Chemical aspects of influence of medical drugs on organism functions

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Some fundamental problems of pharmacology important for setting investigations dealing with the search for new effective drugs are considered. The ways of introduction of drugs into the body, the types and functions of biological membranes, mediators of central and peripheral nervous systems, various receptor systems, and enzyme inhibitors are discussed.

Key words: pharmacology, drugs, biological membranes, agonists, antagonists, inhibitors, mediators, receptors, enzymes, nitric oxide.

This review can be regarded as a sort of introduction into medicinal chemistry. This is a field of chemistry, mainly organic chemistry, whose major lines of investigation include the search for new effective drugs, investigation of the type and the level of biological activity as functions of the compound structure, research into the problems of chemical and/or physicochemical grounds of the drug action on a living organism, and study of the mechanism of drug interaction with biological structures.

It is quite obvious that these investigations can be carried out only jointly by chemists and pharmacologists, the success of studies being largely dependent on the extent to which the scientists of different specialties are able to understand each other and to draw up and implement common plans, *i.e.*, on the extent to which they are professionally ready for cooperation. In this respect, sensible and target-directed approach to the synthesis of biologically active substances is possible only provided that chemists understand the foundations of pharmacology and some aspects of biochemistry and know the most important problems of these branches of science. Without this, a chemist engaged in the development of drugs is limited to "blind screening" whose outcome relies only on fortune and which is therefore relatively inefficient, nonconstructive, and nonproductive.

The goal of this review is to enable the necessary coordination between chemists and biologists. Therefore, the way of presentation of pharmacological information differs greatly from that accepted in pharmacological literature; chemical and physical interactions are discussed in more detail. In this respect, many pharmacological problems are considered less comprehensively and less extensively than this is done in specialized literature. A whole series of biological problems are discussed from the standpoint of their utility in the studies of processes related to the targeted synthesis of drugs. This survey is mainly based on monographs and review publications[1—14] rather than on original publications; however, the latter are also used, although to a limited extent, to illustrate the research investigations.

Penetration of substances through cell membranes. Types of membranes

The interaction of drugs with systems of an organism is based on the formation of bonds with various biosubstrates; it is this primary interaction that governs the further effects up to the medicinal action. It is clear that the main stages are drug transport to the site of action, distribution over organs and tissues, metabolism, and, finally, excretion. Only after a medication has been administered into the organism and its optimal concentration in organs and tissues has been created, can one expect an effective response, which depends on numerous factors. An important factor is the ability of the drug to induce the optimum biological effect, largely determined by the mechanism of its biological action.

Currently, it is accepted to classify the general pharmacology into two main sections, namely, pharmacokinetics, dealing with the problems of drug absorption, distribution, deposition, and excretion and pharmacodynamics, which deals with the biological effects of the introduced drug and investigates the mechanism of its biological action.

The routes of drug administration are divided into enteral (before getting into the general blood-vascular system, drugs pass through the gastrointestinal tract) and parenteral ones (absorption with bypassing the gastrointestinal tract). The enteral routes of drug administration include oral (through the mouth), sublingual (under the tongue), and rectal (through the straight intestine) ones, while the parenteral routes include intravenous, intramuscular, inhalation, and hypodermic injections. In all cases, for acting on the organism, a drug has to overcome a series of biological barriers, the ability of substances to penetrate membranes being largely

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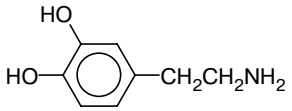
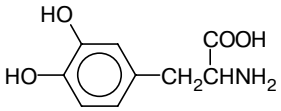
responsible for the efficiency of the use of a medicinal agent.

An impressive example is the search for rational ways of treatment of a serious and widespread disease, namely, parkinsonism. It was found that an important factor provoking Parkinson´s disease is depletion of one of the mediators of the central nervous system, dopamine, in brain tissues. It may seem that the most simple and efficient method for treating this disease is to replenish the dopamine reserves in the brain by direct injection of this preparation, which is rather readily available synthetically. However, this was found to be impossible because the brain is protected from foreign substances (xenobiotics) by a special resisting barrier, namely, the blood—brain barrier (BBB). The brain capillaries are constructed in such a way that polar compounds, to which dopamine certainly belongs, poorly (if at all) cross this barrier.

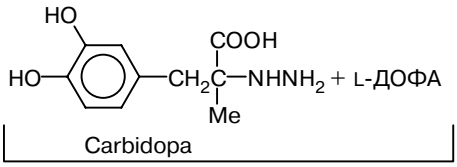


Dopamine



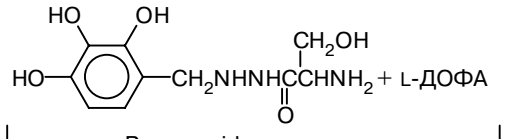
L-DOPA

As a consequence, the routes through which dopamine is to be delivered to the brain become much more complicated. It was found that the amino acid L-(3,4-dihydroxyphenyl)alanine (L-DOPA) is able to cross the BBB by means of active transport (see below). Being a dopamine precursor in the organism, this acid can be decarboxylated in the brain to give dopamine. However, the use of L-DOPA, too, still does not ultimately solve the given problem. The complication is that the required and planned decarboxylation takes place not only in the brain but also at the periphery of the organism (extracerebrally). This not only causes substantial losses of the drug (as noted above, dopamine formed in the peripheral tissues does not enter the brain because of the BBB) but also induces a number of side effects. This problem was largely solved by using inhibitors of peripheral decarboxylaytion, namely, carbidopa and benserazide.



Carbidopa

Nacom



Benserazide

Madopar

Combination of taking L-DOPA with these inhibitors resulted in the development of effective antiparkinsonian remedies called Nacom and Madopar, which are now widely used in clinical medicine.[1,6] The given example (see also below) properly illustrates the fact that simple solutions are not normally typical of pharmacology. Indeed, the system to be corrected by this branch of science is too intricate.

After intake and absorption, the substances enter the blood, which carries them over organs and tissues. Depending on their physicochemical properties, types of resisting biological barriers, and other factors, they are distributed, as a rule, fairly nonuniformly.

In this respect, rather important is the character of bonds arising between the drugs and biosubstrates. Neutral molecules are mainly accumulated in lipids, substances with cationic groups are linked to ribonucleic acids and glycoproteins possessing acidic properties, while compounds with anionic groups are bound to proteins (albumins). Blood serum albumin contains 109 cationic and 120 anionic groups. Despite the predominance of anion-containing fragments, albumin binds anions, probably, due to the higher spatial accessibility of the cationic groups.

The selectivity of distribution plays an enormous role in manifestation of the activity of drugs. For example, tetracyclines are accumulated predominantly in bacterial cells but not in the cells of mammals. The cytoplasmic membranes of bacteria are more permeable for tetracyclines, which induces inhibition of the ribosome protein synthesis in bacteria; this results in the loss of bacteria without substantial toxic effect on the host cells. Yet another example is that most of tumor cells capture uracil much more actively than healthy cells; thus, 5-fluorouracil can be employed as an effective antitumor remedy.

It is clear that the distribution of drugs in an organism depends crucially on their ability to penetrate biological membranes and on the properties and types of the membranes.[2,3,8]

The membranes that need to be penetrated by a substance to exhibit its biological activity are classified in pharmacology into several types. The first type comprises the simplest membranes consisting of lipids and proteins; these are membranes penetrated merely by diffusion. Obviously, in this case, the transfer velocity is determined by the difference between the substance (or substances) concentrations on the two sides of the membrane and the process can take place only until the concentrations become equal, *i.e.*, an equilibrium is attained. It is characteristic of these membranes that the rate of penetration of a substance through them depends, as a rule, on the lipophilicity of the compound; the more fat-soluble the compound transported through the membrane (up to a certain limit), the higher this rate.

The second type of membranes includes those having a specific system facilitating the compound transport through them, *i.e.*, promoting the diffusion. In this

case, too, equal concentrations result in termination of the penetration process. Note that for this type of membranes, no energy consumption during transport takes place. However, the difference from the first type of membranes is that in this case, transfer (moreover, facilitated transfer) of compounds that cannot penetrate the membrane without a transferring agent (a carrier), becomes possible. For example, diffusion of a choline molecule (a remedy for treating liver diseases) through first-type membranes is hardly possible due to the presence of the positively charged tetraalkylammonium group but the specific carrier rapidly delivers choline in the erythrocytes and other cells.

$HOCH_2CH_2N^+Me_3Cl^-$

Choline

It is clear that the permeability of these membranes is limited, for example, by the ability of the carrier to be saturated; in this case, the process is retarded even if the concentrations of the transported substance on the two sides of the membrane are different.

It is significant that the transport can often be inhibited in the presence of substances structurally similar to the main component. In addition, it is very important that carriers are highly chemically specific and, in some cases, they are able to "recognize" their own substrate even in the presence of structural analogs in the medium (including stereoisomers). An additional example (besides choline) of transport through membranes of this type is the transport of D-glucose (as well as other sugars, namely, D-mannose, D-xylose, D-arabinose) into human erythrocytes; it is very important that L-sugars cannot be transported *via* this route.

The third, a fairly important type of membranes includes those membranes that allow transfer against the concentration gradient, so-called active transport, which requires energy consumption. In this case, the carrier can also be saturated. In addition, active transport depends on the temperature, which is a typical feature of energy-dependent processes. There exist quite a few examples of active transport; here, we will cite some of them, namely, the transport of potassium and sodium cations into mammal cells (the positive charge of the sodium and potassium ions does not allow them to penetrate through membranes by simple diffusion). For the same reason, withdrawal of various ionized substances by renal tubules needs active transport. Bacteria capture inorganic ions, sugars, and amino acids in the same way. Accumulation of various substances by some cell organelles also involves this type of membranes (this refers to the sodium, potassium, calcium, and magnesium accumulation in mitochondria against the concentration gradient and iodine accumulation by the thyroid gland). It is noteworthy that active transport makes use of various enzymes, in particular, K^+/Na^+-ATPase is involved in the transfer of these ions into any cells, while Ca^{2+}/Mg^{2+}-ATPase transfers calcium into muscle cells. It is of interest that the carbon dioxide permeability of erythrocyte membranes is controlled by a special ion exchange protein, while the permeability of the nerve and muscle cell membranes varies upon the interaction of acetylcholine with cholinergic receptor.

It is pertinent to mention that there also exist unusual "indirect" ways of substance transport through cell membranes. First of all, these are pinocytosis and phagocytosis. In the case of pinocytosis, a membrane forms a "protrusions", which are subsequently converted into bubbles. The membrane is restored and the bubbles that have formed on the inner side of the membrane turn out to be outside the cell, while those formed on the outer surface find themselves inside the cell. Thus, substances located outside the cell get inside it and, *vice versa*; molecules that are too large to diffuse leave the cell through the membrane. Phagocytosis is similar to pinocytosis; this implies penetration of even larger molecules. Enzymes and hormones are a sort of squeezed out of cells as bubbles surrounded by lipid membranes. For example, this is the way used by an organism to "squeeze out" hydrolytic enzymes of the pancreas as so-called zymogen granules. The bubbles in which a mediator of a central nervous system, acetylcholine, is liberated from nerve endings and the granules in whose form another mediator, noradrenaline, is evolved from the medullary substance of the adrenal glands are of the same origin.

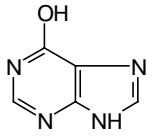
It is fairly interesting to consider the active transport of amino acids from urine to the renal tubules; in this case, the process involves the γ-glutamyl transferase enzyme, which catalyzes the transformation of amino acids and glutathione into γ-glutamyl derivatives, which are able (unlike amino acids occurring in the zwitterion form) to enter the cell. This is followed by hydrolytic cleavage to regenerate the initial molecules.

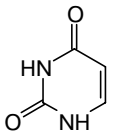
Finally, membranes of the fourth type should also be mentioned; they have the same properties as first-type membranes but contain pores of a definite size. An example is provided by renal glomes, which are permeable for any molecules that are smaller than the albumin molecule (~3 nm).

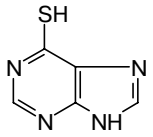
Thus, transport through lipoprotein membranes can take place by different routes. Evidently, in the case of simple membranes, transport through which does not imply energy consumption, diffusion of ions is appreciably hampered, first, because the membrane is charged and, hence, oppositely charged ions "stick" to it, while ions with like charge are repelled from it and, second, because ions in an organism are hydrated, which increases their size by a large factor.

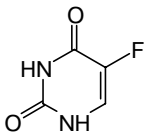
It can be seen from the foregoing that the problems of ionization and lipophilicity are quite important as regards penetration of substances through various membranes and, certainly, they are significant not only for inorganic cations but also for all molecules considered to be biologically active. Without dwelling on the prob-

lems of acid—base relationships and the ability of substances to be distributed between aqueous and oil phases, which are familiar to chemists, we will present only several examples to characterize the importance of this information. It is noteworthy that change in the lipophilicity of substances, *i.e.*, an increase in the possibility of transport through first-type membranes (simple diffusion), and search for compounds capable of being transferred through membranes by means of carriers are important ways of searching for new biologically active compounds. Thus the information on the transport into a cell of compounds such as hypoxanthine and uracil, necessary blocks for the synthesis of xanthine and nucleic cells, has underlain the synthesis of known antitumor preparations, 6-mercaptopurine and 5-fluorouracil.[1—3,8,11—13]

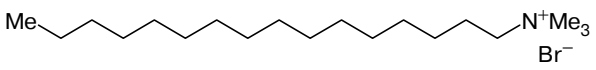

Hypoxanthine


Uracil


6-Mercaptopurine

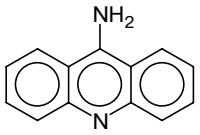

5-Fluorouracil

Here, it is appropriate to note that the ability of some surface active agents to damage cytoplasmatic membranes of bacteria has been used to develop antibacterial preparations in the series of quaternary ammonium salts having hydrophobic substituents with long alkyl chains (normally, C_{12} and longer). An example is cetyltrimethylammonium bromide.[3]

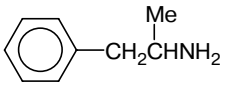


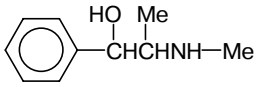
The mechanism of action of this type of compound is related apparently to the formation of large pores in the membranes through which large molecules leave the cells, and, consequently, the cells stop functioning.

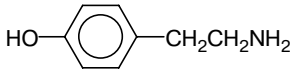
It should be noted that study of acridine derivatives showed that the highest bacteriostatic activity in this series is typical of the most ionized compounds. Indeed, of the aminoacridines studied, the highest activity was found for 9-aminoacridine which is ionized by 99% at pH 7.3. It is the cation concentration (rather than the overall amount of the compound) that governs the bacteriostatic action of acridine derivatives. It is already clear now that aminoacridines are intercalated into DNA (intercalators are compounds that are able to be inserted between the DNA bases owing to planar structure and be retained there owing to hydrophobic and ionic interactions, thus terminating the DNA replication[3]) and inhibit the bacterial DNA-polymerase by linking to matrix DNA. Both mechanisms are due to the possibility of binding of acridine derivatives to DNA, which is enhanced due to ion—ion interaction, typical of cations.[3]

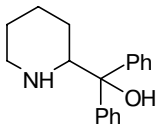

9-Aminoacridine

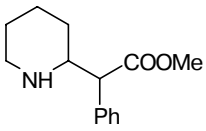
The complex problems associated with interpretation of a series of unclear points in the action of indirect α-sympathomimetics (see below) have been studied by measuring the ionization constants and the distribution between the aqueous and oil phases for amphetamine, ephedrine, meridil, pipradrol, and tyramine[15,16] (Table 1).


(*S*)-Amphetamine


(1*R*,2*S*)-Ephedrine


Tyramine


(*R*)-Pipradrol


(1*R*,2*S*)-Meridil

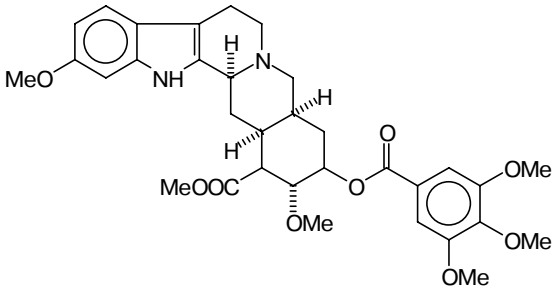
Amphetamine and ephedrine (this preparation exhibits also direct action) occupy a special place among sympathomimetics. In this case, fine distinctions between the biological effects of amphetamine and most of other sympathomimetics come to the forefront. Unlike pipradrol and related preparations, whose central stimulating action decreases dramatically following the elimination of the vesicular noradrenaline depot under the action of reserpine, the activity of amphetamine varies only slightly upon injection of reserpine. Conversely, depression of the synthesis of the noradrenaline

Table 1. Physicochemical properties of α-symphatomimetics

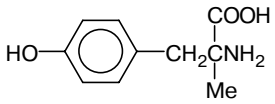
Compound	pK_a	N_n*	k**
Amphetamine	9.93	~0.2	0.21
Ephedrine	9.50	~0.5	0.27
Tyramine	9.16	~0.9	0***
Meridil	8.77	~2.4	1.86
Pipradrol	9.71	~0.3	2.58

* N_n is the fraction of neutral molecules (%) at pH 7.
** k is the partition coefficient in the water—octanol system.
*** Does not pass to octanol.

mediator (by inhibiting the enzymes responsible for its formation from tyrosine in an organism; this is done using an inhibitor of the catecholamine synthesis, namely, α-methyltyrosine) sharply decreases the stimulating activity of amphetamine.



Reserpine



α-Methyl-*p*-tyrosine

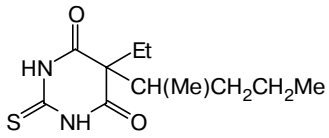
These differences have been interpreted by assuming different localizations of the sites of action of these preparations, either outside or inside the neuronal noradrenaline depots, which is due to different abilities of these drugs to penetrate cell membranes. The lipophilic compounds (meridil and pipradrol) enter the neuronal depot (exogenous reserpine also readily enters it) and act mainly from the inside to liberate the mediator, which then goes to the synaptic gap and causes the effects peculiar to it (in particular, vasoconstriction and vasopressor action).

Meanwhile, hydrophilic preparations (amphetamine, tyramine, ephedrine), which virtually do not pass to the fatty phase, appear to act outside the vesicular depot. Thus, pipradrol and similar preparations act on one type, while amphetamine acts on another type of noradrenaline depots. The major influence of amphetamine is depression of the reverse uptake of the mediator rather than its liberation; this is highly stereoselective: the (*S*)-isomer acts 10—20 types more strongly than the (*R*)-isomer. It cannot be ruled out that amphetamine, which mainly acts from the outside of the vesicular membrane, prevents the mediator from entering the vesicles, while the α-methyl group of the (*S*)-isomer decreases the possibility of back capture due to hydrophobic binding and thus enhances the inhibitory effect of the (*S*)-isomer.[15,16]

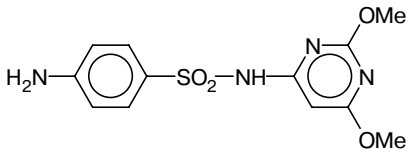
It can be seen from the data (see Table 1) that meridil and pipradrol are much more lipophilic than amphetamine, tyramine, and ephedrine. The latter group of compound virtually do not pass to the fatty phase and, hence, they are hardly able to penetrate the vesicular membranes *via* simple diffusion. Thus, drugs with relatively low lipophilicity act from the outside, while more lipophilic substrates function inside the vesicular depots.

Deposition, excretion, and metabolism of drugs

Thus, arrival of a drug to the site of action, *i.e.*, its ability to penetrate and to bind to cell membranes, is an important factor in manifestation of the biological activity. However, it is obvious that during this journey, some material is inevitably lost due to deposition, metabolism, *etc.* Of course, deposition is determined by physicochemical and structural features of the drugs; for example, lipophilic compounds such as thiobarbiturates are mainly accumulated in the cells of adipose tissues, and sulfamides are linked to albumin. Examples are thiopental, a derivative of thiobarbituric acid (general anesthetic) and a sulfamide drug, sulfadimethoxine, whose formulas are presented below.

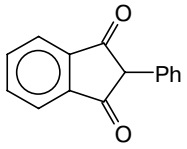


Thiopental

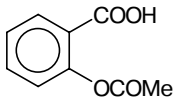


Sulfadimethoxine

Regarding practical application of drugs, it is very important to know the ratio in which various drugs are capable of binding to albumin. For example, combined use of phenindione as an antiocoagulant and aspirin is fairly dangerous because the latter displaces phenindione from the albumin depot and the phenindione concentration increases; the enhanced anticoagulant action may result in bleeding.

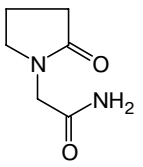


Phenindione



Aspirin

It is evident that one way of drug loss in an organism is excretion; it should be noted that this process is quite individual, being dependent on the type and structure of the preparation. As a rule, drugs come out of an organism in the initial form only partially; most often, prior to excretion, the substances change due to hydrolysis, oxidation, various enzymatic processes, resulting in more hydrophilic compounds. Very rarely, these transformations occur to a low



Piracetam

extent. For example, a known nootropic preparation, piracetam (nootropil), is largely removed from the organism unchanged.

Drugs are excreted by different routes. When they come out with urine, the process is characterized by a special parameter, renal clearance (Cl_R).

$$Cl_R = (C_u/C_p)v,$$

where C_u is the concentration of the substance in urine (mg mL^{-1}), C_p is the substance concentration in blood (mg mL^{-1}), and v is the urination velocity (mL min^{-1}).

The main structural unit of a kidney, nephron, is a U-shaped porous tube located inside another, nonporous tube (kidneys consist of 1.2 million of nephrons). In a nephron, several processes take place, owing to which drugs and drug metabolites are removed from kidneys. Blood that gets into kidneys is filtered in the glomes (fourth-type membranes), which trap all coarsely dispersed substances and polymeric compounds including most of proteins. This filtration is an important mechanism of renal elimination. The renal tubules return some of the filtered fraction to blood (useful substances), while the rest is directed through ureter to the urinary bladder. The rate of drug clearance by kidneys depends substantially on the binding of drugs by blood plasma proteins. Many drugs get from blood into liver in which they undergo partial biotransformation and come out with bile or return to blood either unchanged or as metabolites (including conjugates). Substances evolved with bile to the intestines can come out with excrements, be imbibed back into blood, or be metabolized by bile and intestines enzymes. Drug excretion with bile depends on the molecular mass, the state of liver functions, and the degree of binding of the preparations to proteins. Other routes of excretion include excretion with the breathed-out air, saliva, sweat, tears, and sex secretion.[14]

However, the major route of drug loss is chemical inactivation, namely, metabolism.[3,8] The metabolism pathways are classified into metabolic processes of phases I and II. Phase I includes transformation of the initial preparations into more hydrophilic compounds as a result of various enzymatic processes. An important role in these processes is played by cytochrome P450, which is a set of hemoprotein enzymes controlling the rate of excretion of chemical compounds from an organism and inactivating, in particular, xenobiotics. The enzymatic processes most significant in this respect include oxidative processes, in particular, *N*- and *S*-oxidation, deamination, hydroxylation to give alcohols (*C*-hydroxylation of aliphatic compounds) and phenols (*C*-hydroxylation of aromatic compounds), *O*- and *N*-dealkylation, and so on.[11,13].

An frequently encountered example is deamination induced by oxidative enzymes, monoamino oxidase (MAO) and diamino oxidase (DAO). The action of MAO is discussed below because this enzyme participates in the degradation of catecholamines, mediators of the central and peripheral nervous systems, and inhibitors of this enzyme exhibit substantial biological activity. The results of MAO action can be represented by the following scheme:

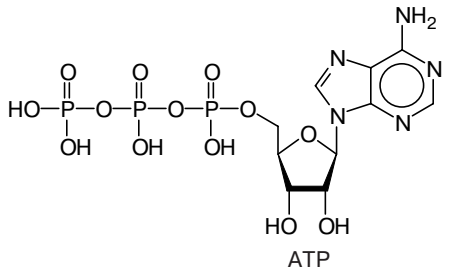
$$RCH_2NH_2 + H_2O + O_2 \longrightarrow RCHO + H_2O_2 + NH_3.$$

It should be noted that other processes can also take place in the liver endoplasmatic reticulum (ER), namely, dechlorination (oxidative and reductive) and the formation of primary amines with participation of the nitroreductase and azoreductase enzymes. In liver, halogen-containing compounds are bonded through the glutathione thiol group. One more important aspect is related to the oxidation of primary and secondary alcohols to carbonyl compounds under the action of alcohol dehydrogenase. For example,

$$EtOH + NAD^+ \rightleftharpoons MeCHO + NADH + H^+.$$

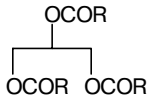
Succinate dehydrogenase converts succinic acid into maleic acid with participation of the Fe^{2+} co-factor.

Speaking about metabolism, one cannot but mention carbohydrate and lipid metabolisms, which are important processes for the functioning of a living organism. The main phase in the metabolism of carbohydrates is glycolysis. Glycolysis takes place for glycogen, animal starch, which is the main glucose store in an organism. Glucose glycolysis can occur without participation of oxygen; in this case, NAD^+ (nicotine adenine dinucleotide) is reduced, thus oxidizing the glyceraldehyde 3-phosphate anion to give 1,3-diphosphoglyceric acid, which then passes into phosphoenol pyruvate; this product is reduced to lactate by the NADH formed in the process. On the whole, glycolysis consists of 11 steps, each using its own specific enzyme; as a result, oxidation of one glucose molecule yields two molecules of adenosine triphosphate (ATP), which is the main accumulator and a versatile transferer of chemical energy.

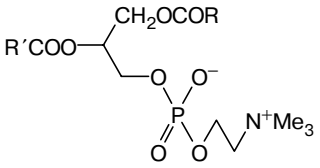


ATP

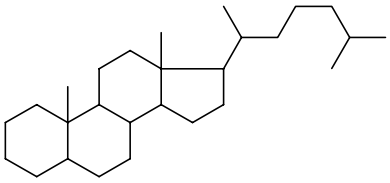
The lipid metabolism includes oxidation of fats (glycerol esters), phospholipids, and steroid compounds.



Fats

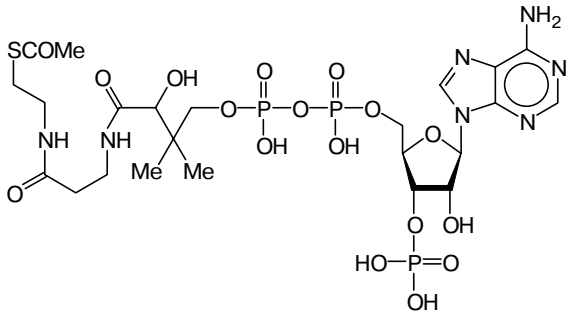


Phospholipids (phosphatidylcholin)



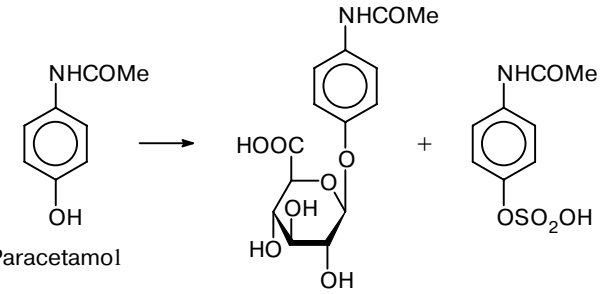
Steroids (cholesterol skeleton)

Fat oxidation occurs in mitochondria and gives rise to simpler molecules (glycerol, pentose, hexose, pyruvate) and, finally, the only "two-carbon group" (acetyl), which is linked to acetyl-co-enzyme A to give acetyl-SCoA, which acts as a "fuel" for the tricarboxylic acid cycle (citric acid cycle or Krebs cycle) and ensures the electron transfer involving the cyctochrome breathing cycle.



Acetyl-CoA

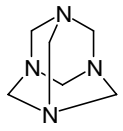
After compounds with reactive functional groups (OH, NH_2, COOH, *etc.*) have formed during the first phase of the metabolism, conjugation involving these groups takes place in phase II to give even more hydrophilic substances, which are rapidly excreted with urine. For example, acetylsalicylic acid is converted into salicylic acid, which is transformed into conjugates through the phenolic hydroxyl. Similarly (also due to the presence of the phenolic hydroxyl), the well-known drug paracetamol is transformed into glucuronide and an ester of sulfuric acid.



Paracetamol

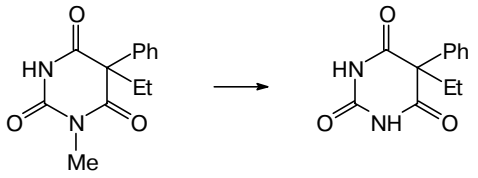
It is clear from the last-mentioned example that division of metabolism into phases is rather arbitrary, and there exist drugs (for example, paracetamol) that directly form conjugates, as well as substances that undergo only phase I and are excreted from the organism by kidneys without conjugation.

The metabolism of drugs is, most often, a way of drug inactivation in an organism. However, there are quite a lot of cases in which metabolic transformations afford compounds possessing higher biological activities.[3,8] However, these metabolites often cannot be used directly for various reasons. For example, they cannot be delivered effectively to the site of action (penetrate the corresponding membranes), they are not sufficiently stable to act as individual drugs, *etc.* However, it is exceptionally important to know what are the true drugs because this provides the possibility of targeted synthesis based on the understanding of the fact what structure is the most appropriate (the most complementary) for interaction with one or another receptor system. An example of this type is the well-known uroantiseptic urotropin, whose role is actually to deliver formaldehyde, which is formed from it in the urinary tract under the action of acids.



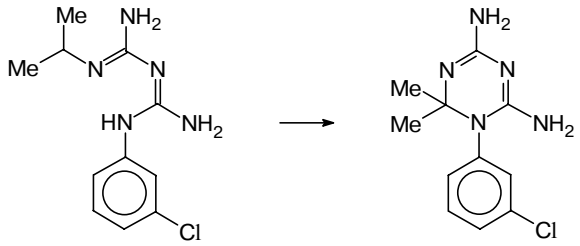
Urotropin

Chloral hydrate $CCl_3CH(OH)_2$ is converted in an organism into the corresponding alcohol, *i.e.*, trichloroethanol CCl_3CH_2OH, while 1-methylphenobarbital is readily converted into phenobarbital in the liver ER.



Phenobarbital

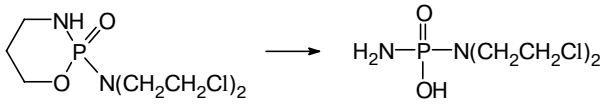
The same process is also typical of a number of other *N*-methyl derivatives of heterocycles. A true drug, dihydrotriazine derivative, is formed in an organism on taking the well-known antimalarial remedy, bigumal.



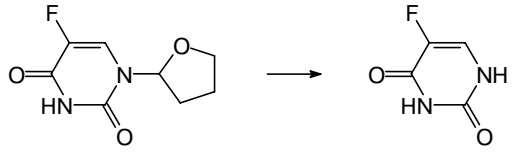
Bigumal

Similar processes involving the formation of more active compounds take place on using antitumor prepa-

rations, cyclophosphan and ftorafur (in the latter case, the known 5-fluorouracil is produced).



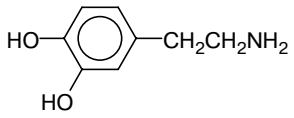
Cyclophosphan



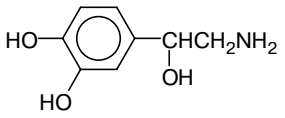
Ftorafur 5-Fluorouracil

Antidepressants

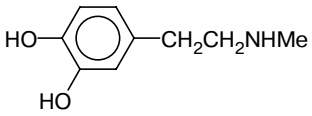
Now we return to the problem of activity of the monoamino oxidase (MAO) enzyme. Not long ago, synthesis and study of MAO inhibitors seemed to be among the most promising routes in the development of drugs for the treatment of mental diseases.[1,6] Indeed, it has been obvious that depletion of the stores of neuromediators such as noradrenaline, dopamine, and serotonin is highly dangerous for mental health and widespread diseases such as depression, schizophrenia, *etc.* develop just because of the lack of these substances in the organism. It appeared that the problem could be solved by activating the central adrenergic processes. At the same time it was found that iproniazid is a strong MAO inhibitor preventing the enzymatic cleavage of mediators of the central nervous system (CNS) as well as their precursors such as tyramine and other endogenic amines.



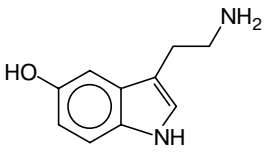
Dopamine



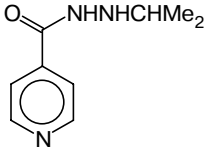
Noradrenaline



Adrenaline

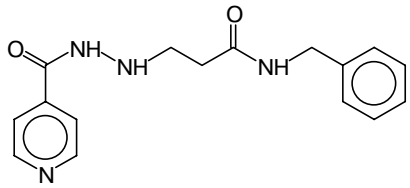


Serotonin



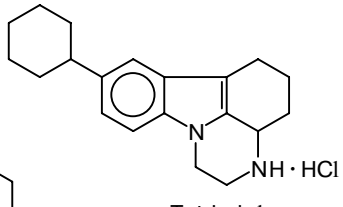
Iproniazid

Unfortunately, it was found that derivatives of isonicotinic acid hydrazide and a series of other MAO inhibitors irreversibly inactivate the enzyme and, although they exert clear-cut antidepressor action, they are highly toxic, cause liver malfunction, and are able to induce the so-called "cheese syndrome" manifested as hypertension, headache, *etc.,* caused by the vasoconstriction effect of compounds (for example tyramine) whose concentration increases upon MAO inhibition. For these reasons, most of irreversible and nonselective MAO inhibitors have now been excluded from the range of preparations meant for medical purposes as antidepressants. Only nialamide is used currently to a certain extent.

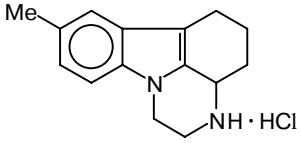


Nialamide

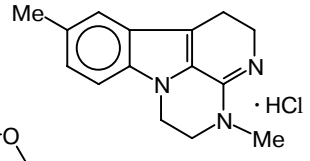
A great progress was attained by the discovery of a new generation of antidepressants, reversible MAO inhibitors. Pyrazidol, which has found wide application in medical practice, was the first representative of this group.[1,6,10] Other drugs of the same type of action are shown below:



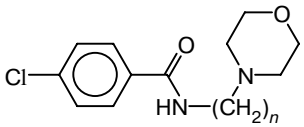
Tetrindole



Pyrazidol



Incazan

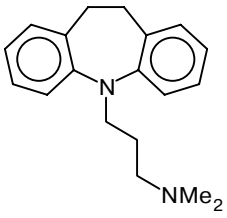


Befol, $n = 3$
Moclobemide, $n = 2$

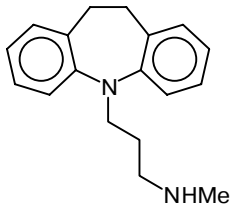
The essence of the activity of most of tricyclic antidepressants (see below) lies in inhibiting the neuronal reverse uptake of neuromediator amines, namely, noradrenaline, dopamine, and serotonin, which results in higher contents of these substances in the synaptic gap region but does not rule out their inactivation, for

instance, by monoamino oxidase. This approach appears more physiological and, indeed, antidepressants with tricyclic structures have occupied a firm place in the medical practice.

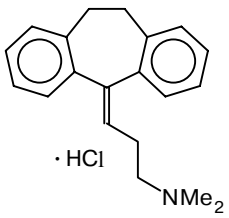
The selectivity in inhibition of the reverse uptake of one or another neuromediator plays a definite role in the degree of manifestation of particular biological effects. Thus it is considered that retardation of the neuronal reverse uptake of noradrenaline results, to a lager extent, in an increase in the psychomotor activity, while that for serotonin results rather in thymoleptic effect (mood brightening). The search for specific sites of binding of antidepressants was performed using [^{3}H]imipramine, which was found to be bound to brain tissue membranes. At present, it is claimed more and more frequently that the effect of antidepressants on cholinergic receptors and histaminergic (see below) brain systems also plays some role in their integrated action. The structures of most important tricyclic antidepressants are shown below:



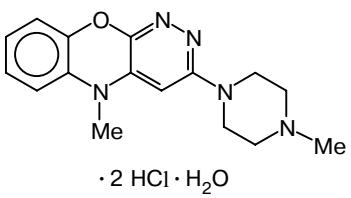
Imipramine



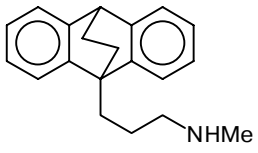
Desipramine



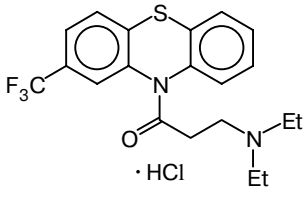
Amitriptiline



Azaphene



Maprotilin

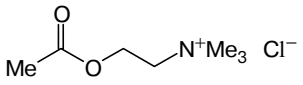


Phthoracizin

Neuromediators and receptors

All effects induced by drugs are either mediated by their interaction with particular systems, called receptors, or are based on liberation from depots of neuromediators, which subsequently act on these receptors.* It is clear that it is mediators that are most adapted structurally for the interaction with receptors, the most promising ways of the search for new drugs being based exactly on realization (and revealing) of structural similarity between new compounds and endogenic compounds, first of all, neuromediators.

Let us consider the most important neuromediators. The first one is acetylcholine, which is involved in the transfer of nerve excitation to the central nervous system, vegetative nerve-knots, and parasympathetic and motor nerve endings.



Acetylcholine chloride

During further discussion, it seems pertinent to consider in more detail the events taking place upon a nerve impulse, which causes evolution of mediators and mediator—receptor interactions, responsible, finally, for biological responses.

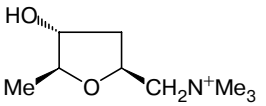
Most of nerve cells (neurons) possess definite properties, which follow from the presence of the main structural components of cells, namely, the cell body, normally shaped like a sphere or a pyramid, dendrites, which are sensitive sprouts serving for transferring a nerve impulse from the periphery to the cell body, and an axon, a nerve cell sprout along which the nerve impulse is transmitted to the periphery. In the synapse region,** axon expands and forms a synaptic platelet, a part of the contact serving for impulse transmission. The Na^+ concentration in the neuron-surrounding medium is much higher than the K^+ concentration, whereas inside the neuron, the situation is opposite. This difference between the ion concentrations on the different sides of a cytoplasmatic membrane gives rise to a negative membrane potential (resting potential) in nerve and muscular cells, *i.e.*, the membrane is a small battery with the negative pole inside. Upon a nerve impulse, the potential difference decreases, the local permeability of the membrane for sodium ions increases, and they enter the axon. The negative potential switches to a positive one, the sodium channels close, and the potassium channels open; the potassium ions come out and the resting potential is thus restored. As this takes place, the ion fluxes depolarize the adjacent section of the membrane, the process is repeated, and the nerve impulse spreads along the nerve fiber.

* Receptors are genetically determinate, mobile, and labile, most often, protein structures, whose functions are to "recognize" a chemical signal and to transform it subsequently into an adequate cell response. In other words, these receptors are material substrates for cell sensitivity and responsiveness.[4]

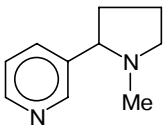
** Synapse is a specialized structure that ensures the transfer of a nerve impulse from the nerve fiber to some cell or muscle fiber or from a receptor cell to a nerve fiber; the space separating the presynaptic and postsynaptic membranes of the synapse, to which mediator is liberated upon a nerve impulse is referred to as the synaptic gap.

In the synapse, a nerve impulse induces liberation of a microquantity of a neuromediator from the presynaptic membrane; this diffuses to the synaptic gap and then interacts with the postsynaptic receptor, which is an effector structure determining the formation of the biological response. If the mediator involved is acetylcholine for which this process has been studied most comprehensively, it is noteworthy that liberation of the mediator is accompanied by generation of a current, which is transmitted to the external membrane of the neighboring muscle fibers. They transmit it inside by virtue of the Ca^{2+} ion reservoir in the sarcoplasmatic reticulum in which the ions are retained by the calsequesterin protein. The arising current induces the liberation of Ca^{2+} ions, which stimulate the subsequent muscle contraction. Similar processes take place upon liberation of noradrenaline. Acetylcholine is the main mediator in the nerve—muscle junction synapses, in ganglionary* sympathetic and parasympathetic synapses, and in postganglionary parasympathetic nerve endings. In postganglionary sympathetic endings, noradrenaline serves as the mediator.

It is very important that the directions of action of mediators in different anatomic units can be strictly opposite. Thus acetylcholine is an exciting mediator in the nerve—muscle junction (depolarization and excitation of nerve cells, contraction of skeletal and smooth muscles) and a retarding, inhibiting mediator in the cardiac muscle. Acetylcholine is a mediator not only at the periphery but in the central nervous system (CNS). The cholinergic receptor is a protein complex, called permease. It should be noted that there exist two sorts of cholinergic receptors, one of them being excited selectively by muscarine and the other, by nicotine. Nicotine is an agonist in the ganglionary and voluntary-muscle endings; it exerts a narcotic and euphoric effects (influence on the CNS) and mimics the action of acetylcholine in the nerve → muscle and nerve → nerve synapses. The nicotinic cholinergic receptor is glycoprotein with the molecular weight (M_w) >50000. It responds rapidly (more rapidly than the muscarinic receptor) to the appearance of a stimulus.



(+)-Muscarine (2*S*,3*R*,5*S*)



Nicotine

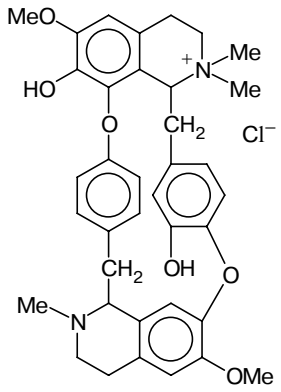
Carbacholine posseses nicotine-like properties; however, pure nicotine agonists are not used in medicine.

$Me_3N^+CH_2CH_2OCONH_2X^-$

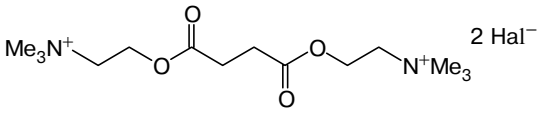
Carbacholine

* Ganglia is a bunch of neurons and nerve fibers, *i.e.*, nerve knots; sympathetic ganglia are located near the spinal cord, while parasympathetic ones are in the vicinity of the organ being innervated.

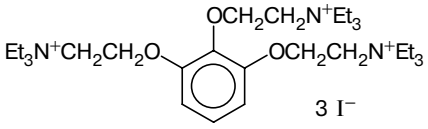
Conversely, antagonists of nicotinic receptors are widely used in surgery. Their use permits a powerful muscle relaxation and, correspondingly, a decrease in the doses of general anaesthetics. These include tubocurarine, dithylinum, gallamine.



Tubocurarine

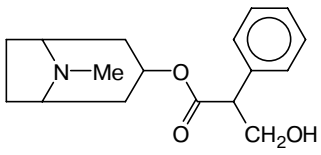


Dithylinum



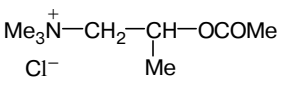
Gallamine

Muscarine mimics the action of acetylcholine, mainly, in parasympathetic postganglionary synapses. The muscarinic receptor (isolated from bovine brain) is actively blocked by a specific agonist, atropine, which is reversibly bound to the receptor and can be displaced by acetylcholine.

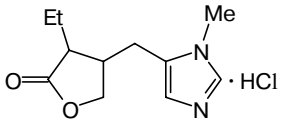


Atropine

Methacholine and pilocarpine are the most typical agonists of muscarinic receptors. Methacholine has an advantage over acetylcholine, namely, it is slowly hydrolyzed by acetylcholine esterase.



Methacholine



Pilocarpine

Speaking about acetylcholine and cholinergic receptors, one should mention acetylcholine esterase, the main enzyme that inactivates acetylcholine. In particular, after liberation of acetylcholine in the synapse and muscle contraction, the excess mediator is destroyed by this enzyme (about $1.5 \cdot 10^{-10}$ mg, *i.e.*, $5 \cdot 10^6$ molecules of acetylcholine per pulse is liberated). Acetylcholine esterase has a basic group with pK_a 7.2 (this might be the imidazole ring of the histidine residue) and an acidic group with pK_a 9.3 (probably, the tyrosyne residue).

Now we consider some data on receptors of another type, namely, adrenergic receptors.[4,15] As has already been noted, (*R*)-noradrenaline is the main mediator of the adrenergic system. Previously, the mediator role has been ascribed to (*R*)-adrenaline, which actually participates to some extent in the transfer of nerve excitation but its major role is that of a hormone involved in various metabolic processes; adrenaline is mainly evolved into tissues rather than to the synaptic gap, where interaction with the receptor takes place.

Adrenergic receptors are classified into two large groups referred to as α- and β-receptors. In terms of the effect strength, substances acting directly on these receptors can be arranged in the following sequences:

α-receptors:

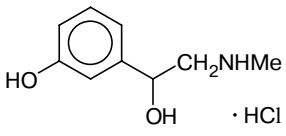
noradrenaline > adrenaline > izadrin > *N*-*tert*-butylnoradrenaline;

β-receptors:

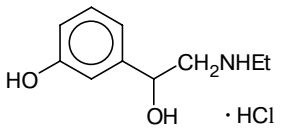
N-*tert*-butylnoradrenaline > izadrin > adrenaline > noradrenaline.

In other words, an increase in the size of the alkyl radical at the nitrogen atom, *i.e.*, an increase in the lipophilicity, enhances the activity toward β-receptors and weakens the action on α-adrenergic receptors. A natural agonist of α-adrenergic receptors is noradrenaline. α-Adrenergic receptors are contained in various tissues; they are largely localized in blood vessels. The action on α-receptors in smooth muscles increases the permeability of cell membranes for inorganic ions. For example, permeability for potassium ions in the intestinal muscles increases, resulting in muscle hyperpolarization and relaxation. In other types of smooth muscles, permeability for Na^+ and Ca^{2+} increases. The activation of presynaptic α-adrenergic receptors entails vesoconstriction and pressor effect, *i.e.*, hypertension. It has now been established that α-receptors (as well as β-receptors) can be divided into two subgroups, namely, α_1- and α_2-receptors. The α_1-adrenergic receptors are mainly localized postsynaptically, while α_2-adrenergic receptors are localized presynaptically (or, in some cases, postsynaptically).

α_1-Adrenergic mimetics (stimulants) exert a vasoconstrictor effect; they are used to increase blood pressure against hypotonia and to exert a general vasoconstrictor effect against rhinites or conjunctivites. A typical representative of this group is mesaton, which acts more weakly than the mediator, noradrenaline, but has a more prolonged effect and, what is very important, it does not stimulate the central nervous system. A similar type of action is found for phethanol.

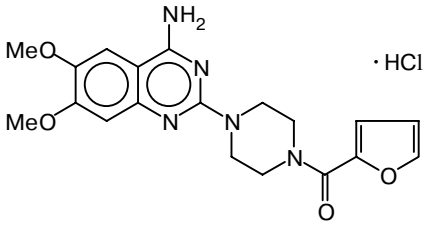


Mesaton

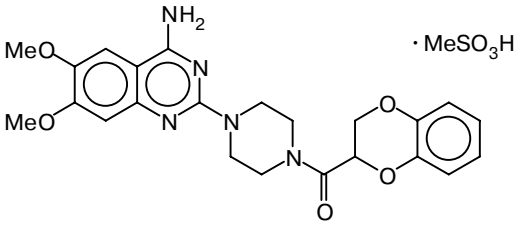


Phethanol

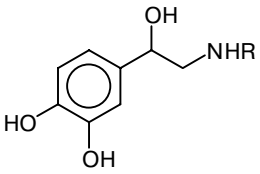
It is clear that α_1-adrenergic blockers exhibit an opposite effect, *i.e.*, they induce dilation of peripheral vessels and are used to treat hypertension. Prazosin and doxazosin are typical drugs of this series, which block the stimulating effect of noradrenaline on vessel α_1-adrenergic receptors and induce vasorelaxation. These preparations are used to treat various forms of hypertension and miction disorders in patients with prostate hyperplasia.



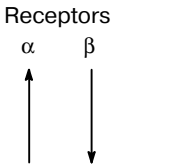
Prazosin



Doxazosin

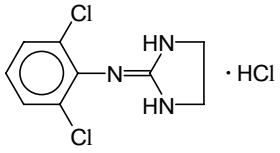


R = H, Noradrenaline
R = Me, Adrenaline
R = $CHMe_2$, Izadrin
R = CMe_3, *tert*-Butylnoradrenaline

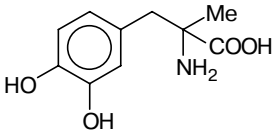


The arrows point to the increase in the activity

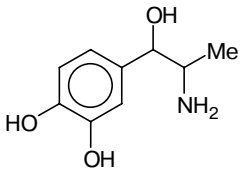
Stimulation of α_2-adrenergic receptors results in adenylate cyclase inhibiting (this requires guanosine triphosphate), decrease in the cAMP level (note that stimulation of α_1-receptors does not affect adenylate cyclase but induces the appearance of a nerve impulse due to liberation of calcium ions). The main representatives of α_2-adrenergic stimulants are the clonidine (clofelin) and methyl-DOPA (Dopegyt) preparations.



Clonidine (Clofelin)



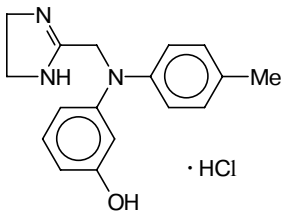
α-Methyl-DOPA (Dopegyt)



α-Methylnoradrenaline

The major application of these drugs is related to their hypotensive effect. First, these drugs induce a short-term pressor effect and then a hypotensive effect, determined by stimulation of the α_2-receptors of brain vasomotor centers, a decrease in impulses from the CNS to blood vessels, and a decrease in the amount of noradrenaline evolved from nerve endings. It is noteworthy that α-methyl-DOPA is actually a prodrug. This preparation passes the BBB and undergoes enzymatic decarboxylation and hydroxylation, being thus converted into α-methylnoradrenaline, which stimulates α_2-adrenergic receptors.

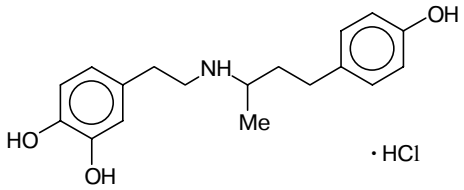
When considering α_2-adrenergic blockers, one should mention phentolamine, which is not, however, a selective drug and inhibits both α_1- and α_2-adrenergic receptors.



Phentolamine

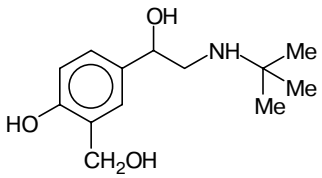
Whereas the typical effects of α-adrenergic receptor stimulation include vasoconstriction, uterus stimulation, and intestinal relaxation, the β-effects include vasorelaxation, uterus muscle relaxation, stimulation of glycogenolysis in muscles, and tachycardia. The β-receptor subtypes are called β_1- and β_2-receptors.

The group of nonselective β-adrenergic stimulants (β_1 and β_2) includes, first of all, *N*-isopropylnoradrenaline (isoproterenol, izadrin), which is a bronchus dilator. β_1-Adrenergic receptor stimulants increase the heart rate and the strength of cardiac contractions, induce distention of coronary vessels, and relax the smooth muscles of the intestines. Dobutamine is a selective β_1-adrenergic stimulant.

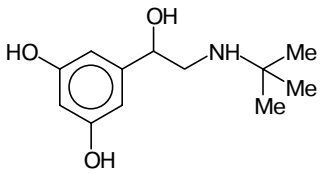


Dobutamine

β_2-Adrenergic receptor stimulants serve for the relaxation of smooth muscles of the bronchi, uterus, and arteries that go to skeletal muscles. Examples of effective β_2-adreno mimetics are salbutamol and terbutaline.



Salbutamol

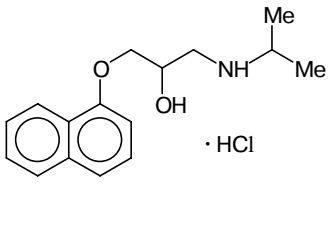


Terbutaline

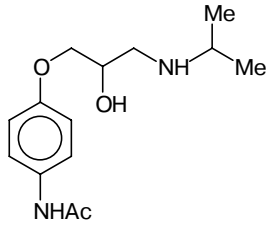
Attention is attracted by the fact that a highly lipophilic substituent must be present at the nitrogen atom (indeed, there exist data that the environment of β_1-receptors is less lipophilic than that of β_2-receptors). One more important conclusion drawn from examination of the structure of β_2-adrenergic stimulants is the decision to avoid a catechol residue as a structural fragment during their synthesis because catecholamines are known to be readily inactivated in an organism under the action of the catechol-*O*-methyl transferase (COMT) enzyme. This approach resulted in highly effective drugs.

At present, β-adrenergic blockers represent one of the major means for treatment and prevention of the ischemic disease, hypertension, and arrhythmia. The effects of β_1-adrenergic blockers include retardation of the heart rate, economization of the myocardium functions, and curing of ischemia, hypertension, and arrhythmia, while those of β_2-adrenergic blockers include contraction of the bronchus smooth muscles and constriction of peripheral vessels. Stimulation of β_1- and β_2-receptors induces adenylate cyclase activation and

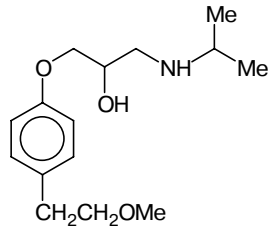
cAMP synthesis involving guanosine triphosphate (the receptors and adenylate cyclase are arranged close to each other; the former are at the external, while the latter are at the internal membrane surface). The antagonists of these receptors (β-adrenergic blockers) inhibit binding of the mediator to the receptor but does not block adenylate cyclase (note that cAMP causes effects similar to those caused by catecholamines). The first β-adrenergic blocker used in practice is propranolol, which is a nonselective preparation that blocks simultaneously β_1- and β_2-adrenergic receptors. Practolol was the first selective (cardioselective) β_1-blocker; later, atenolol and metoprolol have appeared.



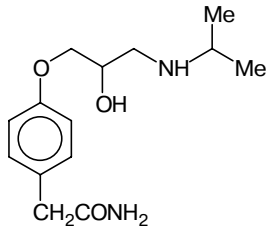
Propranolol (Anaprilin)



Practolol

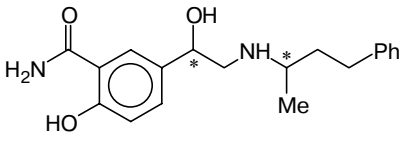


Metoprolol



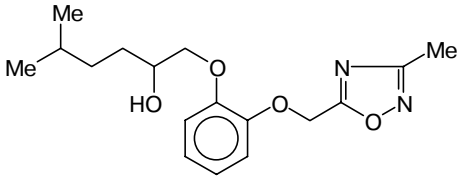
Atenolol

The development of "hybrid" adrenergic blockers acting simultaneously on β- and α-receptors has been a fairly important achievement. Indeed, the α_1-blocking activity (for example, of prazosin) causes side effects such as orthostatic collapse and reflex tachycardia. β-Adrenergic blockers tend to decrease the heart rate, to retard the cardiac contractions and to increase somewhat the peripheral resistance. When labetalol (α_1,β-blocker) is used, the side effects cancel out.



Labetalol

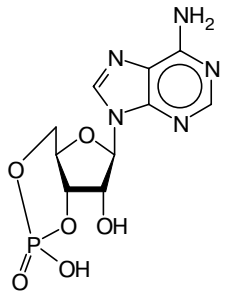
In addition, due to the α-adrenergic receptor blockade, (α+β)-adrenergic blockers have a faster and stronger hypotensive effect; they are used both to treat the ischemic disease and to stop hypertension strokes. Yet another "hybrid" (α+β)-preparation is proxodolol, which has an antiarrhythmic and antihypertensive effects (regarding the latter effect, it surpasses labetalol) and is used in cardiological practice.



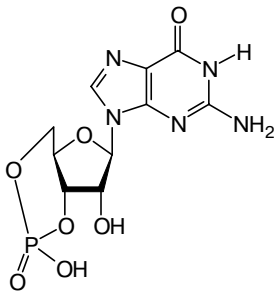
Proxodolol

The foregoing can be summarized in a Table (Table 2).

It appeared pertinent to give here a brief description of so-called secondary messengers, namely cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP).



cAMP

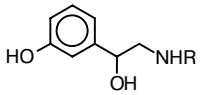
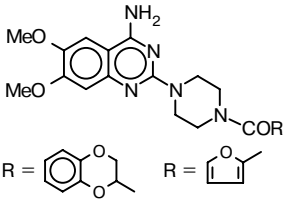
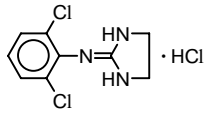
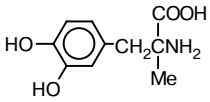
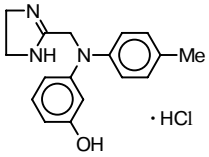
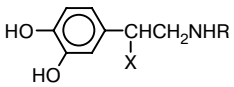
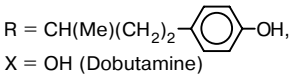
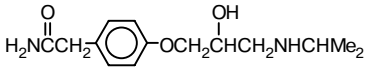
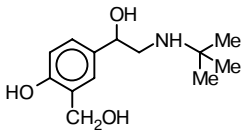
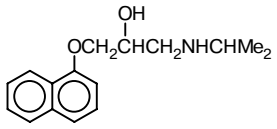


cGMP

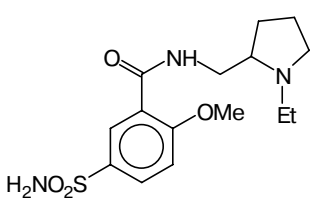
The liberation of cAMP, induced indirectly by catecholamines, results in activation of the protein kinase enzyme, which phosphorylates the specific protein located on the postsynaptic membrane; as a consequence, channels for inorganic cations are opened. Similar effects are also typical of cGMP, both compounds functioning as secondary messengers not only for catecholamines but also for hormones. Opening of the channels gives rise to postsynaptic potentials (as described for mediators), which is responsible for the mediator action of cAMP and cGMP. Note that both cyclic nucleotides play an important role in the control of insulin evolution from the pancreas.

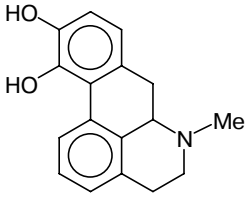
Dopamine is also a neuromediator involved in the transmission of nerve excitation, especially in the central nervous system. In addition, dopamine is a precursor in the biosynthesis of noradrenaline and, further, of adrenaline. Dopamine stimulates the native D_1- and D_2-receptors (D_3- and D_4-receptors are also distinguished but they have been much less studied, see Ref. 17), these receptors being located both in the CNS and at the periphery; they are abundant and play a critical role in controlling many important functions of an organism. The activation of D_1-receptors results in the activation of adenylate cyclase, whereas D_2-receptors are not coupled with adenylate cyclase. The stimulation of D_1-receptors brings about muscle relaxation and vessel dilation. Apomorphine is a weak agonist of

Table 2. α- and β-Adrenergic stimulants and α- and β-adrenergic blockers

Receptors	Stimulation		Blockade	
	Effect	Agonist	Effect	Antagonist
α_1	Vasoconstriction, pressor effect	 R = Me, Mesaton R = Et, Phethanol	Decrease in blood pressure, treatment of hypertension	 Doxazosin Prazosin
α_2	Short-term pressor effect and long-term hypotensive effect	 Clonidine (Clofelin)  α-Methyl-DOPA (Dopegyt)	Vasodilation and hypotensive effect	 Phentolamine
β_1	Increase in the heart contraction strength, coronary vessel dilation	 R = Pr^i, X = OH (Izadrin)  X = OH (Dobutamine)	Decrease in the heart rate and heart contraction strength, treatment of hypertension and ischemic disease	 Atenolol
β_2	Bronchus dilation	 Salbutamol	Increase in the bronchus tone, vasorelaxation	 Anaprilin

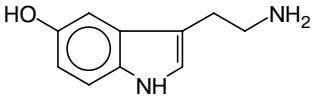
D_1-receptors; sulpiride is a strong antagonist. In addition, sulpiride is a D_2-receptor antagonist, which accounts apparently for its neuroleptic activity.

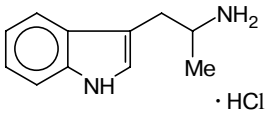

Sulpiride


Apomorphine

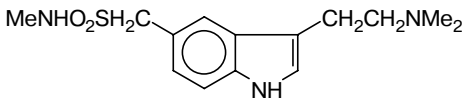
The stimulation of D_2-receptors entails inhibiting of the effect of noradrenaline, unlike that of D_1-receptors; Apomorphine is a strong agonist of D_2-receptors. It is the dopamine deficiency and disorder of the central dopaminergic processes that are considered to be responsible for parkinsonism (see above), which has been the reason for using L-DOPA to treat it (dopamine cannot be used for this purpose because it does not cross the BBB). L-DOPA penetrates through this barrier into the brain, undergoes there decarboxylation, and this replenishes the dopamine stock in the brain. There exists an opinion that schizophrenia is due to a metabolism disorder, resulting in excess dopamine in the brain.

A fundamental progress in neuropharmacology is related to the discovery of the mediator role of serotonin.

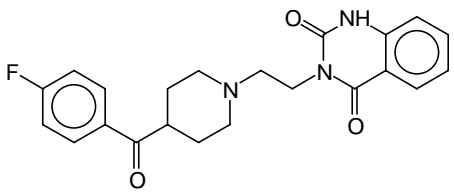

Serotonin


Indopan

Three types of serotonin receptors, 5-HT_1, 5-HT_2, and 5-HT_3, are localized in peripheral organs and in the central nervous system. The endogenic and exogenic serotonin induces contraction of the smooth muscles of blood vessels, gastrointestinal tract, and bronchi, constriction of the peripheral vessels, an increase in the blood pressure, tissue edema, and blood coagulation. A serotonin receptor agonist, indopan, which is structurally related to serotonin, has a psychoactivating and antidepressive action. Another agonist of serotonin 5-HT_1-receptors, sumatriptan, is used as a remedy against migraine, while a serotonin 5-HT_2-receptor blocker, ketanserin, is an antihypertensive remedy.

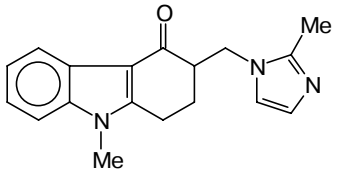


Sumatriptan

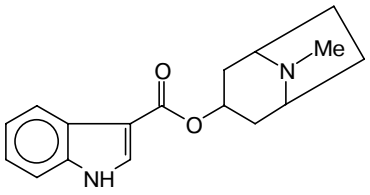


Ketanserin

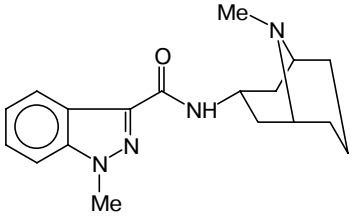
Antiemetics, namely, navoban, zofran, and granisetron, which block 5-HT_3-serotonin receptors, become more and more important, especially in oncology. These drugs are used for prevention and therapy of the complications caused by chemo- and radiotherapy; at present, they have found wide application in clinical practice.



Ondasetron (Zofran, Latran)

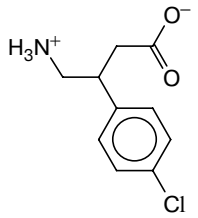


Navoban (Tropisetron)

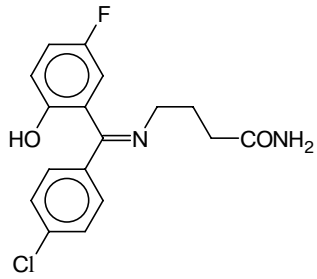


Granisetron

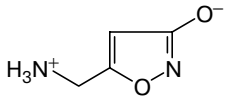
γ-Aminobutyric acid (GABA) is an inhibiting mediator of the CNS and a nerve impulse transferer in the system of inhibitory neurons (glycine and taurine are also inhibitory transferers of this type) in the immediate proximity to the spinal cord; it participates in presynaptic inhibiting processes (GABA is an inhibitory mediator in twelve spinal cord structures). Note that a special monograph has been devoted to mediator amino acids.[12] The pharmacological activity of GABA is related to the influence on the receptor complex incorporating a receptor for GABA, a receptor for benzodiazepines, and a receptor section that binds picrotoxine. These receptors are arranged around the entrance of the channel for Cl ions. Among GABA-receptor agonists, one should mention baclofen, progabide, and muscimol.



Baclofen

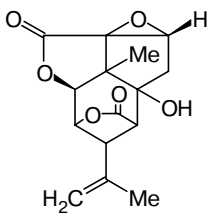


Progabide

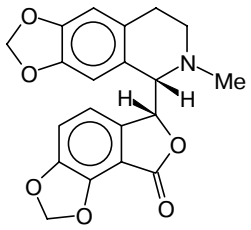


Muscimol

The GABA antagonists include, first of all, the picrotoxine (whose active component is picrotoxinin) and bicuculine alkaloids, which induce cramps.

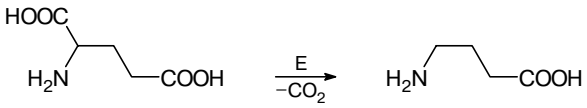


Picrotoxine



Bicuculine

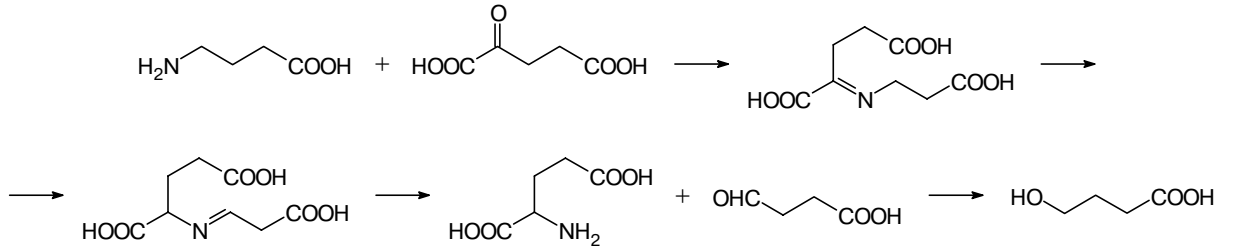
An important physiological function of GABA is to control the brain excitability; the GABA-ergic mediation participates in the formation of the behavioral responses; in particular, it suppresses aggressive behavior. GABA is formed in an organism *via* decarboxylation of L-glutamic acid induced by the glutamate decarboxylase enzyme.[12]



L-Glutamic acid GABA

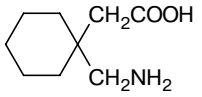
E is glutamate decarboxylase

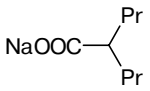
Scheme 1

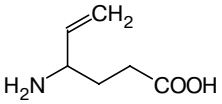


The main metabolic route of GABA in nerve tissue is transamination involving α-ketoglutaric acid. This process is catalyzed by a pyridoxal-dependent enzyme, namely, GABA-transaminase (GABA-T). Transamination furnishes glutamic acid, which is a metabolic precursor of GABA, and succinic hemialdehyde, converted subsequently into γ-hydroxybutyric acid, which is an antihypoxic remedy (Scheme 1).[3,12]

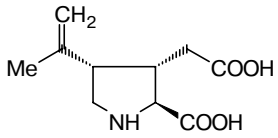
It is this GABA inactivation that became the target process in the investigations directed at the accumulation of the mediator in brain tissues in order to increase its neural inhibitory activity. A search for GABA-T blockers resulted in a series of compounds exhibiting high antiepileptic activity, namely, sodium valproate, gabapentin, and vigabatrin.

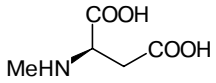

Gabapentin

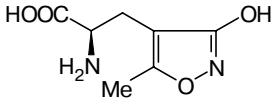

Sodium valproate


Vigabatrin

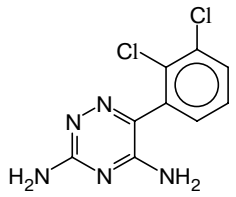
Let us consider briefly the exciting amino acids. It is believed currently that 70% of the central synapses meant for CNS stimulation use L-glutamic acid as the mediator. Excess accumulation of this mediator can induce irreversible damage of neurons and serious pathologies such as Alzheimer's disease, insults, *etc.* The action of glutamic acid is mediated by participation of three types of receptors, kainate receptors (kainic acid is the agonist), HMDA-receptors (*N*-methyl-D-aspartic acid is the agonist), and AMPA-receptors ((*S*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid is the agonist). New investigations devoted to the synthesis of inhibitors of these receptors, which often exhibit pronounced antispasmodic activity, have been described in a number of publications.[18–23] In addition, special glutamate receptors exist.


Kainic acid


N-Methyl-D-aspartic acid


(*S*)-2-Amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propionic acid

The blockade of HMDA-receptors decreases the Ca^{2+} entry into nerve cells, which protects them from damage, and has a therapeutic effect against various CNS diseases. The depression of the central stimulating action of the glutamate stabilizes presynaptic neuronal membranes, blocks the potential-dependent sodium channels, and prevents liberation of exciting amino acids, *i.e.,* glutamic and aspartic acids. The use of this approach culminated in the synthesis of a new highly effective antiepileptic drug called lamotrigin, which inhibits the liberation of these amino acids.[1,6,13]


Lamotrigin

It is worth noting that agonists of AMPA and kainate receptors exhibit high activities as convulsants; recently, a series of compounds with this type of action have been discovered.[24]

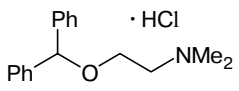
The benzodiazepine receptor to which benzodiazepine drugs are linked is located in the close vicinity of the GABA-binding site. Upon binding, they increase the permeability of neuronal membranes for chloride ions and enhance the GABA-induced stabilization of the cell electric potential, thus decreasing cell excitability.

In the case of some pathologies, for example, anaphylactic shock, burns, or allergic diseases, hystamine is liberated in the organism; it induces a spasm of smooth

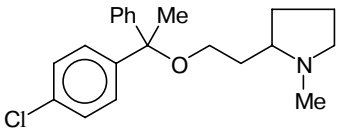
muscles (including bronchus muscles), a decrease in blood pressure, quickening of cardiac contractions, enhancement of gastric juice secretion, and so on. Histamine acts as a mediator in the CNS.

Three types of histamine receptors are distinguished, namely, H_1-, H_2-, and H_3-receptors. Stimulation of H_1-receptors causes spastic contraction of bronchus and intestinal muscles (H_1-peripheral receptors). Stimulation of H_2-receptors promotes secretion of the gastric glands; these receptors participate in the regulation of the uterine, intestinal, and vessel smooth muscle tones. Simultaneously, the H_2-receptors are involved in the mediation of excitation in the CNS (note that H_1- and H_2-receptors play a role in the development of allergic and immune responses). Stimulation of H_3-receptors ensures the central action of histamine.

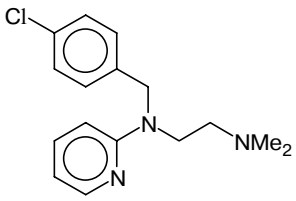
Among H_1-receptor blockers, there exists a large group of effective antiallergic substances, *viz.*, dimedrol, tavegil, suprastin, claritin, phencarol, and bicarphen.



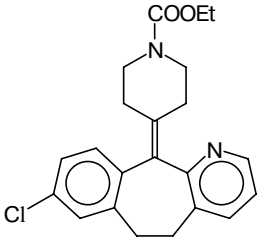
Dimedrol



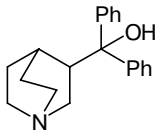
Tavegil



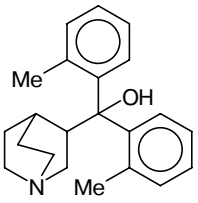
Suprastin



Claritin



Phencarol

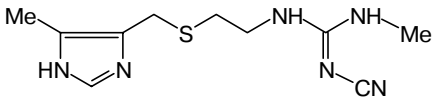


Bicarphen

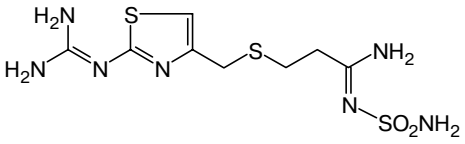
Antiulcer drugs, cimetidine, ranitidine, and famotidine are H_2-receptor blockers.

These compounds depress gastric secretion; famotodine is the most active in inhibiting hydrochloric acid secretion.

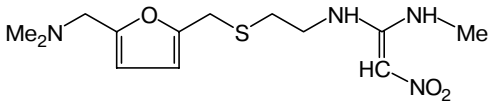
Now we will briefly consider the so-called opiate receptors, which are responsible for the depression of pain sensitivity centers and for the blocking of impulses in the cerebral cortex upon the action of analgesics. The existence of opiate receptors in brain has been demonsrated (in experiments with mice) in a study of



Cimetidine

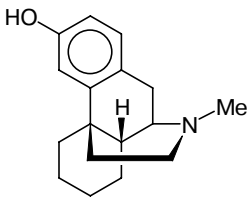


Famotidine

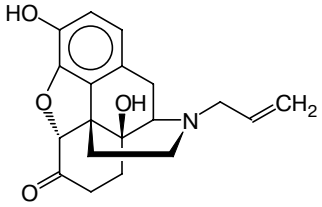


Ranitidine

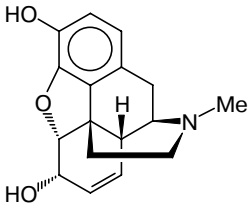
the stereospecific interaction of morphine analogs, *viz.*, levorphanol agonist and naloxone antagonist, with subcell structures in the brain.



Levorphanol



Naloxone

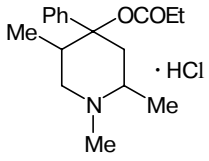


Morphine

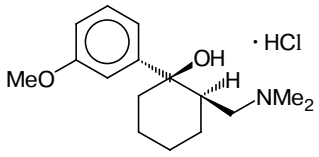
A lipoprotein with a molecular weight (M_w) of 60 000 has been isolated and it was suggested that the agonist (but not the antagonist) induces conformational changes in it, resulting in analgesia (anesthetizing) being the biological response. The endogenous ligands of opiate receptors are represented by neuropeptides, *viz.*, enkephalins (pentapeptides) and endorphins (more complex peptides). Enkephalins and endorphins bind to opiate receptors and have an analgesic effect. This effect is blocked by opiate antagonists, which is a typical feature of agonists. It has been suggested that many exogenous analgesics (but not morphine, which interacts with opiate receptors) are not linked to the receptors themselves but act as inhibitors of enkephalinase, *i.e.*, the enzyme that destroys enkephalins by abstracting the Gly-Phe fragment from them. Thus, these analge-

sics increase the level of endogenous enkephalins and exert an anesthetic effect.

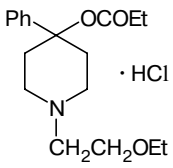
Another series of endogenic analgesic polypeptides are endorphins, which are formed upon hydrolysis of lipotropin in the brain. The most active of these, β-endorphin, which is twice as active as morphine, induces more long-term analgesia, which is removed by naloxone. Some researchers treat enkephalins as neuromediators, and β-endorphin is treated as a hormone that depresses liberation of other neuromediators. Generally speaking, analgesics start to be evolved in a human organism only as the response to pain, *i.e.*, their interaction with opiate receptors can be regarded as a compensatory effect. Mammals have several types of opiate receptors; the most important are μ-receptors through which the analgesic effect of morphine is mediated. Near μ-receptors, δ-receptors are localized. β-Endorphin is able to bind to both types of receptors, whereas enkephalins interact mainly with δ-receptors. Research into the action of opiates led to the conclusion that morphine inhibits adenylate cyclase; the removal of morphine entails strong activation of this enzyme and, as a consequence, the amount of cAMP sharply increases. Generally known is a fairly unpleasant effect of morphine and its analogs, namely, the addiction (psychological dependence). Therefore, much effort has been spent for the search for analgesics that cause no euphoria. Unfortunately, other analgesics such as promedol, tramadol, and a relatively new drug, prosidol, also possess this feature.



Promedol



Tramadol



Prosidol

Inhibitors of the angiotensine-converting enzyme

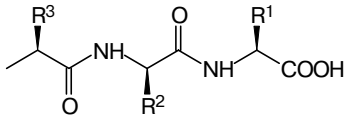
One of the most effective ways of the search for new drugs is to find new enzyme inhibitors, whose high activity in an organism is responsible for particular pathological states. Within the framework of this paper, it is impossible to discuss this point in any detail. Therefore, we will limit ourselves to only one, though quite impressive, example. This is the development of the angiotensine-converting enzyme inhibitors.[25,26] The system that maintains the blood pressure in an organism (kinin system) is responsible for the production of a powerful pressor octapeptide, angiotensine-II, from relatively inactive angiotensine-I.

Asp—Arg—Val—Tyr—Ile—His—Pro—Phe—His—Leu
Angiotensine-I

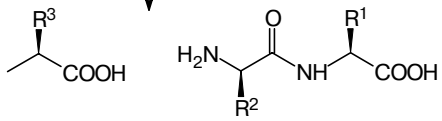
↓

Asp—Arg—Val—Tyr—Ile—His—Pro—Phe
Angiotensine-II

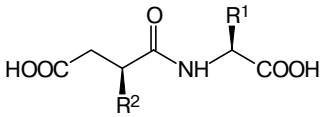
The key enzyme in this transformation is angiotensine-converting enzyme (ACE), which is a regulatory enzyme. This means that it is the products of the enzymatic reaction that act as its inhibitor (in the case where their concentration exceeds the normal concentration needed for functioning of the organism, the opposite relation is observed). The general scheme of the ACE-involving enzymatic process is as follows:



Substrate

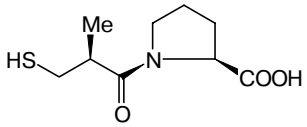


Enzymic reaction products



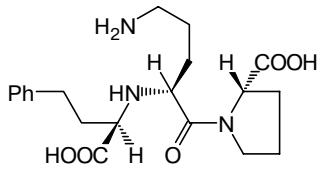
The putative inhibitor

The purpose of the study was to create a structure close to the products of enzymatic reaction and unable to undergo further enzymatic transformations but capable of substituting the substrate in binding to the enzyme, due to the similarity with the substrate, thus blocking (or retarding) the processes of its transformation. Without dwelling on each stage of the study performed, we would like to note that the first effective ACE-inhibiting drug introduced in broad medical practice was capoten (captopril).[25,26]

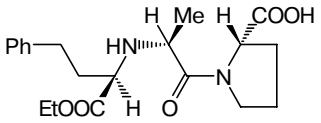


Capoten (Captopril)

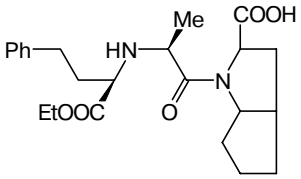
This drug is highly efficient against hypertension and has virtually no influence on normotensive people or



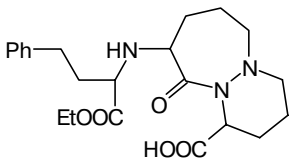
Lisinopril



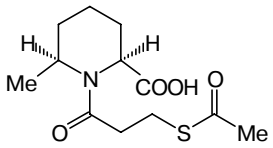
Enalapril



Ramipril



Cilasapril



Metiapril

animals. Detailed analysis of the structure—biological activity relationships, which concerns also stereochemical features of the captopril structure, deserves attention. Table 3 presents data on the change in the degree of enzyme inhibition upon the variation of substituents in the captopril structure.

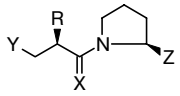
These data point to the enormous role of the SH groups of the terminal fragment, the C=O group, and the L-COOH group. The presence of D-Me is also significant; the removal of this group decreases the activity by an order of magnitude. Other groups able to be coordinated to the Zn^{2+} cation located in the enzyme active site were tested in place of the SH group (it is the strength of the above-mentioned interaction that determines the I_{50} value). The best results were attained with the following substituents: SH (captopril) and NHP(O)(OH)OPh. The stereochemistry of the optical centers is very important; replacement of L-proline by D-proline decreases the activity by 4 orders of magnitude (by a factor of 10000), and replacement of D-Me by L-Me results in a compound an order of magnitude (10 times) less active than captopril.

Thus, the steric factor is exceptionally important for the interaction of neuromediators with the corresponding receptors, for the displacement of mediators from the binding sites to the depot and violation of their reverse uptake, and for the interaction of biologically active compounds with enzymes.

Of other preparations close to captopril in action and more or less related to it structurally, we would like to mention enalapril, lisinopril, ramipril, cilasapril, and metiapril[1].

They all are ACE inhibitors and are used to treat various forms of arterial hypertension.

Table 3.[25,26] Inhibitory activity of captopril derivatives and analogs



X	Y	Z	R	I_{50} (mmol L^{-1})*
O	COOH	L-COOH	H	330
O	COOH	L-COOH	D-Me	22
O	SH	L-COOH	H	0.15
O**	SH	L-COOH	D-Me	0.023
O	SH	H	D-Me	250
H_2	SH	L-COOH	H	240
O	OH	L-COOH	H	>4000

* I_{50} is the concentration inducing a 50% inhibition of the activity of the ACE from rabbit lungs.
** Captopril.

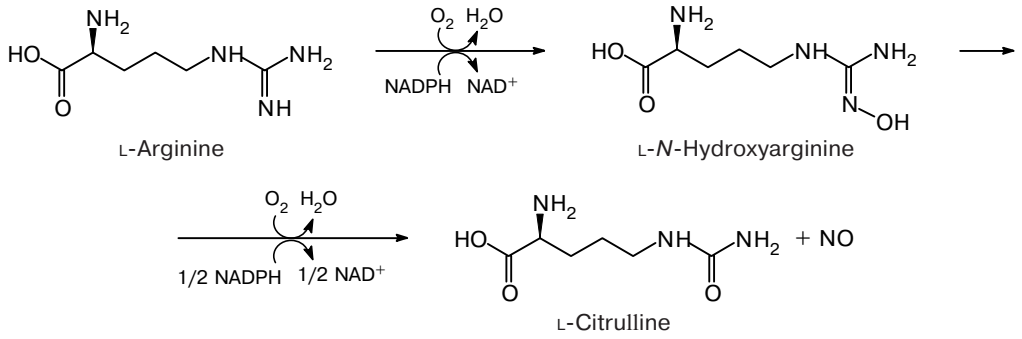
The role of nitric oxide in pharmacology and medicinal chemistry

In conclusion, it appears important to give at least a brief information concerning a new field of pharmacology and medicinal chemistry related to the discovery of one of the most important endogenous substances, nitrogen(II) oxide.[27—31]

Nitric oxide plays an important role in functioning of the vascular system as an endogenous relaxing drug. The liberation of nitric oxide in blood vessels from endothelial cells is due to the increase of the internal level of calcium ions, which initiates biosynthesis of NO. Nitric oxide diffuses to neighboring cells and causes activation of enzymes, namely, soluble guanylate cyclase (SGC), which promotes the transformation of guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP). An increase in the amount of the secondary messenger, cGMP, in a cell causes vasorelaxation and, finally, decrease in the blood pressure. Other important functions of nitric oxide include inhibition of thrombocyte aggregation and positive influence on the immune system, CNS, and the peripheral nervous system. Thus, NO plays a key role in the vascular tone control, participates in the maintenance of the cardiovascular homeostasis,* in the control of

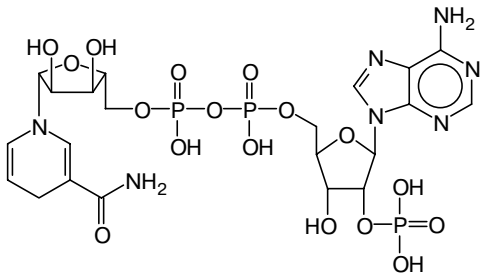
* Homeostasis is a relative dynamic invariability of the internal environment, *i.e.*, blood, lymph, tissue fluid, and stability of the main physiological functions: blood circulation, breathing, heat regulation, metabolism, *etc.* in an organism.

Scheme 2



respiration and immunity, and in the neurotransmitting mechanisms; it is a cytotoxic and cytostatic agent. A whole series of pathological states, for example, cardiovascular, infectious, and inflammatory diseases, thromboses, malignant tumors, urogenital diseases, cerebral disorder upon insults, and so on, can be largely related to either deficiency or overproduction of nitric oxide in the organism. The NO biosynthesis is a result of L-arginine oxidation catalyzed by the NO-synthase enzyme. Two major forms of NO-synthase (NOS) have been described in the literature, namely, the constitutive NOS (c-NOS), which is located in the vascular endothelium and in the brain, and inducible NOS (i-NOS), localized in activated macrophages, *i.e.*, cells capable of active capture and digestion of bacteria, cell remains, and other foreign and toxic species.* The constitutive isoform requires the presence of calcium ions and the calmodulin protein for activation and is subdivided into endothelial and neuronal ones (depending on localization). The former generates NO, which has an influence on the decrease in the blood pressure and thrombocyte aggregation, while the latter (the neuronal enzyme) acts as a neurotransmitter. The main function of i-NOS is immune protection of the organism, *i.e.,* synthesis of nitrogen oxide as a cytotoxic and an antiinflammatory agent. The scheme of NO biosynthesis has been studied fairly comprehensively and looks as follows (Scheme 2) [27,28,30,31].

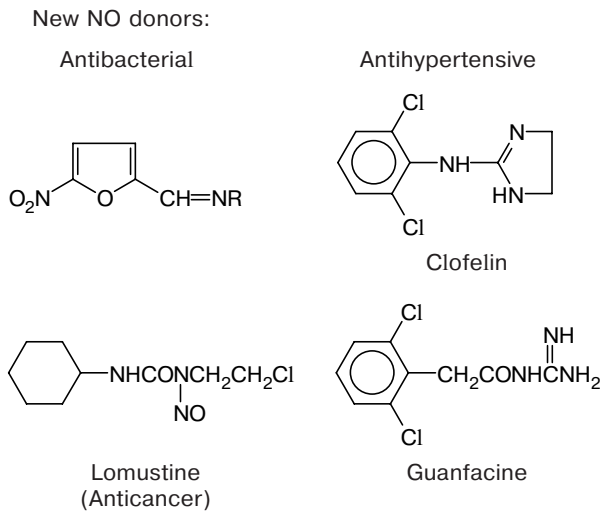
Note that oxidation occurs stereospecifically and only L-arginine (but not D-isomer) is capable of being transformed into NO under the action of NOS. It can be seen from the Scheme that L-*N*-hydroxyarginine is the intermediate product in this process, while L-citrulline is the final process. It was established that the transformation of L-arginine occurs in two steps, the first step, which requires the participation of NADPH and oxygen, yields L-*N*-hydroxyarginine, while the second one, which requires the presence of BH_4 (tetrahydrobiopterin), oxygen, and 0.5 equiv. of NADPH, gives rise to nitric oxide and L-citrulline.



NADPH

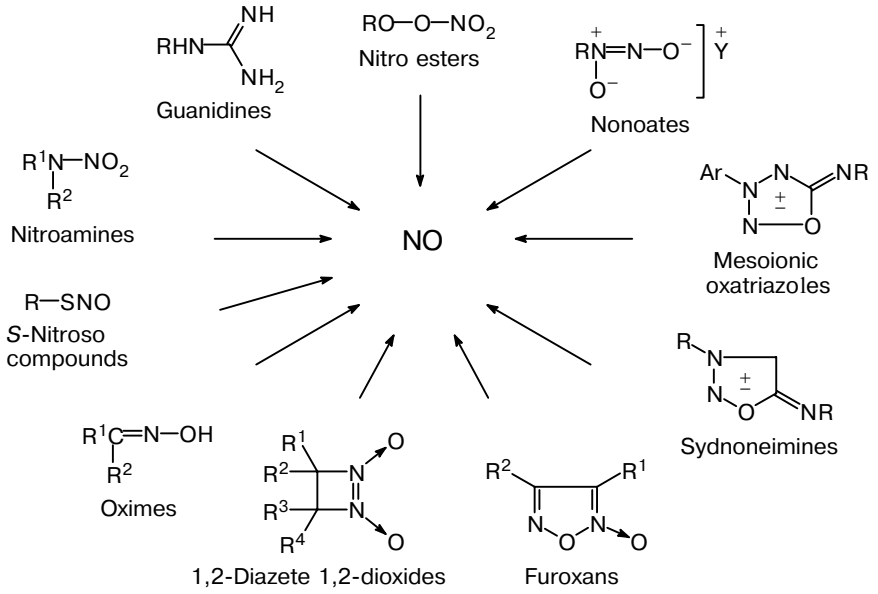
One line of research being actively developed now is the search for various compounds able to serve as nitric oxide generators in the organism, *i.e.*, the search for xenobiotics, whose transformations can result in the formation of NO. The scheme 3 shows the main types of NO donors discovered to date.

A series of new nitric oxide donors has been found recently among known drugs[32,33] and, although it is still unclear whether the main activity of these drugs is related to their NO-donor activity, the mere fact of such a possibility prompts the necessity of detailed analysis of the accepted views on the mechanism of their action.

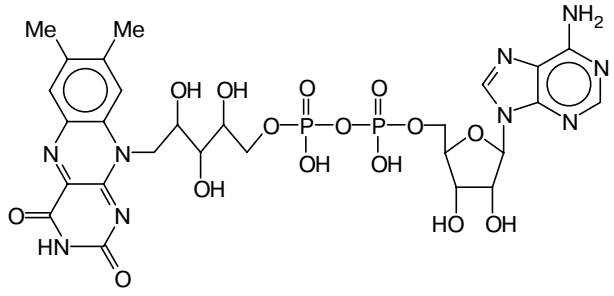


* Constitutive enzymes are those enzymes that occur in cells in constant amounts, irrespective of the metabolic state of the organism. Conversely, the concentrations of inducible (or induced) enzymes in a cell changes; normally, they are present in trace amounts; however, upon the addition of a substrate, the concentration can increase by more than 3 orders of magnitude.

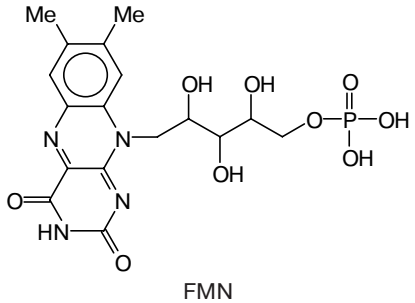
Scheme 3



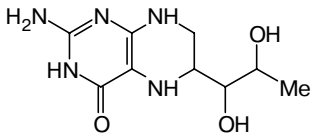
When we speak about nitric oxide donors, the problem is in the way of increasing the amount of nitric oxide in organs and tissues provided that its production in a living organism is insufficient. However, a number of pathological states including cardiovascular diseases, infections, and brain disorders are caused by excess liberation of NO. Undesirable toxicological effects of NO overproduction include extremal hypotension and/or cardiovascular collapse,* cell damage, and the septic shock.** Therefore, in some cases, in is necessary to inhibit the NOS. As noted above, the synthesis of nitrogen oxide is catalyzed by the c-NOS and i-NOS isoforms. All the enzyme isoforms contain FAD (flavin adenine dinucleotide), FMN (flavin mononucleotide), and heme iron as prosthetic groups and require the BH_4 co-factor (5,6,7,8-tetrahydrobiopterin).



FAD

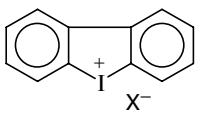


FMN

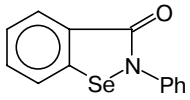


5,6,7,8-Tetrahydrobiopterin (BH_4)

Correspondingly, flavoprotein inhibitors such as iodonium salts and the selenium analog of isothiazole, ebselen, are strong NOS-inhibitors.[30]

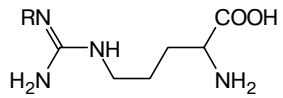


Iodonium salts



Ebselen

The compounds used most often as NOS-inhibitors are arginine derivatives, *viz.*, N^{ω}-methyl- and N^{ω}-nitroarginine:



R = Me (*N*-methylarginine)
R = NO_2 (*N*-nitroarginine)

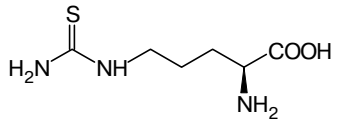
It was found that *N*-methylarginine, which inhibits the macrophage and i-NOS, hampers the development of

* Acute vasodepression.

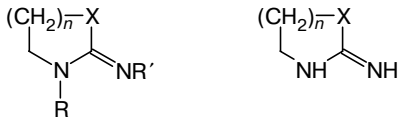
** Septic shock is an acute, life threatening pathological process caused by the formation of suppurative inflammation sites in organs and tissues.

diabetic vascular dysfunctions, *N*-methylarginine and *N*-nitroarginine exhibit an analgesic effect caused by their influence on the CNS; they potentiate the hypertensive action of adrenaline. The nitroarginine itself causes substantial arterial hypertension, which can be partially prevented by L- (but not D-) arginine.

Among other NOS inhibitors, one should mention L-thiocitrulline derivatives (D-isomers are completely devoid of inhibitory activity), which are strong pressor agents *in vivo*, and various amidines.

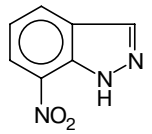


Amidines:



X = $(CH_2)_n$, NR, O, S

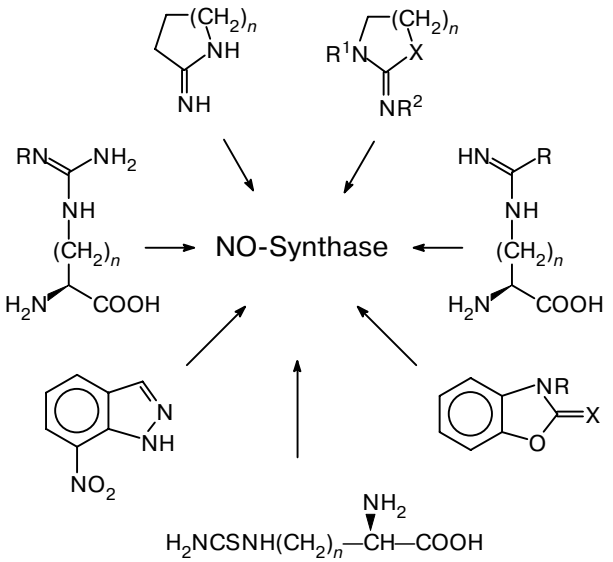
In the series of heterocycles, the greatest interest is aroused by 7-nitroindazole,[30] possessing a high analgesic activity; this compound can presumably serve as the starting point for the development of selective NOS inhibitors acting on the central nervous system and having no cardiovascular effects.



7-Nitroindazole

The general structures of the most popular NOS inhibitors are shown below.

NO-Synthase inhibitors



The development of new nitric oxide generators and specific inhibitors of the NO-synthase isoforms is a new, promising, and rational route to the creation of effective drugs.

* * *

In conclusion, it is noteworthy that the information covered in this review is fragmentary and far from being exhaustive. Suffice it to say that the main problems of particular pharmacology has remained off screen, and only a minor portion of the review is devoted to particular types of drugs and mechanisms of their action.

Actually, the purpose of this review is to provide the general idea of the basic concepts of pharmacology and to demonstrate the possible rational routes of development of both synthetic and theoretical investigations (recall that this paper is meant for chemists) aimed at the search of new effective drugs. We hope that this generalization would promote one of the critical components of research of this type, which is directly dependent on the professional mutual understanding between chemists and biologists.

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