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HISTORY OF PHARMACOLOGY

Pharmacology (from Greek φάρμακον — drug, poison and λόγος — word, knowledge) is a science concerned with drugs and their effects on living organisms; in a wider sense, it is a science studying physiologically active substances in general and their effect on biological systems in particular.

The history of pharmacology is inextricably intertwined with the history of mankind. Prehistoric people relied on their self-preservation instinct to find remedies against diseases. In search for food, ancient people empirically identified presence of medicinal or poisonous properties in plants, berries, sunlight, parts of animals (liver, fat, bone marrow) as well as in minerals, and learned to use them to treat diseases. Drugs were first known only in the form of raw or primitively processed products of mineral, plant or animal origin. As early as in the ancient times, their aggregate knowledge was termed materia medica ("description of medicinal plants").

The primary concern of people was to obtain analgesics. Aborigines of America empirically discovered natural narcotic remedies and used them to alleviate pain. For instance, Aztec healers traditionally used varieties of cacti in the form of juices and infusions; this fact amazed Spanish conquistadors in the 16th century, since Europe did not know any effective methods of analgesia at that time. The medicinal properties of Cinchona bark in treatment of tropic malaria were first discovered by Incas (fig. 1), although the active ingredient of quinine was first extracted from the bark and finally isolated only in 1820.

Tea, rhubarb, castor-oil plant, male fern, santonica wormwood, opium, henbane, tannins and mercury were used for medical purposes. These medications were known back in the old days in China, India, Egypt, and Greece. At about the same time people discovered plants able to irritate the gastrointestinal tract, stimulating properties of the coca leaf, and plants with narcogenic potential such as poppy, cannabis or tobacco.

Use of medications in Ancient Egypt is confirmed by the contents of the medical Ebers Papyrus (circa 1550 BC). The Papyrus contains 900 written formulas of various drugs used in treatment of infectious diseases, respiratory and gastrointestinal tract diseases, cardiovascular disorders, visual and acoustic disturbances. Ancient Egyptian healers used diverse dosage forms such as patches, mixtures, and ointments. Remedies were usually prepared using water from holy springs, honey, milk or vegetable oils as excipients.

Shennong Bencaojing, a treatise on roots and herbs containing description of 365 medicinal plants, was written in China several centuries before the Common Era. It can be regarded as a prototype of the contemporary pharmacopeia. Traditional Chinese medicine discovered such plants as ginseng, magnolia vine, camphor, ginger, rhubarb, tea, aconite, resin, animal origin products such as velvet antlers, gelatin, liver, elephant skin, mineral substances such as iron, mercury, and sulfur. Tibetan physicians knew of such medicinal plants as henbane, camphor, strychnine tree, licorice root, and drugs of mineral origin: iron salts, antimony, copper, and sulfur. The medicinal plant Ephedra (fig. 2) was used in China in the Han dynasty (206 BC — 220 AD) as a remedy against bronchial asthma and bronchitis. Ephedrine was first extracted in 1885 by a Japanese chemist and pharmacologist Nagai Nagayoshi. The drug is still used to treat bronchial asthma, pertussis, rhinitis, atrioventricular block and hypotension.

The first attempt at a systematic classification of the available experience in treatment of patients was made in the 4th

century BC. The ancient Greek physician and philosopher Hippocrates (460–372 BC) collated the existing medical observations and tried to provide them with a philosophical substantiation (fig. 4). Since Hippocrates was not in favor of wide use of medications, he only recommended rational use of simple and effective preparations. He regarded medicine as an experimental science. For treatment purposes he used around 250 medications of plant origin, most of them are used nowadays: barley water, spurge, hellebore etc. and 50 products of animal origin, e.g. honey with vinegar.

He insisted that in taking medicines, one should be mindful, choosing the course of further treatment based on the body's response to the drug. His rule for ethics "First, do no harm" is widely known and recognized.

De Materia Medica ("description of medicinal plants") by a Greek physician Dioscorides (40–90 AD) was a synonym of pharmaceutical science until the 19th century. As antidotes, he advised linseed decoction, rice and various emulsions. He used black nightshade for curing gastric and esophageal burns.

Fig. 1. Cinchona tree and Cinchona tree bark (*Cinchona calisaya*). The antimalarial properties of the bark were known to Indians from ancient times. In Europe, the remedy was first recognized in the 16th century after successful use of Cinchona tree bark extract in treatment of malaria on a wife of the Vice-king of Peru

Fig. 2. Ephedra (*Ephedra vulgaris*). Huangdi Neijing, a medical treatise dating back to circa 1000 BC, recommended use of ephedra, which contains ephedrine for treatment of asthma attacks

Fig. 3. Black henbane (*Hyoscýamus níger*) contains alkaloids scopolamine and atropine. In the Middle Ages the plant was considered extremely toxic

Sleeping within my orchard,
My custom always
of the afternoon,
Upon my secure hour thy uncle
stole,
With juice of cursed hebenon
in a vial,
And in the porches of my ears did
pour
The leperous distilment; whose
effect
Holds such an enmity with blood
of man
That swift as quicksilver it courses
through
The natural gates and alleys
of the body,
And with a sudden vigour doth posset
And curd, like eager droppings into
milk,
The thin and wholesome blood: so did
it mine;
And a most instant tetter bark'd about,
Most lazar-like, with vile
and loathsome crust,
All my smooth body.

Hamlet by William Shakespeare

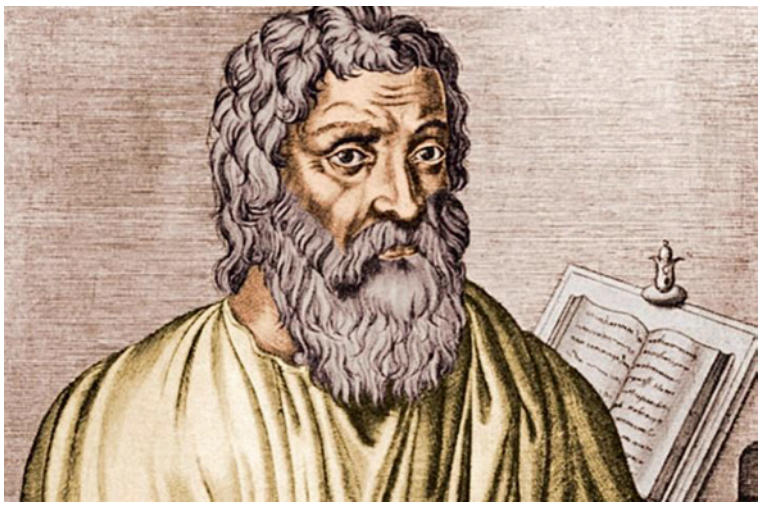

Fig. 4. Hippocrates (460–372 BC)

Pharmacology as a science was further developed in the works of *Galen* (129–204/216 AD), a representative of Roman medicine of the 2nd century AD (fig. 5). Unlike Hippocrates, who believed that nature can offer ready-made drugs, Galen introduced a practice of extraction of "beneficent principles" from natural materials, mostly plants. For these purposes he used wine and vinegar. Nowadays, these preparations (tinctures and extracts) bear the name *galenicals*. Galen's main contribution to pharmacology consisted in refining the methods of drugs preparation. He distinguished three methods of treatment:

1) dietary method, including baths, laxatives, diet, and bloodletting;
2) pharmaceutical method, use of anti-inflammatory, astringent, evacuating, relaxing, "desiccating", stimulating and "pain alleviating" remedies;
3) surgical method.

In order to stay healthy, Galen advised adhering to the concepts "Like cures like" and "The opposite is cured with the opposite".

Avicenna (Abu Ali Husayn ibn Abdillah ibn Sina) (16 August 980 — 18 June 1037) made an outstanding contribution to development of the pharmaceutical science (fig. 6). The scholar's legacy includes a remarkable five volume work *The Canon of Medicine*. The second volume is dedicated to studying of "simple" medications, from the practicing physician's perspective, along with Ibn Sina's teachings about drugs, their nature and trial. The *Canon of Medicine* lists 811 alphabetically ordered drugs of plant, animal and mineral origin, with an indication of their action, methods of application, rules of harvesting and storage. The fifth volume contains a description of "complex" drugs, as well as of poisons and their antidotes. This fundamental work attempts to bind numerous materials into a system and relate them to clinical observations.

Fig. 5. Galen (129–204/216 AD)

Fig. 6. Avicenna (16.08.980–18.06.1037)

Ibn Sina's name is often mentioned in connection with the first use of mercury for treatment of syphilis. The scholar also described symptoms of mercurial stomatitis as a side effect of mercurial treatment.

Paracelsus (1493–1541) offered a rationale for treatment of diseases based on similarity of shape or color of drugs, and organs or juices of the human body. He named the ability to recognize the possible uses of medications by their appearance a "signature" (fig. 7).

Paracelsus considered similarity as the basis for search and selection of "specific" remedies with the "right" action (e.g. mercury for treatment of syphilis). He was the first to extensively use chemical elements (antimony, lead, mercury and gold) as medications. He taught that living organisms consisted of mercury, sulfur, salts and a number of other substances which constitute all other natural bodies. In a healthy person these elements are in equilibrium; and an excess or lack of any of them is an illness. Paracelsus is regarded as the founder of iatrochemistry and the precursor of chemical pharmacology. His most famous quote is "Poison is in everything, and no thing is without poison. The dose makes it either a poi-

Fig. 7. Paracelsus (1493–1541)

Fig. 8. Rudolf Buchheim (1820–1879)

son or a remedy". In the middle of the 16th century the first Pharmacopoeias appeared that listed the drugs used in this state, their composition, therapeutic uses and cost.

Notwithstanding the important work referred to above, pharmacology is held to have emerged as a separate science only when the first university chair was established. This occurred in 1847, when Rudolf Buchheim (1820–1879) was appointed professor of pharmacology at the University of Dorpat (presently Tartu) located within Russia at that time. Lacking outside funding, Buchheim built a laboratory at his own expense in the basement of his house. He is credited with turning the purely descriptive and empirical study of medicines into an experimental science. Buchheim wrote two textbooks on pharmacology and introduced a new system for teaching the pharmaceutical science. His new, more rational drug classification (Physiological Chemical classification) turned the previously chaotic pharmaceutical knowledge into a more logical scheme that was easier to understand and apply in clinical practice (fig. 8).

PHARMACOLOGY IN RUSSIA: BRIEF HISTORY

In ancient Russia, preparation of drugs and treatment of diseases was a function of wise men and later monks. Over time, monasteries started to collect and categorize information about medicinal herbs, and to write manuscripts on pharmaceutical lore. One of the examples of such work is *Izbornik Svyatoslava* ("Svyatoslav's Herbal Anthology") dating back to 1073. In the late 15th century, the feudal Muscovite State emerged as a consolidator of isolated Russian princedoms. The first apothecary's termed *zeleinaya lavka* (herb shop) were established in many cities. Owners of the drugstores, zeleiniks, prepared and sold powders, ointments, tinctures and other remedies. They were often highly educated people with good knowledge of the properties and action of medications, mainly of plants. Their knowledge was captured in handwritten books termed herbals, or zeleiniks, and in those termed vertograds ("flower garden"). The most acclaimed was the one titled **"Blessedly shaded flower garden. Vertograd to health"** (1534) (fig. 9). This *Vertograd* contains a number of examples when a mojo turns into a cure. So, crystal is described as 1) "the one that is chained to the neck… bans away unnecessary sleep"; 2) if someone "thirsty holds it in the mouth, the thirst will be quenched" and 3) the same stone "ground and mixed with fresh honey makes mothers produce more milk".

In 1581, Tsar Ivan the Terrible issued the Decree to open the first pharmacy in Moscow. It served only the Tsar and his court. In order to manage healthcare business, *the Aptekarsky Prikaz* (*Apothecary Supervision office*) was founded in the early 17th century. Among its functions were medicinal plant harvesting, teaching physicians and specialists in drug preparation, providing medicines and treatments to the army, evaluating the medical expertise of doctors and pharmacists arriving in Russia. Apothecary gardens, where people could cultivate medicinal plants, appeared in many cities. During Peter the Great's reign, pharmacology and pharmacy business underwent significant changes: widespread opening of pharmacies, emergence of the pharmaceutical industry associated with apothecary gardens in St. Petersburg on the Aptekarsky Ostrov (which literally means Pharmacy Island), and in Lubny, a town in the Poltava region. In 1701, Czar Peter the Great issued an order to close the herb shops and open eight private pharmacies in Moscow. Simultaneously, the state introduced a monopoly on running pharmacies and eliminated the competition. In the 18th century, state pharmacies continued to exist and expand along with independent private pharmacies. Only pharmacies were allowed to sell medicines. In 1707 the *Aptekarsky Prikaz* was reformed, first into a Pharmacy Chancellery and later into a Medical Board and a Medical Chancellery. The *Aptekarsky Prikaz* organized training practical skills to physicians, manual therapists and pharmacists. Hospital based medical schools were organized to teach medical subjects and pharmaceutical science.

In 1719, a Pharmacy garden was opened in St. Petersburg. Research of new drugs was supported on the state level. In 1720–1721, Russia's first factory of "state medicinal supplies" was founded in St. Petersburg. It was the first state-funded facility manufacturing medications from domestic feedstock. For all intents and purposes Schepin K.I. (1728–1770), lecturer of the Moscow Hospital School who defended a thesis on medicinal properties of bread kvass, may be considered the first Russian professor of pharmacology.

Professor N.M. Maximovich-Ambodik (1744–1812) wrote the first guidebook on medical pharmaceutical science, *Description*

of Medicinal Drugs, which was published in 1783–1788 in St. Petersburg. In 1778 the first state civil Pharmacopoeia in Latin was published in Russia, and in 1866 — in Russian.

It is generally accepted that the founder of domestic pharmacology is Kravkov Nikolay Pavlovich (1865–1924). In 1884 he graduated from the Gymnasium and entered St. Petersburg University as a student of the natural division of the Physics and Chemistry Department. In 1888 he was enlisted with the second year of the Military Medical Academy. Kravkov N.P. worked in laboratories of renowned scientists Sechenov I.M. and Pashutin V.V. The teaching career of Kravkov N.P. is a glorious page in the history of Russian pharmacology. He wrote a two-volume guide entitled *Pharmacology Basics* which went through fourteen editions. The guidebook was in demand with all medical higher education institutions of the country. Kravkov N.P. founded the domestic pharmacology school; his famous students were Anichkov S.V., Zakusov V.V., and Nikolaev M.P.

Zakusov Vasily Vasilievich (1903–1986) worked at the department of pharmacology of the Kirov Military Medical Academy. In 1936 he defended a doctoral thesis on "Respiratory reflexes under the effect of poisons on blood vessels in different vascular regions". He chaired the departments of pharmacology at the First and Third Leningrad Medical Institutions, Kuybyshev Military Medical Academy, and at the First Sechenov Moscow Medical University. For 25 years he was the founding director of the Institute of Pharmacology of the USSR Academy of Medical Sciences, in 1948 was elected a corresponding member, and in 1952 a full member of the USSR Academy of Medical Sciences. Zakusov was the author of the synaptic theory of action of pharmaceutical substances which is being successfully developed by his numerous students and colleagues and is a foundation of the contemporary state of this science. In 1976 he was awarded the Lenin Prize for his cycle of studies in pharmacology of synaptic transmission in cooperation with Anichkov S.V. Most works by Zakusov are dedicated to the two subjects: pharmacology of the nervous system and pharmacology of the cardiovascular system (fig. 10).

Fig. 9. "Blessedly shaded flower garden. Vertograd to health"

Fig. 10. Zakusov V.V. (1903–1986)

The closest apprentice and follower of Professor Zakusov is Kharkevich Dmitry Alexandrovich, Member of the Russian Academy of Medical Sciences, author of numerous brilliant research works in the field of pharmacology of neurotropic drugs. From 1964 to 1998, Kharkevich headed the Department of Pharmacology at the Faculty of General Medicine and Faculty of Preventive Medicine of the First Moscow Medical Institution, and later of the First Sechenov Moscow Medical Academy. For many years he has been the author of Pharmacology textbook for students of Medical faculties.

1. PHARMACODYNAMICS

Pharmacodynamics is a branch of Pharmacology that deals with pharmacological effects, mechanisms, sites and types of action of drugs.

Pharmacological effects of drug are changes in the functions of the body's organ systems in response to the drug therapy.

MS mechanisms of action are ways through which the substances exert pharmacological effects. The main molecular targets of drugs are the following structures:

- receptors;
- enzymes;
- ion channels;
- transport systems.

Receptors are functionally active macromolecules ensuring cellular response to the action of transmitters or other substances. Their binding to the substances with affinity for these receptors (ligands) causes conformational changes in the receptor protein molecule and initiates a cascade of intracellular biochemical reactions that ultimately result in certain effects at the tissue, organ, and systemic levels (pharmacological effects, if the ligand is a MP). Receptors serve as targets for either endogenous ligands (neurotransmitters, hormones, cytokines and other endogenous biologically active substances), or exogenous biologically active substances (including drugs). There are four types of receptors (fig. 1.1):

- ligand-gated ion channels, also termed ionotropic receptors (see fig. 1.1, a);
- G-protein coupled receptors, also termed metabotropic receptors (see fig. 1.1, b);
- Enzyme-linked receptors (e.g. tyrosine kinase) (see fig. 1.1, c);
- Intracellular receptors (receptors regulating transcription of genes) (see fig. 1.1, d).

A. Ion channel coupled receptors. After binding of an agonist or an antagonist to an ion channel receptor, the transmembrane conductance of specific ions increases or decreases within milliseconds, causing a change in the cell membrane electrical potential. Vital activity of the cell strongly depends on Na^+, K^+, Ca^{2+}, Cl^-, and H+ ions. Passage of ions through channels is affected by many antiarrhythmic drugs [Procainamide (Novocainamide♠), Amiodaron, and others], local anesthetics [Procaine (Novocain♠), Lidocaine], anticonvulsants (Phenytoin, Carbamazepine, Lamotrigine). The same mechanism of action is typical of drugs which block calcium channels (Verapamil, Nifedipine, Diltiazem), and activate potassium channels (Minoxidil).

B. G-protein coupled receptors. G-protein coupled receptors are located in the cell membrane and implement their response through the second messenger system. When an agonist binds to the receptor, further signal transduction is performed by the G-protein which regulates the activity of a number of enzymes in a cell or the function of the coupled ion channel. In absence of an agonist, the receptor binds to a G-protein and thus maintains an inactive conformation. The G-protein is a complex of three subunits (α, β and γ). When the receptor is unoccupied, the three subunits are connected together. Receptor activation results in conformational changes, modification of the affinity of the receptor for the G-protein as well as affinity between G-protein components. The β–γ complex disconnects from subunit α in which guanosine diphosphate (GDP) is replaced with guanosine triphosphate (GTP), allowing it to move freely. The freed α-subunit-GTP complex is now able to interact with the target organelle (e.g. adenylate cyclase or ion channel) consuming at the same time the energy of GTP. After this the α-subunit returns to its initial position. By this time, the agonist has disengaged from the receptor, and the entire complex assumes

its initial state. There are several types of G-proteins: G_q protein controls the activity of phospholipase C. Phospholipase

C cleaves phosphatidylinositol diphosphate (PIP_2) into inositol triphosphate (IP_3) and diacylglycerol (DAG), which increase the intracellular calcium content and activate protein kinase C which participates in release of hormones, smooth muscles contraction and in the development of inflammation. This type of G-proteins are involved in development of effects mediated, for instance, through histamine receptors. G_s and G_i, respectively, stimulate and inhibit adenylate cyclase which controls the synthesis of cyclic adenosine monophosphate (cAMP) in the cell. Within a cell, cAMP activates protein kinase A, which regulates a number of intracellular processes.

In addition, the G_i protein activates potassium channels. Examples of these receptors include muscarinic acetylcholine receptors and adrenergic receptors. G_o protein inhibits calcium current.

C. Enzyme-linked receptors. Enzyme-linked receptors usually have a significant extracellular domain which enables binding to ligands (growth factors, cytokines), and an intracellular domain, which is an enzyme (in most cases, tyrosine kinase).

D. Receptors regulating gene transcription. Receptors regulating gene transcription

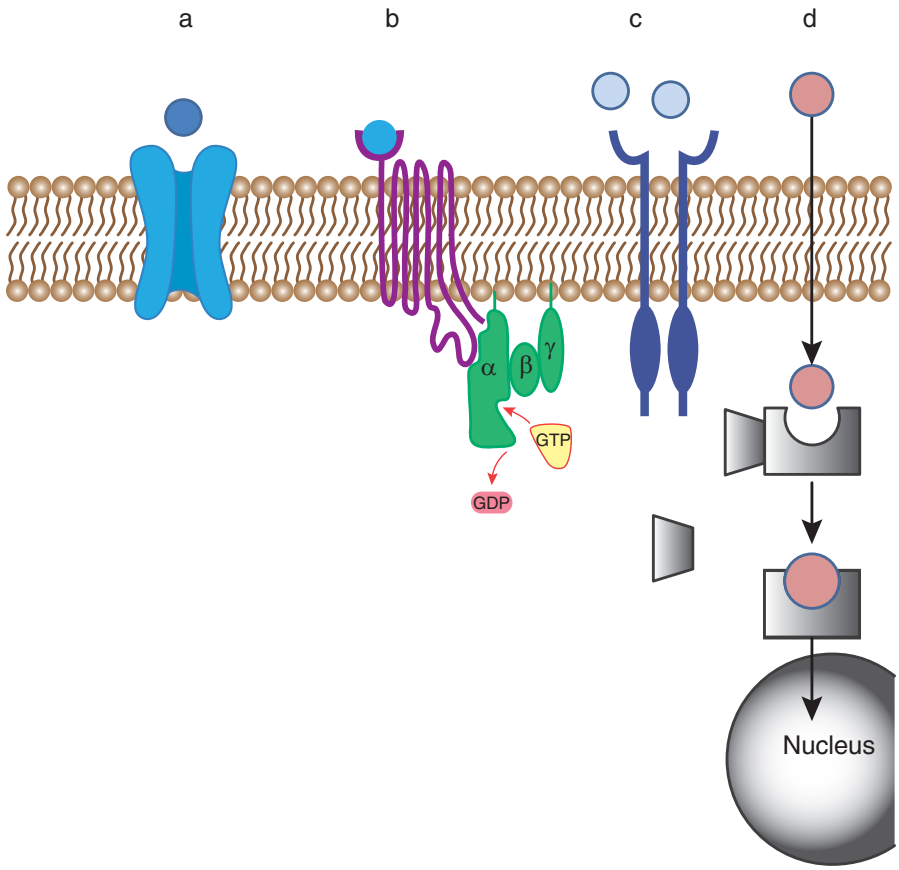

Fig. 1.1. Receptors can be coupled with ion channels (a); with a second messenger system (b); with a membrane enzyme [tyrosine kinase (c)]; or located inside the cell (d)

are termed nuclear receptors. Some of them are located in the cytoplasm and migrate to the nucleus only after binding to a ligand. Specifically, lipophilic glucocorticoids easily pass through the cellular membrane and bind to their appropriate receptors in the cytoplasm, releasing the heat shock protein. The receptor-glucocorticoid complex penetrates the nucleus and stimulates or represses transcription factors.

The strength of a substance binding to its receptor can be described by affinity.

Affinity is the ability of a substance to bind to a biological target (receptor), resulting in a formation of a "substance-receptor" complex. It is a measure of the ligand's ability to bind to the receptor by electrostatic interaction. In accordance with the law of mass action, the speed of reaction is proportional to the product of the reagents' concentrations. Therefore, a drug (L) can form a complex with a receptor (R), defined by the constant k_{+1}. This complex is capable of disintegration at a speed defined by the constant k_{-1}:

$$k_{-1.k+1}.$$

$$L + R \leftrightarrow LR;\ k_{+1}[L][R] = k{-}1\ [LR],$$

where L — ligand; R — receptor; LR — ligand-receptor complex; k_{+1} — association constant; k_{-1} — dissociation constant.

A quotient of the two constants is the equilibrium dissociation constant KD:

$$K_D = \frac{k_{-1}}{k_{+1}} = \frac{[L][R]}{[LR]}.$$

Overall quantity of receptors R_0 includes unoccupied (R) and ligand-bound (LR) receptors: $R_0 = R + LR$. Given that $LR = [L][R]/K_D$, we obtain the following:

$$[R_0] = [R] + [LR] = [R] + ([L][R] / K_D),$$

$$[LR] / R_0 = [L] / ([L] + K_D).$$

Hill–Langmuir equation helps determine receptor occupancy and compare affinity of ligands:

$$[LR] / R_0 = f,$$

where f — receptor occupancy. If $[L] = K_D$, then f = 0.5. Equilibrium dissociation constant K_D is a measure of affinity. It is obvious that K_D is ligand concentration at which 50% available receptors are bound to a ligand.

Consequently, **the dissociation constant (K_D) is numerically equal to the concentration of substance at which half of the receptors in the system are bound to the substance**.

The ability of a substance with binding affinity (a ligand) to activate receptors is termed "intrinsic activity".

Intrinsic activity refers to the ability of a ligand once bound to the receptor to produce a functional response. Depending on the type of interaction between the ligand receptor, a distinction is made between full agonists, partial agonists, antagonists and inverse agonists (which can also be subdivided into full and partial).

The polymorphism of types of ligand-receptor interaction is described by a theory which specifies, as a minimum, two conditions of a receptor: active (R_a) and inactive (R_i), which exist in dynamic equilibrium. The receptor's condition can change either spontaneously or under the effect of a ligand (fig. 1.2).

Agonists (from Greek *agonistes* — rival, *agon* — rivalry) are substances with affinity and intrinsic activity. When interacting with specific receptors, agonists stimulate them, i.e. cause changes in conformation of the receptors, triggering a chain of biochemical reactions inside the cells which results in development of certain pharmacological effects.

Based on this theory, **full agonists** are drugs which bind to receptors and produce the maximal cellular response; intrinsic activity of full agonists amounts to 100%. Full agonists bind to and provide activation of receptors (fig. 1.3, a).

Partial agonists are drugs with the intrinsic activities greater than 0, but less than 100%. In this respect, they bind to receptors; however, not all receptors to which they bind are activated. Therefore partial agonists cannot be as effective as full agonists (see fig. 1.3, b).