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Research progress on calcium-activated potassium ion channels

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Abstract. Potassium ion channels are diverse and widely distributed, playing a key role in a variety of physiological and pathological processes. According to the size of the conductance, they can be divided into large conductive calcium activated potassium channel (BK channel), medium conductive calcium activated potassium channel (IK channel) and small conductive calcium activated potassium channel (SK channel). In recent years, remarkable progress has been made in studying these three ion channels, and a series of therapeutic drugs have emerged. According to the single channel conductance, the BK channel, IK channel and SK channel, and the structure and functions of the three types of channels are introduced respectively. The main structure is composed of a tetrameric protein and a cavity in the center. These three types of potassium channels play a role in various clinical diseases, such as hypertension, Parkinson's, epilepsy and atrial fibrillation. Then in this paper for the existing three channels of therapeutic drugs and their mechanism is introduced and elaborated, more for some small molecule agonists, inhibitors and some toxin compounds, and also for the future research outlook-through the development of corresponding target regulator, reduce the side effects of drugs and adverse reactions, improve the bioavailability of new drugs. It is hoped that through the deeper study of such channels, clinically related diseases can be effectively solved and new breakthroughs can be achieved.

Keywords: BK channel, IK channel, SK channel, therapeutic drug.

1. Introduction

Potassium channel is a class of important proteins that are widely found on the membrane of cell, with the largest number and the widest distribution among numerous ion channels. It plays a series of important physiological roles by regulating potassium ions in and out of the cell membrane, further involved in regulating cell excitability, maintaining ion homeostasis, controlling cell volume and so on. Therefore, the design of a series of drugs acting on potassium channel targets has become the focus of research today.

1.1. Structure and classification of potassium ion channels

According to their conductance size, potassium channel can be divided into large conductive potassium channel (BK channel), medium conductive potassium channel (IK channel) and small conductive

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potassium channel (SK channel). SK, IK and BK channels can be specifically blocked by apamin, clotrimazole, and paxilline respectively.

Large conductance potassium ion channel, also known as BK channel, can induce the change of cell membrane potential and intracellular calcium ion concentration to regulate the potassium ion channel. Opening of BK channels usually causes the outflow of potassium ions from the cell, thereby hyperpolarizing the cells and reducing cellular excitability. The structure of BK channel consists of four subunits, each containing seven transmembrane helix, in which the S0 helix acts separately, the S1-S4 helix is the voltage receptor, which is used to sense the voltage change of the cell membrane, and the S5-S6 helix forms a selective pore. The C terminus of the BK channel has two RCK domains that can bind calcium ions. According to the analytical results of cryoEM technology, the BK channel is wider than the other potassium channels, and it forms a wide funnel-like structure, which contributes to the rapid flow of potassium ions [1].

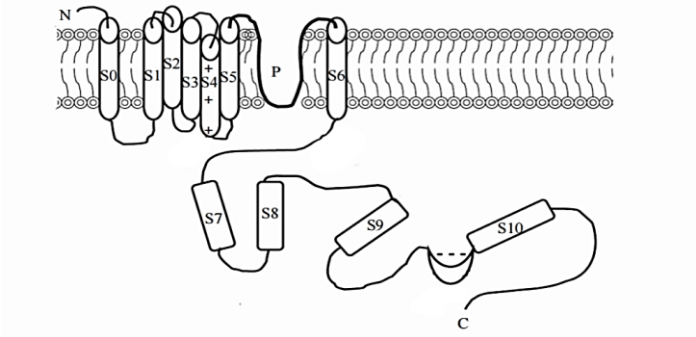

Figure 1. The BK channel structure [1].

Medium conductivity potassium ion channel, also known as IK channel, usually has moderate ion permeability rate. They can be activated by a variety of intracellular signals, such as intracellular calcium concentration, these channels play an important role in regulating cell excitability, maintaining the cell membrane potential stability and participating in neural signaling. The structure of the IK channel is composed of the regulation part KCNE1 and the tetrameric KCNQ1 who is responsible for the formation of. For IK channel, they are mainly expressed in cells of the hematopoietic system, colon, lung, salivary glands and nerve cells of the hematopoietic system [2].

Small conductance potassium channels, also known as SK channels, are a class of potassium channels with low single channel conductance, which are widely distributed in a variety of excitable cells, such as nerve cells, heart and endothelial cells. Members of SK channel can be divided into three subtypes, respectively SK1 channel coded by KCNN1, SK2 channel encoded by KCNN2, SK3 channel encoded by KCNN3 [3]. These channels are sensitive to intracellular calcium concentration, as well as the cell membrane potential, so the channel is also called small conductive calcium activated potassium channel. SK channels typically acts as a tetramer with C4 symmetry, where there is an ion hole at the center of the complex structure, responsible for the selective permeability of potassium ions [4].

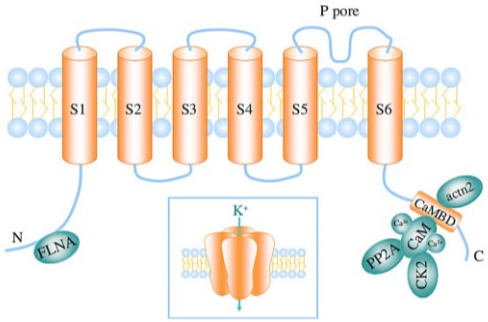

Figure 2. The representation structure of SK channel [4].

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1.2. Function of the potassium ion channels

The main function of potassium ion channel is to maintain the balance between the concentration of potassium ion in intracellular and extracellular fluid. The potassium ion channel allows potassium ion to flow out of the cell membrane and helps to maintain the resting potential of the cell membrane. By controlling the flow of potassium ions, it can regulate the excitability of neurons and muscle cells and avoid excessive excitation. In the nervous system, potassium participates in the transmission of nerve signals, the regulation of action potential repolarization and the rhythm of nerve signals; the opening and closing of potassium channels can change in response to various cellular signals such as calcium concentration and signaling network; some potassium channels play a protective role in neuronal activity to prevent cell damage caused by excessive excitation. In the heart, hERG channels are critical for action potential repolarization in cardiomyocytes, affecting cardiac rhythm and pumping function. In addition, potassium channels also participate in the regulation of cell volume, which is beneficial to maintain the balance of intracellular osmotic pressure.

2. Potassium ion channel-related diseases

2.1. BK channel-related diseases

In the nervous system, BK channels are involved in the repolarization process, further the generation of action potential and excitation of the neural cells. In addition, BK channel is also responsible for the release of neurotransmitters through the presynaptic membrane. With the increasement of intracellular calcium concentration, the cell membrane is depolarized, then, the downstream signal is activated, which directly leads to the elevation of potassium conductance and the hyperpolarization of the cell membrane [5]. The hyperpolarization process is important for the dormancy of signal transmission by closing the Ca2 + channels, thus preparing for the next round of excitation [6]. BK channel dysfunctions are usually associated with epilepsy and cognitive impairment. Epilepsy is a chronic brain disease characterized by recurrent seizures. It can occur in people of any age, and is one of the most common neurological diseases caused by "abnormal firing" of brain neurons. In clinical, the cortical development disorders, brain tumors, head trauma, cerebrovascular diseases, and neurodegenerative diseases are always accompanied by the occurrence of epilepsy. Stimiting encephalopathy, and may also be genetically related. Recent studies suggest that seizures may be related to the abnormal excitation of BK channels: In normal neurons, when hyperpolarized, BK channels may participate in a negative feedback system of neural activity, protecting them from counteracting the damage caused by overexcitability; While seizures occur, the interaction between the core subunit αand the auxiliary subunit βwithin the BK complex is weakened, which leads to the downregulation of β 4 expression and increased neuronal excitatory activity [5].

In the cardiovascular and cerebrovascular system, BK channel is widely recognized to play a vital role in regulating vascular smooth muscle tone, not only involved in the formation of cell membrane potential, but also involved in the regulation of vascular smooth muscle cells, mediate the release of intracellular hormones and neurotransmitters and regulating the vascular wall tension, and also mediate the signal transfer in the proliferation of VSMCs [7].

Cerebral ischemia, also known as transient ischemic attack, is a common acute cerebrovascular disease, usually due to the lack of transient blood supply in the brain, leading to dizziness, tinnitus, severe confusion, blindness and other symptoms in patients. There are many risk factors of cerebral ischemia, such as atherosclerosis, which makes some cerebral arterioles temporary occlusion and hypertension, causing cerebral vasospasm, blood flow, insufficient blood supply. Besides, thrombocytes also make high blood viscosity. insufficient blood oxygen content. Except for these, anemia, heart disease, and myocarditis are causes of transient ischemic attack as well. From the perspective of molecular mechanism, the occurrence of ischemic stroke is a result of excessive calcium ions inflow. Under native state, BK channel locates in the arterial wall of the smooth muscle cells (SMC), and regulate the alteration of cell excitation and rest. When stimulated, calcium ions are accumulated in cells, the BK channel turns to the open conformation and promotes the efflux of potassium ions, thus the

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hyperpolarization of cell membrane. Once the potential in the membrane reaches specified threshold, the cells go back to the rest state, accompanied by the deactivation of calcium ion channel, which is the prerequisite of vasodilation. However, abnormal expression in BK channels will lead to excessive calcium ion accumulation and vasoconstriction, which will lead to the occurrence of cerebral ischemia [5, 7].

2.2. IK channel-related diseases

Medium conductive calcium-activated potassium channel (IK channel) is widely expressed in mammalian body, especially in atrial myocytes, fibroblasts and monocytes / macrophages, and participates in the regulation of various functions such as cell membrane potential formation, cardiomyocyte self-discipline, cell proliferation, cell migration and differentiation. It affects atrial electrical remodeling, atrial fibrosis and macrophage-mediated inflammatory response, and plays important roles in various mechanisms of the occurrence and maintenance of atrial fibrillation [8].

Zhao et al [9]. showed that the expression of IK channels on the membrane of cardiomyocytes could promote the proliferation of cardiac fibroblasts; Wang et al [10]. further explored the role of IK channels in angiotensin (Ang) -mediated fibroblast activation and proliferation, and found that Ang could significantly increase the level and current density of IK channel protein in cardiac fibroblasts. Experimental results show that the inhibition of IK channels may be an effective means to solve the maintenance mechanism of AF.

2.3. SK channel-related diseases

Dysfunction of SK3 channels is one of the factors contributing to neurodegenerative diseases, but its molecular biological basis is currently unknown. By means of immunohistological analysis, researchers found that the arrangement of SK3 channels in both the CA1 and CA3 layers of neuron-degenerated mouse hippocampal are disrupted. These features suggest that SK3 ion channels are involved in various central nervous system dysfunction, like schizophrenia, Alzheimer's disease, or other psychotic / neurodegenerative disorders. Although the current understanding of the role of SK3 channels in brain diseases is limited by the lack of modulators of specific SK3 channels, SK3 channels remain undeniable as one of the potential drug targets [11].

SK2 channels, also a subtype of SK channel, are mainly expressed in cerebellar Purkinje neurons and are also important for the regulation of neural activity [12]. The loss of firing accuracy in Purkinje neurons underlies the symptoms of motor dysregulation such as spinocerebellar ataxia and essential tremor, which has been demonstrated in transgenic mice. In human body cells, loss-of-function mutations in the KCNN2 gene also cause neurodevelopmental motor disorders such as cerebellar ataxia and tremor.

Both ion channels of SK2 and SK3 isoforms were expressed in cardiac cell plasma membrane and mitochondria, with more abundant atrial SK2 channels compared to the ventricles, while SK3 channels were expressed at similar levels in the atrial ventricle. In normal physiological conditions, SK3 channels are regulators of ventricular repolarization, whose dysfunction may affect the cardiac conduction system. Meanwhile, several studies have shown that SK channel also plays an important role in atrial repolarization and participates in the maintenance of atrial fibrillation. SK channel blockers can prolong atrial ERP without affecting QT interval, so SK channel blockers may become new targeted therapeutic agents against atrial fibrillation. However, some studies have suggested that excessive inhibition of SK channel expression may similarly increase the susceptibility to AF [13].

Other studies have found that SK3 channel subtype is expressed in vascular endothelial cells, through the perception of blood flow shear force (friction between blood flow and endothelial cell layer, parallel to the long axis, physiological level shear protection against vascular endothelial cells) increased, release of nitric oxide, leading to an increase in local Ca2+ concentration. Ca2+ is released from the endoplasmic reticulum and then entered through transient receptor potential (TRP) channels, a Ca2 + channel in vascular endothelial cells. Activation of SK3 channels induces hyperpolarization of vascular endothelial cells and spreads to the vascular smooth muscle cell layer, causing hyperpolarization of

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endothelial-derived factors (EDH), leading to vascular dilation. Whereas genetic defects in SK3 channels in mice impair EDH responses and cause hypertension, suggesting a role for endothelial SK3 channels in blood pressure regulation [14].

3. Potassium ion channel target drugs

3.1. BK channels related to the drugs

The biaromatic thiourea derivative NS11021 is a potent BK channel agonist (open agent), which promotes the opening of the voltage-dependent BK channel mainly by slowing the inactivation dynamics of the channel, which can increase the opening probability of the channel, thus exerting the role of antihypertensive and vascular relaxation. According to preclinical studies, NS11021 has potential applications in treating hypertension [15].

The benzimidazole derivative NS1619, another BK channel agonist, promotes potassium ion efflux by increasing the open probability of the channel, resulting in hyperpolarization of the cell membrane. NS1619 Activation of BK channels can not only relax blood vessels, affect blood pressure regulation and local blood flow perfusion, but also participate in the nervous system, to regulate the release of neurotransmitters and neuronal excitability, with an impact on the transmission and integration of neural signals [16].

3.2. IK channels related to the drugs

Clotrimazole is a spectrum of antifungal drug that is also an inhibitor of IK channels. It was found to regulate the tone of vascular smooth muscle through the IK channel, with a potential cardiovascular therapeutic effect. TRAM-34 is a potent, selective Ca2+ -activated K+ channel inhibitor with a kD value of 20 nM, which is 200 to 1500-fold more selective for other ion channels and does not inhibit cytochrome P450. Unlike Clotrimazole, TRAM-34 selectively inhibits IKCa 1 without blocking the cytochrome P450 enzyme (CYP3A4). TRAM-34 effectively inhibited the cloned IKCa 1 channel in IKCa 1-transfected COS-7 cells and also inhibited IKCad currents in human T lymphocytes and T84 cells.

3.3. SK channels related to the drugs

Apamin Is a naturally occurring polypeptide toxin and is a specific blocker of SK channels. It is usually used in some basic studies to explore the physiological function of SK channels. However, due to the limitations of its toxicity and pharmacokinetic properties, its application in the clinic is hindered, and it is only suitable for the establishment of laboratory disease models. NS8593 is a novel SK channel inhibitor with higher selectivity and better pharmacokinetic properties. In zoological experiments, NS8593 showed potential therapeutic effects for cardiovascular and neurological diseases. NS13001 is a potent, selective, positive allosteric modulator with orally active SK channels. NS13001 For SK2 and SK3, the EC50 of the channel is 1.8 μ M and 0.14 μ M, respectively. NS13001 Is expected as a potential therapeutic agent for the treatment of spinocerebellar ataxia type 2 (SCA2) and possibly other cerebellar ataxia [17].

4. Conclusion

In conclusion, all three potassium channels are associated with various diseases, and most are diseases of the nervous and cardiovascular systems, such as epilepsy, Alzheimer's disease, hypertension, etc. Nowadays, the treatment means are often some small molecule chemical drugs, as agonists or inhibitors of this target, but in the future, the research focus may be more on the modulators of these targets, so as to strengthen the activity of drugs, reduce toxic side effects and adverse reactions. As an important regulator of cellular physiological functions, potassium channels have significant implications for in-depth understanding of life processes and disease mechanisms. With the continuous progress of research technology, the understanding of potassium ion channel will be more comprehensive and in-depth, which will certainly bring new breakthroughs for the treatment of related diseases.

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