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Editorial Review

Applications of K +channel modulators in clinical practice: Review

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Abstract:

Ion channels present in plasma membrane & intracellular organelles of all cells play an important role in maintaining cellular integrity, smooth muscle contraction, secretion of hormones & neurotransmitters. Among these K^+ channels are the most abundant having important role in cardiac repolarization, smooth muscle relaxation, gastrointestinal peristalsis & insulin release etc. K^+channels are grouped into families based on their structures as well as physiological & pharmacological criteria.

The opening & closing of K^+ channels are modulated by many compounds like ATP, ADP, and Nitric oxide. Channel modulators are the substances which modulate the opening or closing of channels. There are number of methods like electrophysiological, Biochemical, Animal experiments to study these ion channels & channel modulators.

K^+ channels are associated with diseases like Diabetes, epilepsy & long QT syndrome etc. The diverse nature of K^+ channels offers the opportunity for new drug development. This review covers such methods with their conclusion & tries to highlight the importance of application of K^+ channel modulators in clinical practice.

Keywords: K^+ channels, channel modulators

Introduction:

During last decade there is observed advanced research , largely because of two major technical advances:(1) single-channel recording techniques, which have permitted the measurement of currents from individual ion channels in a variety of tissues, and (2) molecular cloning, which provides sequence information about the structural composition of the proteins comprising ion channels. [1]Both these techniques and the availability of cloned receptors have significantly advanced our understanding of the manifold function of ion channels that selectively allow the movement of potassium ions (K^+) across the cell membrane and that are essential for regulating excitability of tissues. [2]

Electrophysiology:

Electro physiologists had knowledge about the basic concepts that there were specialized membrane structures that allow the selective movement of sodium and potassium across the membrane. The first detailed analysis of this process appeared in Hodgkin and Huxley's classic investigations into the components of the squid giant axon action potential in the late 1940s and early 1950s. These studies recognized the importance of the movement of K^+out of the cell to produce rapid repolarization of the cell membrane after a depolarizing spike. They also specially identified a “leakage” current, a component of which was a result of the passage of K^+, that draws the membrane potential toward the equilibrium

potential for K^+([approximate]-90 mV in most cells). The search of compounds such as the organic cation tetraethylammonium (TEA^+) and barium ions that block K^+currents in neural and cardiac tissues further characterized these currents. [3]

Basic Mechanisms

The way in special which K channels help stabilize the excitability of tissues relies on several key electrophysiologic concepts. Briefly, the resting membrane potential for a given cell is a function of the differential distribution of the most abundant common ions (Na^+, $K^+$and Cl^-) between the inside and the outside of the cell. This differential distribution is maintained primarily by energy-consuming ion transporters such as $Na^{+/K+}$ATPase.[4]

K channel modulators in clinical use :

Specific modulation of individual K^+ channel types therefore offers an enormous potential for the development of physiological tool compounds and new drugs. To name just a few examples, K^+ channel modulators are already clinically used as drugs for the treatment of type-2 diabetes and cardiac arrhythmia and are widely pursued in academia and the pharmaceutical industry as novel targets for epilepsy, memory disorders, chronic pain, cardiac and brain ischemia, hypertension, bladder over-reactivity, immunosuppression and cancer. In this review we will first give an overview of K^+ channel pharmacology in general and then discuss the medicinal chemistry of the K^+channels which constitute targets for the treatment of neurological disorders (Kv7.2–7.5, KCa1.1, KCa2.1–2.3) and autoimmune diseases (Kv1.3, KCa3.1) in more detail.[5]

K^+ channels have equilibrium potential close to −80 mV. They are therefore ideally suited to set the resting membrane potential, a task they perform in most cells. In neurons and other excitable cells, K^+ channels are also crucial for determining the shape, the duration, and the frequency of action potential firing. In order to adjust these functions to the specific requirements of a particular neuron, the different K^+ channels often show subfamily-specific patterns of cellular and subcellular localization. For example, Kv1 channels are predominantly found on axons and nerve terminals, Kv2 channels in the soma and in dendrites, Kv3 channels in dendritic or axonal domains, and Kv4 channel in somatodendritic membranes.6,7,8

Potassium channels are essential in both excitable and non-excitable cells for the control of membrane potential, regulation of cell volume, and the secretion of salt, neurotransmitters and hormones. They are integral membrane proteins that allow the selective, diffusional passage of potassium ions across biological membranes, and are capable of up to 10,000-fold selectivity of potassium over sodium.[8,9]

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