Short-acting** (up to 6–8 hrs, intake 3–4 times a day) — I generation (verapamil, diltiazem, nifedipine, etc.)
- **Medium-acting** (8–12 hrs, intake 2 times a day) — isradipine, felodipin, etc.
- **Long-acting** (up to 24 hrs, intake ones a day) — retarding forms of verapamil, diltiazem, isradipine, nifedipine and felodipine
- **Extra-long-acting** (antihypertensive effect prolongs over 24–35 hrs, intake once a day) — amlodipine

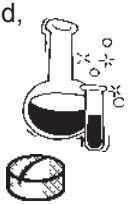
INDICATIONS FOR CALCIUM CHANNEL BLOCKERS

- Supraventricular extrasystoles and tachyarrhythmias, especially on reentry mechanism, atrial flutter and fibrillation *(verapamil, diltiazem)*
- IHD: exertional angina pectoris, Prinzmetal's angina *(verapamil, diltiazem, DCCB of II generation)*
- Arterial hypertensions
- Disturbances of cerebral circulation, migraine *(nimodipine, cinnarizine)*
- Disturbances of peripheral blood circulation, Raynaud's disease *(amlodipine)*
- In complex therapy of CNS diseases: Alzheimer's disease, senile dementia, alcoholism, vestibular disorders *(nimodipine)*
- For prevention of cold bronchial spasm
- For removal of hiccup (at the expense of supression of the diaphragmal muscles spastic contraction)

CALCIUM CHANNEL BLOCKERS

Advantages over other drugs

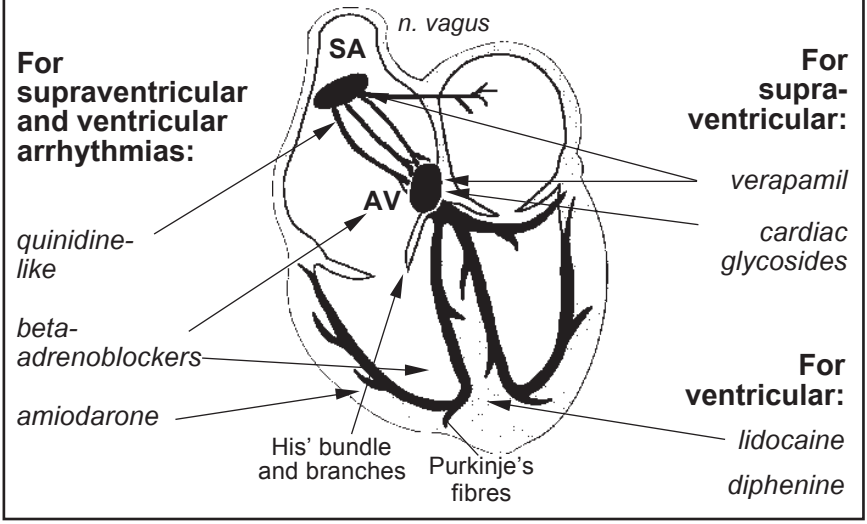
- Metabolically neutral (have no negative influence on lipid, carbohydrate metabolism, electrolyte balance)
- Do not ↑ tone of bronchi (like β-adrenoblockers)
- Do not ↓ intellectual, physical and sexual activity; do not cause depressions
- Improve quality of life



Adverse effects

- **Verapamil, diltiazem:** arrhythmogenicity (bradyarrhythmias, AV-block, etc.), heart failure, edema of shins and ankles
- **Vasotropic:** hypotension; tachycardia (nifedipine), with marked atheroclerosis — "steal syndrome"
- Reddening of the face, vertigo, headache, visual impairment, gingival hyperplasia, GIT and liver disorders, cough, dyspnea, etc.

DIRECTION OF ANTIARRHYTHMIC DRUGS ACTION



Topic 13

ANTIANGINAL DRUGS. COMPLEX THERAPY OF MYOCARDIAL INFARCTION

Breast pang *(angina pectoris)* — it is
a disease from which one can suffer for
30 seconds or 30 and more years long
Freidberg

CLASSIFICATION OF ISCHEMIC HEART DISEASE (IHD)

1. **Sudden coronary death** (ICD-X — 146.1)
2. ***Angina pectoris*** (ICD-X — 120.0): *stable efforts angina* (I II III, IV functional class — FC); rest angina prectoris (of minor exertions) is referred to III, IV FC as well; *vasospastic angina pectoris* (spontaneous, Prinzmetal's); *unstable angina pectoris* (revealed for the first time up to 28 days; progressing; early postinfarction one)
3. **Acute myocardial infarction** (AMI) (ICD-X — 121.0) with indicating the onset date, localization, complications: *with the Q wave presence* (transmural); *without the Q wave* (microfocal); *subendocardiac; indefinite; recurrent* (from 3 to 28 days); *repeated* (up to 28 days); *acute coronary insufficiency*
4. **Cardiosclerosis (with indicating the HF stage and type of arrhythmia):** *focal* (ICD-X — 125.2) (postinfarctic; not conditioned by MI); *diffuse* (ICD-X — 125.0)
5. **A painless form of IHD** (ICD-X — 125.6)

ANTIANGINAL DRUGS

Drugs which are capable by one or another way to liquidate a conflict between providing myocardium with O_2 and its consumption

Ethiopathogenesis of IHD

- **Metabolic factor** — stress, loadings, intoxication
- **Vascular factor** — atherosclerosis, etc.
- **Neurospastic factor** — "splinters in the vegetative nervous system" (cholecystitis, peptic ulcer, osteochondrosis, etc.)
- **Myocardial and hemodynamic** — focal and diffuse defeats of myocardium
- **Blood** — worsening of blood rheology

as a result:

⇒ increase of myocardial need in O_2

⇒ reduction of its delivery to myocardium

CLASSIFICATION OF ANTIANGINAL DRUGS

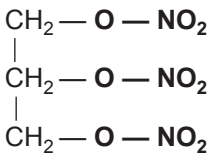
- **Diminishing myocardial need in O_2 and improving its blood supply**
  - *Nitrovasodilatators:* nitrates (nitroglycerine and its prolonged forms) and sidnonimines (molsidomine)
  - *Ca^{2+}-channel blockers:* verapamil, nifedipine
  - *Activators* (nicorandil) and *blockers* (amiodarone) of K^+-channels
- **Diminishing myocardial need in O_2:** *β-adrenoblockers (propranolol, atenolol)*
- **Improving O_2 delivery to myocardium (coronarolytics):** *myotropic* (dipiridamol, papaverine, etc.) and *reflectory action* (validol)
- **Increasing myocardial resistance to hypoxia:** *antihypoxants, antioxidants, anabolics, etc.*

NITRATES

- **Nitroglycerine and its prolonged forms:** sustac-mite (forte), nitroderm, trinitrolong, nitro-mac, etc.
- **Isosorbide dinitrate** (iso-mac, isocet, nitrosorbide, etc.)
- **Isosorbide mononitrate** (isomonate, olicard, etc.)

Physical-chemical properties

- Simple ethers of nitric acid containing **O–NO_2**
- Well-soluble in alcohol, ether, chloroform
- Tablets of nitroglycerine are unstable *(1–2 months)* ⇒ storage in a tightly closed glass package **(!)**



HISTORY OF NITRATES CREATION

1846 Ascanio SOBRERO synthesized nitroglycerine

1847 Constantin HERING obtained the tablets of nitroglycerine and determined therapeutic doses

1857 Thomas BRUNTON applied inhalation amyl nitrite with retrosternal pains at angina pectoris

1879 William MURRELL offered a sublingual application of nitroglycerine for angina pectoris attacks arrest

A. Sobrero

A. Nobel

PHARMACOKINETICS OF NITRATES

Introduction: nitroglycerine — sublingually ***(only in a seating position!)***, its prolonged forms — transdermal, transbuccal (≈ 8 hrs), isosorbide mono- and dinitrate — per oral

Bioavailability: in nitroglycerine with per oral administration — 10–20% (*first pass elimination* — inactivation by nitrate reductase)

Peak of concentration: nitroglycerine — *2 min*, signs in 15–20 min; $T_{1/2}$ prolonged forms and isosorbide mono- and dinitrate — 1–3–8 hrs

Biotransformation: in the liver, conjugating with the glucuronic acid, *nitroglycerine* → *dinitrate* → *mononitrates* (active metabolites)

Excretion: by kidneys, mainly as denitrated metabolite glucuronides

PHARMACODYNAMICS OF NITRATES

Hemodynamic effects of nitrates are similar to action of endothelial vasodilative factor — nitrogen oxide (NO)

Physiological role of NO

- Interacts with guanilate cyclase, haemoglobin, causes destruction of DNA, blocks the synthesis of nucleic acids and ATP, inactivates enzymes of respiratory chain of mitochondria, etc.
- ↓ ABP, improves blood supply of organs
- ↓ thrombocyte aggregation
- The mediator function through the nitroxidergic neurons at the periphery (↓ tone of vessels, adjusting of GIT motility and secretion), in the CNS (processes of long-term memory, recognition, etc.)
- NO of macrophages renders a toxic effect on bacteria, viruses, tumour cells, ↓ lymphocyte proliferation, etc.

MECHANISM OF NITRATES ACTION NITRATES

NITRATES
with renewal into nitrites
with participation of
SH-groups of glutathione

as well as the following:

- ↑ prostacycline products
- ↓ vasomotor center *(clonidine mechanism)*

As a result:

✓ vasoconstrictive action
✓ relaxation of bronchial tubes, GIT, uterus, urinary system
✓ antiaggregate action

endothelial cells
→ **NO** ← from L-arginin
↓
↑ guanylate cyclase
↓
GTP → ↑ cGMP
↓ *system of protein kinase*
light chains of myosin – PO_4 → light chains of myosin
actin ↓ contraction
↓ **relaxation of all types of smooth muscles**

NITRATES

Dilatation of peripheral arteries *(↓ post-loading)*
↓ systemic peripheral resistance
↓ stroke volume of the left ventricle
↓ ABP
↓ resistance to blood flow

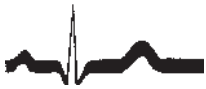
Dilatation of the peripheral veins *(↓ pre-loading)*
↓ venous return to the heart
↓ volume of blood and final diastolic pressure in the left ventricle
↓ size of the heart and tension of myocardial wall
↓ work of the heart
↓ myocardial need in O_2

Dilatation of large coronary arteries
↓ central coronaroconstrictive reflexes
↓ diastolic tension of the wall
↑ coronary blood flow
↑ blood supply of ischemized zones

antianginal effect

ANTIANGINAL ACTION OF NITRATES

- **Venous dilatation** of systemic circulation ⇒ depositing blood in the venous vessels and ↓ venous pressure (↓ *pre-loading*), and ↓ resistance of coronary vessels with ↑ in them of blood flow during diastole ⇒ **↓ myocardial need in O_2 + improvement of coronary blood flow**
- **Arterial dilatation** of systemic circulation and ↓ ABP (↓ post-loading) ⇒ **↓ heart work and myocardial need in O_2**
- **Dilatation of large coronary arteries** ⇒ redistribution of blood flow to the ischemized zones of the myocardium



INDICATIONS TO NITRATES ADMINISTRATION

- **IHD:** angina pectoris (*acute attack* — 1–2 tablets by 0,0005 g of nitroglycerine; with the purpose of *prophylaxis* — prolonged forms, isosorbide mono- and dinitrate), AMI
- **Chronic heart failure**

Drug	Way of introduction	Onset, min	Duration	Application at IHD	
				Attack	Course
Nitroglycerine (tabl., caps., solution)	Sublin-gually	1–2	10–30 min	+	–
Nitroderm (plaster)	On the skin	15–30	About 24 hrs	–	+
Isosorbide dinitrate	Sublingually, per os	3–10 20–60	1–12 hrs	±	+
Isosorbide mononitrate	Per os	30 min – 2 hrs	4–14 hrs	–	+

NITRATES

Criteria of efficiency:

- ♦ Mild headache, ↑ HR by 7–10 per a min, ↓ SAP by 10–15%
- ♦ ↓ attacks rate, ↑ tolerance to physical exercise, disappearance of ischemia on ECG

Adverse effects

- **Orthostatic hypotension**
- **Reflectory tachycardia** (prevention of β-adrenergic blocking agents)
- **Throbbing headaches** (venous dilatation of brain-tunics) ↑ **intracranial pressure, reddening of the face and neck**
- **Development of tolerance** ("Monday" disease)
- **Syndromes of "early negative afteraction"** (a single dose) and **"rebound"**
- **Local irritating action**
- **Rare methemoglobinemia (more frequent nitrites), ↑ intraocular pressure**

TOLERANCE TO NITRATES

Reasons

- ♦ Disturbance of nitrates reduction because of glutathion resources exhaustion in the vascular endothelium
- ♦ Accelerated inactivation cGMP with phosphodiesterase (PDE)
- ♦ Reflectory activation of the sympathetic nervous system
- ♦ Worsening of renal blood flow with increasing of circulated blood volume

Methods of prevention

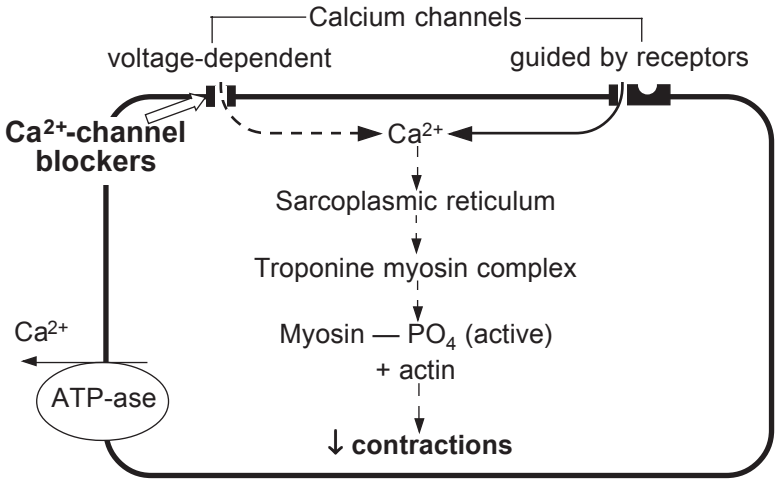
- ↑ doses of drugs (temporal effect)
- They prescribe nitrates of average term before expected physical loading with 10–12 hour interval (nitrates free interval)
- They alternate with calcium channel blockers
- Correctors — SH-group donators (unithiol, ACC), inhibitors ACE (captopril), diuretics

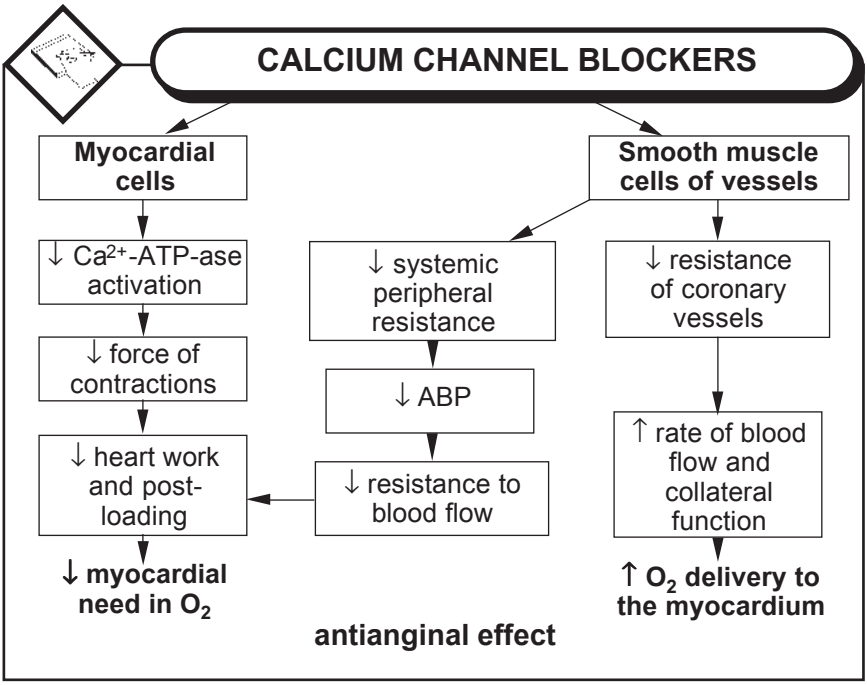
CLASSIFICATION OF CALCIUM CHANNEL BLOCKERS*

- **I type (cardiotropic)** *(phenylalkylamine derivatives)*: I generation verapamil (phynoptine), II generation — gallopamil, etc.
- **II type (vasotropic):**
  - **General action:** *dihydropyridine (DCCB) derivatives:*
    I generation — nifedipine (fenigidine, corinfar)
    II generation — nifedipine-GITS, amlodipine, nimodipine, isradipine, nicardipine, etc.
  - **Cerebrovasotropic** — diphenylpiperasine derivatives: I generation — cynnarizine (stugerone), II generation — flunarisine (nomigrain), as well as some dihydropyridine derivatives (nimodipine)
- **III type** — mixed (benzothiazine derivatives): I generation — diltiazem, II generation — clentiazem

* — full characteristics of the group is in the Topic 12

CALCIUM CHANNEL BLOCKERS AND MYOCARDIUM





COMPARATIVE DESCRIPTION OF CALCIUM CHANNEL BLOCKERS

Index	Verapamil, Dialtizem	Dihydropyridine CCB	
		I generation	II generation
Coronary blood flow	↑	↑↑	↑↑
ABP	↓	↓↓	↓↓
HR	↓	↑	–
AV-conduction	↓	–	–

CALCIUM CHANNEL BLOCKERS

Indications

- IHD: effects angina pectoris, Prinzmetal's. If it is associated with tachycardia — verapamil, dialtizem, if with bradycardia, arterial hypertension — DCCB, especially of the II generation
- Supraventricular extrasystole and tachyarrhythmia *(verapamil, diltiazem)*
- Arterial hypertension
- Disturbances of cerebral circulation, migraine *(nimodipine, cinnarizine)*
- Disturbances of peripheral circulation, Raynaud's disease *(amlodipine), etc.* (Topic 12)

Adverse effects

- **Verapamil, diltiazem:** arrhythmogenicity (bradyarrhythmia, AV-block, etc.), heart failure, oedemas on shins and ankles
- **Vasotropic:** hypotension; tachycardia (nifedipine), with pronounced atherosclerosis — "steal syndrome"
- Reddening of the face, dizziness, headache, visual impairment, gingival hyperplasia, disorders of the GIT, liver, cough, shortness of breath, etc.

ACTIVATORS OF POTASSIUM CHANNELS

Nicorandil (nicotinamide nitrate)

opening of K^+-channels

↓

K^+ outflux from the cell

↓

hyperpolarization

↓

voltage-dependent Ca-channel do not open

↓

↓ Ca delivery to the cell

↓

↓ smooth muscles tone

↓

✓dilatation of coronary vessels

✓dilatation of peripheral arteries and veins with ↓ ABP, pre- and postloading

+ cardioprotective, antiaggregate action

ACTIVATORS OF POTASSIUM CHANNELS

Indications

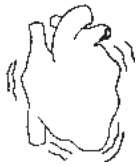
- ♦ IHD: vasospastic and stable angina pectoris *(nicorandil)*
- ♦ Arterial hypertension, resistant to treatment by other drugs *(other representatives of this group — minoxidil, diazoxid)*

Adverse effects

- Worsening of the clinical course of arrhythmias caused by the circular wave of excitation (reentry)
- Like in nitrates — headache, dizziness, orthostatic hypotension, moderate reflectory tachycardia
- Dyspepsia

POTASSIUM CHANNEL BLOCKERS

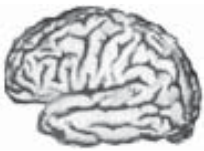
Amiodarone, sotalol



- ♦ **K^+-channel** blockade
- ♦ **Na^+- and Ca-channel** blockade
- ♦ **β- and α-adrenolytic action** (without a complete blockade)

⇒

- "-" chrono-, dromo-, bathmotropic effects
- Saving energy resources of myocardium (↑ creatininsulfate, adenosine and glycogen)
- ↓ myocardial need in O_2



- ↓ peripheral vascular resistance and ABP (moderate)
- Coronary vasodilatation

POTASSIUM CHANNEL BLOCKERS

Amiodarone

Indications

- ♦ IHD: angina pectoris
- ♦ Tachyarrhythmia (refer to Topic 12)

Adverse effects

- **Arrhythmogenic action** (AV-conduction abnormality, ↓ HR, etc.), **hypotension**
- **With prolong administration (cumulates, $T_{1/2}$ up to 100 days!):**
  - ✓ neurological disorders (tremor, ataxia, paresthesias)
  - ✓ hypo-, hyperfunction of the thyroid gland
  - ✓ lung fibrosis
  - ✓ dysfunction of the liver, constipation
  - ✓ yellow-brown deposits in the cornea, visual impairment
  - ✓ photodermatitis (grey-blue discolouration), photosensitization, etc.

BETA-ADRENOBLOCKERS AT ISCHEMIC HEART DISEASE

- ♦ **Nonselective (β_1+β_2):** propranolol (anapriline), nadolol, timolol
- ♦ **Selective (β_1):** atenolol, metoprolol, bisoprolol, acebutolol, celiprolol
- ♦ **With the intrinsic simpathomimetic activity (ISA):** oxprenolol, pindolol

I. Antianginal action — ↓ myocardial need in oxygen

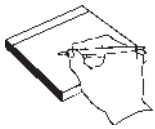
- ↓ sympathetic influences ⇒ ↓ HR, force of contraction and ABP
- ↑ duration of diastolic perfusion
- Improvement of perfusion of subendocardiac layer and myocardium on the whole
- Redistribution of blood flow to the ischemized zones of the myocardium, collateral circulation
- Limitation of microvascular defeats of the myocardium

BETA-ADRENOBLOCKERS AT ISCHEMIC HEART DISEASE

II. Cardioprotective action

- ↓ lipolysis with free fatty acids (FFA) oxidization term limitation ⇒ stabilization of cellular and lysosomal membranes
- Antioxidant properties
- Facilitates dissociation of oxyhemoglobin
- Releases prostacycline from the vascular endothelium ⇒ antiaggregate action

III. Stress-protective action



Indications

- IHD with predominance of nervous-metabolic factor in pathogenesis

IMPROVING O_2 DELIVERY TO MYOCARDIUM (coronarolytics)

- **Myotropic action (vasodilatators):**
  - **PDE inhibitors** — *isoquinoline derivatives:* drotaverin (no-spa), papaverin; *different chemical groups:* carbocromen (intencordin)
  - **adenosinergic and PDE inhibitors** — dipyridamol (curantil), lidoflazine, etc.
  - **antagonists of adenosine (purine) receptors and PDE** inhibitors — purine derivatives (methylxanthine): theophylline, aminophylline (euphylline), etc.*
- **Reflectory action** — validol (25–30% mentol solution in the mentil ether of isovaleric acid)

* Theobromine, caffeine, pentoxiphylline (trental), etc. belong also to methylxanthines (refer to Topic 16)

CORONAROLYTICS OF MYOTROPIC ACTION

- **Adenosinergic** (dipyridamol)
  - Inhibitors of adenosinedesaminese and reuptake of adenosine ⇒ ↑ adenosine level:
    - ✓in the myocardium ⇒ *coronarolytic action* (adenosine release at hypoxia and dilates coronary vessels)
    - ✓in red blood cells and endothelial cells ⇒ *antiaggregate* (+ ↑ cAMP due to phosphodiesterase inhibition and prostacycline action potentiation)
- **Adenosine receptors antagonists and PDE inhibitors** (refer to Topic 16)
  - ↑ level of intracellular cAMP ⇒ vasodilatating action on the coronary vessels and a number of other effects including adverse ones

CORONAROLYTICS

Indications

- **Limited by:**
  - ✓sclerotic changes of coronary arteries
  - ✓"steal phenomenon": dilatation of small arteries, precapillars and improvement of blood flow in healthy tissues, instead of ischemized, where reserve of their dilatation is already exhausted *(dipyridamol, carbocromen, etc.)*
  - ✓cardiostimulation with ↑ myocardial need in O_2 *(PDE inhibitors)*
- **Individual, in particular:**
  - stable angina pectoris of mild degree *(dipyridamol)*
  - IHD assosiated with ↓ contractile activity of myocardium, etc. *(PDE inhibitors)*
  - for diagnosis of zones with lowered perfusion with coronarography *(dipyridamol)*

PROMOTING MYOCARDIAL RESISTANCE TO HYPOXIA

- **Antihypoxants** — trimetazidine (preductal), mildronate, ATP-long, phosphaden, neotone, cocarboxylase, riboflavine, ascorbic, nicotinic acid, etc.
- **Antioxidants** — tocoferol, dibunole, essenciale, etc.
- **Anabolic** — *steroidal* (retabolil, nerobol), *nonsteroidal* (riboxine (inozine), potassium orotate)
- **Normalizing electrolyte metabolism** — panangin (asparcam)

PRINCIPLES OF MYOCARDIAL INFARCTION COMPLEX THERAPY

- **Removal of pain syndrome** — narcotic analgesics
- **Prevention and treatment of thrombi formation** — anticoagulants, fibrinolytics, antiaggregants
- **Removal of fear, emotional excitation** — neuroleptics, tranquilizers
- **Removal of cardiac rhythm disorders** — antiarrhythmic
- **Limitation of necrosis** — nitrates
- **Removal of disturbances of electrolyte and acid base balance (ABB)** — sodium bicarbonate, panangin, etc.
- **Renewal of contractile activity of the myocardium** — cardiac glycosides
- **Fight with hypotonia** — adrenomimetics, analeptics, blood substitutes
- **Prevention of vomiting** — neuroleptics

Topic 14

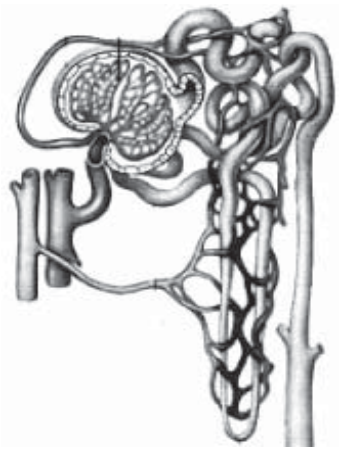
DIURETIC DRUGS. COMPLEX THERAPY OF HEART FAILURE. URICOSURIC DRUGS

DIURETICS

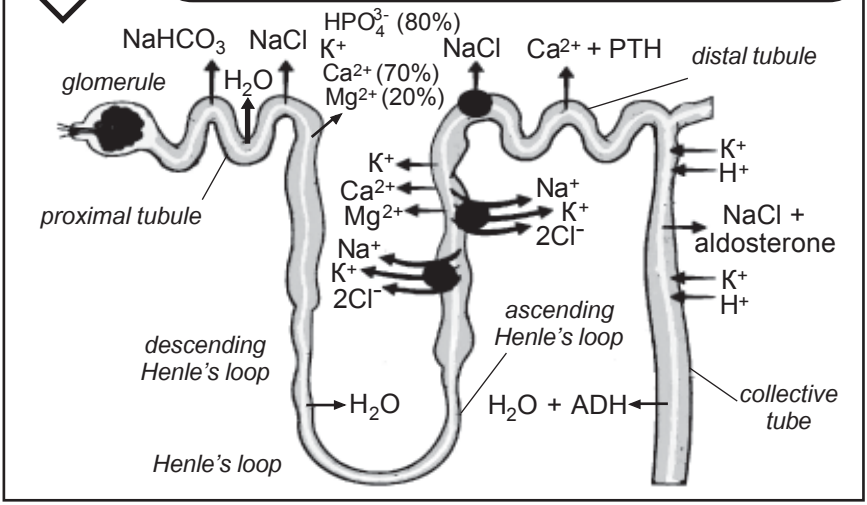
Substances of herbal, inorganic and synthetic origin which increase diuresis

by the way of:

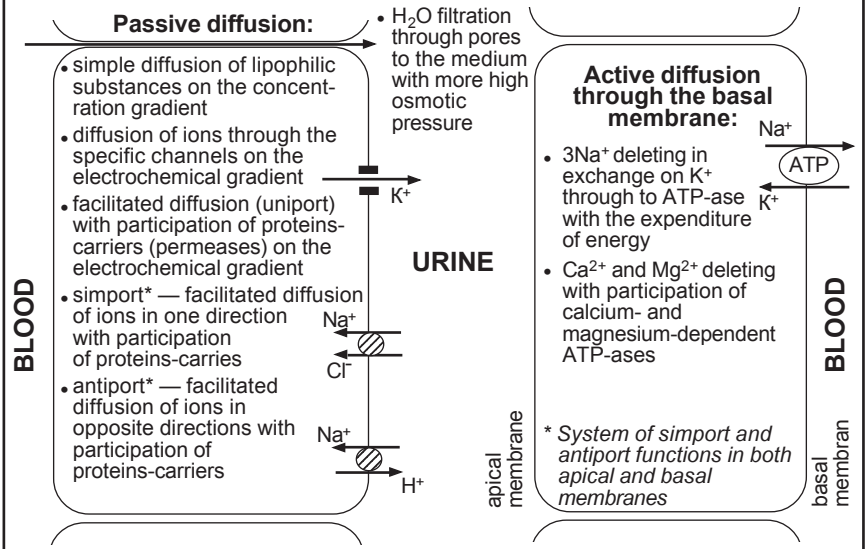
- **enhancement of filtration** (primary urine formation)
- **inhibition of electrolyte reabsorption processes** (foremost Na^+ and Cl^-) **and water in renal tubules** (secondary urine formation)



TUBULAR SYSTEM OF THE KIDNEY



TYPES OF SUBSTANCES TRANSPORT IN KIDNEYS

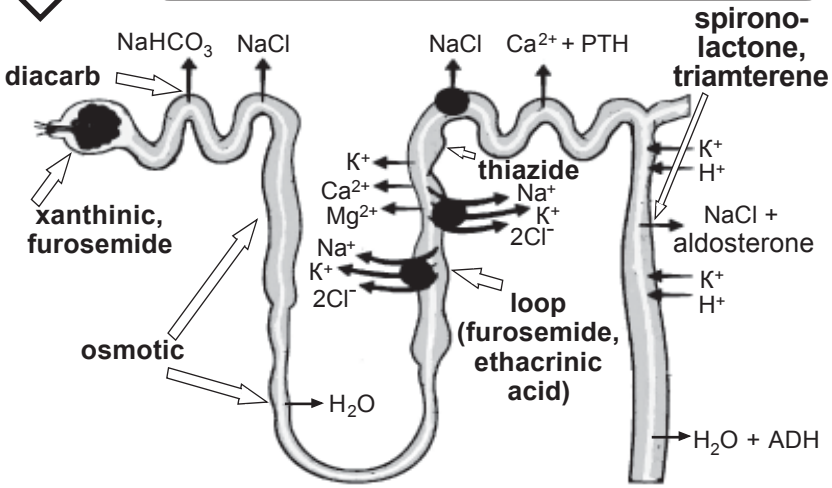


CLASSIFICATION OF DIURETICS

According to chemical structure and mechanisms

- **Inhibiting transport of sodium from tubular lumen to the cell (apically):**
  - *aldosterone antagonists* — spironolactone (veroshpirone)
  - *sodium channels blockers* — triamterene
- **Braking transport of sodium from cell through the basal membrane:**
  - *inhibitors of carboanhydrase* — diacarb (acetazolamide)
  - *loop* — furosemide, bufenox, xipamide, torasemide, etacrin acid, etc.
  - *sulfonamides thiazide* (hydrochlorthiazide) and *thiazide-like* (oxodoline, clopamide, etc.)
- **Acting along the whole length of tubules**
  - *osmotic* — mannitol, urea
  - *acidifying* — ammonium chloride
- **Changing blood supply of kidneys:** xanthines — aminophylline, theophylline
- **Herbal origin**
- **Combined** — moduretic, triampur

SITES OF DIURETICS APPLICATION



CLASSIFICATION OF DIURETICS

According to localization of action in nephrone

- ↑ **filtration mainly in tubules** — *xanthine*
- ↓ **reabsorption mainly:**
  - ✓ in proximal convoluted tubules — *carboanhydrase inhibitors*
  - ✓ in proximal tubules, descending Henle's loop — *osmotic*
  - ✓ in the ascending Henle's loop — *strong acting ($3Na^+ – C^+ – Cl^-$ simport inhibitors) furosemide, ethacrinic acid*
  - ✓ in distal tubules *($3Na^+ – Cl^-$ simport inhibitors) — thiazide, thiazide-like*
  - ✓ in distal convoluted tubules and collective tubes — *potassium-sparing*

According to the character of action

- **Hydrouretics** (causing mainly water diuresis) — *osmotic*
- **Saluretics** (primarely inhibiting reabsorption of sodium and chlorine) — *loop, thiazide and thiazide-like, carboanhydrase inhibitors*

CLASSIFICATION OF DIURETICS

According to force of action (sodium excretion, %)

- **Strong:** *loop* (15–25%) — furosemide (lasix), ethacrynic acid (uregit), bufenox (brinaldix), xipamide, thorasemide
- **Middle force:**
  - ✓ *thiazide and thiazide-like* (5–10%) — hydrochlorthiazide (hypothiazide), cyclomethiazide (navidrex), clopamide, indapamide
  - ✓ *osmotic* (5–8%) — mannitol
- **Weak action (3–5%):**
  - ✓ *potassium-sparing* — spironolactone, triamterene, amiloride
  - ✓ *carboanhydrase inhibitors* — diacarb (acetazolamide, diamox)
  - ✓ *different* — xanthine, herbal

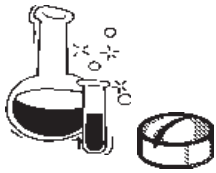
CLASSIFICATION OF DIURETICS

According to speed and duration of action:

- **Rapid and short-term effect:** loop, osmotic
- **Middle force and duration:** thiazide, potassium-sparing (triamterene), inhibitors of carboanhydrase, xanthinic
- **Postponed and long-acting:** thiazide-like, potassium-sparing (spironolactone)

According to influence on acid-base balance of blood

- Causing **marked metabolic acidosis**: carboanhydrase inhibitors, ammonium chloride
- Resulting in **moderate metabolic acidosis**: potassium-sparing
- Promoting **moderate metabolic alkalosis**: thiazide and thiazide-like loop



CLASSIFICATION OF DIURETICS

According to influence on potassium excretion*:

- **Strong potassiumuretics (diuresis/potassiumuresis = 1/1):** thiazide, thiazide-like, carboanhydrase inhibitors
- **Middle potassiumuretics (diuresis/potassiumuresis=1/0.75):** loop
- **Small potassiumuretics (diuresis/potassiumuresis=1/0.25)**: osmotic
- **Potassium-sparing**

* The K^+ loss is to great extant conditioned by the rise of its secretion on the electrochemical gradient in the ending departments of distal tubules and collective tubes due to depression by diuretics of Na^+ reabsorption in the higher located departments of nephrone

According to influence on calcium excretion

- ↑ **Ca^{2+} excretion** (hypocalciemia): loop
- ↓ **Ca^{2+} excretion** (hypercalcemia): *thiazide, thiazide-like*

XANTHINE DIURETICS

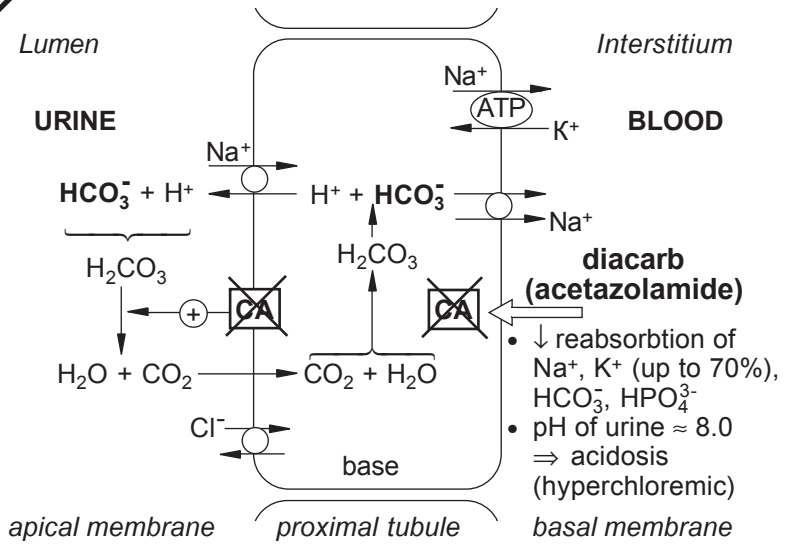
Aminophylline (euphylline), theophylline

Mechanism of diuretic action

- Improvement of general and renal hemodynamics, dilatation of renal arterioles
- ↑ renal blood flow
- ↑ gromerular filtration rate
- Reduction of nephrocytes contact with urine, ↑ its flow along the system of tubules
- ↑ quantity of functioning glomerules
- ↓ sodium reabsorption in proximal tubules and water in the descending loop

They have also cardiostimulating, vasodilatating, spasmolytic, broncholytic action *(refer to Topic 16)*

CARBOANHYDRASE INHIBITORS



diacarb (acetazolamide)

- ↓ reabsorbtion of Na^+, K^+ (up to 70%), HCO_3^-, HPO_4^{3-}
- pH of urine ≈ 8.0 ⇒ acidosis (hyperchloremic)

CARBOANHYDRASE INHIBITORS

Indications

- Hypochloremic alkalosis
- Glaucoma, glaucomatous crisis
- Hydrocephaly, epilepsy
- Acute mountain sickness

Adverse effects

- **Hypokaliemia!** (drowsiness, paresthesia, paralytic ileus, nephropathy, arrhythmias)
- **Hyperchloremic acidosis** (a 3–4-day break in therapy!)
- **Phosphate calculi and calcium citrate formation in the kidneys**
- **↓ Gastric juice**
- **Allergy, agranulocytosis**

OSMOTIC DIURETICS

Mannit (mannitol), urea

Mechanism of action

- ↑ **renal blood supply** (↑ formation of vasodilatating factors — prostaglandin E_2, prostacycline)
- Filtrate well in glomerules, but being high-polar substances, do not reabsorb in tubules and **↑ osmotic pressure of urine ⇒ ↓ water reabsorption**
- Work mainly **in proximal tubules, descending Henle's loop, and collecting tubes as well**
- Moderately ↑ excretion of **Na^+ H^+, K^+, Mg^{2+}, Ca, Cl^-, NCO_3^-, phosphates, can cause both alkalosis and acidosis**
- **Dehydratating effect:** after i.v. introduction at first ↑ osmotic pressure of blood ("drawing of liquid" from tissues, useful with edema of the brain) ⇒ ↑ of circulated blood volume decreasing as diuretic effect develops

OSMOTIC DIURETICS

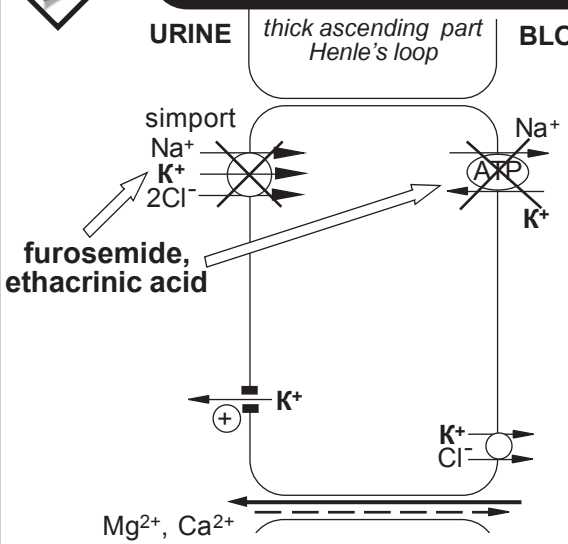
Indications to mannit

- ♦ Edema of the brain (effect is practically instant — by 60–90% ↓ intracranial pressure)
- ♦ Acute poisonings (forced diuresis)
- ♦ Acute necrosis of renal tubules associated with shock, infections, hemolytic reactions, poisoning
- ♦ Acute attack of glaucoma

Adverse effects

- Urea penetrating through the tissue barriers (including BBB and mannit at the traumatic edema of the brain — **rebound phenomenon** (secondary hydratation of the brain, ↑ intracranial pressure)
- **Urea** — irritating action on veins, necrosis in case of subcutaneous contact
- **Overdosage** — strong dehydratation with ↓ ABP, thromboses, thirst, hallucinations

LOOP DIURETICS



- ↓ reabsorption of **Na^+, Cl^-, K^+, Mg^{2+}, Ca^{2+}, H^+, HCO_3^-, HPO_4^{3-}**
- ↓ tissue respiration
- ↑ **prostaglandin** synthesis
- ⇒ ↑ renal blood flow
- dilatation of veins and arteries ⇒ ↓ ABP and unloading of the left ventricle **(like nitroglycerine)**

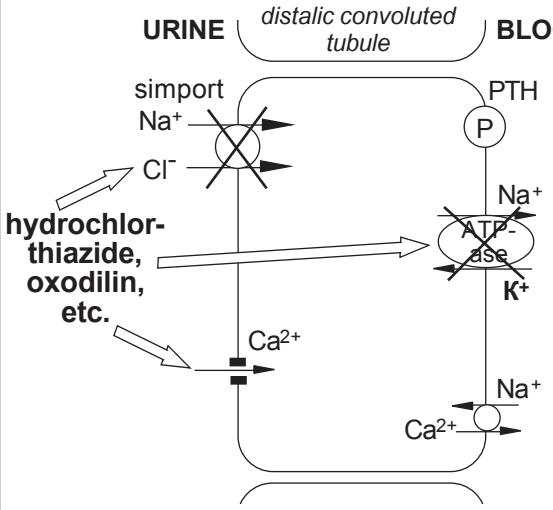
INDICATIONS TO LOOP DIURETICS

- Acute and chronic cardiovascular insufficiency
- Pulmonary edema, cardiac asthma
- Cerebral edema
- Cirrhosis of the liver with portal hypertension and ascitis
- Acute and chronic renal failure, eclampsia
- Arterial hypertension, hypertensive crisis
- Poisonings (forced diuresis)
- Glaucomatous crisis
- Hypercalciemic crisis

ADVERSE EFFECTS OF LOOP DIURETICS

- Hypokaliemia, hypocalciemia, hypomagnesemia
- Hypochloremic alkalosis
- Dehydratation, sudden profuse diuresis (6–10 l)
- Orthostatic hypotension
- Hyperglycemia
- Ototoxicity (disturbances of endolymph content)
- Exacerbation of gout
- Interstitial nephritis, formation of phosphate precipitate
- Atherogenicity
- Acute pancreatitis (seldom)
- Allergy, photosensitization
- Leukopenia, thrombocytopenia

THIAZIDE AND THIAZIDE-LIKE DIURETICS



- ↓ reabsorption **Na^+, Cl^-, H^+, K^+, Mg^{2+}**
- ↑ **Ca^{2+}** in blood
- significantly ↓ **HCO_3^- and phosphates**
- disturb renal bioenergetics
- ⇒ does not change (worsen) renal blood flow
- ↑ renin secretion ⇒ ↑ aldosterone
- ↑ ADH

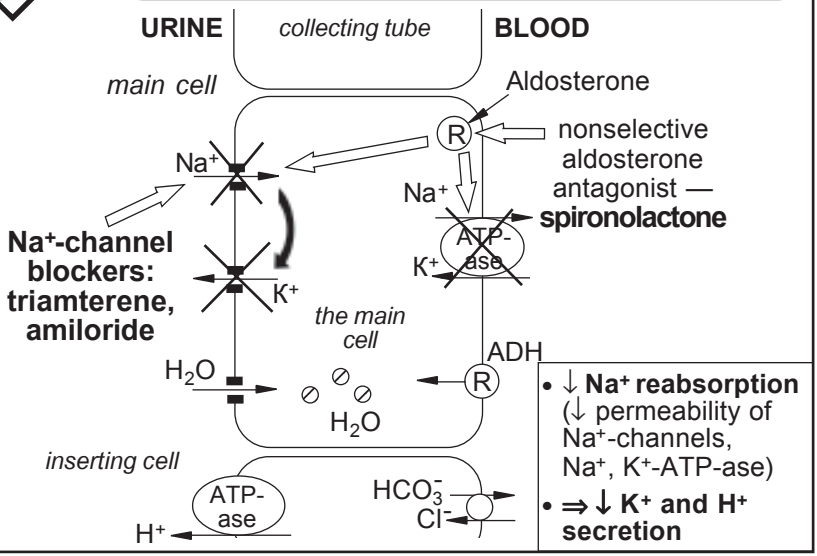
INDICATIONS TO THIAZIDE DIURETICS

- Chronic heart failure (↓ pre-loading)
- Arterial hypertension (in the complex therapy)
- Cirrhosis of the liver with portal hypertension and ascites
- Nephrosis, nephritis (moderate severity)
- Toxicosis of pregnant women
- Hypocalciemia (nephrolithiasis with hypercalciemia)
- Diabetes insipidus
- Subcompensated glaucoma
- Bromism (↓ binding with Br)

ADVERSE EFFECTS OF THIAZIDE DIURETICS

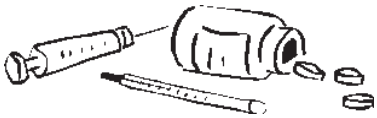
- Hypokaliemia, hypomagnesemia (arrhythmogenic action)
- Hyponatriemia (↑ ADH, ↑ thirst)
- Hypercalcemia
- Metabolic alkalosis
- Hyperlipidemia (atherogenicity)
- Violation of tolerance to carbohydrates
- Hyperuricemia
- Orthostatic hypotension
- Allergy, photosensitization, dermatitis, thrombocytopenia
- Anorexia, exacerbations of pancreatitis, cholecystitis
- ↓ libido, impotence
- Fatigue, paresthesias, xanthopsia

POTASSIUM-SPARING DIURETICS



INDICATIONS FOR POTASSIUM-SPARING DIURETICS

- Hypokaliemia
- Heart failure
- Arterial hypertension *(in combinations with thiazides)*
- Primary (tumour, etc.) and secondary hyperaldosteronism (heart failure, cirrhosis of the liver, etc.) — *spironolactone*
- Poisoning by lithium — triamterene, amiloride



ADVERSE EFFECTS OF POTASSIUM-SPARING DIURETICS

- Hyperkaliemia
- Hypochloremic acidosis
- Gynecomastia, impotence, menstrual cycle disorder *(spironolactone)*
- Diarrhea, gastritis, gastric ulcer with bleeding *(spironolactone)*
- Skin rash, thrombocytopenia
- Tremor, ataxia *(spironolactone)*
- Hypotension *(triamterene)*
- Acute renal failure, nephritis *(triamterene)*, urolythiasis *(triamterene)*
- Macrocytic anaemia *(triamterene)*

HERBAL DIURETICS

Field horse-tail — *Equisetum arvense*
The herb contains: alkaloids (equizetine, nicotine, 3-metoxipyridine), saponine equizetonine, flavonoids, organic acids (aconite, apple, oxalic), fatty oil (3–3.5%), essential oil, great number of salts of silicic acid, vitamines C, B, carotin, bitters, resins, tannins, etc.
An extract of herb is recommended as diuretic, hypotensive, antianflammatory, hemostatic (with pulmonary, uterine, renal, haemorrhoidal, nasal bleeding), promotes slags washing out from an organism, and also locally as an antiseptic, etc.

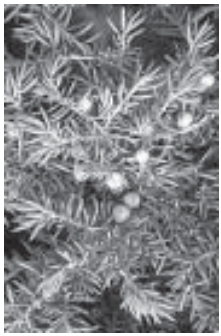
Bear berry — *Arctostaphylos uva-ursi*
Basic agents are in the leaves — phenologlycosides (arbutine, methylarbutine), which split in an organism into hydrochinon and methyhydrochinone.
As an antiseptic and diuretic substance (↑ filtration) it is a part of diuretic tea, is used with diseases of kidneys and urinary tracts (pielonephritis, urolithiasis, cystitis).

Silver birch — *Betula pendula*
The buds *(gemmae)* contain: essential oil up to 6%, vitamine C, saponins, bitter, tannins, resin, tartatic sugar; leaves (folium): + carotin, nicotine acid, glycosides, triterpenic alcohols, inozit. The buds and leaves also contain flavonoids, have phytoncide properties. Betulole (which makes the rind white and protects from penetration of different fungi), glycosides, saponins, tannins, essential oils are found in the rind. Fructose and glucose, apple acid, protein and unknown aromatic substance are an organic part of birch sap.
The extract and decoction of buds have diuretic, antiseptic, cholagogic, sudorific, anti-inflammatory, wound-healing action.
A leaves extract is used as a diuretic, with disorders of the nervous system — as a stimulant, at renal colic, icterus — as an antianflammatory and vitamine agent.

HERBAL DIURETICS

Pheasant's eye — *Adonis vernalis*
The herb contains: cardiac glycosides (cimarin, adonitoxins, etc.), saponins, adonidoside, adonil acid, chinones, phytosterine and cumarins. According to the character of action on the heart the drugs of Pheasant's eye occupy intermediate position between strofantine and foxglove. Besides the cardiotonic action, it has diuretic, sedative effects.

Common Juniper — *Juniperus communis*
The berries and needles contain an essential oil (no less than 0.5% of cadinene, camfene), sugar, organic acids (apple, formic and acetic), microelements (manganese, iron, copper and aluminium), resins and other substances; pine-needle — 266 mg% of ascorbic acid.
It is used as a diuretic (as a rule in combination with potassium acetate), and also as antimicrobial, cholagogic, expectorant, antitoxic, improving digestion, anti-inflammatory agent, etc. It has strong insecticide action. It is established that the volatile substances of Common Juniper kill about 30% of microorganisms containing in the air.



Orthosifon stamen (kidney tea) — *Orthosiphon stamineus*
Evergreen half-bushes with the branchy stems. The leaves contain saponins, diterpene ethers (orthosifols), glycoside orthosifonin, coffee acid derivatives, flavonoids (eupatorin, sinensetin, scutellarin, salvigenin), essential oil, are rich in potassium salts.
Is a strong diuretic; excretes urea, urinary acid, chlorides from an organism; normalizes metabolism. It is aplied at urolithiasis, cholecystites, gout, atherosclerosis, and also as a mild antihypertensive agent.

HERBAL DIURETICS

Cowberry — *Vaccinium vitisidaea*

The leaves contain about 9% of glycoside arbutine, hydrochinone, ursolic, tartaric, gallic, quinine acid; tannin, hyperozide (hyperin), tannins (2–9%), phytoncides. In the berries of cowberry — sugar (about 10%), vitamine C (15–30 mg%), carotin, organic acids: lemon, apple, oxalic, benzoic, acetic, glioxil, pyruvic, oxipyruvic, etc. The seeds contein up to 30% of fatty oil, containing linoleic and linolenic acids.

As decoctions and tea the leaves are used with urolithiasis, cystites, as a diuretic and antiseptic mean; the leaves extract has more strong diuretic properties; fresh, soaked berries cowberry water are used at subacid gastrites; are effective with arthrites, diarrhea.

Wild strawberry — *Fragaria vesca*

The extract of leaves and fruits are used as a diuretic mean; for treatment of gout, cholelithiasis and urolithiasis. The fruits, in addition, are used as a vitaminic substance, and a strawberry leaf is known as a substitute of tea.

In England the old doctors tell: “The doctor has nothing to do at the place where they eat strawberry and whortleberry.”

Bachelor’s buttons — *Centaurea cyanus*

The flowers contain glycosides centaurine, cichoriine, cianine making the herb blue; tannins, etc.; there are alkaloids in fruits.

The flowers as extracts, decoctions and fluid extract strengthen diuresis, excretion of substances participating in stone formation (calcium, inorganic phosphorus, urinary acid), render cholagogic, antimicrobic, spasmolytic effect, have antitumor activity.

HERBAL DIURETICS

Parsley — *Petroselinum crispum*
The fruits contain essential oil, up to 22% of fatty oil (mainly glycerides of petrozelin acid); flavonic glycosides; leaves — essential oil, luteoline, apigenine, carotin, ascorbic acid; flowers — quercetin, cempferol; roots — apigenine.
The herb and seeds have diuretic properties and strengthen salts excretion from an organism (epiole and miristicine presence in the herb).
It is used with renal and cardiac diseases, urolithiasis and inflammatory processes in the urinary bladder; diseases of the liver, dyspepsia, meteorism, etc.

Glabrous ruptur-wort — *Herniaria glabra*
The herb contains cumarin and its derivatives umbelliferon and gerniarin; flavonoids — quercetin, routine, quercetin triglycoside, quercetin arabinoside, quercetin galactoside, isoramnetin ramnoglucoside; triterpenic saponin, hard essential oil and signs of alkaloids.
Is used as a diuretic with diseases of the kidneys, urinary bladder and as an astringent.

Different herbal tea (examples): bachelor's buttons (flowers) — 15 g; bear berry (leaves) — 45 g; juniper (berries) — 15 g. A table spoon this mixture is filled up with 200 ml of boiling water, let it draw for 20 min and filter. One should administer by a table-spoon 3–4 times per a day.
Diuretic tea: bachelor's buttons, bear berry, glabrous ruptur-wort, St-John's-wort, corn stigmae, calendula, camomile, liquorice, parsley seed. Method of preparation: 2 table spoons of tea (8–10 g) are filled up with 0.5 l of boiling water, let it draw for 1.5 hrs. One should administer by 0.5 glass 3 time per a day 30 min before the meal.
Renal tea (with inflammatory renal diseases): birch leaf, glabrous ruptur-wort, lovage, horse-tail, bear berry, cowberry, leaf of raspberry, sage, flowers of Danewort, tansy, St-John's-wort, three-color violet, common centaury, bur-marigold, leaf of strawberry, root of parsley. Method of preparation: 2 table spoons of tea (8–10 g) are filled up with 0.5 l of boiling water, let it draw for 1.5 hrs. One should administer by 0.5 glass 3 time per a day 30 min before the meal.

St. John's-wort

GENERAL PRINCIPLES OF DIURETICS ADMINISTRATION

- **Daily diuresis during treatment must not exceed 2–2.5 l**
- **Rational choice with taking into account:**
  - intensity of edematous syndrome
  - disbalance of hemodynamics
  - state of initial electrolyte balance
  - features of pharmacological characteristics of a diuretic, its adverse effects (administration in the first half of day!)
  - individual tolerance
- **"Medicinal vacations"**
- **Combined diuretics**
- **Full value diet and drink regimen**
- **In urgent cases —** i.v. introduction of strong and fast-acting diuretics
- **Control and correction of electrolyte and acid-base balance**

CHRONIC HEART FAILURE (CHF)

This is a syndrome arising at systolic and/or diastolic dysfunction accompanying with chronic hyperactivation of neurohormonal systems and has the following clinical manifestations: dyspnea, palpitation, limited physical activity, edema

Classification

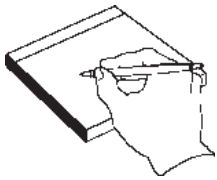
- **I functional class (FC)** — there are no limitations of physical activity and influence on quality of life
- **II FC** — moderate limitation of physical activity: common physical activity leads to fatigue, dyspnea or pain in the heart area
- **III FC** — pronounced limitation of physical activity: even a little physical loading results in appearance of marked clinical symptoms
- **IV FC** — any physical activity causes discomfort: the symptoms of CHF arise even at rest and intensify with a slightest physical loading

THERAPY OF HEART FAILURE

- **Basic:**
  - ✓ ACE inhibitors
  - ✓ diuretics, as well as selective antagonists of aldosterone receptors: ellerenone (inspra)
  - ✓ cardiac glycosides
  - ✓ β-adrenergic blockers (with ACE inhibitors): bisoprolol, carvedilol, methoprolol-retard
- **Assisting:** antagonists of receptors to angiotensine II, CCB (amlodipine)
- **Additional** (in definite clinical situations): vasodilatators (nitrates, CCB), antiarrhythmic, nonglycoside cardiotonics, antiaggregants, indirect anticoagulants, corticosteroids, synergists of cardiac glycosides — vitaminic drugs (thiamine, cocarboxylase, piridoxine, nicotine acid, tocopherol), cardiotrophic (glucose, steroidal and nonsteroidal anabolic drugs)

ANTIGOUT DRUGS

- **↓ synthesis of urinary acid:**
  - ✓ depressing xanthine oxidase — *allopurinol*
  - ✓ with different mechanism of action — *benzobromarone*
- **↑ excretion of urinary acid (uricosuric):**
  - ✓ ↓ reabsorption of urinary acid in renal tubules — *benzobromarone, probenicide, anturane, urodane, kebuzone*
  - ✓ shifting urine pH to the alkaline side — *uralit, soluran, magurlit*
  - ✓ combined — *allomarone*
- **↑ excretion of nitrous slags:** *urolesan, phytolysine, cystenal*
- ***Applying with acute attack of gout:*** NSAIDs *(butadione, indomethacine, colchicine, glucocorticoids)*



Topic 15

DRUGS REGULATING ARTERIAL BLOOD PRESSURE. HYPOTENSIVE AND HYPERTENSIVE DRUGS

DISTURBANCES OF VASCULAR TONE

- ↑ system tone — **hypertension**
- ↓ system tone — **hypotension**
- Change of the tone causing **disturbances of local** (regional) **blood flow** — cerebral, peripheral, etc.

Arterial hypertension

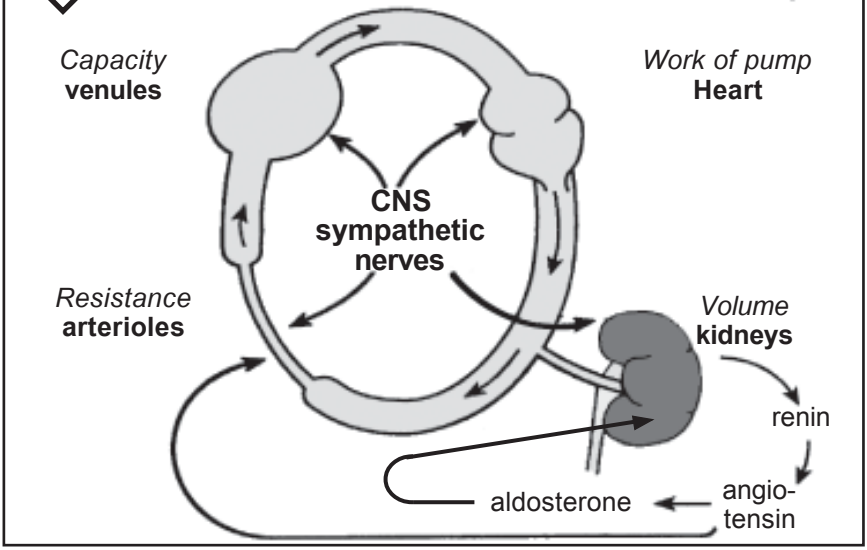
- **Primary (essential) — hypertension:** in 20–40% patients with boundary AH (neurocirculatory dystonia of hypertensive type, diagnosed on the basis of three times fixed within a week ↑ SAP up to 159 mmHg, DAP up to 94 mmHg, without the signs of target organs damage (the nervous system, the heart, the eyes, the kidneys)
- **Secondary — symptomatic** (vascular: dilatation ot the renal artery as a result of renal diseases, etc.; initially humoral: pheochromocytoma, Cushing's disease, etc.)

The correct choice of hypotensive therapy depends on knowledge of etiology, basic links of AH pathogenesis being an object of medicinal influence!

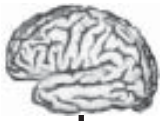
CLASSIFICATION OF HYPERTENSION

Stages	ABP, mmHg	
	SAP	DAP
N	101–139	61–89
Boundary AH	140–159	90–94
I stage — mild (functional, transitory)	160–179	95–109
	There are no signs of target organs damage	
II stage — moderate (initial organic defeats, labile)	180–199	110–119
	Hypertrophy of the left ventricle, constriction of retinal arteries, etc.	
III stage — severe (organic defeats, stable)	> 220	> 120
	Disorders of cerebral, coronary, renal circulation	

BLOOD PRESSURE REGULATION



HYPOTENSIVE DRUGS



I. Neurotropic: tranquilizers, neuroleptics, psychosedatives

II. On the synaptic transmission:

central α_2-adrenomimetics *(clonidine, methyldopa)*

selective agonists of imidasoline receptors *(moxonidine)*

α- and β-adrenoblockers

sympatholytics

serotoninoblockers

ganglionic blocking agents

III. On the water-salt metabolism: diuretics, ACE inhibitors, antagonists of angiotensin II receptors

IV. Myotropic (vasodilatators): nonselective *(papaverin, no-spa, etc.)*, selective *(Ca^{2+}-channel blockers, K^{+}-channel activators, etc.)*

DEMANDS TO A HYPOTENSIVE DRUG

- To cause stable fall of ABP, to be effective with administration per os
- To act protractedly (24 hrs), preserving the circadian rhythm of ABP with normalization of the morning level
- To promote reduction of organ defeats (hypertrophy of the left ventricle)
- Not to cause orthostatic hypotension
- Not to have cardio-, neurodepressive properties and development of tolerance to drugs
- Not to retain sodium in an organism
- Not to provoke ABP rise after a withdrawal ("rebound" hypertension)
- To improve quality of life of patient, preventing development of complications and lethal outcome

CENTRAL α-ADRENOMIMETICS

Clonidine (hemitone), methyldopa, guanfacin

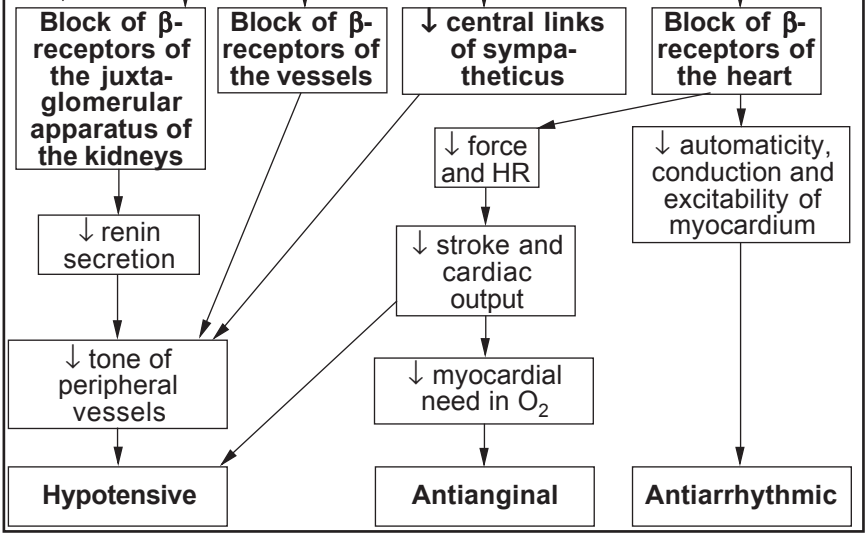
- ↓ arteries and ↓ peripheral resistance (greater in the vertical position)
- ↓ HR and minute blood volume — MBV (greater in the horizontal position)
- Prevents hypertrophy of the left ventricle and heart failure
- ↓ vessels of the kidneys, the brain, the heart
- ↓ secretion of rennin and activity of RAS
- + *sedative, nootropic, analgesic, hypothermic effect*

Adverse effects

✓ Drowsiness, vomiting, constipations, dry mouth, initial ↑ ABP (i.v.), bradyarrhythmias, etc.

✓ Rebound syndrome, tolerance to therapy, worsening the AH clinical course and quality of life

β-ADRENOBLOCKERS



β-ADRENOBLOCKERS

Pharmacokinetics

- **Absorption:** well absorbed, peak of concentration is in 1–3 hrs
- **Bioavailability:** first pass elimination
- **Distribution** is even, lipophilic (anapriline, metoprolol, etc.) well penetrate through the HEB
- **Excretion** with urine (different $T_{1/2}$)

Indications

- Arterial hypertensions
- Ischemic heart disease
- Tachyarrhythmia
- Glaucoma — *timolol*
- Hyperthyroidism — *propranolol*
- Neurological disorders (migraine, alcoholic abstinence) — *propranolol*

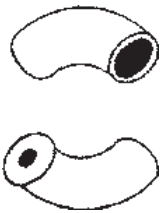
β-ADRENOBLOCKERS

Adverse effects

- **CVS: arrhythmogenic action** (AV-conduction abnormality, bradycardia, etc.), **heart failure, hypotension, edemas** (↓ renin)
- **Bronchial spasm**
- **Spasm of coronary and peripheral vessels** ("intermittent claudication")
- **Hypoglycemia**
- **Dysfunction of the thyroid gland** (↓ triiodothyronine)
- **Atherogenic action**
- **↓ thrombocyte aggregation**
- **↑ intestinal peristalsis**
- **Contraction of pregnant uterus**
- **Receptor desensitization**
- **Rebound syndrome** with ↑ myocardial ischemia

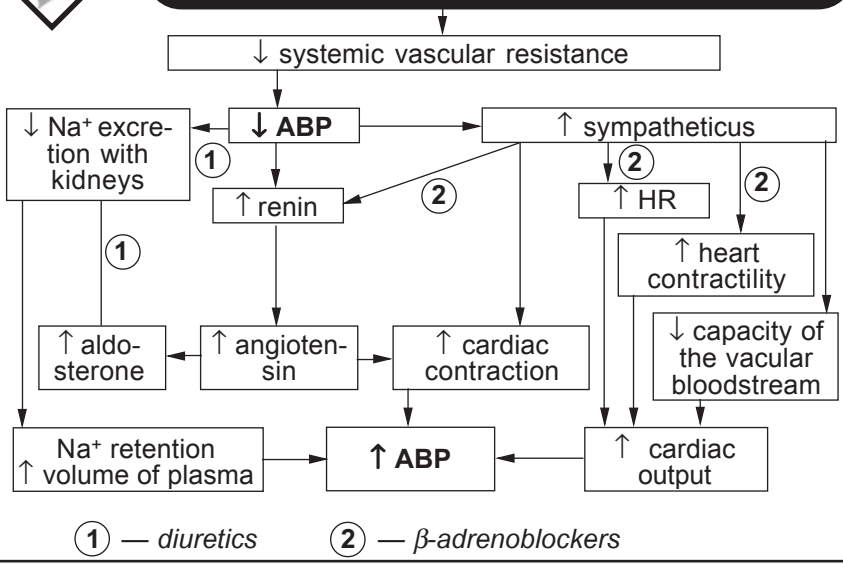
MYOTROPICS (VASODILATATORS)

- **Arterial:** apressin (hydralazine), activators of potassium channels, vasotropic calciun channel blockers, etc.
- **Arterial and venous:** papaverine, drotaverine (no-spa), α-adrenoblockers, ganglionic blocking agents, nitrates (sodium nitroprusside), etc.



Majority of myotropic drugs are intended for hypertensive crisis arrest and additional therapy in the AH complex treatment!

VASODILATATORS



MYOTROPICS (VASODILATATORS)

- **Nonselective** (refer to Topic 16)
  - *PDE inhibitors:*
    - ✓ derivatives of isoquinoline — papaverine, no-spa (drotaverine)
    - ✓ + *antagonists of adenosine receptors:* xanthine derivatives — theophylline, aminophylline (aminophylline)
  - *Mixed mechanism of action* — apressine (hydralazine), dibazole, nicotinic acid and its derivatives, etc.

- **Selective**
  - *Calcium channel blockers* — nifedipine, diltiazem
  - *Potassium channel activators* — minoxidil, diazoxide
  - *Nitrogen oxide donators* — sodium nitroprusside

MYOTROPICS OF MIXED ACTION

Apressine (hydralazine)

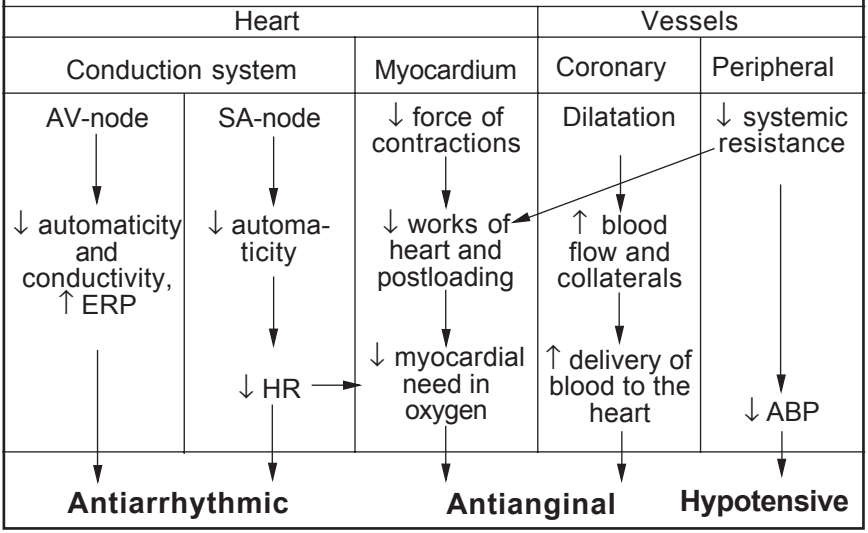
- **Pharmacodynamics:**
  - dilates arterioles due to release of nitric oxide (without causing orthostatic phenomena)
  - dilates arteries of the heart, the brain, the kidneys
- **Pharmacokinetics:** well absorbed (90%), but first pass elimination especially in rapid acetylators (15%); in blood is bound with ketoacides forming hydrazones
- **Indications:** per os for treatment of mild and moderate AH (effect comes in 45 min), heart failure (↓ postloading) in complex with reserpine (adelfan) + hydrochlorthiazide (adelfan-ezidrex) + i.m. (in 20–30 min), i.v.
- **Adverse effects:**
  - *hemodynamic:* hypotension, nausea, edemas, reflex tachycardia, reddening of the face, "coronary steal" syndrome
  - *immunological* reactions on the type of systemic lupus erythmatosus
  - *hypovitaminosis* B_6 (hydrazone): polyneuritis, paresthesia, thrombocytopenia
  - *tolerance, with withdrawal* — initial high ABP

CLASSIFICATION OF CALCIUM CHANNEL BLOCKERS

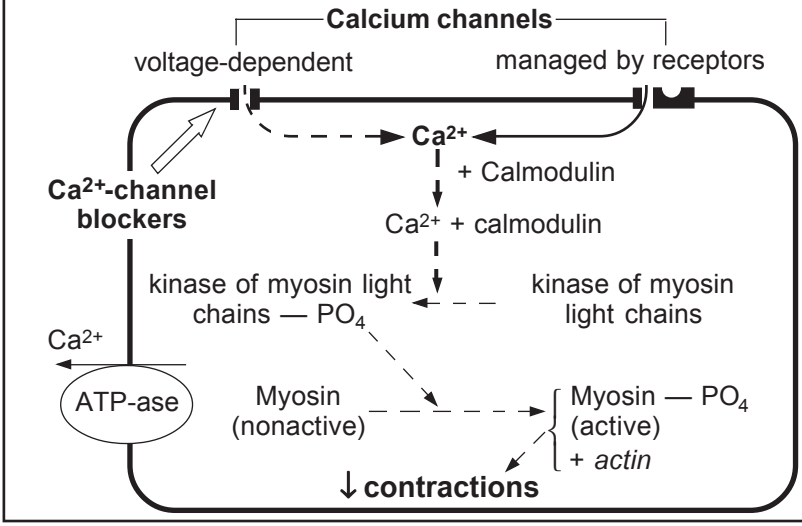
- **I type — cardiotropic** *(phenylalkylamine derivatives)*: I generation — verapamil (finoptine), II generation — hallopamil, etc.
- **II type (vasotropic)**
  General action: *dihydropyridine derivatives* (DCCB):
  - I generation — nifedipine (fenigidine, corinfar), II generation — nifedipine-GITS, amlodipine, nimodipine, isradipine, nicardipine, etc.
  - *Cerebrovasotropic — diphenylpiperasine derivatives*: I generation — cinnarizine (stugerone), II generation — flunarizine (nomigrane), as well as some *dihydropiridine derivatives* (nimodipine)
- **III type — mixed** *(benzothiazine derivatives)*:
  I generation — diltiazem,
  II generation — clentiazem

* — full characteristics of the group is in the Topic 12

CALCIUM CHANNEL BLOCKERS



CALCIUM CHANNEL BLOCKERS AND SMOOTH MUSCLES OF ARTERIES



PECULIARITES OF HYPOTENSIVE EFFECT OF CALCIUM CHANNEL BLOCKERS

- ↓ SBP and DBP
- + moderate diuretic and sodiumuretic action
- ↑ blood flow to vital organs (the heart, the brain, the kidneys), ↑ microcirculation
- ↓ hypertrophy of the left ventricle (sign of efficacy)
- ↓ ABP proportional to the dose, in therapeutic doses have a slight influence to normal ABP, do not cause orthostatic phenomena
- I generation of DCCB — ABP variability + reflex tachycardia
- II generation — maximal antihypertensive effect of retarding forms of I generation of all the CCB develops after 2–4 week therapy without pause; amlodipine — after 4–8 weeks

CALCIUM CHANNEL BLOCKERS

Indications

- AH, especially with the presence of concomitant diseases (diabetes mellitus, bronchial asthma, renal diseases, gout, etc.)
- Disturbances of cerebral circulation, migraine (nimodipine, cinnarizine)
- Disturbances of peripheral circulation, Raynaud's disease (amlodipine)
- Etc. (refer to Topic 12)

Adverse effects

- **Verapamil, diltiazem:** arrhythmogenicity (bradyarrhythmia, AV-block, etc.), heart failure, edemas on shins and ankles
- **Vasotropic:** hypotension; tachycardia (nifedipine), with marked atherosclerosis — «steal syndrome»
- Reddening of the face, dizziness, headache, visual impairment, gingival hyperplasia, disorders of the GIT, liver, cough, shortness of breath, etc.

ACTIVATORS OF POTASSIUM CHANNELS

Minoxidil, diazoxide

Opening of K^+-channels

↓

K^+ outflux from the cell

↓

Hyperpolarization

↓

Voltage-dependent Ca-channels do not open

↓

↓ Ca^{2+} delivery to the cell

↓

↓ tone of smooth muscles

↓

Vasodilatation

↓

↓ ABP

ACTIVATORS OF POTASSIUM CHANNELS

Indications

- **Reserve drugs at AH:**
  - ✓ severe forms, stable to treatment by other drugs *(minoxidil, diazoxide)*
  - ✓ hypertensive crisis *(diazoxide)*
- **IHD:** vasospastic, stable angina pectoris *(nicorandil)*

Adverse effects

- Tachyarrhythmia with ↑ myocardial need in O_2 ⇒ danger of myocardial infarction, unstable angina pectoris
- Heart failure, pulmonary hypertension, pericarditis, cardiac tamponade
- Orthostatic hypotension
- Reversible hypertrichosis ⇒ *minoxidil (rigein)* at alopecia
- Hyperglycemia
- Disturbances of peripheral, cerebral circulation, etc.

DONATORS OF NITRIC OXIDE

Sodium nitroprusside + Endothelial cells → **NO**

Adverse effects:

- ✓ orthostatic hypotension
- ✓ reflex tachycardia
- ✓ rebound syndrome
- ✓ metabolic intoxication (cyanides, thiocyanides)
- ✓ hypovitaminosis B_{12}, etc.

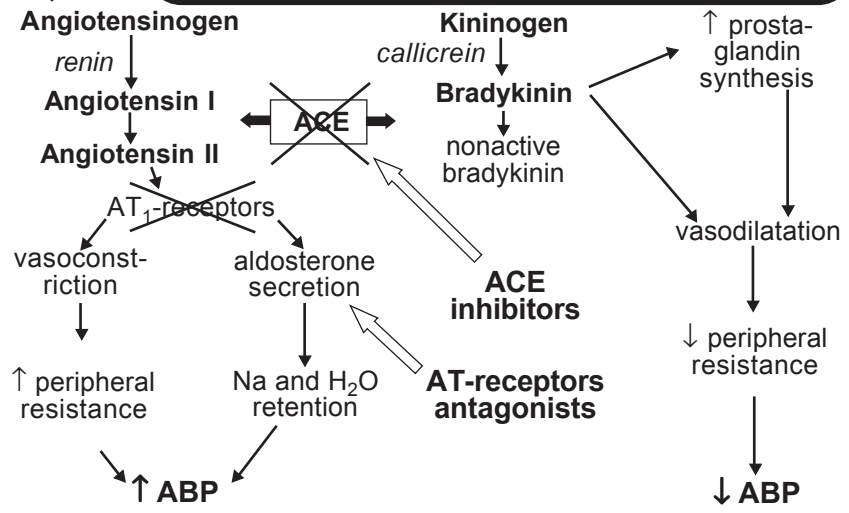
↑ guanylate cyclase

GTP → ↑ cGMP

↓ content of Ca^{2+} cytozole free ions

Smooth muscles relaxation

DRUGS AFFECTING THE RENIN ANGIOTENSINE SYSTEM (RAS)



DRUGS AFFECTING THE RENIN-ANGIOTENSIN SYSTEM

- **Angiotensin-converting enzyme inhibitors (ACE inhibitors):**
  - short-acting (6–12 hrs), containing a sulfhydryl group — *captopril (capoten)*
  - long-acting (24 hrs), containing a carboxyl group — *lisinopril, enalapril, perindopril, ramipril, etc.*
  - ultralong-acting (36 hrs), containing a phosphoryl group — *fosinopril*
- **Antagonists of angiotensin II receptors:** *losartan, valsartan, etc.*

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

HISTORY OF CREATION

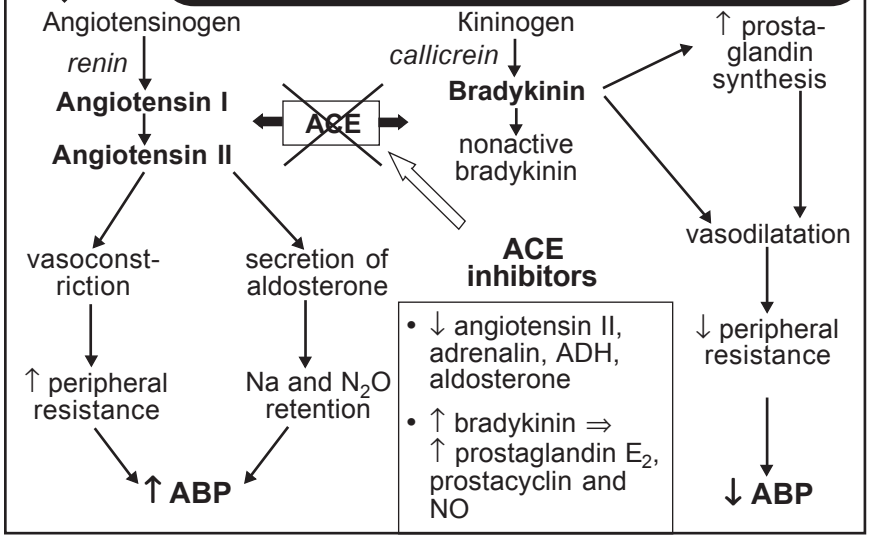
1971 B. RUBIN in the laboratory of the firm "Squibb" created the first ACE inhibitor teprotide — a polypeptide separated from the poison of the Brazilian snake jararaca

1975 at the same laboratory D. W. CUSHMAN and M. ONDETTI synthesized the first peroral ACE inhibitor — capropril

1998 ACE inhibitors were named the "golden standard in therapy of cardiovascular diseases" (the XII World Congress of Cardiologists)

The ACE inhibitor positive effect on quality and prognosis of life of patients was confirmed during the following years at numerous clinical researchers

ANGIOTENSIN CONVERTING ENZYME INHIBITORS



PHARMACODYNAMICS OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS

As a result of ↓ *plasma* RAS activity

- ↓ arteries and veins *(↓ pre- and postloading)*
- ↑ renal blood flow and gromerular filtration, ↓ hypokaliemia *(diuretic, nephroprotective)*
- HR normalization at tachycardia, antiarrhythmic effect
- ↓ coronary vessels, ↑ myocardial blood supply
- ↓ vessels of the brain

As a result of ↓ *tissue* RAS activity

- ↓ dilatation and hypertrophy of the heart
- ↑ synthesis of ATP, creatinphosphate, glycogen
- angioprotective action
- ↑ perception, cognitive activity

PHARMACODYNAMICS OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS

As a result of *metabolic* effects:

- Antiaggregation action
- Antiatherosclerotic
- ↓ lipids peroxidation *(captopril)*
- ↑ tolerance to glucose *(ramipril)*

Indications

- Arterial hypertention (AH during menopausa — *moexpril*)
- CHF, IHD *(perindopril, ramipril)*, including acute myocardial infarction (?)
- Chronic renal failure *(enalapril, ramipril)*
- Diabetes mellitus, prophylaxis of stroke *(ramipril)*

PHARMACOKINETICS OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Absorption: in per os intake the onset of captopril action is in 30–40 min (with sublingual — in 10 min); in all the rest — in 2–6 hrs: slow and incomplete absorption + all ACE inhibitors, except for captopril and lisinopril — **"prodrugs"** ⇒ with diseases of GIT, liver ↓ of the effect

Bioavailability: in majority 10–65%; in some drugs (captopril, moexpril, cylasapril) depends on the meal intake: captopril on an empty stomach — 75%, during the meal — 35%

Binding with proteins: lisinopril — 5%, captopril — 30%, phosinopril — 95%

Distribution: enalapril, phosinopril, trandolapril — lipophylic ⇒ well penetrate through the tissue barriers, including BBB

Biotransformation: prodrugs in the liver and/or GIT mucosa form active metabolites (...prelates)

Excretion: by kidneys as usual ⇒ ↓ dose with renal failure; ramipramil, fosinopril, trandolapril have 50% with bile; $T_{1/2}$ of captopril — 6–12 hrs; the rest — 24–36 hrs

INHIBITORS OF ANGIOTENSIN CONVERTING ENZYME

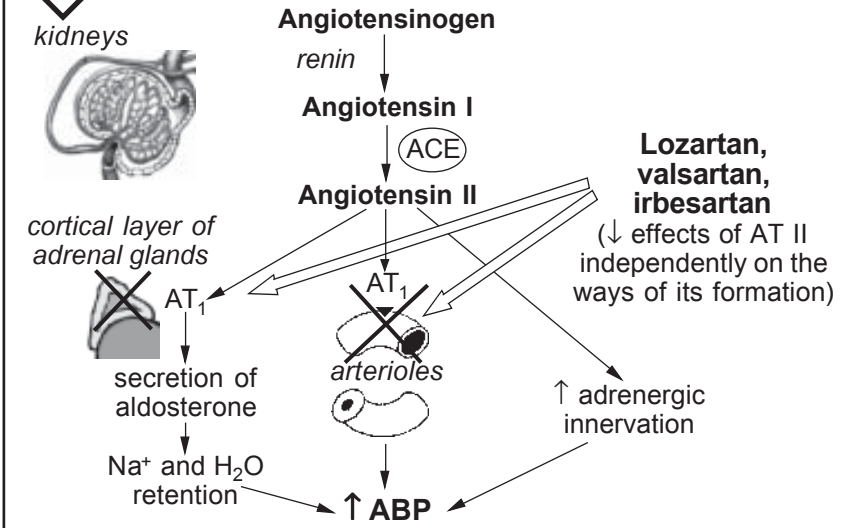
Adverse effects

- Dry cough (dry rales!)
- Hypotension (initial doses)
- Disturbances of renal function (proteinuria, edemas). nephrotoxicity rises NSAIDs
- Hyperkaliemia
- Alteration of taste, "burned tongue" syndrome
- Skin allergic reactions, angioneurotic edema, urticaria, photosensitization
- Importance, gynecomastia (lisinopril, captopril, etc.)
- Embryotoxicity

STIMULATION OF AT_1-RECEPTORS

Organs	Effects of angiotensin II
Heart	↑ contractity, hypertrophy, coronary vessels constriction
Peripheral vessels	Constriction with ↑ ABP, hyperplasia and hypertrophy of smooth muscles
Adrenal glands	↑ aldosterone secretions ↑ Na^+ reabsorption, K^+ secretion ↑ catecholamines
Kidneys	Constriction of the renal artery, ↓ renin
Hypophysis	↑ ADH secretion
Hypothalamus	↑ thirst center
Simpathetic NS	↑ noradrenaline secretion

ANTAGONISTS OF AT_1-RECEPTORS



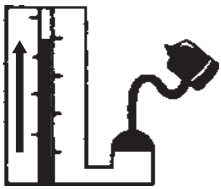
PHARMACODYNAMICS OF AT_1-RECEPTORS ANTAGONISTS

- ↓ common peripheral resistance of vessels and ABP *(↓ post-loading)*
- ↓ SAP and DAP (on 6–20% in 5–6 hrs during 24 hrs)
- ↓ HR, hypertrophy of the left ventricle
- Nephro- and angioprotective action
- Sodiumuretic and uricosuric action
- ↓ aldosterone, noradrenaline, adrenaline
- ↑ renin, angiotensin I and II (by the principle of feed-back)
- **In contrast to ACE inhibitors**
  - ✓ does not change the level of bradykinin, prostaglandin, prostacyclin, K^+ content in the blood
  - ✓ adverse effects are less expressed

GENERAL PRINCIPLES OF ARTERIAL HYPERTENSION TREATMENT

- ↓ ABP not below working values
- Choice of drug with taking into account:
  - individual features
  - severity of disease
  - extent of hemodynamic disturbances, etc.
- To begin with monotherapy («simple» treatment, if possible 1 tablet a day)
- In case of ineffectiveness — turn to combination of drugs with different mechanism of action (low doses)
- Gradual therapy withdrawal (rebound syndrome)
- The newest drug is not proved to be the best one!
- The low-sodium diet (3–5 g), ↓ excessive weight
- To have patience and learn a patient to be patient

PHARMACOTHERAPY OF ARTERIAL HYPERTENSION



- **I stage** ***(monotherapy)***
  - ✓ β-adrenoblockers, *or*
  - ✓ diuretics, *or*
  - ✓ calcium channel blockers, *or*
  - ✓ ACE inhibitors
- **II stage** ***(2 drugs combination)***
  - ✓ β-adrenoblockers + diuretic
  - ✓ β-adrenoblockers + calcium channel blockers
  - ✓ diuretic + ACE inhibitors
  - ✓ diuretic + calcium channel blockers
- **III stage** ***(3 drugs combination)***
  - ✓ β-adrenoblockers + diuretic + inhibitors ACE
  - ✓ β-adrenoblockers + calcium channel blockers + diuretic
  - ✓ diuretic + ACE inhibitors + calcium channel blockers (or prasosin)
  - ✓ with resistance additionally — methyldopa, minoxidil, clonidine

HYPERTENSIVE CRISIS

Drug	The way of application	Effect onset, min	Duration, hrs
Sodium nitro-prusside	i.v.	The beginning of infusion	The end of infusion
Diazoxide	i.v.	1–5	1–12
Apressine	i.v.	5–10	4–6
Nifedipine	i.v.	1–5	3–6
	Sublingual	15–30	3–6
Captopril	"-"	10	6–12
Labetalole	i.v.	1–5	6–24

if necessary also

- ✓ furosemide (lazix) i.v.
- ✓ neurotropic — diazepam (i.v.), aminasine (i.v., i.m.), magnesium sulfate (i.v.), etc.

CLASSIFICATION OF HYPERTENSIVE DRUGS

- **Adrenomimetics** — adrenaline, ephedrine, noradrenaline, mesatone
- **Dopaminomimetics** — dopamine
- **Glucocorticosteroids** — hydrocortizone, prednizolone
- **Mineralocorticosteroids** — DOXA
- **Analeptics** — caffeine, cordiamine, sulfocamfocaine
- **Drugs affecting the angiotensine system** — angiotensinamide
- **Adaptogens** — drugs of eleuterococcus, ginseng, leuzea, etc.

Topic 16

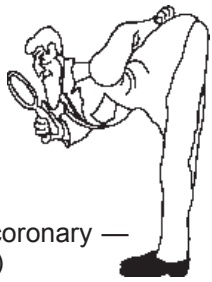
MYOTROPIC DRUGS

MYOTROPIC DRUGS

Drugs which are able to decrease the tone of smooth cells of cavital organs and vessels

From the practical point of view for the removal of pathologically ↑ tone of:

- **Cavital organs:**
  - biliary-, urinary tracts, GIT — *spasmolytics*
  - bronchial tubes — *broncholytics (dilatators)*
  - uterus — *tocolytics*
- **Vessels** — vasodilatators:
  - for ↓ system ABP as *antihypertensive*
  - with disturbances of peripheral circulation (coronary — *coronarolytics*; cerebral, lower extremities)



MYOTROPIC DRUGS

Depending on nature of spasm

- **Drugs which**
  - **↓ influence of spasming innervation:** parasympathetic ⇒ **M-cholinoblockers** (for the cavital organs), ***ganglionic blocking agents*** (for vessels); alfa-adrenergic for vessels ⇒ ***α-adrenoblockers***
  - **↑ inhibiting influences:** through presynaptic β_2-adrenoreceptors ⇒ ***β_2-adrenomimetics*** (refer to proper topics)
- **Myotropic spasmolytics of wide spectrum** influencing the universal mechanisms of contraction **(inhibit)** or relaxation **(activate)** of smooth muscle fibers *nonselectively* and *selectively* (specifically on seperate links — donators of nitric oxide, calcium channel blockers, activators of potassium channels, etc. (refer to Topic 15)

MYOTROPIC DRUGS

- **Nonselective action:**
  - **Inhibitors of phosphodiesterase** — *isoquinoline derivatives:* opium alkaloid papaverine and its synthetic analog drotaverine (no-spa); *different chemical groups**: carbocromen (intencordine)
  - **Antagonists of adenosine (purine) receptors and PDE inhibitors** — *purin derivatives (methylxanthine)*: theophylline, aminophylline, etc.
  - **Adenosinergic** — dipyridamol (curantil), lidoflazine, etc.*
  - **Mixed mechanism of action** — apressin (hydralazine), dibazol, the nicotinic acid and its derivative, etc.**

* — refer to Topic 13
** — refer to Topic 15

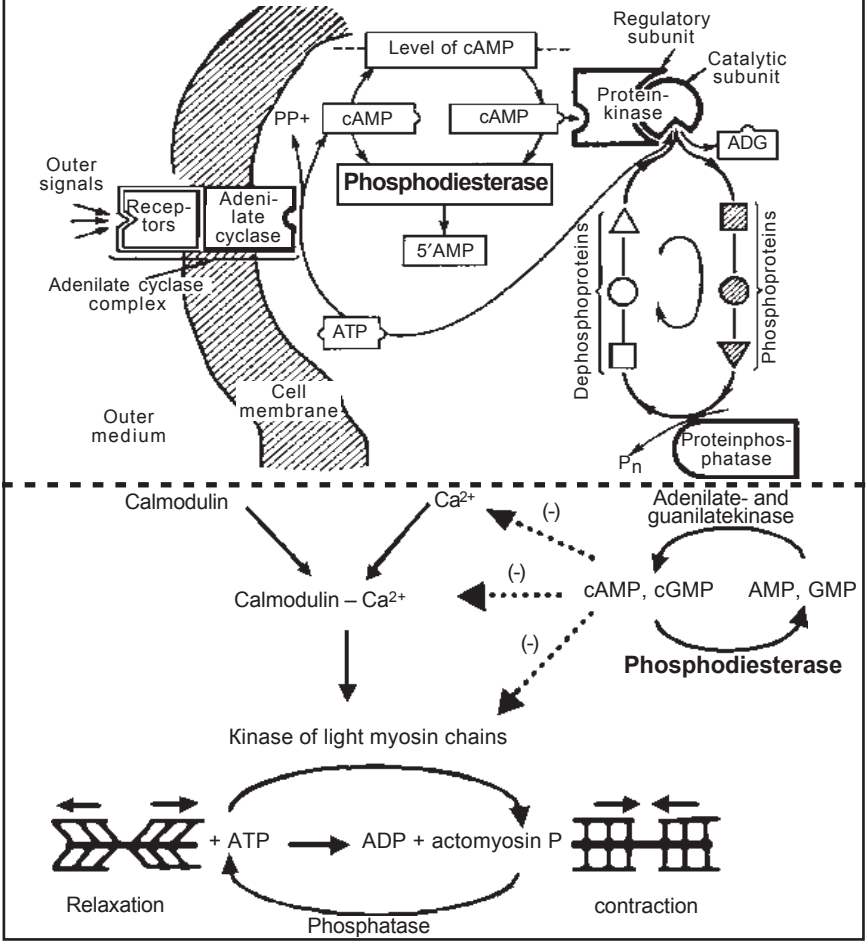
INHIBITORS OF PHOSPHODIESTERASE

- **By the structure there are 11 types of PDE**

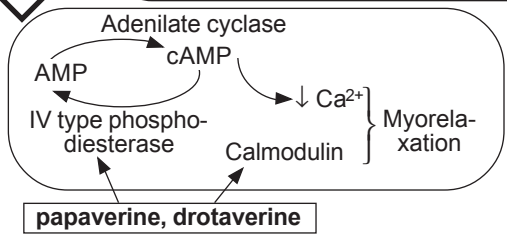
Isoenzyme PDE (substrate)	Tissue distribution	Functional role of substrate
PDE1 (cAMP, cGMP)	The brain, cardiomyocytes, myocytes of vessels, internal organs, skeletal muscles, liver	Muscle relaxation, gustatory sensation, olfaction
PDE2 (cAMP, cGMP)	Adrenal cortex, cavernous bodies; myocytes of the heart, internal organs, skeletal muscles, the brain	Olfaction, adrenal cortex's hormones secretion
PDE3 (cAMP, cGMP)	The myocytes of the heart, internal organs; thrombocytes, liver, fatty tissue, kidneys, cavernous bodies	Contraction of cardiomiocytes, secretion of insulin, regulation of lipid exchange, thrombocyte aggregation
PDE4 (cAMP, cGMP)	The brain, testicles, thyroid, lungs, mast cells, myocytes of vessels, internal organs, skeletal muscles	Inflammation, smooth muscle tone, development of depression, thyroidal hormones secretion, reproductive function
PDE5 (cGMP)	Cavernous bodies, myocytes of vessels, internal organs, thrombocytes, gastrointestinal tract	Erection, smooth muscle tone, thrombocyte aggregation
PDE6 (cGMP)	Retina (rods, coni)	Transmission of signal to the visual organ
PDE7 (cAMP)	Myocytes of the heart, skeletal muscles, T-lymphocytes	T-cells activating, contraction of skeletal muscles, metabolism
PDE8 (cAMP)	Many organs and tissues, the ovary, testicles, colon, brain	The T-cells activation
PDE9 (cGMP)	Many organs and tissues, the spleen, small intestine, brain	Unknown
PDE10 (cAMP, cGMP)	The brain, testicles, thyroid	Transmission of signal in the dopaminergic fibres
PDE11 (cAMP, cGMP)	Myocytes of the vessels, internal organs, heart, skeletal muscles, cavernous bodies, prostate, testicles, liver, kidneys	Unknown

INHIBITORS OF PHOSPHODIESTERASE

- **By substrate activity and dependence on coenzymes — 4 type:** *Ca^{2+}-calmodulindependent* — in the cardiac muscle, brain tissue; activity ↑ in presence of Ca^{2+}; *cGMP-modulated* — in the nervous system, cortical substance of adrenal glands (steroidal hormones biosynthesis regulation), the cardiac muscle, some types of smooth muscles, thrombocytes, fatty cells, hepatocytes; *cAMP-specific* — in the reproductive system (cavernous bodies), in the kidneys, lymphocytes; *cGMP-specific* — in the lungs, thrombocytes, in the cells of rods and coni of the retina



INHIBITORS OF PHOSPHODIESTERASE



Nonselective inhibition of PDE (more frequent with III and IV types) ⇒ ↑ level of intracellular cAMP ⇒ opening of Na^+- and Ca^{2+}-channels ⇒ *spasmolytic action*

Indications

Symptomatic therapy in complex!

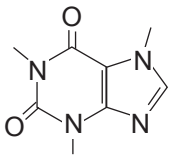
- **With spasms of cavitary organs:** repid relief of colics (i.m., s.c., rarely i.v. in combination with M-cholinolytics, analgesics); in the complex medical treatment of chronic diseases of GIT (cholecystitis, gastroduodenitis, spastic colitis, etc.), kidneys (urolithiasis, cystitis, etc.), uterus and ovaries
- **Rapid relief of hypertensive crisis**
- **Disturbances of coronary and cerebral circulation** (in combination with nicotinic acid — nicoverine, nicoshpan, etc.)

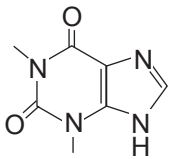
DERIVATIVES OF XANTHINES

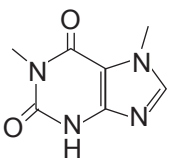
(oxidized purines, analogs of urinary acid)

✓ **Alkaloids:** caffeine *(1,3,7-trimethylxanthine)*, theobromine *(3,7-dimethylxanthine)*, theophylline *(1,3-dimethylxanthine)*

✓ **Half-synthetic**: *aminophylline (theophylline + ethylenediamine!), diprophylline, pentoxiphylline (trental, agapurine), etc.*


Caffeine


Theophylline


Theobromine

Sources of obtaining

- **Caffeine:** tea (about 5%), coffee (2–2.5%), cola nut (2%), etc., as well as by the synthetic way from the urinary acid
- **Theobromine:** seeds of chocolate tree (2%)
- **Theophylline:** tea

PHARMACODYNAMICS OF XANTHINES

- Relaxation of smooth muscles:
  - GIT ⇒ *spasmolytic effect*
  - bronchi ⇒ *broncholytic effect* (especially theophylline: + ↓ histamine release + ↑ contractility of diaphragm)
  - cardiac vessels ⇒ *coronarolytic effect* (theophylline)
  - vessels of the lungs, kidneys, skeletal muscles
- ↑ cardiac activity (force, contractility) ⇒ *cardiostimulating* effect
- ↑ CNS ⇒ *psychostimulating effect* (caffeine, to lesser extent theophylline)
- *Diuretic effect* (weak; at the account of ↑ blood flow, filtration, ↓ reabsorption)
- ↑ gastric secretion
- ↓ thrombocyte aggregation ⇒ *angioprotection* (pentoxyphylline)
- ↑ lipolysis, glycogenolysis, basic exchange
- *Immunomodulating, anti-inflammatory* (theophylline)

PHARMACODYNAMICS OF XANTHINES

Mechanism of action

- **↑ intracellular level of cAMP** in the CNS, heart, smooth and skeletal muscles, fatty tissue, thrombocytes and other tissues:
  - ✓ concurrent antagonists of adenosine receptors A_1 (subtype of purine receptors of the first order P_1) ⇒ ↑ **synthesis of cAMP**
  - ✓ inhibit PDE (in large doses), that ↓ **inactivation of cAMP and cGMP**
- Inhibition of “slow” calcium channels (theophylline)

PHARMACODYNAMICS OF XANTHINES

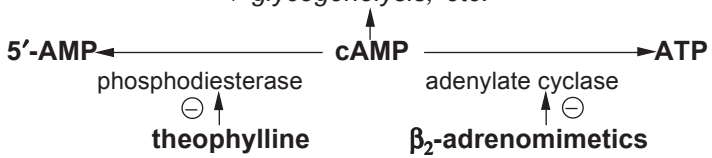
I. Concurrent blockade of adenosine receptors owing to similiarity with adenosine

Types of purine receptors	Their sub-types	Function
P_1 (adenosine)	A_1	By means the G-protein ↓ *adenylate cyclase and* ↓ *level of cAMP*, block Ca^{2+}-channels and K^+ permeability of membranes, ↓ secretion of neuromediators ⇒ • ↓ CNS (↓ motor activity, breathing, antianxious effect) • ↓ CVS (↓ HR, AV-conduction) • ↓ renal blood flow and secretion of renin • ↓ lipolysis in the fatty tissue
	A_2	↑ *adenylate cyclase,* ↑ *synthesis of cAMP* ⇒ vascular dilation, ↓ aggregation of thrombocytes
	A_3	Is not finally cleared up
P_2 (react on ATP)	P_{2x}	Open Na^+, K^+, Ca^{2+}-channels
	P_{2y}	Is not finally cleared up

PHARMACODYNAMICS OF XANTHINES

II. Nonselective inhibitors of phosphodiesterase

Broncho-, vasodilatation, ↓ release of mediators, ↑ glycogenolysis, etc.



Adverse effects

- *Associate with unselective action and numerous concomitant effects:* hypotension, dizziness, tachycardia, arrhythmias, dyspepsia, vomiting, etc.
- *Aminophylline (due to diethylamine)* — exfoliative dermatitis, fever, etc.

Topic 17

DRUGS AFFECTING BLOOD CIRCULATION AND MICROCIRCULATION

ANGIOPROTECTORS

(protecting vessels) — a diverse group of drugs applied with systemic and peripheral angiopathias — atherosclerosis, diabetes mellitus, alcoholism, etc.

"Atherosclerosis is a varied combination of arterial intima changes consisting in accumulation of lipids, complex carbohydrates and elements of blood and products of its disintegration, fibrous tissue and calcium deposits resulting in the vascular wall damage and disturbances of hemodynamics"

The following conditions belong to disease atherosclerosis (ICD-X):

- **arteriolosclerosis**
- **arteriosclerotic disease of the vessels**
- **ateroma**
- **degeneration:** arterial, arteriovascular, vascular
- **obliterating senile endarteritis:** arteritis, endarteritis

CLASSIFICATION OF ANGIOPROTECTORS

- **Hypolipidemic:** ↓ lipid synthesis; ↓ cholesterol absorption; bilious acids absorption; ↑ catabolism and excretion of sterols
- **Hyperalfalipoproteinemic:** difenine, bioflavonoids
- **Stabilizators of atherogen lipoproteids**: heparin, hondroitinsulfate
- **Antiaggregants:** ↓ cyclooxygenase, ↓ phosphodiesterase and adenosindesaminase, blockers of receptors on thrombocytes
- **Antioxidants:** direct and indirect action
- **Endotheliotropic**
- **Vasotropic calcium channel blockers**

FACTORS CONTRIBUTING TO ATHEROSCLEROSIS DEVELOPMENT

- High level of cholesterol in blood because of excessive income with food, damages of liver receptors which are responsible for its removal (heredity, chronic alcoholism)
- Rise of arterial pressure and as a result cholesterol easily penetrates through the endothelium
- Damage of endothelium (tobacco smoking, chronic stress, drugs)
- Rise of glucose level (diabetes mellitus)
- Slowing of blood flow (sedentary life-style)

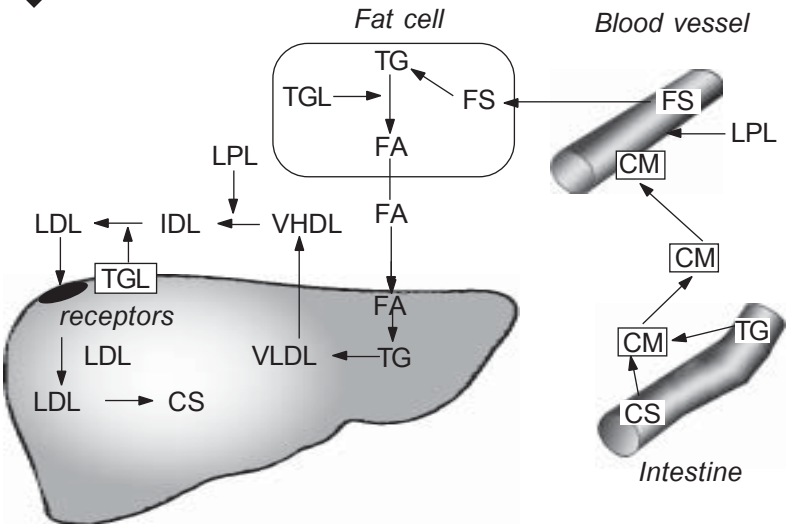
LIPOPROTEINS (LP)

Lipo-proteins	Diameter, nm	Chole-sterol, %	Triglyce-rides, %	Athero-genicity
CM	80–500	6	90	–
VLDL	30–80	17	**55**	+
IDL	25–35	30	40	++
LDL	18–28	**55**	8	**+++**
HDL	5–12	20	5	Antiathero-genic

Functions:

- *Chylomicrons (CM)* — transport of exogenous (food) triglycerides (TG)
- *Very low density lipoproteins (VLDL)* — endogenous TG transport
- *Intermidiate density lipoproteins (IDL)* — endogenous TG and cholesterol (CS) transport
- *Low density lipoproteins (LDL)* — CS transport to the tissues
- *High density lipoproteins (HDL)* — CS transport from the tissues

METABOLISM OF LIPOPROTEINS



HYPERLIPOPROTEINEMIAS

Types:
I — CM
II a — LDL
II b — LDL + VLDL
III— IDL
IV— VLDL
V — CM + VLDL

CS norm in the blood:
3.0–5.2 mmol/l (men)
3.0–6.2 mmol/l (women)
TG: 0.5–2.0
LDL: < 4.1
HDL: 0.97–1.96 and less

The most atherogenic are II, III, IV types of hyperlipoproteinemia

- **Primary** (genetic)
- **Secondary** (acquired):
  - ↑ TG — diabetes mellitus, chronic renal failure (CRF), chronic diseases of liver, alcoholism, obesity
  - ↑ TG + ↑ CS — hypothyreosis, nephrotic syndrome
  - ↑ TG + ↓ HDL — β-adrenoblockers, thiazide diuretics, per oral contraceptives

CLASSIFICATION OF HYPOLIPIDEMIC AGENTS

- **Inhibitors of bilious acids absorption:** *anion-exchange resins resins or bilious acids sequerstants (cholestiramine, cholestipol)*
- **Inhibitors of CS absorption:** linoleamide (clinolamide)
- **Inhibitors of lipid synthesis (CS, TG):**
  - *statins* or inhibitors of reductase hydroximethyl-glutaric coenzyme A — HMG-A (lovastatin, simvastatin, etc.)
  - *fibrates* (bezafibrate, gemfibrozol, etc.)
  - *different:* nicotinic acid (niacin); biguanides; enduracine; probucol
- **Promoting sterols catabolism and excretion:** *linetol, lipostabil, polisponine, polyunsaturated fatty acids (PUFA), thyroidine*

ANION-EXCHANGE RESINS

Cholestiramine, colestipol

- Bind bilious acids in the intestine, preventing their reabsorption after biliary excretion
- ⇒ ↓ CS, ↑ quantity of LDL receptors
  ⇒ ↓ LDL and ↑ HDL in the blood

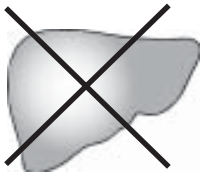
Adverse effects:

- **GIT** — nausea, vomiting, constipation or diarrhea, meteorism, abdominal pain, etc.
- **Drug absorption disorders:** thiazides, cardiac glycosides, phenobarbital, *etc. (an hour before and 4 hrs after the administration)*

STATINS

Lovastatin, simvastatin, fluvastatin, etc.

- Inhibit reductase hydroximethylglutaric coenzyme A (HMG-A)
- ⇒ ↓ synthesis CS in the liver
  ⇒ ↓ CS; ↑ quantity of receptors LDL
  ⇒ ↓ LDL, VLDL, TG and ↑ HDL in the blood



Adverse effects

- **GIT** — nausea, vomiting, meteorism, stomach aches, constipation or diarrhea, cholestasis, hepatitis, pancreatitis
- **Nervous system** — insomnia, headache, dizziness, fatigue, muscular seizures, bleard vision

STATINS

Adverse effects

- **Musculoskeletal system** — rigidity, myopathy (rarely rabdomyolisis, acute necrosis of skeletal muscles)
- **Cardiovascular system** — hypotension
- **Hematosis** — hemolytic anaemia, leukopenia, thrombocytopenia, ↑ erythrocyte sedimentation rate (ERS)
- **Urinary and sexual systems** — proteinuria, renal failure caused by rabdomyolisis, impotence
- **Visual organs** — opacity of lens
- **Skin** — itching, alopecia, dermatomyositis, eczema
- **Allergic reactions** — vasculitis, arthritis, urticaria, lupus-like syndrome, angioneurotic edema, photosensitization, toxic epidermal necrolysis

FIBRATES

Bezafibrate, hemfibrosil, fenofibrate, etc.

- ↓ CS synthesis in the liver and VLDL secretion in the blood, ↑ CS excretion with bile
- ⇒ ↓ CS, LDL, VLDL, TG and ↑ HDL in the blood

Adverse effects

- **GIT** — nausea, vomiting, stomach pain, diarrhea, meteorism, formation of cholesterol gall-stones (!)
- **Musculoskeletal system** — myositis, myasthenia in shins
- **Hematosis** — anaemia, leukopenia, eosinophilia, thrombocytopenia
- **Allergic reactions** — urticaria

EFFECT ON LIPOPROTEINS

Drug	CS	TG	VLDL	IDL	LDL	**HDL**
Anion-exchange resins	↓↓	↑	↔	↔	↓↓	↑
Statins	↓↓↓	↓	↓↓↓	↓	↓↓↓	↑
Fibrates	↓	↓↓↓	↓↓↓	↓	↓	↑↑
Nicotine acid	↓	↓↓↓	↓	↓	↓	↑
Probucol	↓	↔	↔	↔	↓	↓

HYPOLIPIDEMIC THERAPY IS RECOMMENDED TO PERSONS

- With identified IHD or diseases of peripheral vessels
- After coronary artery grafting
- Burdened family anamnesis with coronary vessels disease
- Suffering from obesity
- Suffering from diabetes mellitus
- Suffering from hypertension
- Those having hyperlipidemic stigma *(arcus corneal senilis)* at the age < 40 and xanthomas at any age
- Family anamnesis is burdened with hyperlipidemia

PRACTICAL ASPECTS OF TREATMENT

↓ **only CS** — drugs, ↑ excretion of bilious acids
— fibrates or statinis

↓ **CS and TG** — fibrates or derivatives of nicotine acid

↓ **only TG** — fibrates or derivatives of nicotine acid or lipostabil, linetol

- ♦ Considering contraindications
- ♦ Considering patient's anamnesis
- ♦ Regular control upon lipid content of the blood *(dose correction)*
- ♦ The combination of drugs of given groups (statins, fibrates, niacin), as well as with a number of other ones (indirect anticoagulants, macrolids, immunomodulators, etc.), increase the risk of side effects development!

OTHER ANGIOPROTECTORS

Stabilizators of atherogenic lipids — heparin, sulfate chondroitine A, polyanions

- ♦ Class of mucopolysaccharides, activating (stabilizing) lipoproteids in the dispersion state, prevent from binding with vascular intima, brake thrombogenic mechanisms of atherogenesis

Antioxidants

- ✓ **Direct action:** fat-soluble — tocopherol acetate, aevit, ubiquinole, dibunole; water-soluble — ascorbic acid, bioflavonoids (routine, quercetine); thiole — glutathion, cistamine, lipamide, lipoic acid
- ✓ **Indirect action:** precursor of glutathion (glutaminic acid, complamine), inductors of peroxidase (sodium selenit)
- ♦ ↓ free-radical oxidization of organic compounds (including lipids) by the molecular oxygen

OTHER ANGIOPROTECTORS

Antiaggregants

- ✓ ↓ **Synthesis of thromboxane A_2:** COX inhibitors (acetylsalicylic acid, aspirin-cardio); inhibitors of thromboxanthine synthetase (dazoxiben)
- ✓ **Blockers of receptors on thrombocytes:** ADP (ticlopidine, clopidogrel); thrombocyte activating factor — TAF (ketotifen, tanacan); serotonin (ketanserin), glycoproteine type IIb/IIIa (reopro, lamifiban, tirofiban, etc.)
- ✓ **PDE inhibitors + adenosine desaminase** (↑content of cAMP and adenosine in thrombocytes): dipyridamol, pentoxyphylline
- ✓ ↑ **activity of prostacycline system** (↑ prostacycline receptors): epoprostenol
- ♦ Prevent from aggregation, adhesion, thrombocytar blood clot forming, secretion with thrombocytes of biologically active substances (BAS)

OTHER ANGIOPROTECTORS

Endotheliotropic

- ✓ ↓ **activity of bradykinin** (↓ aggregation, ↑ fibrinolysis): parmidin (anginin, prodectin, veranterol)
- ✓ **Antigialuronidase** (↑ stability of capillaries, ↓ their permeability): etamsilate (dicinone), calcium dobesilate, troxevasine (venorutin)

- ✓ **Herbal:** escin, escuzan, androxone, Ginco Biloba

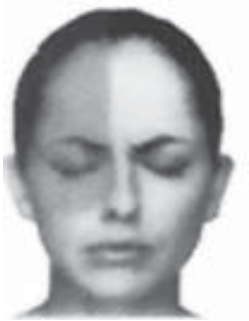
- ♦ Prevent from endothelial contractility and desquamation, its inhibition with beta-lipoproteids, preserve endothelial cover with a thin layer of glycocalix (polysaccharide) and fibrin

THERAPY OF CEREBRAL CIRCULATION DISTURBANCES

- **Myotropic (spasmolytics)** — *drugs of periwinkle* (vinpocetin (cavintone), vincamine), *derivatives of xanthin* (theophylline, pentoxiphylline), *derivatives of isoquinoline* (papaverine, drotaverine), *dibazol*, *nicotine acid and its derivatives* (xanthinole nicotinate (complamine), nicoshpan), etc.
- **Alfa-adrenoblockers** — *drugs of ergot alkaloids* (dihydroergotamine, dihydroergotoxin, etc.) and their analogs (nicergoline (sermion)
- **Calcium channel blockers** — nimodipine, cinnarizine, flunarizine
- **Antagonists of serotonin** — metisergid, peritol, pizotifen (sandomigran), etc.
- **Improving metabolic processes** — *nootropics* (aminolone, piracetam, picamilone), *protein hydrolizates* (cerebrolysine, actovegine)
- **Thrombolytics** (antiaggregants, anticoagulants, fibrinolytics) and **inhibitors of fibrinolysis** (aminocapronic acid)

MIGRAINE

- ♦ The disease characterized by strong pulsating, as a rule, one-sided headache which lasts for 4–72 hrs
- ♦ Frequently the pain is precedes by “aura” (visual, speech disturbances, stomach-aches, etc.)
- ♦ As a rule takes place in young women
- ♦ Has a congenital character
- ♦ The attack can be provoked by stress, fatigue, alcohol, menstruation, etc.
- ♦ Frequency of attacks — from 1 time a year up to 2 and more times a week
- ♦ *Pathogenesis* of vasomotor disorders is not finally cleared up



PHARMACOTHERAPY OF MIGRAINE

- **For treatment of attacks**
  - Specific (antimigraine) action: *alfa-adrenoblockers* (drugs of *ergot alkaloids* — ergotamine, dihydroergotamine) and *agonists of serotonine (5-HT_1) receptors* (sumatriptan, zolmitriptan, etc.), caffeine
  - Nonspecific (analgesic) action: NSAIDs (paracetamole, acetylsalicylic acid, naproxen, indometacine), *antiemetics* (dopaminolytics — metoclopramide, etc.)
- **For prophylaxis:** *beta-adrenoblockers* (propranolol), *anticonvulsants* (carbamazepin, derivatives of valproic acids), calcium channel blockers (cinnarizine, nimodipine), *antidepressants, 5-HT_2 receptors antagonists* (metisergid, pizotifen, peritol, etc.), *caffeine, NSAIDs, clonidine, magnesium sulfate, etc.*

PHARMACOTHERAPY OF PERIPHERAL CIRCULATION DISTURBANCES

- **Alfa-adrenoblockers:** tropafen, pyrroxan, etc.
- **Myotropic:** derivatives of xanthine (aminophylline, instenon, pentoxyphylline (trental), xanthinole nicotinate), isoquinoline derivatives (papaverine, drotaverine hydrochloride), benzofurane derivatives (fenicaberan), imidazole derivatives (dibazole), herbal and animal origin (andecalin, etc.)
- **Angioprotectors:** hypocholesterinic, endotheliotropic, etc.

CONTENTS

Godovan V. V.

Pharmacology in pictures and schemes : a handbook : in 2 volumes / V. V. Godovan ; ed. by V. I. Kresyun. — Odessa : The Odessa National Medical University, 2011. — Vol. 1. — 272 p. — English.

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This handbook consists of two volumes and contains the questions of general and special pharmacology, history of drugs creation, modern classifications of pharmacological groups, generalized data of pharmacokinetics, pharmacodynamics and pharmacotoxicodynamics of drugs applied in the modern medical practice. The material is highlighted in integration with other medicobiological and clinical disciplines. A schematic representation of drug action mechanisms and the effects occurring as a result of it occupies a special, unique place in the book.

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Vladlena Vladimirovna Godovan belongs to a new generation of the Odessa school of pharmacologists and clinical pharmacologists headed by a Corresponding Member of the National Academy of Medical Sciences of Ukraine, Honoured Worker of Science and Technology of Ukraine, professor V. I. Kresyun. Vladlena Vladimirovna occupies a prominent place in it. Doctor of medical sciences, professor of the General and Clinical Pharmacology Department, dean of the Medical faculty of the Odessa National Medical University, scientific secretary of the Odessa department of the Ukrainian Pharmacologists Association, a leading research worker of the State Expert Center of the Ministry of Health of Ukraine, scientific secretary of a specialized council. Basic directions of her scientific activity are search and creation of drugs on the basis of natural metabolites of a human organism, including co-ordinating compounds of germanium with bioligands; elaborations in the field of clinical pharmacology of hepatoprotectors and drug usage safety.

She is an author of more than 300 scientific works, including 2 monographs, 35 training handbooks, manuals, dictionaries in Ukrainian, Russian and English, 18 patents of Ukraine and certificates of authorship.