Visceral Sensory Systems and their Functional Organization

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PREFACE

For normal functioning, humans and animals must continuously receive information about changes in their surrounding environment and their own internal environment and respond promptly to it. In this regard, in the process of evolution in the body of animals and humans, special systems have arisen, for which the name sensory systems is most often used nowadays. Accordingly, the sensory systems of animals and humans were divided into two groups: extrasensory systems and sensory systems of the internal environment—visceral sensory systems. Extrasensory systems provide humans and animals with a capacity for spatial orientation, communication, food search, escape from a predator or vice versa, victim pursuit, etc. Visceral sensory systems serve to maintain constancy within the physiological limits of the parameters of the internal environment—homeostasis. Due to its great importance, the study of sensory systems has been the subject of continuous and close attention by researchers of various specialties for many decades. Periodically accumulating experimental data on sensory systems, as a rule, are systematized and formalized in the form of reviews or separate monographs. It should be noted here that when presenting the material on sensory systems, more attention was paid to extrasensory systems. Data on visceral sensory systems were presented to a lesser extent. This was due to a number of reasons. In particular, at the initial stages of research on sensory systems (the beginning of the 20th century), there was an opinion expressed by the famous english physiologist and anatomist, the creator of the modern doctrine of the autonomous nervous system, D.N. Langley, that the internal organs receive only efferent innervation and, accordingly, visceral sensory systems should not exist. In addition, in the first animal experiments and clinical examinations in humans to study sensitivity to various stimuli of internal organs, ambiguous and contradictory data were obtained. In addition, when studying the sensitivity of internal organs, there were more methodological difficulties than when studying the external sensory structures of the body. The certainty of the existence of visceral sensory systems was introduced in the last 30-40 years of the last century by the results of the work of a russian physiologist—Nobel laureate I.P. Pavlov. At that time, the main method that was used to study the mechanisms of functioning of the sensory systems of animal organisms was the method of conditioned reflexes developed by

Pavlov. Here, first of all, it should be noted the systematic research of teams of employees led by academician K.M. Bykov and academician V.N. Chernigovsky. In the experimental work of Bykov and his colleagues, fundamentally important data were obtained indicating that visceral sensory systems or internal analyzers according to Pavlov contain the same departments and function on the same principles as extrasensory systems or external analyzers. These works were a powerful incentive for the intensification of research on visceral sensory systems. In the middle of the last century, methods began to be applied that made it possible to move on to the study of visceral sensory systems at the cellular and molecular level. The study of visceral sensory systems began to "catch up" with the study of extrasensory systems. As a result, by now a lot of new data has accumulated on various issues of sensory systems of internal organs, which is of great interest to physiology. Based on experimental data, a special course of lectures for students of St. Petersburg State University "Physiology of visceral sensory systems" was developed and a book of the same name was written.

CHAPTER 1

A BRIEF HISTORY OF THE DEVELOPMENT OF RESEARCH ON SENSORY SYSTEMS

A necessary condition for the existence of humans and animals is the continuous receipt of information about changes in their surrounding environment and their own internal environment and prompt response to it. In this regard, in the process of evolution in humans and animals, special systems have emerged, called **sensory systems.** However, sometimes these systems are referred to as sensory **organs or analyzers**. Currently these terms serve to define the same systems, including: common auxiliary structures, peripheral, perceiving (receptor) link, conducting part, central department and feedback link. Sensory systems that transmit information to the body about changes in the external environment are called **extrasensory systems** and, accordingly, transmit information from internal organs—**visceral sensory systems**.

The systematic study of sensory systems began in the middle of the 19th century with the study of human extrasensory systems. Works on this topic were primarily associated with the names of outstanding European physiologists **P. Bugger, C. Bell, I. Muller, E. Weber, G. Fechner,** and **G. Helmholt.** It should be noted here that, according to a number of scientists of that time, it was believed that objects or their physical components, which are perceived by the senses, directly enter the central nervous system. For example, the image of an object decreases due to the optical system of the eye and enters the central nervous system along the optic nerve to the "sensorium" (Fig. 1.1). Sound vibrations, spreading through the structures of the middle and inner ear, reach the auditory nerve and pass through it as through a sound pipeline to the "sensorium." However, the scottish physiologist and anatomist **C. Bell (1811)** was the first to state that "external objects by themselves do not enter the brain. Neither color nor vibration propagate along the nerve, but bodies have some effect on the senses, so that we see, hear, smell, etc." At the same time, the merit in formulating this idea in the form of a complete scientific theory and experimental substantiation belongs to the german physiologist **I. Muller**,

who put forward a number of fundamentally important provisions regarding the functioning of the senses.

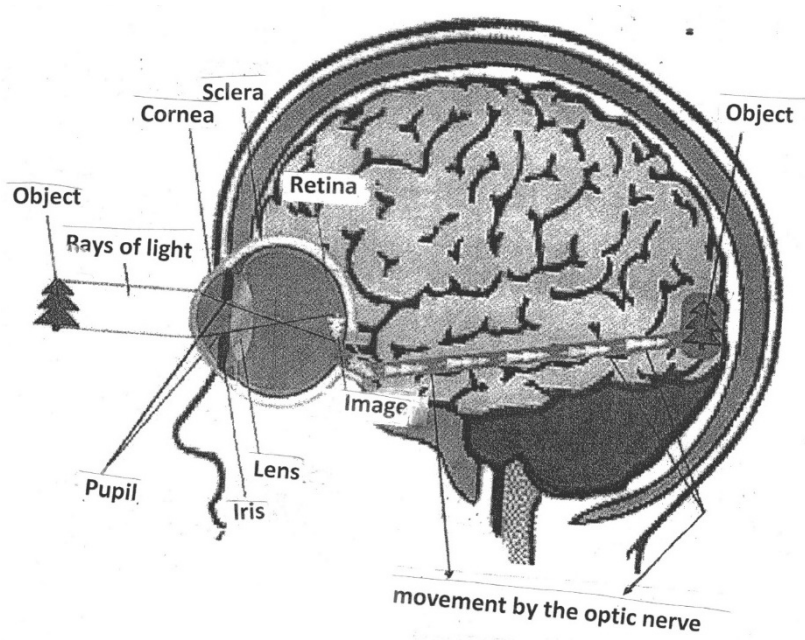

Fig. 1.1. The scheme of object perception in the human visual sensory system

$$\Delta S = c\Delta R / R$$

Where **c** is the proportionality constant. The introduction of **c** into the equation assumes, according to G. Fechner, the equality of all minimum increases in sensation (sense) from the threshold to the maximum amplitude of the irritating stimulus. As a result of simple mathematical transformations and assumptions, Fechner obtained:

$$S = k \lg R \; G.$$

Fechner called this expression E. Weber's law. Later it was called the Buger-Weber-Fechner law, which is formulated as follows: the magnitude of sensation is proportional to the logarithm of the magnitude of irritation.

The formula of the Buger-Weber-Fechner law is derived under a number of conditional assumptions and, above all, the formula requires compliance with the ratio of the formula of the Buger-Weber law, i.e., **ΔR / R** – const. However, numerous subsequent experiments have shown that the ratio is not constant over the entire range of irritation intensity. In this regard, in the 50s of the 20th Century, the american psychophysiologist S. Stevens, based on the results of his examinations conducted on humans using sound, light and electrical stimuli, proposed the law of the power function. According to this law, the sensation that arises in response to the stimulation of any sensory system is proportional to the degree of intensity of the stimulus

$$\mathbf{S = a\ (I - R^x)}$$

Where **S** is the sensation, **I** is the intensity of the stimulus, **R** is the intensity of the threshold irritation, **x** is the exponent, and **a** is a constant, the value of which depends on the selected units of measurement. The exponent of **x** varies depending on which sensory system is being studied. So, for example, according to Stevens, the indicator for light stimuli is 0.33, for the perception of the smell of heptane 0.6, for the taste of sodium chloride 1.3. It should be pointed out that at present both the Buger-Weber-Fechner law and Stevens' law are used in psychophysics as a power function. According to this law, the logarithmic or power ratio is extremely important for the functioning of sensory systems. In particular, the sensitivity of the sensory system increases with low-amplitude irritating stimuli and "coarsens" with sufficiently strong stimuli, thereby ensuring the normal functioning of the sensory system, protecting it from damage. The logarithmic or power-law relationship between irritation and sensation is also valid for animal sensory systems.

The beginning of research on visceral sensory systems also occurred in the middle of the 19th century and this is due to Russian physiologist I.**M. Sechenov**. In 1863, Sechenov's famous book **"Reflexes of the Brain"** was published in Russia. In it, he described the existence of a special "dark" muscular feeling, which, apart from skeletal muscles, is characteristic primarily of all hollow internal organs. Sechenov pointed out that a "dark" sensation arises in the organs of the thoracic and abdominal cavities, forming "a vague gross feeling (probably from all organs of the body equipped with feeling nerves), which we call in a healthy person a sense of general well–being, and in a weak or sickly person - a sense of general malaise." Sechenov called these special feelings systemic and even singled them out into a special group. At the same time, the initial studies of visceral sensory organs have not received the same development as the study of

sensory organs that perceive information from the external environment. There could be several reasons why. In particular, at the initial stages of research on visceral sensory systems (the beginning of the 20th century), there was an opinion expressed by the famous english physiologist and anatomist, the creator of the doctrine of the autonomous nervous system—D.N. Langley, that internal organs receive **only efferent** innervation and, accordingly, visceral sensory systems should not exist. In addition, in the first animal experiments and clinical examinations of human sensitivity to various stimuli of internal organs, ambiguous and contradictory results were obtained. Thus, some of the initial information about the sensitivity of internal organs was the data of K. Bichat (Bichat, 1802). In experiments on dogs, he irritated the abdominal viscera (cut, stabbed) and at the same time did not observe signs of pain. However, later a number of other researchers (Mayer, Pribram, 1872) reported that an increase in blood pressure was found, accompanied by a slowing of the pulse with mechanical irritation of the mucous and serous membranes of the stomach in dogs and cats. The same thing was observed with bloating of the stomach. The clinical examinations of K. Lennander (Lennander K, 1901, 1902, 1904) deserve attention. Lennander carried out his observations on humans during various surgical operations. Lennander came to the conclusion that most of the internal organs—the liver, omentum, gallbladder—are not sensitive even to intense influences. Touching the intestines (thick and thin) and mesentery, incision, stretching of the intestines were not perceived subjectively. Following the work of Lennander, a number of experimental works on animals appeared. Here, first of all, it is necessary to note the experiments of K. Kast and C. Meltzer (Kast K, Meltser C, 1907), which subjected Lennander's surveys to experimental verification. The abdominal cavity of a dog, cat or rabbit was opened under ether anesthesia, and then the experimenters waited for anesthesia to pass, only after that they examined pain, tactile, temperature and other types of reception. It was found that touching a heated glass rod, squeezing the intestines with fingers, and tweezing various internal organs (intestines, kidney, uterus, bladder) caused a pronounced reaction in animals.

Certainty in the existence of visceral sensory systems was introduced by the results of the work of russian physiologists. Here, first of all, the systematic research of academicians Bykov and Chernihivsky should be noted, which began in the last 30-40 years of the last century. The main method used to study the mechanisms of the functioning of animal organisms was the method of conditioned reflexes developed by I.P. Pavlov. The first study in the formation of visceral conditioned reflexes to irritation of receptors of internal organs can be considered to be the work of Bykov and Alekseev-

Berkman (1926), in which both an unconditional stimulus (diuresis) and a conditional one (infusion of fluid into the gastrointestinal tract) were interoceptive, i.e. acting on receptors of internal organs. It should be noted here that this work gave rise to a whole direction in the physiology of conditioned reflexes. Experimental work on this topic was summarized in Bykov's book **"The cerebral cortex and internal organs. M., 1947**". Numerous studies by Bykov and his collaborators testified that visceral sensory systems or internal analyzers according to Pavlov contain the same departments and function on the same principles as extrasensory systems or external analyzers. At the same time, it should be noted that for methodological reasons, psychophysical examinations on human visceral sensory systems have not been carried out.

It should be noted that psychophysical examinations of human extrasensory systems, as well as studies using the method of conditioned reflexes in humans and animals, have allowed us to obtain data on the patterns of the functioning of sensory systems in general. However, the issue of cellular mechanisms that ensure the operation of extraterrestrial and visceral sensory systems seemed to be extremely important. According to I. Muller, what are the "special states" caused in the nerves and felt as sensations? How their transmission, processing and analysis take place in the central nervous system ("in the sensorium"). Unfortunately, the lack of appropriate methods pushed back the beginning of these studies to the middle of the 20th century, when more advanced electrophysiological methods, as well as methods of experimentation with single nerve fibers and cells, began to be widely used in physiological practice.

In the study of transformation processes, the energy of an irritating stimulus in sensory systems at the cellular level, two periods can be distinguished. The beginning of **the first period** is associated with the research of the famous english physiologist, Nobel laureate E.D. Adrian. In a series of studies conducted at the beginning of the 20th century using an electrophysiological method on receptors of extrasensory systems, muscle and skin mechanoreceptors and receptors of visceral systems—lung mechanoreceptors, Adrian and his colleagues discovered that receptor formations, like neurons, send numerous series of impulses—action potentials (PD) of the same amplitude, the frequency of which varies with changes in the parameters of the irritating stimulus (mechanical stimulus). The data of these studies were summarized in his famous monograph: **"The basis of sensation", 1928. Adrian** made a fundamentally important conclusion that the encoding of information in the external and visceral receptors is carried out using a frequency electrical code. Along with this,

the position was expressed about the existence of stationary (as opposed to discrete nerve impulses) electrical excitation in receptors. In particular, in the conclusion of his monograph, Adrian wrote: "Irritation arises suddenly, and its strength remains constant. The excitation process in the receptor gradually fades away, and as it fades, the intervals between pulses in the sensitive fiber become larger. As a result of some process taking place in the central nervous system, the impulses integrate, and the strengthening and weakening of sensation becomes a fairly accurate copy of the rise and fall of the excitation process in the receptor."

Adrian's idea of a graduated electrical excitation process in sensory receptors was further developed by the English physiologist B. Katz (Katz, 1950 a, b) and the Swedish physiologist R. Granit and colleagues (Granit, 1970) in experiments on receptors of extrasensory systems: respectively on mechanoreceptors—muscle spindles of a frog and photoreceptors of a water beetle Dytiscus. At the same time, similar experiments were conducted by Mexican physiologists R. Alvarez-Builla and J. Ramirez de Arellano (1953), as well as English physiologists J. Gray and M. Sato (1953) on a visceral mechanoreceptor—a Pacini body prepared from the mesentery of a cat. These studies can be considered the beginning of **the second period** of the study of sensory systems. In these works, the concept of generator potential was put forward. Its essence was as follows: an irritating stimulus causes the appearance in the sensory receptor of only a slow graduated potential or, in modern terms, an analog electrical response. Spreading electrotonically, it causes the generation of impulse activity (PD) in nerve fibers, i.e.,it is converted into a digital response. As an illustration of this concept, the results of experiments on the registration of electrical signals from muscle receptors (muscle spindles) of a frog, photoreceptors of a water beetle (Dytiscus) and a Pacini calf were used. A mechanical stimulus (stretching of the muscle) pressing on the Pacini body caused the generation of two types of electrical signals: a slow potential arising at the location of nerve endings (receptor) and superimposed rapid oscillations–PD, the electrogenesis of which was concentrated in the nerve fiber that formed the nerve endings (Katz B, 1950 a, b; Alvares-Buylla R, Ramires de Arellano J, 1953; Gray J, Sato M, 1953). The light stimulus caused the photoreceptors of the water beetle to generate similar types of electrical signals: a slow potential arising at the location of photoreceptor cells and overlapping PD, the electrogenesis of which was concentrated in nerve structures. In this regard, the graduated electrical response of the receptor can be considered, according to Muller, a "special state" (at least its electrical part) that occurs in the receptor (the peripheral part of the sensory system). This condition is transmitted to the central nervous system (sensorium) using a series of PD.

The works of Katz, Gray, Sato, Almirez-Builla, and Ramirez de Arelano served as a powerful impetus for the intensification of the study of sensory systems at the cellular and molecular level, first in animals, and then the improvement of methods allowed for examinations in the peripheral and central departments of human sensory systems (Vallbo A, 2018). In addition to the electrophysiological method, other methods began to be used to study extrasensory and visceral sensory systems, in particular methods of molecular biology, electron microscopy and histochemistry, and methods of genetic engineering. This made it possible to intensify research on the conduct and processing of sensory information in various parts of the nervous system, including the cerebral cortex at the cellular and molecular levels. It is important to note that by the end of the 20th century, the study of visceral sensory systems had "caught up" with the study of extrasensory systems.

Experimental data obtained in studies of extrasensory and visceral sensory systems allowed us to define the sensory system and its main functions. **"The sensory system is defined as a set of common auxiliary formations, sensory receptors, nerve pathways and centers, the irritation of which in humans and animals leads to the appearance of a specific feeling characteristic of this sensory modality" (Altman, 2009).** All parts of the sensory system are in one way or another under the control of neurohumoral feedback.

The main functions of the sensory system are to provide humans and animals with the ability to detect, distinguish and identify signals from the outside world and the internal environment, or, in other words, the formation of sensory images. In turn, the realization of these functions leads to a certain state and (or) motor behavior of the body. At the same time, the assessment of one's own behavior and the behavior of external objects is the basis of thinking (Altman, 2009).

In Fig. 1.2 in accordance with the definition, a block diagram of the sensor system is presented

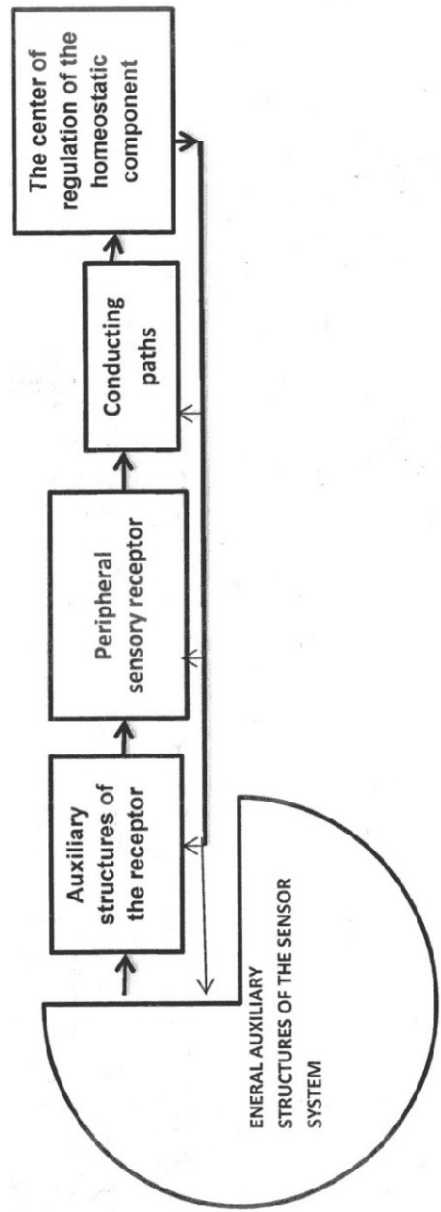

Fig. 1.2 Block diagram of the sensor system.

In the following chapters, the functional characteristics of visceral sensory systems will be presented in detail. At the same time, as mentioned above, according to the results of numerous studies of extrasensory and visceral sensory systems, the energy of an adequate stimulus in the receptors of sensory systems is converted into an electrical signal (a special state according to Muller). This signal is transformed and transmitted to the central nervous system also by means of electrical signals. In view of the importance of this process, it is advisable for a better understanding of the functioning of visceral sensory systems to briefly focus on the processes of electrogenesis in the cellular structures that make up sensory systems (Fig. 1.2.): **the sensory receptor, nerve fibers and nerve cells, and various synaptic structures.**

CHAPTER 2

ELECTROGENESIS IN THE CELLS OF ANIMAL ORGANISMS: GENERAL PROVISIONS

2.1 Passive ion transport

All animal cells are covered with a membrane that consists of a lipid bilayer with protein inclusions. The thickness of the membrane is 8-10 nm. Lipids form the base of the membrane matrix, into which proteins are immersed. In addition, cell membranes in most cases contain carbohydrates, which can be attached to lipids (glycolipids) or proteins (glycoproteins) (Fig. 2.1).

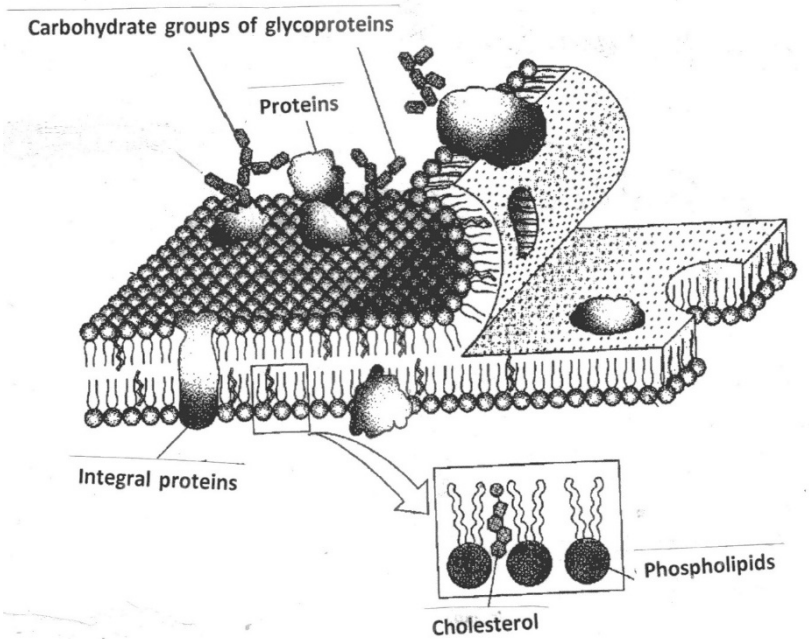

Fig. 2.1 Schematic representation of a cell membrane section obtained using the freeze-chipping technique.

Due to the fact that the extracellular and intracellular media are almost exclusively aqueous, the lipid molecules forming the bilayer membrane are arranged so that their hydrophilic ends face the aqueous medium, and the hydrophobic ends face each other and are isolated from the aqueous extracellular medium and from the intracellular volume. Thus, membrane lipids are retained by hydrophobic forces and electrostatic interactions of their hydrophilic end section.

In addition to lipids, the cell membrane contains proteins. In most cases, proteins are immersed in the lipid layer and figuratively "float" among lipids and mainly phospholipids, forming a kind of mosaic in the liquid phospholipid matrix. Accordingly, this concept of the biological membrane structure has been called the "liquid mosaic" model. In some cases, proteins permeate the entire bilayer and come into contact with both extracellular and intracellular spaces (transmembrane proteins). In other cases, proteins are attached to the membrane by a fatty acid chain, a phospholipid, or a prenyl group (Fig. 2.2).

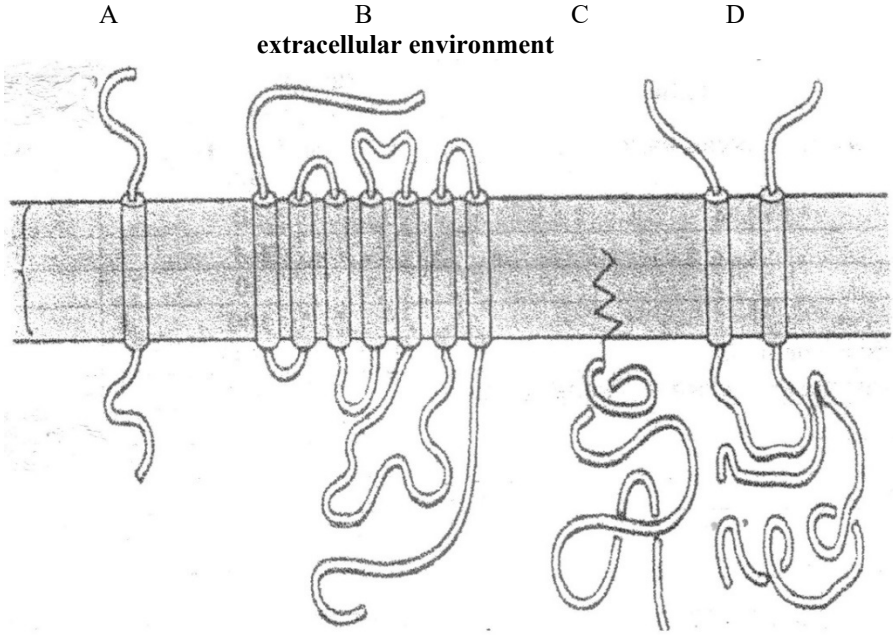

Fig. 2.2. Some examples of protein-membrane bonding.

The cylinders inside the membrane are marked with α-helices. **A**—single α-helices pass through the membrane; **B**—numerous α-helices pass through the membrane; **C**—the protein is connected to the cytoplasmic part of the bilayer by a fatty acid chain or prenyl group; **D**—the protein immersed in the membrane is non-covalently bound to another protein in the cytosol.

Transmembrane proteins are arranged in such a way that hydrophobic spirals are immersed in the membrane, and hydrophilic ones in aqueous ones—intracellular or extracellular volumes. This provides the ability for proteins to stay (anchor) in the membrane. Transmembrane proteins can form hydrophilic pores in the membrane - ion channels, providing passage through the membrane of a number of inorganic ions. We will discuss the structure of ion channels in more detail at the end of the section. It should also be noted here that the presence of ion channels in the membrane was the basis for the occurrence of electrical potentials on the cell membrane.

In studies of the electrical activity of nerves and muscles conducted at the beginning of the last century, it was found that a potential difference is recorded between the electrodes located on the altered (damaged) and intact parts of a nerve or muscle. Moreover, the electronegative site was the damaged part, for example, an incision of a nerve or muscle. Further improvement of the electrophysiological technique and, in particular, the appearance of microelectrodes, thin glass pipettes filled with electrolyte with a tip diameter of 2-1 microns, which could be injected through the membrane into the cell without damaging the cell, as well as electronic amplifiers with high input resistance confirmed the presence of a potential difference in living cells through the membrane. At the same time, the inner part of the membrane turned out to be electronegative with respect to the outer one.

Of great importance for electrophysiological research was the discovery of a "convenient" object"—a giant squid axon with a diameter of 500-600 microns. The use of a giant axon made it possible not only to measure the transmembrane potential difference with high accuracy, but also to squeeze out the axoplasm by subjecting its composition to chemical analysis and, in particular, to measure intracellular ion concentrations. Subsequently, measurements of the membrane potential and determination of the intracellular ionic composition were carried out on other mammalian nerve and muscle cells (Table 2.1). The presence of a potential difference across the cell membrane indicated that the membrane is permeable to ions. The negative polarity of the inner side of the membrane and the high intracellular

concentration of potassium ions (Table 2.1) indicated the main role of potassium ions in the formation of the transmembrane potential difference.

Table 2.1. Intracellular ionic composition of various mammalian cells

Ions	**Intracellular concentration**	**Extracellular conctynhftion**
1. Giant squid axon	**mM/kg H_2O**	**mMkg H_2O**
K^+	**400**	**20**
Na^+	**50**	**440**
Ca^{2+}	**0,4**	**10**
Mg^{2+}	**10**	**54**
Cl^-	**100**	**560**
Organic ions	**≈385**	**–**
2. Mammalian muscle cells	**mM**	**mM**
K^+	**155**	**4**
Na^+	**12**	**145**
Mg^{2+}	**30**	**1–2**
Ca^{2+}	**1–2**	**2,5–5 (only 10^{-4} in free form**
Cl^-	**4**	**120**
Organic ions	**≈150**	**–**
3. Cat motor neuron	**mM**	**mM**
K^+	**150**	**5,5**
Na^+	**15**	**150**
Cl^-	**9**	**125**

In particular, the presence of pores or channels in the cell membrane that are permeable only to potassium ions allows these ions to move along a concentration gradient into the extracellular medium. However, there will be no movement, since diffused ions with a positive charge are not compensated by the flow of ions with an opposite charge. This will immediately lead to the creation of a retarding electrostatic force with a negative sign on the inside of the membrane. An electrochemical equilibrium will be established on the membrane between the electrical work that needs to be performed by a small number of ions to cross the boundary in one direction, and the osmotic work required to move the same number of ions in the opposite direction. A number of assumptions and simple mathematical calculations that allowed us to determine the formula

by which the membrane potential can be calculated for this situation (for more information, the calculation of the membrane potential is given in the book by Nobel laureate B. Katz "Nerve, muscle, synapse" 1966). The formula is a variant of the well-known equation, physicochemist, Nobel Prize winner V.G. Nernst derived for calculating electrode potentials and has the following form:

$$Em = -\frac{RT}{nF}\lg\frac{[K]o}{[K]i} \qquad (1),$$

where Em is the membrane (equilibrium) potential), R is the gas constant, T is the absolute temperature, F is the Faraday number, n is the valence of the ion, [K] is the concentration of potassium ions, the icons o, i mean the concentration, respectively, outside the membrane and inside the cell. It should be noted that the Nernst equation is the most famous and most often cited equation in the biological literature.

Thus, the membrane potential according to the Nernst formula, is determined only by the ratio of concentrations of potassium ions inside and outside the cell. Indeed, in early studies of the effect of potassium ion content on the membrane potential of living cells, it was found that a change in their extracellular concentration significantly changed the magnitude of the transmembrane potential difference. While variations in the concentrations of other ions did not significantly affect the magnitude of the membrane potential. At the same time, as the methods for recording the electrical activity of cells improved, it turned out that there was a discrepancy between the recorded value of the membrane potential and calculated according to the Nernst formula with variations in the concentration of potassium ions in the extracellular medium. Figure 2.3 presents data from the seminal work of A. Hodgkin and R. Keynes (1955), in which the intracellular membrane potential of the squid axon, was measured when the extracellular concentration of potassium ions changed. The ratio calculated by the Nernst formula (dashed line) does not hold for low concentrations of potassium ions (solid line). This allowed us to assume that the cell membrane is permeable to other ions and mainly to sodium ions and contains the corresponding ion channels.

The dotted line is drawn at an angle of inclination equal to 58 mV for a tenfold change in the extracellular level of potassium ions in accordance with the Nernst equation. Due to the presence of membrane permeability for sodium ions, experimental data (solid line) differ from theoretical data, especially at low concentrations of potassium ions. Along the ordinate axis is the amplitude of the membrane potential in millivolts (values of the

membrane potential with a negative sign), along the abscissa axis is the concentration of potassium ions in millimoles (mM): (from Hodgkin A, Keynes R, 1955).

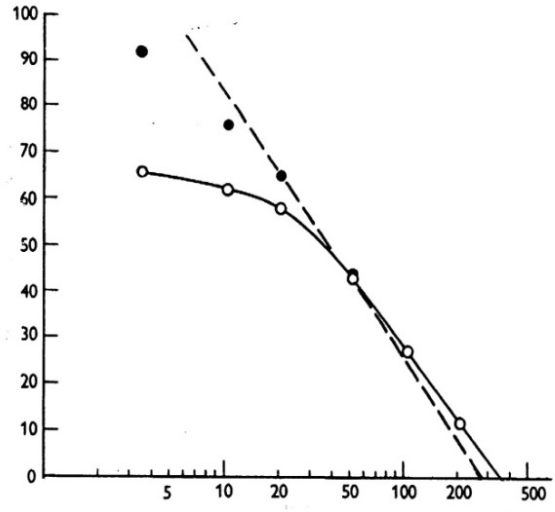

Fig. 2.3 Dependence of the membrane potential of the squid axon on the extracellular concentration (semi-logarithmic scale) of potassium ions.

To consider the role of sodium permeability, let us first turn to the model of an ideal cell located in an environment with a high concentration of sodium ions and low potassium ions. The concentration of potassium ions inside the cell is higher than outside, and vice versa, the concentration of sodium ions is lower than in the extracellular medium. Since there are only channels for potassium ions in the membrane, the membrane potential will be equal to the potassium equilibrium potential according to the Nernst equation. When sodium permeability (the presence of sodium ion channels) and permeability to chlorine ions (the presence of chlorine ion channels) are introduced into the model, sodium ions will tend into the cell due to their concentration gradient, as well as the negative polarity of the inner side of the membrane. As sodium enters, a positive charge accumulates on the inner surface, and the membrane begins to depolarize. As a result, the equilibrium for potassium ions is disrupted and potassium ions begin to move into the extracellular space. With increasing membrane depolarization, the driving force for sodium entry decreases, while for potassium it increases. The process continues until both ion fluxes balance each other. At this point, the

change in the membrane potential stops, since no charge accumulation occurs. The value of the membrane potential will be located between the potassium and sodium equilibrium potentials and will be determined by potassium and sodium currents of equal magnitude and directed in opposite directions. Chlorine ions are also involved in this process, but the equilibrium potential of chlorine adjusts to the new value of the membrane potential by changing its intracellular concentration. As the cation currents come into equilibrium, the intracellular concentration of chlorine ions will increase until the total chlorine current becomes zero. If we assume the permeability of the membrane, in addition to potassium ions for sodium and chlorine ions, additional parameters should be added to the Nernst formula and the formula will change its appearance accordingly. Research on this issue was initiated by D. Goldman (1943), and then independently conducted by Hodgkin and Katz (1949). The authors made the assumption that the voltage gradient (i.e., the electric field) is evenly distributed across the membrane. As a result, for the first time in the work of Hodgkin and Katz, a new formula appeared in its finished form, taking into account the permeability of the cell membrane except potassium ions for other ions. This equation is called the constant field equation or the Goldman, Hodgkin, Katz equation

$$\mathrm{Em} = -\frac{RT}{nF}\, lg\, \frac{\mathrm{Pk[K]o+PNa[Na]o+PCl[Cl]i}}{\mathrm{Pk[K]i + PNa[Na]i+PCl[\ Cl]o}} \qquad (2),$$

where Em is the membrane (equilibrium) potential), R is the gas constant, T is the absolute temperature, F is the Faraday number, n is the valence of the ion, in square brackets, respectively, the concentrations of potassium [K], sodium [Na] and chlorine [Cl] ions. P is the ion permeability coefficient.

It follows from the formula that, with insignificant values of PNa, PCl, the permeability to sodium and chlorine ions can be neglected and the formula is converted into the Nernst formula. It is important to note here that if the membrane potential is determined only by the Nernst formula, then in accordance with the formula it can be established in the presence of one open potassium channel. In this case, a change in the membrane potential can occur only with variations in extracellular concentration of potassium ions or temperature. The presence of sodium and chlorine channels in the membrane along with potassium ion channels significantly expands the electrical response of the cell to various stimuli. The presence of sodium and chlorine channels in the membrane along with potassium ion channels significantly expands the electrical response of the cell to various stimuli. Let's explain this using an equivalent electrical circuit for a cell membrane

having potassium, sodium and chlorine channels (Fig. 2.4A) The diagram shows three separate conductive ion channels. Each channel corresponds to an EMF, which is the equilibrium potential for a given ion and corresponds to the difference in the transmembrane potential difference, which balances the ion's tendency to diffuse along its concentration gradient. For sodium and potassium ions, the electric polarity is opposite to the concentration difference, and for chlorine ions, the electric polarity and concentration gradient have the same direction. The (electromotive force) EMF value for each ion is determined by the Nernst equation. It should be noted that in many nerve tissues, the main potential-forming ions on the membrane are potassium and sodium ions. Chlorine ions are passively distributed in accordance with the membrane potential and are not potential-forming. Therefore, the equivalent electrical circuit in Fig. 2.4A can be simplified by leaving only the permeability to potassium and sodium ions in the membrane (Fig. 2.4B). Accordingly, formula 2 is transformed and will look like this

$$\mathrm{Em} = -\frac{RT}{nF}\, lg\, \frac{\mathrm{Pk[K]o} + \mathrm{PNa\ [Na]o}}{\mathrm{Pk[K]I} + \mathrm{PNa[Na]i}} \qquad (3)$$

For a better understanding of the role of sodium and potassium permeability, which simultaneously exists in the cell membrane, we will use the electric circuit proposed by Nicholls, Martin, Wallace, and Fuchs (2001) to form the membrane potential. In Fig. 2.4C (1) there is an electrical circuit simulating the electrical circuit of the cell membrane, shown in Fig. 2.4B. Two batteries are connected in series and give current **I** in the same direction (shown by arrows). Let's assume that the power supply V_1 simulates the potassium E_k equilibrium potential, and the power supply $V_2 – E_{Na}$ equilibrium potential. R1, R2 are, respectively, the internal resistances of the power supplies, representing the values opposite to the conductivities g_k, g_{Na} . The resistances R_1 and R_2 are connected in series. What is the potential difference between points **b** and **d** (which represent the internal and external environment of the membrane)? The voltage drop across the two resistances between **a** and **c** is: $V_1 + V_2 = 100$ mV + 50 mV = 150 mV. The current **I** flowing from **a** to **c** through the resistance R_1 and R_2 is equal to: $I = V_1 + V_2 / R_1 + R_2$ =150 mV /100000 ohms = 1.5 μA. When the current I = 1.5 μA passes through the resistance R_1 = 10000 ohms, the potential $I \cdot R_1 = (V_1 + V_2 / R_1 + R_2) R_1$ drops at 15 mV. Since point **a** is positive with respect to **b**, the potential difference between the inner and outer sides will therefore be $V_1 - I \cdot R_1$ = 100 mV - 15 mV = 85 mV. You can get the same result by calculating the potential drop after the current passes through R_2. In this

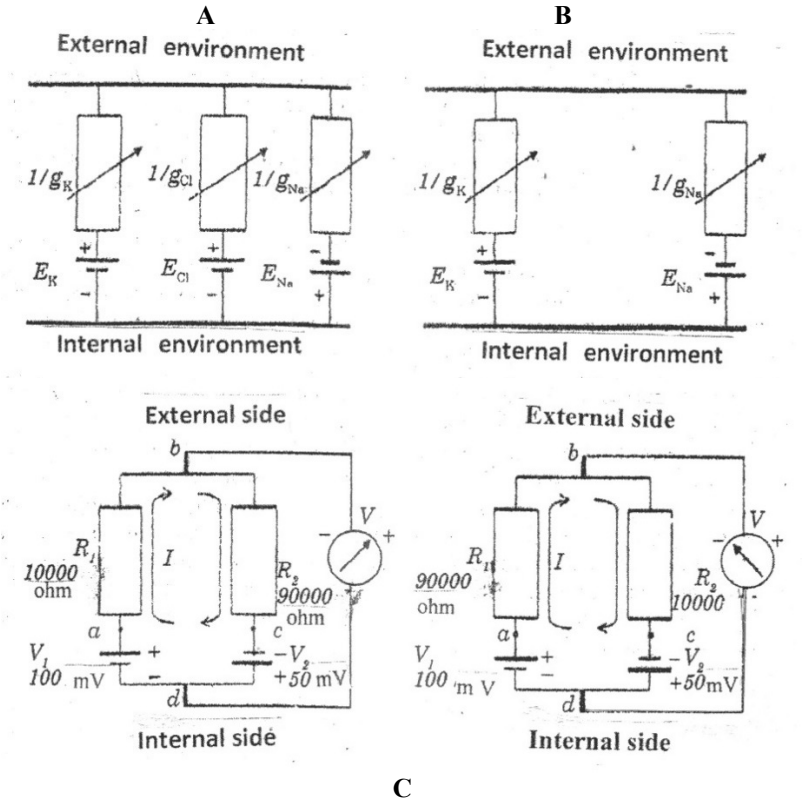

Fig. 2.4. Electrical circuit of the cell membrane (A, B) and an electrical circuit simulating the electrical circuit of the cell membrane (C) (from Nicholls J, Martin A, Wallace B, Fuchs P, 2001)

A. gK, gCl, gNa – conductivities for potassium, chlorine and sodium ions; 1/gK, 1/gCl, 1/gNa - values inverse to conductivities, variable resistances, respectively, for potassium, chlorine and sodium ions. E_k, Ecl and E_{Na} are the equilibrium potentials for potassium, chlorine, and sodium ions calculated using the Nernst formula B. The same designations for remote conductivity and equilibrium potential for chlorine ions. **C** is an electrical circuit simulating the electrical circuit of a cell membrane on **B**. V1, V2 – power supplies, R1, R2 – internal resistances of power supplies, I – current in the circuit, V – potential logger in the circuit between points d and b.

case, the voltage drop across the resistance R_2 will be 1.5 μA · 90,000 ohms = 135 mV. Add it to V_2 since the point **c** is negative with respect to **b**, we get that 135 mV+ (-50 mV) = 85 mV. Thus, the potential between **b** and **d** has a single value of 85 mV with a negative sign on the "inside". The diagram of Fig. 2.4**C** (1) simulates a membrane situation where the conductivity to potassium ions significantly exceeds the conductivity to sodium ions and the membrane potential is determined mainly by the equilibrium potential for potassium ions.

In Fig. 2.4**C** (2) R_1, R_2 are reversed. Since the total resistance in the circuit remains the same, the current should also be the same as in Fig. 2.4C (1), i.e.,1.5 μA. This scheme simulates the situation on the membrane when the conductivity for potassium ions is significantly less (resistance is greater) than the conductivity for sodium ions. Now the potential drop after the current passes through the resistance R_1 is 90,000 ohms · 1.5 μA = 135 mV. Point **a** is positive with respect to **b**. The potential difference between the inner and outer sides, therefore, will be equal to 100 mV -135 mV = -35 mV. We get the same value by calculating the potential drop after the current passes through R_2. In this case, the voltage drop across the resistance R_2 will be 1.5 μA · 10000 ohms = 15 mV. Add it to V_2, since the point **c** is negative with respect to **b**, we get that 15 mV+ (-50 mV) = -35 mV.

The potential between **b** and **d** has a single value of -35 mV with a plus sign on the "inside". The diagram in Fig. 5**C** (2) simulates a situation on a membrane when the conductivity to sodium ions significantly exceeds the conductivity to potassium ions and the membrane potential is determined mainly by the equilibrium potential for sodium ions. Thus, the potential in an electrical circuit (let's call it Vm) (Fig. 2.4B) between the "inner" and "outer" sides can be determined by the formula:

$$\mathrm{Vm} = \mathrm{V1} - \frac{(\mathrm{V1+\ V2}) \cdot \mathrm{R1}}{(\mathrm{R1 + R2})} \quad (4)$$

Converting formula (4) we get

$$\mathrm{Vm} = \mathrm{V\,1} - \frac{\mathrm{V1\ (R2/\ R1\ )-V2}}{\mathrm{1\ +R2\ /\ R1}} \qquad (5)$$

A simple electrical circuit in Fig. 2.4**C** and formula (5) illustrates an important point in membrane physiology: the membrane potential can vary widely as a result of changes in its permeability (opening or closing of ion channels), while electrical sources determined by equilibrium potentials for ions remain unchanged.

2.2 Active ion transport

The studies initiated in the middle of the 20th century by Hodgkin and Keynes (1955) on the role of active ion transport in the formation of membrane potential turned out to be fundamentally important for elucidating the nature of the membrane potential of cells. It should be noted here that the membrane potential is fully determined by the Goldman, Hodgkin, Katz formula, it is necessary to achieve electrochemical equilibrium for each ion and, accordingly, the condition that all ion currents through the membrane are equal to zero would be fulfilled. However, it was found that in reality the cell gradually loses intracellular potassium and sodium ions diffuse inside from the extracellular medium. As a result, the ion concentrations on both sides of the membrane will equalize and the membrane potential will disappear. Therefore, it turned out that in addition to maintaining concentration ion gradients in the cell, there is an active ion transport carried out by a sodium-potassium pump. Schematically, one of the variants of the ion pump is shown in Fig. 2.5A. When studying the mechanisms of active transport, it was found that energy is needed for its functioning, and in particular the energy of ATP, which is released from ATP using an ion-activated ATPase. With the help of a pump, sodium and potassium ions are transferred in a certain proportion in the direction opposite to their passive movement, as opposed to the continuous flow of sodium ions into the cell and potassium out. Depending on the conjugacy of ion transport, the operation of the pump can be electrically neutral, for example, 1 Na+ is output outside and 1 K+ inside the cell, and does not contribute to the value of the membrane potential due to the passive permeability of the membrane to ions. The operation of the pump can be electrogenic, for example, 3 Na+ are output to the outside, and 2 K+ to the inside of the cell. In this case, the membrane potential will be shifted towards its increase in absolute magnitude (towards hyperpolarization). Calculations (Nicholls J.G. et al., 2003) show that the contribution can reach -11 mV.

For the membrane potential of the cell, taking into account the existence of active transport in the cell, Mullins and Noda (1963) later derived the Mullins-Noda formula:

$$\text{Ем} = -\frac{RT}{nF}\lg\frac{rPK[K]o+PNa[Na]o}{rPK[K]i+PNa[Na]i} \qquad (6)$$

where **r** is the ratio of the number of ions carried by the ion pump, the other designations in the formula are the same as in the formula of Goldman,