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Signal function of potassium channels – clinical aspects

Potassium (K^+) channels are the most diverse class of ion channels, and are important for regulating neuronal excitability and signaling activity in a variety of ways. They are major determinants of membrane excitability, influencing the resting potential of membranes, wave forms and frequencies of action potentials, and thresholds of excitation. Voltage-gated K^+ cannels exist not as independent units merely responding to changes in transmembrane potential but as macromolecular complexes able to integrate a plethora of cellular signals that fine tune channel activities. There are a wide variety of therapeutic agents that are targeted to non-K^+ channels, but result in unintended block of K^+ channels. This K^+ channel block can result in potentially serious and sometimes even fatal side effects.

Key words: K^+ channels; cumulative inactivation; ancillary subunits; neuronal signaling; genetic diseases.

INTRDUCTION

Potassium (K^+) channels are major determinants of membrane excitability, influencing the resting potential of membranes, wave forms and frequencies of action potentials, and thresholds of excitation. Potassium channels fulfill important function in many signal transduction pathways in the nervous system. Voltage-gated K^+ channels are key components of multiple signal transduction pathways. The functional diversity of potassium channels far exceeds the considerable molecular diversity of this class of genes. A distinctive combination the of K^+ channels endows neurons with a broad repertoire of the excitable properties and allows 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 second messenger pathways activated by neurotransmitters and other stimuli. K^+ channels are among the most frequent targets of the actions of several signaling system [1, 7, 20, 28]. Since potassium (K^+) channels mediate outward K^+ currents and increase the membrane conductance, they tend to hyperpolarize the cell and attenuate the effects of excitatory stimuli.

Ion channels are not only crucial in healthy individuals, but several of them have been implicated in disease, either genetic or acute. The possible treatments to channel associated disease will be accelerated if we understand in detail how channels are implicated in the physiology of the cell and if we could design modifications that restore normal function [4]. For example several human genetic diseases, such as pathologies involving cardiac arrhythmias, deafness, epilepsy, diabetes, and misregulation of blood pressure, are caused by disruption of K^+ channel genes [20].

Genetic suppression of K channel activity in mice causes epilepsy. Also pharmacological blockade of K^+ channels, e.g. with 4-aminopyrine or barium, readily causes epileptic seizures. There are a wide variety of therapeutic agents that are targeted to non-K^+ channels, but result in unintended block of K^+ channels. This K^+ channel block can result in potentially serious and sometimes even fatal side effects /e.g. cardiac arrhythmias/ [5].

K^+ CHANNELS AND INTEGRATION OF THE SIGNALS IN NEURONS

Diversity among different members of the K^+

channel family is related mainly to the various ways in which K^+ channels are gated open. Some K^+ channels are ligand gated, which means that pore opening is energetically coupled to the binding of an ion, a small organic molecule, or even in some cases a protein. Other K^+ channels are voltage gated, in which case opening is energetically coupled to the movement of a charged voltage sensor within the membrane electric field. Therefore, the different kinds of K^+ channels open in response to different stimuli: a change in the in the intracellular Ca^{2+} concentration, the level of certain G- protein subunits in the cell, or the value of the membrane voltage.

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

The general mechanisms of ion channel targeting are of considerable interest. Historically, K^+ channels targeting and cellular localization were believed to involve primarily protein-protein interactions. However, there is increasing interest in the potential role for cellular lipids in the regulation of channel localization, which is the result of a revised view of membrane organization in which the traditional fluid mosaic model has been updated to reflect a developing appreciation of 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 ion channel localization more closely. Lipid rafts are specialized membrane microdomains that are rich in sphingolipids and cholesterol. These rafts have been implicated in the organization of many membrane-associated signaling pathways. Biochemical and functional evidence indicate that K_v channels, in addition to other ion channels, localize to lipid raft microdomains on the cell surface [26].

A precise control of neuronal action potential patterns underlies the basic functioning of the central and peripheral nervous system. This control relies on the adaptability voltage gated of potassium, sodium and calcium channel activities. The importance of voltage-gated ion channels in mediating and sculpting electrical signals in the brain is well established. Theoretical and experimental reports explore how neurons can respond to changing inputs by adjusting their firing properties, through the modification of voltage–gated ion channels Regulation of transcription and translation of the relevant genes exerts significant conrol over the phenotype of individual neurons. Many types of channels and receptors are expressed in the nervous system, contributing to the complex and diverse functional repertoires of neurons [30]. Complex processing and integration of the signals observed in neurons are facilitated by a diverse range of the gating properties of the ion channels in this cell type, particularly of the voltage-gated K^+ channels [4, 14, 16, 22, 25, 32].

Recent evidence indicates that the neuronal message is persistently filtered through regulation of voltage–gated ion channels [10]. 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 the ion channels in this cell type, particularly of the voltage-gated K^+ channels. A distinctive combination of ion channels endows neurons with a broad repertoire of the excitable properties and allows each neuron to respond in a specific manner to a given input at a given time. 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^+ cannels exist not as independent units merely responding to changes in transmembrane potential but as macromolecular complexes able to integrate a plethora of cellular signals that fine tune channel activities. Proteins that associate with K^+ channels may do so dynamically with regulated on- and off-rates or they may be constitutively complexes for the lifetime of the channel protein. The functional result of interactions with these accessory proteins includes altered channel assembly, trafficking, protein stability, gating kinetics, conduction properties, and responses to signal transduction evens [27]. Although a single type of K^+ channel α-subunit is often present in a variety of different organs, the kinetic behavior and conformational changes of α-subunits are often modulated by co-assembly with ancillary subunit. The expression of ancillary subunits varies between organs, as well as between regions of an organ [13]. This diversity of 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 factors such as development, changes in hormonal state, ischemic conditions, etc., which can also modulate the electrophysiology and pharmacology of native potassium currents [5]. K^+ channels encompass numerous ancillary subunits, and many can be assembled with heteromers of multiple subunits and splice variants, rendering the combinatorial diversity of voltage-gated ion channels truly staggering [29].

Potassium current diversity contributes to the specificity of neuronal firing patterns and may be achieved by regulated transcription, alternative RNA splicing, and posttranslational modifications. (Alternative splicing is seen in nearly all metazoan organisms as a means for producing functionally diverse polypeptides from a single gene [6].

A single neuron can be broadly divided into three interrelated modules: input, integration, and output. Historically, voltage –gated ion channels were postulated to pay a crucial role at the output end of a neuron. A passive integrator feeds an algebraic sum of its inputs to a nonlinear device (the cell body), which fires action potentials depending on the inputs they receive. The role of various voltage – gated ion channels in modulating the single action potentials and their bursts have been teased apart, and significant information is available about the activation, deactivation, and inactivation dynamics of various ion channels within those millisecond periods. Later, equipped with the knowledge that there are conductance's that are active subthreshold and that dendrites possess ion channels, the role of voltage- gated ion channels in the integration module received attention. Experimental and theoretical evidence is accumulating on how ion channels could contribute to integration of synaptic inputs with and without dendrites or back propagating action potentials [29, 14, 33].

Potassium channels located in the dendrites of hippocampal CA1 pyramidal neurons control the shape and amplitude of back-propagating action potentials, the amplitude of excitatory postsynaptic potentials and dendrite excitability. Non- uniform gradients in the distribution of potassium channels in the dendrites make the dendritic electrical properties markedly different from those found in the soma [14].

K^+ channels activity is modulated by external and internal K^+ ions. Elevation of $[K^+]_0$ may occur just through high levels of neuronal activity and through specific actions of neurotransmitters on glial cells. Some of the

affects of changes in $[K^+]_0$ can be attributed to the shift in the K^+ equilibrium potential, which modifies both the resting potential of the cells and driving force for K^+ current. Variations in $[K^+]_0$ have been implicated in pathogenic of several disorders, such as epileptyform seizures and electrical instability of the heart following acute ischemia. These changes might occur through the modulation of K^+ channels by $[K^+]_0$ and modulating the firing pattern of neuron as a function of $[K^+]_0$ [7].

Two distinct molecular mechanisms for K^+- channel inactivation have been described: N – type, which involves rapid occlusion of the open channel by an intracellular tethered blocker, and slow C-type, which involves a slower change at the extra cellular mouth of the pore. The two mechanisms must be coupled in some way [3, 21]. Recent experiments show that slow C-type inactivation can be further divided into P-type and C-type. The slow inactivation of K^+ channels can be strongly influenced by permeating ions. The cumulative inactivation of voltage-regulated K^+ channels is thought to be due to P/C-type inactivation state, from which recovery is slow [17, 18, 24]. Cumulative inactivation of the appears to be state-dependent and voltage – independent. Cumulative inactivation, which is similar in its mechanisms to that in K^+ channels, is manifested in Ca^{2+} channels [31]. One of the main causes of frequency – dependent spike broadening during repetitive discharges is cumulative inactivation of certain K^+- channels. Such spike broadening can modify several aspect of neuronal signaling [2, 19, 23, 25].

TEA ions have been useful probes of the structure and function of K^+ channels, perhaps because TEA is positively charged, like K^+ ions, and about the same size as a hydrated K^+ ion. External TEA block many types of K^+ channels but with 1000- fold range of effective concentrations [15, 34]. Much of this difference can be attributed to the amino acid at a single position in the outer entrance to the pore [21](MacKinnon, Yellen 1990). Recent molecular dynamic simulation and electrostatic calculations suggested that the external TEA binding site in K^+ channels is outside the membrane electric field. TEA-binding site formed by a bracelet of pore-lining aromatic residues. The center of the bracelet could bind a TEA through a cation-p orbital interaction [9,15,34].

The K^+- dependent conformational alteration that resulted in a change in $[TEA]_0$ potency was correlated with the effect of K^+ on inactivation rate. As $[K^+]_0$ was increased, $[TEA]_0$ potency and effects of $[K^+]_0$ on inactivation rate saturated at the same $[K^+]_0$ as the effect on $[TEA]_0$ potency. These results suggest that the different channel conformations, which are associated with different $[TEA]_0$ potency, can affect the rate of slow inactivation.

The architecture of the pore establishes the physical principles underlying selective K^+ conduction [11]. The selectivity filter is an integral part of the inactivation mechanisms. The selectivity filter is the site, which K^+ influenced the channel conformation [8, 12, 24].

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СИГНАЛЬНА ФУНКЦІЯ КАЛІЄВИХ КАНАЛІВ – КЛІНІЧНІ АСПЕКТИ

Механізми інтегрування сигналів у нейронах деякою мірою пов'язані з функціонуванням різноманітних типів іонних каналів. Особливо важлива роль належить калієвим каналам. Певна сукупність цих каналів властива кожному типу нейронів і забезпечує різноманітні прояви збудливості, що дає змогу нейрону у певний час специфічно відповідати на вхідний сигнал. Властивості багатьох різновидів калієвих каналів можуть модулюватися дією вторинних посередників, нейромедіаторами або іншими стимулами. Калієві канали являють собою найбільш розповсюджені мішені для дії низки сигнальних систем. Фармакологічні впливи на калієві канали, використовують як терапевтичні засоби.

Ключові слова: калієві канали, кумулятивна інактивація, супутні субодиниці, нейрональні сигналізація, генетичні захворювання.

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СИГНАЛЬНАЯ ФУНКЦИЯ КАЛИЕВЫХ КАНАЛОВ – КЛИНИЧЕСКИЕ АСПЕКТЫ

K^+ каналы являются важнейшими детерминантами мембранной возбудимости. Они определяют потенциал покоя мембран, частоту и характер протекания потенциалов действия, порог возбуждения. Потенциалуправляемые K^+ каналы не являются независимыми структурами, которые отвечают на изменения мембранного потенциала. Они представляют макромолекулярные комплексы, способные интегрировать совокупность клеточных сигналов, влияющих на активность каналов. K^+ каналам принадлежит важная роль в осуществлении преобразований сигналов в нервной системе. Функциональное многообразие каналов намного превышает многообразие генов, кодирующих K^+ каналы. Такие генетически обусловленные заболевания человека как определенные типы аритмий, глухота, эпилепсия, диабет, расстройство регуляции кровяного давления – обусловлены нарушениями в генах K^+ каналов.
Ключевые слова: K^+ каналы, кумулятивная инактивация, сопутствующие субъеденицы, нейрональная сигнализация, генетические заболевания.

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