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Review

Voltage-dependent BK and Hv1 channels expressed in non-excitable tissues: New therapeutics opportunities as targets in human diseases

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ABSTRACT

Voltage-gated ion channels are the molecular determinants of cellular excitability. This group of ion channels is one of the most important pharmacological targets in excitable tissues such as nervous system, cardiac and skeletal muscle. Moreover, voltage-gated ion channels are expressed in non-excitable cells, where they mediate key cellular functions through intracellular biochemical mechanisms rather than rapid electrical signaling. This review aims at illustrating the pharmacological impact of these ion channels, highlighting in particular the structural details and physiological functions of two of them — the high conductance voltage- and Ca^{2+}-gated K^+ (BK) channels and voltage-gated proton (H_v1) channels- in non-excitable cells.

BK channels have been implicated in a variety of physiological processes ranging from regulation of smooth muscle tone to modulation of hormone and neurotransmitter release. Interestingly, BK channels are also involved in modulating K^+ transport in the mammalian kidney and colon epithelium with a potential role in the hyperkalemic phenotype observed in patients with familial hyperkalemic hypertension type 2, and in the pathophysiology of hypertension. In addition, BK channels are responsible for resting and stimulated Ca^{2+}-activated K^+ secretion in the distal colon.

H_v1 channels have been detected in many cell types, including macrophages, blood cells, lung epithelia, skeletal muscle and microglia. These channels have a central role in the phagocytic system. In macrophages, H_v1 channels participate in the generation of reactive oxygen species in the respiratory burst during the process of phagocytosis.

Contents

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1. General features of voltage-dependent ion channels structure

Ion channels are highly specialized membrane proteins whose main function is to provide a permeable path to passage of ions across the cell membrane of living cells. They form ion-conducting pores that open in response to different kind of stimuli, such as changes in the membrane potential, ligand binding, membrane stretch and temperature [1,2].

Ion channels that open their ion-conductive pore in response to changes in the membrane potential are known as voltage-gated ion channels [2]. Most of them share a basic membrane topology with an α-subunit composed of six membrane spanning segments (6-TM, Fig. 1A) including monomeric ion channels with four domains (24 TM segments) such as voltage-gated sodium (Na_v) and calcium (Ca_v) channels; and tetrameric ion channels formed by four 6-TM monomers. The latter group is represented by voltage (K_v) and calcium (K_{Ca}) gated potassium channels, bacterial voltage-gated sodium channels (bNa_v) and transient receptor potential (TRP) channels [2,3]. The first four TM segments (S1–S4) of each 6TM-subunit form the voltage-sensing domain (VSD), while the two last TM segments (S5 and S6) of each subunit conforms one common and centrally located pore domain.

Here we focus on two voltage-dependent ion channels that resemble 6-TM voltage-gated channels but with some special features: the high conductance voltage- and Ca^{2+}-gated K^+ (BK) channels (Fig. 1B); and voltage-gated proton (H_v1) channels, which are composed by the equivalent 4 first TM of voltage-gated channel, i.e, are homologous to the VSD (Fig. 1C).

2. Structural details of the high conductance voltage- and Ca^{2+}-activated K^+ (BK) channels

The BK channel is the only member of the voltage-gated ion channel family with an α subunit containing an additional TM segment (S0, Fig. 1B). As a particular feature, BK channels display very large single channel conductance (~250 pS in 100 mM symmetrical K^+) [4–6]. The conducting pore is built by a tetramer of BK channel α-subunit can be divided into two main regions: the transmembrane (S0–S6 segments) and the intracellular C-terminus region (Fig. 1B). The transmembrane region has a topology that resembles that of K_v channels with the addition of an extra hydrophobic TM segment at the NH_2 terminus, called S0, which faces the extracellular side [7]. The voltage sensor domain (VSD) of the BK channel is formed by the first four TMs segments, S1–S4, which are connected by a linker (S4 and S5 linker) to the pore domain in the S5 and S6 TMs segments. The intracellular C-terminus region comprises about two-thirds of the protein, containing several site for alternative splicing and a stretch of negatively charged amino acids (aspartates) dubbed as the 'Ca^{2+} bowl'. This region has the ability to sense changes in Ca^{2+} concentration inside the cells. The cytoplasmic domain of each α-subunit can be divided into two principal structures, both homologous to the 'regulator of K^+ conductance' (RCK). These two tandem C-terminal RCK domains form a gating ring that encompasses the eight RCK domains from the tetramer of BK α-subunits [8].

After the crystallization of the K_vAP channel by MacKinnonís group in 2003 [9], many other groups were able to solve the structures of different voltage-gated ion channels. While the structure of the full-length BK channel remains elusive, despite experimental efforts to clarify it, the intracellular RCK domains that participate in intracellular Ca^{2+} channel regulation were successfully resolved at 3.1 Å [10,11]. The structure reveals four intracellular domains, the RCK2 domain being twisted with respect to RCK1, very similar to those of the MthK channel (a bacterial K^+ channel which also has a RCK domain) and they are part of the gating ring of this channel [12]. In these domains there are three Ca^{2+} binding sites, including a Ca^{2+} bowl [10,11]. The Ca^{2+} bowl is located in the RCK2 domain and forms a typical metal binding motif called EF-hand-like motif. The residues involved in Ca^{+2} binding are Asp 367, Glu 374 and Glu 399 in human BK [10]. The neutralization of negatives charged residues induces a conformational change in the channel stabilizing the open state [13]. The only reliable information about the structure of BK channel transmembrane segments has been obtained by cryo-electron microscopy (cryo-EM)[14]. This technique has provided some details about the channel structural features in lipid environment [14]. In this study, purified BK channels were reconstituted into liposomes, and measurements of K^+ flux were obtained as a functional assay of the purified proteins. The authors captured thousands of images from frozen liposomes containing BK channel particles and after an elaborated image processing "tour de force", they obtained a 3D reconstruction of the BK channel at 20 Å [14]. The low-resolution structure of the internal domains is consistent with previous crystallographic experiments. Furthermore, the structural arrangement obtained for the different transmembrane domains were similar to other K_v channels where the VSD are surrounding the pore domain. Given the current advances in cryoelectron microscopy [15] in which researchers had solved the structure of very large ion channels at atomic resolution, it could be envisioned that in the near future the BK channel structure will be solved at a high resolution.

3. Structural details of voltage-gated proton (H_v1) channels

The molecular identity of a family of voltage-gated proton channels, called H_v1 (Human Voltage-gated proton channels) or VSOP (Voltage-sensing domain only protein) channels, was identified less than 10 years ago by two independent groups [16,17]. H_v1 channels, were cloned from mouse, chicken, zebrafish, human and the sea squirt *Ciona intestinalis* [16,17], and were found to be formed by 4 transmembrane segments, with the N and C terminus facing the intracellular side of the membrane (Fig. 1C). When $H_v1$channels were first sequenced, they displayed a statistical significant sequence identity to the voltage-sensing domain (VSD) of voltage-gated potassium (K_v) channels, with the particularity that they lack the typical pore domain. However, it was not clear how $H_v1$channels containing only a VSD could make a functional channel. The molecular determinants of their function have started to be identified after initial experimental difficulties with the attainment of a crystal structure with proton channel characteristics; this structure has provided important clues on H_v1 structure [18]. It must be clarified however that this structure was obtained in the close state, which is of great value but does not provide information on the open state, and we still have to rely on molecular models to further understand the function structure relationship in the open versus closed state. In this respect, many models have been con-