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POTASSIUM CHANNELS AND SIGNAL TRANSDUCTION PATHWAYS IN NEURONS

The article is dedicated to the 90th anniversary of the outstanding Ukrainian physiologist academician Platon Kostyuk, who devoted himself to ion channel research.

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Potassium (K^+) channels constitute the most diverse class of ion channels; these channels are especially important for regulation of the neuronal excitability and provide signaling activity in a variety of ways. These channels are major determinants of the membrane excitability, influencing the resting potential of the membranes, waveforms and frequencies of action potentials, and thresholds of excitation. Voltage-gated K^+ channels do not exist as independent units merely responding to changes in the transmembrane potential; these are macromolecular complexes able to integrate a great variety of cellular signals that provide fine tuning of channel activities. Compounds that change K^+ channel properties are commonly employed as therapeutic agents in a number of pathologies, in particular, arrhythmias, cancer, and neurological disorders (psychoses, epilepsy, stroke, and Alzheimer's disease).

Keywords: potassium channels, signal function, neurological disorders.

INTRODUCTION

It is clear that the impact
of ion channel research on our
understanding of the nervous
system is only starting. (F.Bezanilla, 2008).

Academician Platon Kostyuk in his monograph published by the Physiological Society ("Plasticity in nerve cell function," 1998) demonstrated that the most unique feature of the nervous system can probably be described as *plasticity*. For years, long-lasting plasticity of synaptic transmission was the favorite mechanism to account for information storage in the brain. Calcium signals participate in an extremely complicated intracellular machinery that is capable of controlling structural and functional properties of the neurons [1-3]. Recent evidence indicates that the neuronal message is also persistently filtered through regulation of the functioning of voltage-gated ion channels. Changes in the expression level or biophysical properties of ion channels may alter a large range of functional processes such as dendritic integration, spike generation, signal propagation via the dendritic and axon, and regulation of the plasticity thresholds [4-7].

Potassium channels (K^+ channels) have at present been identified in virtually all types of cells in all organisms where they are involved in a great variety of physiological functions. These channels are ubiquitous and critical for life. They are found in *Archaebacteria*, *Eubacteria*, and eukaryotic cells, both plant and animal; their amino acid sequences can be very easily recognized because K^+ channels always contain a highly conservative segment called the K^+ channel signature sequence. This sequence forms a structural element known as the selectivity filter; it prevents passage of Na^+ ions but allows K^+ ions to move through the membrane at rates approaching that of the diffusion limit. The K^+ selectivity filter catalyses dehydration, transfer, and rehydration of a K^+ ion within about ten nanoseconds. This physical process is absolutely crucial for the production of electrical signals in biology. Within a certain time interval, the selectivity filter contains two K^+ ions about 0.75 nm apart. This configuration promotes the ion conduction by exploit-

ing electrostatic repulsive forces to overcome attractive forces between K^+ ions and the selectivity filter. The architecture of the channel pore determines the physical principles underlying selective K^+ conduction [1-4]. This is the hallmark of K^+ channels, namely the nearly perfect selectivity for K^+ ions over Na^+ ions in the setting of very high K conduction rates. In some members of the family of voltage-gated K^+ channels, the removal of internal and external K^+ allows Na^+ ions to permeate through the pore [8-12].

POTASSIUM CHANNELS AND INTEGRATION OF THE SIGNALS IN NEURONS

Effective control over the phenotype of individual neurons is based on the regulation of transcription and translation of the relevant genes, and such control is provided perfectly. Many types of channels and receptors are expressed in units of the nervous system, contributing to the complex and diverse functional repertoires of functioning of the neurons [12]. Complex processing and integration of the signals observed in neurons are facilitated by a variety of gating properties of different ion channels, particularly of those of voltage-gated K^+ channels [6].

Potassium (K^+) channels form the most diverse class of the ion channels. These channels are crucially important for the regulation of neuronal excitability and for the formation of signaling activity in a variety of ways. These channel structures are major determinants of the membrane excitability; they influence the resting potential on the membranes and modulate the waveforms and frequencies of action potentials (APs) and thresholds of excitation. Voltage-gated K^+ channels are key components of multiple signal transduction pathways. The functional diversity of K^+ channels is much more extensive than the molecular diversity of the respective class of the genes. A distinctive combination of K^+ channels endows neurons with a broad repertoire of the excitation properties and allows each neuron to respond in a specific manner to a given input within a given time interval. The properties of many channels can be modulated by second messenger pathways activated by neurotransmitters and other types of stimuli. Potassium channels are among the most frequent targets for the actions of several signaling systems [11-14].

The diversity of different members of the K^+ channel family is related mainly to various ways in which K^+ channels come from the closed state to the open one. Some K^+ channels are ligand-gated, which means that pore opening is energetically coupled with an ion, a small organic molecule, or even a protein molecule. Other K^+ channels are voltage-gated; in this case, opening is energetically coupled to the movement of a charged voltage sensor within the membrane electric field. Therefore, different kinds of K^+ channels open in response to different stimuli, namely to changes in the intracellular Ca^{2+} concentration, to levels of certain G-protein subunits in the cell, or to a value of the membrane voltage.

The specificity of information is generally encoded by the kinetics of the frequency, duration, bursting, and summation of APs. A neuron (or a specific axon, or a dendrite), when it is necessary to change its firing pattern, can rapidly regulate the gating behavior of the existing channels. If longer-term modifications of the firing patterns are required, the cell may alter the transcriptional expression of the ion channel genes for providing diverse functions. The number of K^+ channel genes is relatively large; the diversity of endogenous K^+ current phenotypes observed in various excitable cells is, however, much greater. Additional processes such as alternative splicing, posttranslational modification, and heterologus assembling of pore-forming subunits in tetramers contribute to extend the functional diversity of a limited repertoire of the K^+ channel gene products. Even greater diversity can be achieved through interactions between K^+ channel proteins and accessory proteins or subunits [15-19].

General mechanisms of ion channel targeting are of considerable interest. Historically, targeting and cellular localization of K^+ channels were believed to be primarily related to protein-protein interactions. However, there is increasing interest in the potential role of cellular lipids in the regulation of K^+ channel localization, which was determined by a revised view on the membrane organization. The traditional fluid mosaic model has been modified to reflect the developing appreciation on the membrane lipid heterogeneity. The existence of membrane microdomains, particularly those referred to as lipid rafts, has motivated investigators to examine the role of protein–lipid interactions in the ion channel localization more closely. Lipid rafts are specialized membrane microdomains rich in sphingolipids and cholesterol. These rafts have been implicated in the organization of many membrane-associated signal pathways. Biochemical and functional studies indicated that K_v channels are in close spatial relations with lipid raft microdomains on the cell sur-

face [15].

Precise control of the neuronal AP patterns underlies the basic functioning of the central and peripheral nervous systems. This control relies, to a significant extent, on the adaptability of voltage-gated potassium, sodium, and calcium channels. The importance of voltage-gated ion channels in mediating and sculpting electrical signals in the brain is well established. Theoretical and experimental reports described how neurons can respond to changing inputs by adjusting their firing properties, and these events are mediated by modification of voltage-gated ion channels [5]. Recently obtained evidence indicates that neuronal output messages are persistently filtered through regulation of voltage-gated ion channels [14]. There are many genes encoding the pore-forming subunits of the "classical" voltage-gated ion channels in mammalian neurons.

Complex processing and integration of the signals observed in neurons are facilitated by a diverse range of the gating properties of ion channels typical of this cell type, particularly of those of the voltage-gated K^+ channels. Distinctive combinations of ion channels endow neurons with a broad repertoire of excitation properties and allow each neuron to respond in a specific manner to a given input at a given moment. The properties of many K^+ channels can be modulated by second messenger pathways activated by neurotransmitters and other stimuli.

It is now widely recognized that voltage-gated K^+ channels exist not as independent units merely responding to changes in the transmembrane potential but as macromolecular complexes able to integrate an enormous multiplicity of cellular signals providing fine tuning of channel activities. Proteins associated with K^+ channels may do so dynamically with regulated on- and off- rates, or they may be constitutive components of the complexes determining the lifetime of the channel protein. The functional results of interactions with these accessory proteins include alteration of the channel assembling, trafficking, protein stability, gating kinetics, conduction properties, and responses to signal transduction events [17]. Although a single type of the K^+ channel α subunit is often present in a variety of different organs, the kinetic behavior and conformational changes of α subunits can be modulated by co-assembling with an ancillary subunit. The expression of ancillary subunits varies between organs, as well as between regions of one and the same organ [19]. This diversity of the ancillary subunit expression, therefore, contributes to the diverse assortment of potassium currents recorded from native tissues. In addition, relative expression of K^+ channels and their associated ancillary subunits can be affected by a number of factors. The latter change in the course of development, with modifications of the hormonal state, under ischemic conditions, etc., these factors also modulate the electrophysiology and pharmacology of native potassium currents [17]. Potassium channels encompass numerous auxiliary subunits, and many channels can be assembled with heteromers of multiple subunits and splice variants, rendering the combinatorial diversity of voltage-gated ion channels truly staggering [6].

Potassium currents contribute in a diverse mode to the specificity of neuronal firing patterns. The composition of these currents may be determined by regulated transcription, alternative RNA splicing, and post-translational modifications. Alternative splicing is obvious in nearly all metazoan organisms as a means for producing functionally diverse polypeptides from a single gene [16].

As is generally accepted, a neuron can be divided into three interrelated modules, namely the *input, integration core,* and *output.* Historically, voltage-gated ion channels were postulated to play a crucial role at the *output* part of the neuron. A passive integrator feeds an algebraic sum of *inputs* of the neuron to a nonlinear integrating device (cell body), which fires APs depending on the *inputs* it receives. The role of various voltage-gated ion channels in modulating single APs and their bursts have been teased apart, and significant information is available on the activation, deactivation, and inactivation dynamics of various ion channels within millisecond-order time intervals. Later on, equipped with the knowledge that there are conductances active in the subthreshold states and that neuronal dendrites possess the respective ion channels, the role of voltage-gated channels in the integration module began to attract special attention. Experimental and theoretical evidence is being accumulated on how ion channels could contribute to integration of synaptic inputs localized on and outside of the dendrites or to back-propagating APs [18, 20]. Potassium channels located in the dendrites of hippocampal CA1 pyramidal neurons control the shape and amplitude of back-propagating APs, the amplitude of excitatory input effects, and the dendrite excitability. Non-uniform gradients in the distribution of K^+ channels on the dendrites make the dendritic electrical properties markedly different from those found in the soma [21].

Ion channels are not only crucial in neurons of healthy individuals; several types of these channels have been implicated in the pathogenesis of certain diseases, both genetic and acute. The successfulness of searching for possible treatments of channel-associated diseases will be higher if we understand in detail how channels, including K^+ ones are implicated in physiology of the cell and if we will be able to design modifications that restore normal functions of the channels [10]. For example, several human genetic diseases involving cardiac arrhythmias, deafness, epilepsy, diabetes, and misregulation of the blood pressure, are caused by disruptions of the K^+ channel genes [9].

The K^+ channel activity is modulated by external and internal K^+ ions. Elevation of the $[K^+]_O$ may occur just through high levels of neuronal activity and through specific actions of neurotransmitters on glial cells. Some of the effects of changes in the $[K^+]_O$ can be attributed to shifts in the K^+ equilibrium potential, which modify both the resting potential in the cells and the driving force for K^+ currents. Variations in the $[K^+]_O$ are implicated in the pathogenesis of a few disorders, including epileptiform seizures and electrical instability of the heart following acute ischemia. These changes might occur through $[K^+]_O$-determined modulation of K^+ channels and changes in the firing pattern of the neuron due to shifts in the $[K^+]_O$ [9].

Two distinct molecular mechanisms for K^+ channel inactivation have been described. These are an N-type mechanism related to rapid occlusion of the open channel by an intracellular tethered blocker, and a slow C-type mechanism involving a slower change at the extracellular mouth of the pore. These two mechanisms should be coupled in some a way [22]. Recent experiments showed that slow C-type inactivation can be further divided into P-type and C-type. Slow inactivation of K^+ channels can be strongly influenced by permeating ions. Cumulative inactivation of voltage-regulated K^+ channels is thought to be due to the P/C-type inactivation state, the recovery from which is slow [23-25]. Cumulative inactivation of K^+ channels appears to be state-dependent and voltage-independent. Cumulative inactivation, similar in its mechanisms to that of K^+ channels, is manifested in Ca^{2+} channels [26]. One of the main causes of the frequency-dependent spike broadening during repetitive discharges is cumulative inactivation of certain K^+ channels. Such AP broadening can modify a few aspects of neuronal signaling [27-29].

Tetraethylammonium (TEA) ions have been for many years used as effective probes in the research of the structure and functions of K^+ channels. This is, perhaps, due to the fact that TEA ions are positively charged (similarly to K^+ ions) and have about the same size as hydrated K^+ ions. External TEA blocks many types of K^+ channels, but within an about 1000-fold range of effective concentrations [30-31]. This difference can mostly be attributed to certain amino acid residue at a single position in the outer entrance to the pore [32]. Results of recent molecular dynamic simulations and electrostatic calculations allowed researchers to suggest that the external TEA binding site in K^+ channels is localized outside with respect to the membrane electric field. The TEA-binding site is formed by a bracelet-like complex of pore-lining aromatic residues. The center of the bracelet can bind a TEA ion via a cation-π orbital interaction [30-31, 33].

The K^+-dependent conformational alteration that resulted in a change in the $[TEA]_O$ potency correlates with the effect of K^+ on the inactivation rate. As the $[K^+]_O$ increased, the $[TEA]_O$ potency and inactivation rate also increased. The effects of $[K^+]_O$ on epy inactivation rate became saturated at the same value of $[K^+]_O$ as the effect on the $[TEA]_O$ potency did. These results suggest that different channel conformations associated with different $[TEA]_O$ potencies can affect the rate of slow inactivation. The selectivity filter is an integral part of the inactivation mechanisms. The selectivity filter is the site through which K^+ ions influence the channel conformation [31, 34, 35].

Potassium channels mediate outward K^+ currents and increase the membrane conductance; they tend to hyperpolarize the cell membrane and attenuate the effects of excitatory stimuli. Potassium channels are, therefore, normally regarded as inhibitory, i.e., they reduce the neuronal excitability. Genetically provoked suppression of K^+ channel activity in mice causes the development of epileptiform activities. Pharmacological blocking of K^+ channels, e.g., with 4-aminopyridine or barium, readily evokes epileptic seizures. Compounds having K^+ channel blocking properties are commonly employed as therapeutic agents for a number of conditions such as arrhythmias, cancer, and neurological disorders, including psychoses, epilepsy, stroke, and Alzheimer's disease. There is a wide variety of therapeutic agents targeted to non-K^+ channels but providing an unintended block of K^+ channels. This type of K^+ channel blocking can result in potentially serious and sometimes even fatal side effects (e.g., in the case of cardiac arrhythmias) [17].

CONCLUDING REMARKS

Regulation of transcription and translation of the relevant genes exerts significant control effects on the phenotype of individual neurons. Many types of channels and receptors contributing to diverse functional repertoires of the neurons are expressed in the nervous system. Complex processing and integration of the signals observed in neurons are facilitated by an extensive range of the gating properties of ion channels in this cell type, particularly of voltage-gated potassium channels.

Potassium channels form the most diverse class of ion channels; these channels are crucially important for the regulation of neuronal excitability and signaling activity in a variety of modes. They are major determinants of the membrane excitability, influencing the resting potential on the membranes, waveforms and frequencies of action potentials (APs), and thresholds of excitation. Potassium channels fulfill important functions in many signal transduction pathways in the nervous system. Voltage-gated K^+ channels are key components of a number of signal transduction pathways in the cell. The functional diversity of these channels exceeds many times the considerable molecular diversity of the respective genes. Distinctive combinations of the properties of K^+ channels endows neurons with a broad repertoire of their excitation properties and allow each neuron to respond in a specific manner to a given input at a given time. The properties of many channels can be modulated by secondary messenger pathways activated by neurotransmitters and certain other stimuli. Potassium channels are among the most frequent targets for the actions of several signaling systems. Potassium channel activity is significantly modulated by external and internal K^+ ions. Significant elevation of the $[\ K^+\ ]_O$ may occur just through high levels of neuronal activity and through specific actions of neurotransmitters on glial cells [1].

The information contained in spike timing is available immediately rather than after an averaging integration period. Furthermore, timing of the AP patterns can potentially transmit even more information than timing of individual constituent spikes. If longer-term modifications of the firing patterns are required, the cell may alter the transcriptional expression of ion channel genes.

The selectivity of ion channel pores has generally been regarded as the fixed one. However, recent studies on various classes of ion channels challenged the generality of this idea and showed that some ion channels can significantly modify their ion selectivity, and normally impermeant ions begin to permeate under some certain circumstances. This phenomenon represents both a new functional aspect of physiology of ion channels and allows one to propose a suggestion on novel ways by which channels may process information in the nervous system [35]. Ion channels are not only crucial molecular membrane objects in healthy individuals; some of them have been implicated in the pathogenesis of different diseases, either genetic or acute [19].

This publication was not associated with any experiments on animals or tests involving human subjects; therefore, it does not require confirmation of compliance with existing ethical standards from this aspect.

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КАЛІЄВІ КАНАЛИ ТА ШЛЯХИ ПЕРЕДАЧІ КЛІТИННИХ СИГНАЛІВ В НЕЙРОНАХ

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Р е з ю м е

Калієві канали виконують важливі функції у великій кількості шляхів передачі клітинних сигналів у нервовій системі. Складна обробка та інтеграція сигналів, котрі спостерігаються в нейронах, полегшуються через наявність великого набору воротних властивостей іонних каналів, зокрема таких властивостей потенціалкерованих калієвих каналів. Специфічні сполучення калієвих каналів забезпечують нейронам широкий репертуар характеристик збудливості та дозволяють кожному нейрону відповідати специфічним чином на дію конкретного вхідного сигналу в конкретний момент часу. Властивості багатьох калієвих каналів можуть модулюватися під дією шляхів вторинних месенджерів, активованих нейротрансмітерами та стимулами інших видів. Калієві канали формують найбільш різноманітний клас іонних каналів. Ці канали істотно важливі для регуляції збудливості нейронів та сигнальної активності, що здійснюється різним чином. Дані канальні структури є основними детермінантами збудливості мембрани, впливаючи на потенціал спокою мембран, форму та частоту потенціалів дії та пороги збудження. Потенціалкеровані калієві канали

не існують як незалежні одиниці, в основному відповідальні за зміну мембранного потенціалу; це макромолекулярні комплекси, здатні інтегрувати колосальну кількість клітинних сигналів, котрі реалізують тонку настройку активності каналів. Сполуки, котрі змінюють властивості калієвих каналів, широко використовуються як терапевтичні агенти в таких випадках, як аритмії, ракові захворювання та неврологічні розлади (психози, епілепсія, інсульти та хвороба Альцгеймера). Цілями значної кількості терапевтичних агентів є канали, що не відносяться до калієвих, але «ненавмисно» блокують саме калієві канали. Таке блокування калієвих каналів може зумовлювати потенційно дуже серйозні або навіть смертельні побічні ефекти.

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