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The role of ion channels in the vital functions of the cell

Abstract

The cell ion channels are complex protein structures with molecular systems of opening, closing, selectivity, inactivation and regulation. The purpose of this review is to generalize and systematize literature data on the structural and functional characteristics of ion channels and methods for studying their activity. Violations of their activity can lead to a change in the functioning of the cell and the whole organism as a whole, therefore, further study of the structural and physiological characteristics of ion channels is promising and relevant.

Keywords: ion channels, methodological approaches to definition

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Introduction

Cell ion channels are complex protein structures with molecular systems of opening, closing, selectivity, inactivation and regulation. They perform a number of functions. Many modulators of cell metabolism also exert their effect through ion channels. By providing transport of ions and water through the membrane, intracellular concentration of calcium ions, they regulate the pH and volume of the cell. Often being receptors, channels are included in the systemic regulation of the functions of individual cells, organs and systems of the body as a whole. Ion channels are of particular importance in excitable cells. They provide the formation of the resting membrane potential (MP), excitability, as well as active or passive depolarization, initiate the release of hormones and contraction of muscle fibers. The activity of ion channels underlies the generation and propagation of action potential in neurons, which are necessary for the transmission of excitatory and inhibitory impulses. Ion channels take part in the processes of information transfer from one nerve cell to another, including exocytosis of synaptic vesicles with the release of a mediator and its interaction with the receptors of the postsynaptic membrane, provide fine-tuning of pre- and postsynaptic activity by feedback and retrograde signals. These processes underlie the most complex integrative functions of the brain, short-term and long-term synaptic plasticity, participating in memory mechanisms.[1–5] The proteins forming the channels are transmembrane and their extracellular sites and the pore of the channel itself are available for the action of extracellular chemical agents, both natural and artificial (pharmacological). Therefore, the study of the molecular mechanisms of ion channel blockade is necessary for pharmacology and medicine in general. One of the main problems of modern pharmacology is the lack of information about the molecular basis of the action of drugs. In order to predict the effect of certain drugs in physiological and pathological conditions, it is necessary to study the structure of ion channels and the mechanisms of their interaction with ligands at the molecular level.[6] The purpose of this review is to generalize and systematize the literature data on the structural and functional characteristics of ion channels and methods for studying their activity.

The main types of ion channels

All channels of excitable cells can be divided into two main types. The first type is the channels of rest, which spontaneously open and close without external influences. They are important for generating MP at rest. The second type is the so–called gate channels gate-channels (gate – gates). At rest, these channels are closed and can open under the influence of certain stimuli that can act directly on the channel or through a system of secondary intermediaries. Some varieties of such channels take part in the generation of electrical signals of excitable cells, action potentials (PD), synaptic and receptor potentials.[1,7]

Most ion channels are characterized by selectivity, that is, only specific ions pass through a certain type of channels. On this basis, sodium (Na), potassium (K), calcium (Ca), chlorine (Cl) channels are distinguished. The selectivity of the channels is determined by the size of the support, and it and its hydrate shell, the charge of the ion, as well as the charge of the inner surface of the channel. Non-selective channels can pass several different ions at once, for example, potassium and sodium or chlorine and potassium. There are channels through which all ions and larger molecules can pass.[7,8–13] The ion channel is characterized by two states – open and closed, and the transition from one state to another occurs instantly and the opening occurs only for a certain time. The time of the open state of the channel varies randomly, but its average time is a characteristic value for this type of channels. Some ion channels open quite often at rest and the probability of finding such channels in the open state in an inactive cell is relatively high. Activation of such channels by an adequate stimulus dramatically increases the likelihood of their opening. According to the activation method, all known ion channels can be divided into four groups. Some channels specifically respond to physical changes in the cell membrane of a neuron. The most prominent representatives of this group are potential-activated channels. Examples are the K^-, Na^-, Ca^-channels sensitive to the potential on the membrane, which are responsible for the formation of AP, opening when a certain potential is reached on the membrane.[14,15]

The group of channels activated by physical changes includes mechanosensitive channels that respond to mechanical influences (stretching or deformation of the cell membrane).[16] Ion channels of another group, ligand-activated, open when chemicals activate special receptor binding centers on the channel molecule. Such channels are divided into two subgroups depending on whether their receptor centers are intracellular or extracellular. Ligand-activated channels responding to extracellular stimuli are also called ionotropic receptors. They include channels sensitive to neurotransmitters and are directly involved in the transmission of information in synaptic

structures. Ligand-activated channels activated from the cytoplasmic side are sensitive to changes in the concentration of specific ions and intracellular ligands. For example, Ca^- activated K^- channels are activated by a local increase in the concentration of intracellular calcium. Such channels play an important role in cell membrane repolarization during AP completion. In addition to Ca^{2+} ions, cyclic nucleotides are typical representatives of intracellular ligands. Cyclic GMF is responsible for the activation of Na channels in the retinal rods, playing an important role in the work of the visual analyzer.

The classification of channels by activation method is largely conditional. Some ion channels can be activated only with a few impacts. For example, Ca^- activated K^- channels are also sensitive to potential changes, and some potential-activated ion channels are sensitive to intracellular ligands.[1,17] Metabotropic receptors are a complex of proteins consisting of the receptor protein itself, which binds to the neurotransmitter, G-protein, which, when activated, interacts with effector proteins – enzymes or ion channels, changing their activity. In the inactive form, the G-protein exists as an αβγ-heterotrimer binding guanidine diphosphate (GDF).Upon binding of the receptor protein to the ligand, the α-subunit is activated, which has a high affinity for guanidine triphosphate (GTP) and low affinity for the β-complex.as a result, the α-subunit releases GDF, attaches GTP and detaches from the β-dimer.

In the state of a complex with GTP, the α-subunit activates or inhibits various intracellular enzymes such as phospholipase A2, which catalyzes the release of arachidonic acid, adenylate cyclase, which catalyzes the synthesis of cAMP from ATP, guanylate cyclase, which catalyzes the synthesis of cGMP from GTP, phospholipase C, which cleaves phosphatidylinositol-4,5–diphosphate of the membrane to inositol- 1,4,5-triphosphate (IF3) and diacylglycerol (DAG). As a result, the level of secondary mediators – Ca^{2+} ions, cAMP, cGMP, IF3 and DAG - changes, which leads to the activation of the corresponding protein kinases: cAMP-dependent protein kinases (A-kinases), cGMP-dependent protein kinases (G-kinases), Ca^- calmodulin-dependent protein kinases (B-kinases) and Ca^- phospholipid-dependent protein kinases (C-kinases). Activation of protein kinases causes phosphorylation of ion channels and can initiate their opening or closing. In some cases, the β-dimer can interact with the subunits of ion channels, causing stimulation or inhibition of their activity. In this case, the G-protein directly interacts with ion channels. Unlike the ionotropic receptor, the metabotropic receptor is able to contact sequentially with many tens and hundreds of G-protein molecules, which, in turn, activate a large number of enzyme molecules, leading to a sharp increase in the response. This leads to the activation of a large number of ion channels and a prolonged physiological response.[18–21]

Sometimes an adequate stimulus can deactivate ion channels that were active at rest. Activation or deactivation of a channel means an increase or decrease in the probability of its opening, and not an increase or decrease in the time of the open state of the channel. In addition to the activation and deactivation processes, the ion current through the channel is regulated by other processes. The ion channel can go into a conformational state in which the usual activating stimulus is not able to cause the opening of the channel. For ion channels activated by potential, this state is called inactivation. According to the rate of inactivation, rapidly inactivating and slowly inactivating ion channels are distinguished. For channels responding to chemical stimuli, this condition is known as desensitization. Termination of the ion current through the channel may also occur when the channel is open. This happens if a large molecule binds to the ion channel and closes the pore. Another example is the blocking of channels with magnesium or cadmium ions. These cations, binding to the channel in the area of its mouth, prevent the penetration of other cations. Each channel is characterized by conductivity and permeability. The magnitude of the current passing through the ion channel is a direct reflection of the velocity of charged ions. The conductivity of the ion channel depends on two factors: the permeability of the channel and the concentration of ions near the mouth. In the absence of ions, there is no current. The permeability of the channel is determined by the peculiarities of the passage of ions through the channel. One of the possible mechanisms of ion movement is diffusion through an aqueous medium filling the channel pore. Penetrating ions interact with ion channel proteins. In solution, due to the presence of charge, the ions are always covered with a hydrate shell. If the ion channel pair is narrow, a certain amount of energy is needed to free it from the associated water molecules and allow it to penetrate through this section. In the channel and it can be an object of attraction or repulsion by the charges of the channel wall. The interaction of the ion with the walls of the ion channel can lead to peculiar "jumps" of the ion from one binding center to another. Such ion interactions can affect ion selectivity and the permeability of ion channels.[5,16,22]

Movement of ions through an open channel (conductivity)

The movement of ions in the channel is provided by the presence of two driving forces: chemical and electrical. The chemical driving force is determined by the difference in ion concentrations outside and inside the cell. The concentration of ions outside and inside the cell is not the same, which is due to the operation of special membrane transport systems-carriers (pumps). The electric driving force depends on the potential on the membrane. If the K^- channel is open, and there is a concentration gradient for potassium on the membrane, then K^+ ions begin to move through the channel and exit the cell. K^+ ions carry positive charges, so the membrane is positively charged from the outside, and the loss of positive charges by the cell leads to the appearance of a negative charge on the inner surface of the membrane. As a result, a potential difference is formed on the membrane (with a negative charge inside), resulting in an electric driving force that causes K^+ ions to enter the cell. As a result, the chemical force is balanced by the electric force, and the movement of K^+ ions through the channel stops. The electric potential on the membrane, which stops the movement of K^+ ions through the K^-channel along the concentration gradient, is called the equilibrium potential for potassium. There are selective channels in the membrane for Na^+, Ca^{2+} and Cl^- ions. The equilibrium potential depends only on the concentration of ions on both sides of the membrane.[1,3]

Principles of molecular organization of ion channels

The use of modern research methods has made it possible to determine the molecular structure of most of the known ion channels and to identify the functional significance of their elements. Any channel consists of several structural and functional parts responsible for opening, closing, selectivity, inactivation, regulation. The pore-forming part of the ion channel is a polypeptide organized in the form of several identical transmembrane domains, or several protein subunits, which can be either the same or different in structure. All channels in the pore-forming subunits have regulatory domains binding to various regulatory molecules. Channels have the property of selectively passing ions, which is realized in the narrowest part of the channel, the so-called selective filter. Cation-selective channels often have negatively charged residues in the region of the selective filter, which attract positive and repel negative ions.

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Many ion channels have one or more auxiliary subunits that play a modulatory, structural, or stabilizing role. These subunits can be divided into two main classes. One class consists of completely cytoplasmic intracellular subunits that do not have transmembrane domains, the other contains one or more transmembrane domains.[1,5]

Regulation of ion channels

The activity of ion channels can be regulated by a number of factors. Changes in the membrane potential not only stimulates potential-activated channels, but also modulates the operation of other types of ion channels. The channels are regulated by chemical ligands that can bind to the channels from both the extracellular and intracellular sides of the membrane. Inactivation of some potential-activated channels requires the entry of Ca^{2+} ions. Ca^{2+} ions can inactivate the channel either by directly binding to the channel site, or by activating the enzymes of their inactivation by protein dephosphorylation.

The channels can also be adjusted by pressure or tension (mechanically). In this case, the energy associated with the stretching of the membrane is transferred to the channel via the cytoskeleton or directly by changing the tension of the lipid bilayer. The rapid gate mechanisms of the channels can be regulated by long-term changes in the metabolic state of the cell. Some channels are sensitive to intracellular ATP levels, while others have gate properties that change in response to changes in the redox state and extracellular pH. Ion channels are targets of a number of intracellular mediators, which are formed as a result of activation of cascades of intracellular reactions: cyclic nucleotides, protein kinases, gaseous mediators, arachidonic acid, its metabolites and other fatty acids.[15,16,19]

Experimental methods of ion channel research

Registration of integral currents and potentials

The movement of ions through a huge number of different ion channels of the membrane forms an integral transmembrane current, which causes a redistribution of charge on the membrane and changes in potential. In this case, it is possible to register either changes in the potential on the membrane as a result of current flow, or current registration. Electrophysiological methods of recording the potential and current flowing through the membrane of an excitable cell can be conditionally divided into intracellular and extracellular. Metal electrodes or glass micropipettes (microelectrodes) are usually used for this.[23]

Fixing the potential

For these purposes, the technique of two-electrode potential fixation was used for the first time. The potential difference between the reference electrode placed in an isotonic sodium chloride solution and the measuring electrode is fed to the input of the operational amplifier, where it is compared with the command potential set by the experimenter. In the case of a difference in these potentials, a current injection compensating for this difference occurs through another electrode, which is measured by an ammeter. This value will be equal to the total value of all ion currents through the membrane. Further development of these ideas led to the creation of the currently main experimental method for studying the properties of ion channels – the method of local potential fixation (Patch clamp).[23,24]

Method of local fixation of potential

It allows recording the amplitude of ion currents of single channels due to the formation of a gigaohm contact between the glass electrode and the cell wall. Thus, a fragment of the membrane enclosed in a micropipette is isolated from the external environment, which reduces the noise of the captured signal. There are the following varieties of this method, depending on which the necessary electrolyte composition is selected in a micropipette:

Whole-cell

Pressure is applied to the pipette in such a way as to disrupt the integrity of the isolated membrane segment. After that, the composition of the cytoplasm is aligned with the electrolyte composition of the micropipette.

Cell-attached

This configuration differs only in the occurrence of gigaomic contact with a slight deformation of the membrane without a clear violation of integrity. Both electrodes are located on the same side of the membrane. To set the transmembrane potential difference (external – pipette electrode), it is necessary to use washing solutions, which creates difficulties due to the multicomponent cytoplasmic composition

Inside-out

An isolated section of the membrane is torn from the cell, and this system is immersed in a washing solution close in content to the cytoplasm. Then the potential difference on the membrane is strictly equal to the potential difference between the electrodes. A feature of this configuration is the ability to register a single channel.

Inside-in

The transition from the "Whole-cell" configuration is carried out by slow removal of the micropipette, due to which, after the rupture of the uninsulated sections, the membrane closes in an inverted form. As with the use of "Inside-out", the method allows the study of single channels.[15,18,23,24]

A combined quantum-classical method is used to calculate the energy profiles of ions in channels. For this purpose, the following methods are used: calculation of ion energy profiles (force fields of molecular mechanics) and functional characteristics of channels (theory of absolute rates of Eyring reactions), combined quantum-classical method, method of "energy alignment" of tertiary protein structures (construction of chirally modified model channels with modified primary structure, structurally and functionally equivalent to the corresponding natural channels).[9]

Molecular modeling of ion channel operation

This method contributes to the development of a more precise pharmacological effect on the cell, as it is used for the design of new drugs of medical importance. The ion conduction model allows a purposeful approach to the creation of qualitatively new ligands that provide an incomplete block of ion channels. Molecular modeling consists in finding the structural template of the channel, aligning its amino acid sequences and constructing the model itself. The calculations use the approximation of atom-atomic potentials, taking into account the dependence of the dielectric constant on the distance.[6,25–27]

Conclusion

Cell ion channels are complex protein structures with molecular systems of opening, closing, selectivity, inactivation and regulation. Violations of their activity can lead to changes in the functioning of

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the cell and the whole organism as a whole. The development of new methods for studying the work of ion channels can be used to study the effects of drugs and other chemical agents on the body, as well as to search for new effective pharmacological drugs, the active centers of which are ion channel receptors.

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None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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