A BK (Slo1) channel journey from molecule to physiology

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Calcium and voltage-activated potassium (BK) channels are key actors in cell physiology, both in neuronal and non-neuronal cells and tissues. Through negative feedback between intracellular Ca^{2+} and membrane voltage, BK channels provide a damping mechanism for excitatory signals. Molecular modulation of these channels by alternative splicing, auxiliary subunits and post-translational modifications showed that these channels are subjected to many mechanisms that add diversity to the BK channel α subunit gene. This complexity of interactions modulates BK channel gating, modifying the energetic barrier of voltage sensor domain activation and channel opening. Regions for voltage as well as Ca^{2+} sensitivity have been identified, and the crystal structure generated by the 2 RCK domains contained in the C-terminal of the channel has been described. The linkage of these channels to many intracellular metabolites and pathways, as well as their modulation by extracellular natural agents, has been found to be relevant in many physiological processes. This review includes the hallmarks of BK channel biophysics and its physiological impact on specific cells and tissues, highlighting its relationship with auxiliary subunit expression.

Introduction

BK channels are members of a family of Ca^{2+} and voltage-dependent potassium channels. They are constituted by a tetramer of α subunits that form the conducting pore and are encoded by the *slo1* gene. In several tissues, BK channels have been observed to be modulated by auxiliary subunits, which confer important physiological performance to the channels. BK channels are ubiquitously expressed in cell membranes of mammalian tissues, where they couple signals that result from differences in membrane

voltage and intracellular Ca^{2+} concentration, which are both key actors in the physiology of nervous and non-nervous cells. In this review we provide an overview of BK channel function and its relationship with structural cues, the voltage sensor domain and gating properties of the channels, as well as its crosstalk with its auxiliary subunits.

A Short Story about How BK Channels Were Identified

The first evidence of a K^+ permeability induced by increases in intracellular calcium concentration was obtained in red blood cells.[1] Later, a calcium-dependent K^+ current was reported from experiments where Ca^{2+} was injected in motoneurons, resulting in both an increase in membrane conductance and a decrease in cellular excitability.[2] Moreover, the removal of external Ca^{2+} was found to decrease a voltage-dependent K^+ current in mollusk neurons.[3,4] A few years later, these currents were defined as being carried by a calcium-dependent potassium current,[5] after which their critical role in neuronal firing properties and hyperpolarization was soon acknowledged.[6]

The year 1981 was the *annus mirabilis* of BK channel research, since abundant expression of these channels was found in skeletal muscles and chromaffin cells. Single channel recordings from skeletal muscle and chromaffin cells[7,8] as well as the reconstitution of a calcium-dependent K^+ channel in bilayers[9] revealed the large conductance of BK channels, which ranges within 200 pS. This magnitude gave rise to the names MaxiK or BK, thus representing the large conductance potassium channel.[10] With the advent of the giga-seal patch clamp technique[11] and the possibility of isolating and patching small cells, BK channels were soon found and described in liver, lymphocyte, epithelium, exocrine, and endocrine glands as being linked to excitation-secretion coupling.[8,12-14] Marty et al. discovered that channels of different conductance give rise to Ca^{2+}-dependent potassium currents in rat lacrimal glands and named the largest conductance type channel *BK*.[15] By that time, another important finding regarding this channel's localization was made, namely that it is abundantly
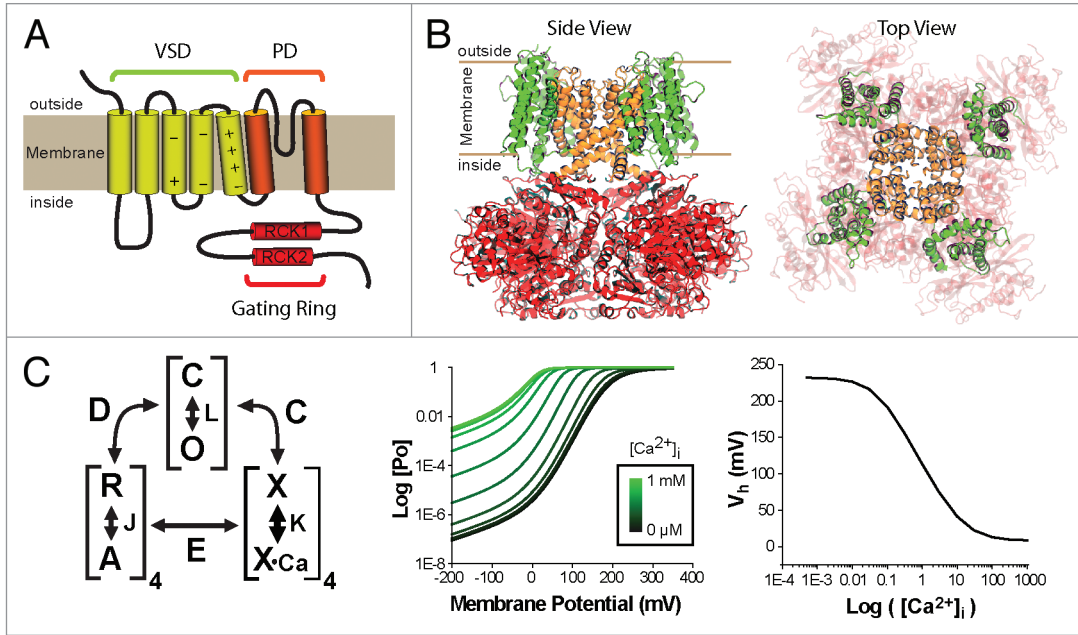
Figure 1. Structural and functional characteristics of BK channels. (**A**) Schematic topology of 1 BK channel α subunit. (**B**) Homology model of BK channel from the side (left) and top (right). The transmembrane domain is a homology model of MthK (PDB 1LNQ) and the cytoplasmic domain corresponds to the crystal structure of the human BK channel gating ring. (**C**) HA allosteric model of BK channel activation. Activation of pore, voltage sensor and calcium sensor domains are described by L, J and K equilibrium constants. D, C and E are allosteric constants that couple with each functional domain (left). The calcium (middle) and voltage (right) dependence of open probability is also described by the HA allosteric model in a semi-logarithmic scale at different [Ca^{2+}].

expressed in smooth muscles.[16] Experiments in neurons soon demonstrated that the BK channel is an essential component for neurotransmitter release in presynaptic terminals.[17] In addition, BK channels serve as negative feedback pathways in neurons during membrane depolarization and changes in intracellular Ca^{2+} concentration.[18,19] Contemporaneously, Miller et al., discovered Charybdotoxin (ChTX), which is a scorpion toxin that is able to block BK channels with nM affinity.[20] However, other K$^+$ channels are also sensitive to ChTX, thus encouraging the search for a more specific toxin. Consequently, the Iberiotoxin (IbTx) was isolated from the scorpion venom and was shown to be a more specific blocker with a high degree of affinity to BK channels.[21]

A calcium-sensitive component of the potassium currents was soon identified in *Drosophila*, which was later shown to correspond to the *slowpoke* allele.[22] The *slowpoke* was then isolated, cloned and expressed in heterologous systems, and shown to indeed produce BK channels.[23,24] The BK mammalian counterpart was soon cloned, and it was demonstrated that general molecular characteristics of BK channels are evolutionarily conserved from fly to mouse.[25]

Functional BK channel diversity is quite frequent and is attained by alternative splicing of the α subunit, interaction with auxiliary subunits and other partners, post-translational modification, and trafficking.[18,19,26] This review focuses on questions and advances related to the main and auxiliary subunits of BK channels, the molecular mechanisms proposed for gating that are governed by the voltage sensing domain and, finally, their relevance in certain cell physiology and pathophysiology events.

The Structure of the Slo Channels

The family of Slo channels is composed by the following three main members: (1) the BK channel, also known as Slo1; (2) Slo2 (with 2 variants: Slick and Slack), underlying Na$^+$ and Cl$^-$-activated K$^+$ channels; (3) and Slo3 (also called KSper), giving rise to the H$^+$ activated K$^+$ channel.[19] The HUGO gene nomenclature, common names and locations for the 3 variants of Slo channels mentioned above are presented in **Table 1**.

Slo channels are homotetramers of 4 pore-forming α-subunits, whose topology resembles that of voltage-gated K$^+$ (K$_V$) channels, but also include a large C-terminal cytoplasmic domain and an extra transmembrane segment (S0), as in the case of Slo1 and Slo3.[27,28] The C-terminus appears to confer ion sensitivity to the different members of this family.[19] In fact, Ca^{2+} binding sites and regulatory domains have been identified in this region of the BK α subunit (**Fig. 1**). This subunit, containing about 1200 amino acids, also includes critical structural features of the channel such as ion permeation, gating, and modulation by other proteins and intracellular ions. The functional channel is composed of a tetramer of α subunits and a putative tetramerization domain, which has been described in the C-terminal region of the channel. This domain is near the pore region and is termed *BK-T1*.[29]

Electron cryo-microscopy studies have provided some insights about the channel's structure in its native lipid environment. By averaging thousands of images of structures obtained from frozen vesicles, a 3D reconstruction was made with an approximate resolution of 20 Å.[30] The general architecture of the channel resembles that of Kv channels, with the exception of

Table 1. SLO family channels

Channel or subunit	Alternating names	Gene symbol (human)	Location	Estimated conductance
SLO1	BK, K_{Ca}, Maxi-K, K_{Ca}1.1, Big Potassium	KNCMA1	10q22.3	100–270 pS
SLO2.1	Slick, K_{Na}, K_{Ca}4.2, sodium activated potassium channel, sodium and chloride activated ATP sensitive potassium channel	KCNT2	1q31.3	60–140 pS
SLO2.2	Slack, K_{Na}, K_{Ca}4.1 EIEE14, ENFL5	KCNT1	9q34.3	100–180 pS
SLO3	K_{Ca}5.1, Slowpoke homolog 3, pH-sensitive maxi potassium channel	KCNU1	8p11.2	8p11.2 pS

large protrusions in the external aspect of the channel that may correspond to the S0 and N-terminal regions of the protein.

Calcium Sensitivity, Voltage Sensor, and Gating Mechanisms

Structure and function studies on calcium and divalent cation sensitivity

Many studies have revealed that Ca^{2+} binding promotes a leftward shift of the steady-state open probability of BK channels (**Fig. 1C**).[7,8,31] The channels' affinity to Ca^{2+} has been determined to be between 1–10 μM,[32,33] and was later found to be regulated by modulatory proteins and metabolic conditions.[34] Colocalization of Slo1 channels with VDCC (voltage-dependent calcium channels) appears to be essential for Slo1 channel activation since to raise the channel open probability to reasonable values ($P_o \geq 0.5$) at membrane voltages in the range -50 to 0 mV requires range of Ca^{2+} concentrations of 10 μM or more.[35] Colocalization of BK and VDCC channels has been found in hair cell (**Fig. 3A**, middle).[36,37] Similarly, BK channels can form macromolecular complexes with VDCC channels in neurons.[38] Moreover, cytosolic Ca^{2+} per se is able to open the channels.[39] Current models have proposed that voltage sensing is more effectively translated into channel gating (opening) as intracellular calcium increases, thus imposing channels to open at more negative voltages than when Ca^{2+} is not present.[31,33,39,40] **Figure 1C** illustrates BK Ca^{2+}-dependence curves at different membrane voltage.

The first site within the C-terminus to be identified as a high affinity Ca^{2+} binding site in BK channels was dubbed the Ca^{2+} bowl.[41] This Ca^{2+} bowl contains several acidic residues (T273 to Q910 in mSlo1) that dramatically alter the channel's Ca^{2+} sensitivity when mutated.[42-44] Soon after this finding, multiple sites of high Ca^{2+} affinity in the large intracellular proximal part of the C-terminus of the channel were reported.[45-48] This region, conserved among prokaryotes and similar to TrkA domains that regulate K^+ conductance in many prokaryotic cells, was established as the K^+ channel conductance regulator and named the RCK domain (**Fig. 1A** and **B**). BK channels contain 2 RCK domains in tandem in the C-terminus of the α subunit, located in positions 340 to 610 for RCK1, and 640 to 1055 for RCK2, as was described for the human BK channel.[49,50] The crystal structure of a Ca^{2+}-gated K^+ channel in bacteria, called MthK, revealed the existence of 4 RCK domains that co-assemble in a solution forming a ring. The conformation of this ring changes upon Ca^{2+} binding and is known as the gating ring.[49,51] Each RCK domain contributes to the binding of 3 Ca^{2+} ions, providing a total of 24 Ca^{2+} ions bound to the ring in the MthK channel.[52] The RCK domain structure of the MthK channel has also been identified with Cd^{2+} bound to the ring,[53] uncovering a large negatively charged surface in the C-terminal region. Neutralization of the charges in the RCK domain induces a change in the channel conformation that facilitates channel opening.[53] The structure of the BK channel with and without bound Ca^{2+} has shown that Ca^{2+} stretches the intracellular region of the channel, thus transferring a conformational change to the coupling produced between voltage sensors and gating.[50,52] The structural determinations of the BK RCK domains with 3 Å resolution[50] displayed that each α subunit contains a pair of RCK domains in the C-terminus portion, and that the Ca^{2+} bowl resides within the distal RCK domain (**Fig. 1A** and **B**). Hence, as initially proposed for prokaryotes, eukaryotes also have an octameric gating ring in the intracellular C-terminal region of the channel, thus conferring its Ca^{2+} dependence.[50,54] Spectroscopy and particle-scale optical dynamic light scattering analysis revealed a significant reduction and reverse in the gating ring radius upon Ca^{2+} binding in the BK channel.[55] Furthermore, measurements by FRET also indicated that Ca^{2+} binding to the RCK domains induced changes in the gating ring, which seem to be significantly greater than those hypothesized by crystallography.[56]

In addition to calcium, other divalent ions have been reported to bind to the Ca^{2+}-sensing sites of the BK channel, and some like Ba^{2+}, Mg^{2+}, Zn^{2+}, and Cd^{2+} have been reported bind in crystallographic experimental approaches.[48,53,57,58] The Mg^{2+} site is of particular interest, since it is formed by an interdomain composed of membrane spanning domains and cytoplasmic portions that are mostly located in its RCK1 domain.[46,59] Mg^{2+} ions that are bound to this site repel R213 residue in the S4 transmembrane segment, hence facilitating the active configuration of the voltage sensor and, consequently, the channel opening.[59,60]

The voltage sensor in BK channels

Early experiments in BK channels suggested that they could be activated by voltage in the absence of intracellular divalent cations.[61] Their structural similarity to Kv channels, as observed by cloning the α subunit of the BK channel in *Drosophila* and mice, suggested the presence of a voltage sensor domain (VSD)
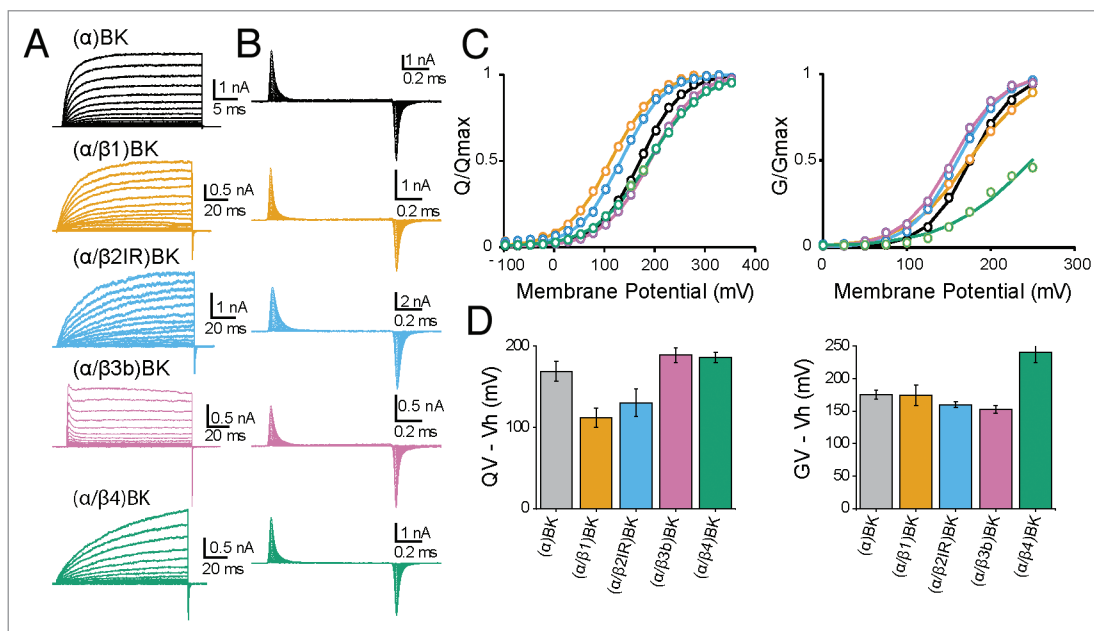
Figure 2. Ionic and gating currents for (α)BK and (α/βx)BK channels. (**A**) Representative families of ionic currents evoked by voltage steps of 50 ms for (α)BK and 120 ms for the α/βx complexes, ranging from 0 to 250 mV in 10 mV steps. Currents were recorded in 1 mM symmetrical K^+ and ~5 nM Ca^{2+}. (**B**) Gating currents elicited by 1 ms pulse duration to increasing voltages from -90 to 350 mV in increments of 10 mV; pulse duration was set to reach a quasi-steady-state. (**C**) Gating charge-voltage and conductance-voltage relationships for (α)BK and (α/βx)BK channels. Q-V and G-V curves correspond to (α) BK (black), (α/β1)BK (orange), (α/β2IR)BK (light blue), (α/β4)BK channels (bluish green). (**D**) Quantification of Vh and z obtained from fits to Q-V relations (values represent mean ± S.D).

(**Fig. 1A**), putatively lying in a conserved positively charged S4 transmembrane spanning segment of the protein.[23-25] The first direct demonstration that BK channels possess an intrinsic voltage sensor came from gating current measurements in the absence of intracellular Ca^{2+}.[39,62,63] The gating or sensing currents of BK channels proceed within a very fast time frame and have weak voltage dependence (~$0.7e_0$/voltage sensor) compared with those found in Kv and Ca^{2+} channels. Auxiliary proteins and other agents can directly affect the voltage-dependence and kinetics of the gating currents.[64,65] Studies on BK channels expressed in heterologous systems have also shown that several mechanisms are involved in channel gating based on voltage differences and Ca^{2+} changes.[33,62,66,67]

The S4 segment of BK channels has three positively charged residues (**Fig. 1A**), but only one (i.e., the R213) seems to contribute to the total amount of gating charges. Other important amino acid residues of the voltage sensor, including D153 and R167, are located in the S2 segment. However, the D186 residue, which is also involved in charge movements of the gating current, is present in the S3 segment of the channel.[68] The structural rearrangements of the voltage sensor during BK channel activation have also been studied by using the voltage clamp fluorometry technique. In this technique,[56,69] fluorescent probes are attached to cysteine residues in a region thought to undergo conformational changes during voltage sensor charge movements. Changes in the environment where the probe is located may result in changes in fluorescence intensity, which is recorded together with electrophysiological determinations. When the fluorescent probe is introduced in the S3-S4 region of the protein, measurements of voltage-dependent

changes that correlate with fluorescence fluctuations can account for the conformational changes in the voltage sensor during channel activation. Nevertheless, extremely slow conformational changes were unexpectedly revealed by the fluorescent labeling of position 202 of the S4 segment, which might be explained due to the interaction of the fluorophore with nearby tryptophan 203.[69] The quenching of the fluorescent probe diminished with W203F mutation, suggesting that this residue acts as an intrinsic fluorescence quencher. Based on these results, it has been hypothesized that a possible secondary structure of the voltage sensor in the BK channel in the S3-S4 region, placing amino acids L204, G205, and L206 within the extracellular portion of the S4 helical transmembrane segment.[70] Fluorescent labeling of tryptophan introduced residues that showed that the voltage sensing domain (VSD) of the S4 segment moves away from the S1 and S2 segments, while S2 gets closer to the S1 segment during voltage-dependent activation gating.[71] The S0 segment seems to play a pivot-like role, by which the S4 segment moves upward during depolarization, thus facilitating the opening of the channel.[72] All together, these results allowed for hypothetical interpretations of how the BK channel might function and how Ca^{2+} and voltage sensing can be incorporated so as to understand the BK channel as an allosteric protein.[73]

Mechanisms of gating: allosteric linkage of channel opening to voltage and calcium sensitivity

One of the most successful models that explains the behavior of BK channels is the one developed by Horrigan, Cui, Cox and Aldrich in a series of papers by the end of the 90s.[33,62,67,74] Following the Monod-Wyman-Changeux scheme of channel

Table 2. Alternative splicing variants of BK channels and modulatory subunits

Channel or subunit		Gene symbol (human)	Location	Tissue expression
BK$_{Ca}$		KCNMA	10q22.3	*Zero:* brain, kidney, thymus, stomach, muscle, small intestine, testis, adrenal gland, uterus, prostate, pituitary, breast virgin, breast pregnant, breast lactating, embyo (9.5, 12.5, 19 d) *STREX (e21):* brain, heart, kidney, spleen, thymus, stomach, muscle, small intestine, lung, testis, adrenal gland, pancreas, uterus, prostate, pituitary, breast virgin, breast pregnant, breast lactating, breast involuting, embryo (8.5, 9.5, 12.5, 19 d) *e22:* spleen, liver, muscle, small intestine, skin, uterus, prostate, breast virgin, breast pregnant, breast lactating, breast involuting, embryo (9.5, 12.5, 19 d) *Δe23:* brain, heart, kidney, spleen, thymus, liver, stomach, muscle, small intestine, lung, testis, skin, adrenal gland, pancreas, uterus, prostate, pituitary, breast virgin, breast pregnant, breast lactating, breast involuting, embryo (8.5, 9.5, 12.5, 19 d)
β subunit	β1	KCNMB1	5q34	smooth muscle, aorta, trachea, kidney, urinary bladder, brain
	β2	KCNMB2	3q26.32	spleen, placenta, pancreas, heart, kidney, uterus, chromafin cells, brain, dorsal root ganglia
	β3	KCNMB3	3q26.3-q27	*β3a:* spleen, placenta, pancreas, heart, kidney; *β3b:* spleen, pancreas, kidney, heart, brain, placenta, lung, liver, testes; *β3c:* spleen, prostate, placenta, liver, kidney, pancreas, ovary, brain, lung; *β3d:* spleen, testes, placenta, kidney, pancreas, brain, lung
	β4	KCNMB4	12q	brain, neuronal tissue, kidney, bladder smooth muscle
γ subunit	γ1	LRRC26	9q34.3	cerebellum, brain (whole), fetal brain, testis, aorta, mucosa, lung, trachea, prostate, thyroid gland, thymus, salivary glands, acinar cells, epithelial cells, hair cells (inner ear), arterial smooth muscle cells
	γ2	LRRC52	1q24.1	testis, skeletal muscle, placenta, sperm cells, kidney, lung, prostate, thyroid gland, salivary gland
	γ3	LRRC55	11q12.1	brain (whole: mitral cell layers of olfactory bulb, medial habenular nuclei of thalamus, ventral tegmental area, substantia nigra, cortex), fetal brain, placenta, uterus, testis, liver, spleen, lung, thymus, skeletal muscle, prostate, kidney, adrenal gland, salivary gland, thyroid gland, trachea
	γ4	LRRC38	p36.21	cerebellum, brain (whole), fetal brain, placenta, uterus, testis, skeletal muscle, aorta, spleen, trachea, prostate, thyroid gland, thymus, salivary gland, adrenal gland

allosteric modeling, the authors proposed that the channel subunit can undergo closed to open transitions in the absence of Ca^{2+} or membrane depolarization. They also proposed that Ca^{2+} binding or membrane depolarization produces conformational changes that are allosterically coupled to the channel gate, hence facilitating its opening (**Fig. 1C**).[39]

BK Channel Diversity

Alternative splicing of BK channels

There is a single gene encoding the α subunit of BK channels, in contrast with other members of the voltage-dependent potassium channel family. The structural and functional diversity of BK channels has been established by alternative splicing of the *slo1* gene and based on the association with auxiliary subunits that are encoded by multiple genes (**Table 2**). Many groups have described alternative gene *slo1* splicing that can produce the α subunit of the BK channel with different functional properties and tissue distribution.[75-78] Interestingly, the analysis of alternative splicing in BK channels showed that constitutive exons are conserved among different species of the same phylum, while alternative exons are not.[78] Across phyla, some sites of the *slo1* gene appear to be more susceptible to alternative splicing than others, thus suggesting a convergent evolution at this level.[78] A major determinant of splicing in BK channels is the STREX complex (stress-axis hormone-regulated exon) that changes the ability of the channel to respond to calcium, oxidation and phosphorylation shifts.[79,80] It is worth noting that alternative splicing of the *slo1* gene is critical in determining the localization of the BK channel in the plasma membrane or in intracellular organelles.[81,82] Interestingly, it is yet to be known whether the α subunit of intracellular BK channels is associated with auxiliary subunits and, if it were, the question would arise as to what auxiliary subunits are involved.[82]

Another important question is how interaction among alternative exons regulates BK channel function. An attempt to answer this question was made taking advantage of the worm *Caenorhabditis elegans*.[83,84] The *C. elegans* BK channel gene has only 3 sites for alternative splicing (A, B, and C), and encodes 12 splice variants.[83] The splice site enable the insertion of exons encoding part of the RCK1 (exons A1 and A2) and sections of the RCK1-RCK2 linker (exons B0, B1, B2, C0, and C1). Functional studies of all isoforms show that the A1 and A2 exons regulate channel gating kinetics and Ca^{2+} sensitivity but only if alternate exons are inserted in sites B or C. For example, a shift of about 40 mV in the voltage dependence arises if the variant (A1; B0; C1) is expressed compared with (A2; B1; C0). The biophysical properties of these splice variants, plus eventually co-expression with auxiliary proteins, could prove to be essential for some physiological processes, such as voltage shift of that magnitude alters behavior and decrease synaptic transmission.[85,86]

Post-translational modifications

Most post-translational modifications described in BK channels are related to the addition of hydrophobic groups for membrane localization. Palmitoylation of BK channels has been reported to be critical for PKA inhibition to occur in these channels.[87] This modification could regulate BK channel localization and its modulation by other proteins.[88,89] Particularly, the S0-S1 linker palmitoylation appears to be fundamental to plasma membrane localization.[88] The molecular determinants for α subunit palmitoylation have been located in a polybasic domain upstream of palmitoylated cysteine residues in splice variants of the C-terminal region of the channel. Mutations of residues in this polybasic domain prevents palmitoylation, thus generating a reduction in the channel's voltage sensitivity.[90]

BK channels are also modulated by strong and reversible protein phosphorylation in native tissues. The phosphorylation by cAMP-dependent protein kinase (PKA) activates BK channels in smooth muscle cells and neurons, but inhibits channel activity in anterior pituitary cells.[91-95] This diversity of PKA actions is due to a differential regulation of different splice variants of the BK channel by phosphorylation. PKA has shown to activate BK channel formed by α subunits that lacks the stress-regulated exon (STREX) and inhibits homotetramers formed by α subunits containing the STREX exon.[96,97] The increase in BK channel activity is mediated by direct phosphorylation of serine 869 (serine 899 in some isoforms) in the C terminus, in which the phosphorylation of all four serine 869 residues in the tetrameric channel is required. PKA-mediated phosphorylation of a single serine residue of the STREX insert leads to channel inhibition independent of the presence of serine 869.[96,97] On the other hand, PKC inhibits BK channel activity and Src has been reported to increase channel activity (for a review see ref. 98).[98] The exhaustive study performed by Yan et al., showed the presence of 30 Ser/thr phosphorylation sites, 23 of which are located in the C terminus and 4 are found on splice insertions.[99]

BK Channel Auxiliary Subunits

β-subunits

Four types of β auxiliary subunits of the BK channel have been identified thus far in mammals. All of them share a similar predicted topology, containing 2 transmembrane segments called TM1 and TM2, short intracellular N and C-terminal regions, and an extracellular loop of about 100 amino acids containing four cysteines. β1, β2, and β3 exhibit high degrees of homology, whereas β4 is genetically more distant from all β subunits. Although to a different degree, β subunits can modify Ca^{2+} sensitivity, voltage dependence and gating properties of BK channels (**Fig. 2**). It has been estimated that the most likely stoichiometry in which α and β subunits interact is that of one β subunit per α subunit.[100] Despite the breadth and depth of BK channel research, some important questions remain unanswered with regards to how BK channels interact in native systems, such as the following: (1) are there BK channels with less than 4 β subunits in native cells?; (2) do different types of β subunits co-exist in the same channel? In some tissues more than 1 type

of β subunits are present.[101,102] Hence, the overall question that arises is whether subunit heterogeneity could eventually be an additional source of functional diversity.

The main site of surface interaction between α and β subunits appears to involve the S0 segment of the α subunit.[103] There have been experiments in which amino acids in the TM1 and TM2 segments of the β subunits as well as in different transmembrane segments of the α subunit were substituted by cysteines. These experiments showed that cross-linking between TM2 and S0 occurs with high efficiency; whereas TM1 crosslinks with S1 and S2 occur to same extent.[104,105] Co-immunoprecipitation experiments and TOXCAT assays with the β2 subunit have suggested that TM1 binds to the S1 α subunit segment.[106] Consequently, S0, S1, and S2, which are part of the VSD in BK channels, appear to interact with the TM1 and TM2 segments of the β subunits. These interactions suggest that conformational changes of the VSD during channel activation would be influenced by the presence of β subunits and could be the cause of the β1, β2 and β4 effects on gating currents (see **Fig. 2**).

Early studies using *Xenopus* oocytes as expression systems showed that the β1 subunit induces an increase in apparent sensitivity to Ca^{2+}, a decrease in voltage dependence, and a deceleration of the macroscopic kinetics of α subunits in BK channels.[64,107,108] The β1 subunit also modifies the pharmacological properties of the channel, such sensitivity to alcohols,[109] estrogens,[110] and omega-3 polyunsaturated fatty acids.[111] The affinity of scorpion toxins to BK channels is also increased by the β1 subunit and its presence is needed for internal binding to the channel opener dehydrosoyasaponin-I (DHS-1).[112,113] The β1 subunit is encoded by the *kcnmb1* gene, which is located in chromosome 5q35.1 in the *Homo sapiens*. This subunit is mainly expressed in vascular smooth muscles, but it is also found in the urinary bladder and in some regions of the brain (see **Table 2**).

The β2 subunit, encoded by the *kcnmb2* gene, also increases Ca^{2+} and voltage sensitivity, slows down kinetics,[65,114-116] and induces a fast and complete inactivation of BK channels.[115,117] The N-terminus of the β2 subunit (residues 1 to 45) blocks the BK channel by interacting with a receptor site in the α subunit, which becomes accessible once the channel is in the open state.[115,117,118] The 3D structure of the β2 subunit N-terminus was established by NMR.[119] The structural analysis of the first 45 amino acids of the N-terminus shows that it consists of 2 well-defined domains connected by a flexible linker (see **Fig. 3A**, lower). Residues 1 to 17 form the so-called "ball domain," and residues 20 to 45 generate the "chain" and, thus, provide a structural explanation to β2-mediated BK channel inactivation. Fluorescent labeling of BK channels formed by α and β2 subunits has shown that β2 expression results in a shift of the F-V curve toward more negative membrane potentials, which is consistent with the shift promoted in the G-V activation curve.[114] F-V curves from BK channels carrying a fluorescence probe in the VSD domain are shifted due to the co-expression of the β2 subunit, which is independent from the presence of the N-terminal inactivating gate. This result suggest that in α/β2 channels, interaction does not produce VSD charge immobilization, as in the case of Shaker K^+ channels, where N-type inactivation produces sharp charge
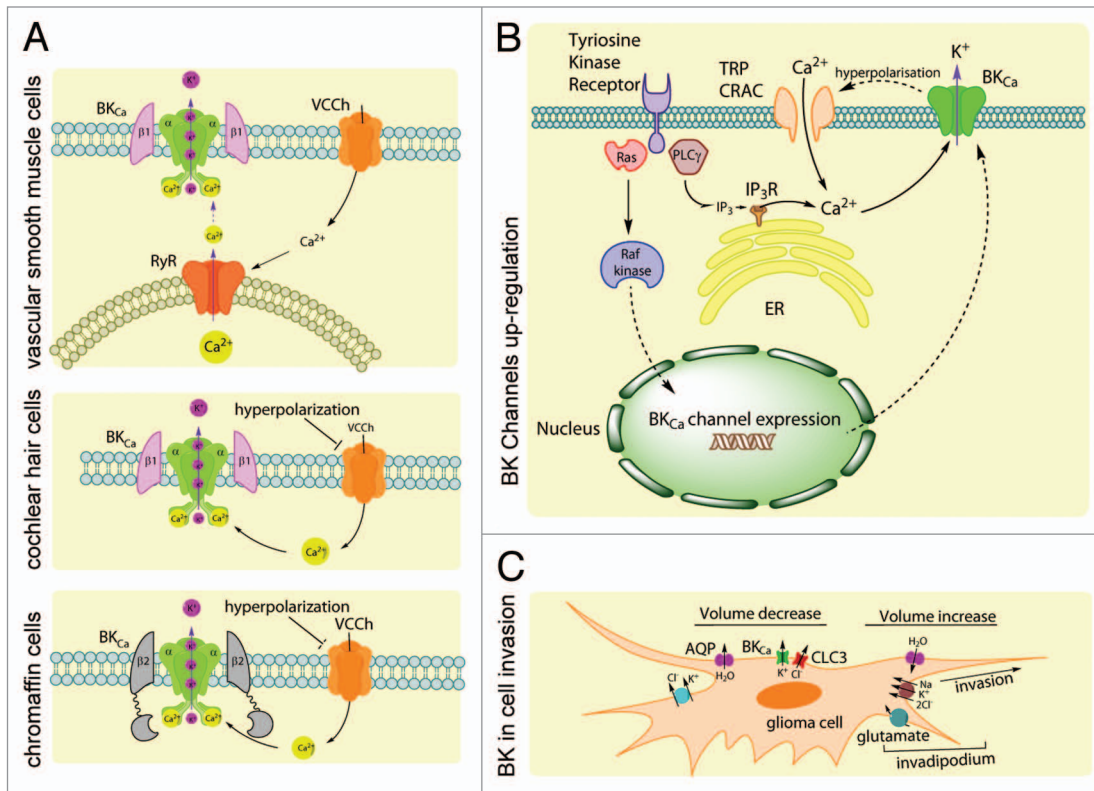
Figure 3. Proposed role of BK in physiology and pathology. (**A**) Cartoon representation of α and β subunits of BK channels co-expressed in vascular smooth muscles (upper), cochlear hair cells (middle) and chromaffin cells (lower). In VSM cells β1 subunits confer calcium sensitivity during the coupling of calcium sparks and outward currents. In chromaffin cells β2 subunits induce deceleration in BK current deactivation, consequently producing repeated firing in cells. In auditory hair cells, co-expression with β2 allows to tune the cells in a characteristic firing frequency. (**B**) BK channel expression has been found to be upregulated in tumors, such as prostate, glioma, and astrocyte cancer types, thus correlating with cell proliferation and malignancy coupled to calcium signaling and protein kinase activation. (**C**) BK channels play an active role in volume changes during cell invasion, acting in orchestration with other transporters and channels. The expression of these channels is relevant in glioma cells, because they migrate long distances through the brain.

immobilization.[114] However, this result may also be interpreted differently, considering that only half of the gating charges are located in the S4 segment, and that only 1 charge present in this segment (i.e., R213) suffers displacement during activation. This would be contrary to what has been observed in the Shaker K$^+$ channel, where 4 positively charged residues move across the entire electric field. β2 also induces an instantaneous outward rectification, suggesting that the β2 external loop approaches the BK pore in order to alter the α subunit ion conduction features.[116] It is worth noting that the N-terminus of β2 prevents the surface expression of this subunit and hinders the surface expression of the α subunit by stimulating endocytocis.[120] This fast inactivation by β2 appears to be responsible for the fast inactivating phenotype of BK channels in chromaffin cells and CA1 hippocampal neurons.[121,122] At least 2 splice variants of this β subunit have been identified in the pancreas and are known as β2a and β2b. Splice variant β2b does not confer inactivation to BK channels and it yields currents almost identical to those observed from the α subunit alone.[123] β2b is the predominant variant in the pancreas and is also present in kidneys, spleen, adrenal chromaffin cells, dorsal root ganglia, and brain (see **Table 2**).

The β3 subunit was cloned and expressed by 3 different groups, thus identifying 4 splice variants (*a* to *d*).[116,124,125] Unlike β1 and β2, none of the β3 subunits were observed to alter calcium sensitivity or voltage dependence of the α subunit.[116] Of the 4 splicing variants, only *a*, *b*, and *c* induced partial inactivation.[116,126,127] Albeit incomplete, this inactivation is faster than the one induced by the β2a subunit. Although to a small degree, the β3b subunit consistently seems to speed activation at low Ca^{2+} concentrations and produce an inward rectification of BK channel currents, which is regulated by the extracellular segment of this subunit.[126] The N-terminal region of β3, which is related to BK channel inactivation, seems to be non-conserved among different species.[128] The gene encoding this subunit in *Homo sapiens* is *kcnmb3* and it is located quite close to *kcnmb2* in chromosome 3q26.3-q27. This subunit is expressed in adrenal chromaffin cells, kidneys, the heart, brain, spleen, lung, liver, testis, and other tissues (see **Table 2**).

The human β4 subunit was cloned almost at the same time as β3[124,125] and its sequence is more distantly related to the other β subunits.[124,129] β4 has been seen to alter calcium sensitivity of the channel in a complex manner.[124,130] At low Ca^{2+} concentrations, this subunit decreases apparent Ca^{2+} sensitivity, but increases it at

high Ca^{2+} concentrations. This has been observed as a reduction in open probability compared with the α subunit alone at low Ca^{2+} concentrations and as a rise in open probability at high Ca^{2+} concentrations when the subunit is present.[124,130,131] β4 also slows down kinetic activation and deactivation, allowing for a more prolonged control over repolarization after the depolarization of the plasma membrane. This property is observed in the brain as a reduction of dentate gyrus excitability and protection against seizures,[132] and seems to be related to phosphorylation-dependent changes.[133] Palmitoylation of the β4 subunit in the amino acid residue C193 of the β4 C-terminus has been observed to regulate the expression of BK splice variants containing the putative trafficking motif REVEDEC in the C-terminus of the α subunit.[80,134] Despite these actions, the β4 subunit is able to downregulate the surface expression of BK channels in brain.[135] This subunit is responsible for some of the features that are unique to neuronal BK channels, such as low affinity to scorpion toxins and sensitivity to ethanol.[129,136] It is important to note that the effects of ethanol over the BK features also depend on the location of the channel in different neuronal compartments. For example, in the nucleus accumbens, which is a brain area known to be involved in addiction, somatic channels (but not dendritic BK channels) increase the open probability that is governed by compartimentalized β4 expression in somas.[137] Similar effects were also observed in the hypothalamic-neurohypophysial system, where β1 expression predominates and where channels in the soma and dendritic compartments are insensitive to IbTx, in contrast to those found in the nerve terminal (β4 expression is higher in nerve terminals). In addition, these channels are highly activated by ethanol.[138] Accordingly, spiny neurons isolated from mice, showed low tolerance to alcohol, but cells derived from β4 knockout mice exhibit chronic tolerance to ethanol, even at the behavioral level.[139] β4 is expressed almost exclusively in the brain, but it has also been found in kidneys and genito-urinary smooth muscles (see **Table 2**).[140,141] The *kcnmb4* gene encodes the β4 subunit in humans and is located in chromosome 12q15.

Previous studies revealed that the modulation of the apparent Ca^{2+} sensitivity mediated by the β1 subunit was not due to an increase of the affinities of the Ca^{2+}-binding sites, but rather to a Ca^{2+}-independent effect.[142,143] These studies suggested that β1 alters the BK voltage- sensing properties. Measurements of gating currents in the BK channel α subunit alone or in combination with different types of β subunits revealed that β1, β2 and β4 stabilize the voltage sensor in its active conformation, whereas β3 has no effect on voltage sensor equilibrium.[64,65,144] It has been recently proposed that coupling between α and β subunits is mediated by electrostatic forces between the following three interaction sites: (1) a PI site that accounts for pre-inactivation; (2) an E site, which enhances Ca^{2+} sensitivity of the α subunit; (3) and an ECaB site, which couples the α subunit Ca^{2+} bowl to the gating process through the β2 subunit.[145] According to these results, the binding energy between the α and β2 subunits is mainly electrostatic, suggesting a close interaction between the β2 subunit extracellular loop with the pore gate and the voltage sensor in the α subunit.

It should be highlighted that β subunits may also bind to other members of the Slo family. In fact, Slo3 has been found to be able to bind to the β4 subunit.[146] However, although all 4 β subunits are able to co-assemble with the Slo3 channel, only β4 has been observed to produce significant changes in the surface expression of the Slo3 channel.

In summary, 4 different auxiliary β subunits are expressed in mammalian tissues. A functional conserved domain among β1, β2, and β4 subunits stabilize the active configuration of the channels, while increasing the energy barrier that separates closed from open states.[147] The importance of the β subunits is not only related to the modulation of Ca^{2+} sensitivity and voltage-dependent gating of the α subunit, but also to the fact that they act as a target "sites/receptors" for different agents that could modulate BK channel function, such as protein, toxins, blockers or openers. Consequently, their significance is also related to channel trafficking and expression in cellular surface. These subunits also play a critical role as receptors for estrogens and steroids.[110] The BK channel responds to steroids in a manner that does not only depend on the nature of the ligand, but also on the type of β subunit associated to the channel.[148] Lipids like omega 3 polyunsaturated fatty acids with vasoactive properties have also been shown to activate BK channels in a β subunit-dependent manner.[111]

γ subunits

In addition to β subunits, there are other auxiliary subunits that have been described in terms of their ability to modulate BK channel α subunits, which are known as γ subunits. Pioneers in the study of these subunits are Yang and Aldrich, who identified conserved leucine-rich repeat proteins (LRRCs) that can dramatically modify BK channel activation features.[149,150] The first γ subunit described was LRRC26 (γ1), which induces a Ca^{2+}-independent leftward shift of ~140 mV in the opening probability vs. voltage curve, with V_h ~18 mV.[150] Within the framework of Horrigan's model for BK channel activation, this result can be interpreted as γ subunits improving coupling between the activation of the voltage-sensor and channel opening. Several paralogous proteins of LRRC26 (γ1), such as LRRC52 (γ2), LRRC55 (γ3) and LRRC38 (γ4), have been identified.[150] Although all γ subunits have been seen to modify V_h values for BK channel activation, their effects extend to different degrees, thus being LRRC26 (γ1) and LRRC52 (γ2) the subunits that cause greater effects.[150] Thus far, γ and β subunits do not appear to co-assemble at the same time with α subunits. The LRRC52 (γ2) subunit has also been found to interact with other Slo channels, like Slo3 in testis.[151]

Endogenous Signaling Molecules

Several small endogenous molecules such as heme, carbon monoxide and oxygen reactive species are able to modulate BK channels (for an excellent review see ref. 150).[152] In particular, haem, a stable protein prosthetic group acutely modulates BK channels and it does so by binding to CKACH sequence located in the linker that join together the RCK1 and RCK2 domains.[153-155] It has been suggested that interaction of heme with the RCK1-RCK2 linker may expand the gating ring, hindering

the interactions between the ring and the voltage sensor domain that occur during BK channel activation.[156] Although the physiological role of heme binding to BK is still unclear, its binding is modulated by the redox state of the cell suggesting that the channel activity can be widely different in hypoxic and normoxic conditions.[157]

BK Channel Pharmacology: Blockers and Openers

Slo1 channels have been observed to be blocked by the scorpion toxins ChTx and by the highly selective IbTX.[20,158] These scorpion toxins act as pore blockers occluding conduction pathways of the α subunit in BK channels. A positively charged side chain of lysine 27 in ChTx has been identified as the blocking particle in the molecule.[159] In addition, a quite potent blocker isolated from scorpions is known as kaliotoxin, which inhibits BK channel opening with a K_D of approximately 20 nM.[160] Paxilline is another high-affinity blocker of the channel, which is a tremorgenic mycotoxin that has been described as an extremely potent BK channel blocker with a K_D also in the nM range.[161] BK channels are also very sensitive to the administration of tetraethylammonium in the extracellular side of the channel, with K_D ~250 μM.[162-164] This high sensitivity is due to the presence of a phenylalanine ring in the boundaries of the external mouth of the selectivity filter.[165,166]

Furthermore, a number of BK channel *openers* have been identified, including the synthetic benzimidazolone derivative NS1619, and the natural modulator dihydrosoyasaponin.[167] It is worth mentioning that the compound NS11021 is a Slo1 channel activator that has shown to have better specificity and 10 times higher potency compared with NS1619, which is one of the most broadly applied Slo1 openers.[168]

BK Channels in Smooth Muscles

The main function of BK channels in vascular physiology is to reduce contractile responses to excitatory stimuli by increasing in the concentration of intracellular Ca^{2+}. Myogenic tone control, vasorelaxation induced by Ca^{2+} sparks, endothelial factors or exogenous and endogenous vasoactive agonists also involve BK channel activation.[169-172]

There are numerous reports indicating that BK channels participate in the endothelium-dependent hyperpolarization of vascular smooth muscle cells, for which nitric oxide (NO) appears to be an important BK channel activator.[173] NO activation of BK channels is linked to cGMP-activated kinases.[174,175] NO is produced by endogenous synthases like eNOs in endothelia.[176] Other endothelium-derived factors, such as cytochrome P450-derived epoxyeicosatrienoic acids, prostacyclin and lipoxygenase derivatives produce the relaxation of smooth muscle cells by activating BK channels.[177]

Additionally, redox agents such as H_2O_2, have also been shown to have an inhibitory effect on BK channels by decreasing their open probability.[178] The inhibitory action of reactive oxygen species (ROS) has been compared with β1 function impairment.[179] However, the β1 subunit enhances the ability of

oxidative regulation of the BK channel.[180] In general, CO is a potent BK channel activator composed of vascular myocytes and carotid body glomus cells. It has been suggested that a motif in the BK C-terminal region is a binding region for CO, promoting its gating changes independently of redox changes (an excellent review on endogenous signaling molecules that modulate BK activity can be read in Hou et al., 2009).[152]

BK channels work as transducers and coupling agents between the endothelium and vascular smooth muscles, communicating diverse chemical signals generated in the endothelium to the vascular smooth muscle tone, thus controlling blood vessel caliber and flow.[181] BK channel activation in smooth muscles is tightly related to endothelium activity through NO/cGMP-dependent protein kinase I (PKGI).[182] This has profound implications in many tissues and organs, where smooth muscle activity plays important roles in regulating pressure, volume and flow. **Figure 3A** shows a general view of BK in smooth muscle physiology.

Other types of smooth muscle cells

BK channels are also important in other kinds of smooth muscle cells. In the uterus, for instance, they participate in the control of myometrial cell membrane potentials,[183] their expression being under hormonal control.[184] Thus, a significant downregulation of the BK α subunit is observed in rat myometrium at the end of pregnancy, likely enhancing the myometrial excitability needed during labor and parturition.[184]

As in vascular smooth muscles, BK channels can regulate the tone and contractility of airway smooth muscles by providing a negative feedback mechanism. In human bronchial smooth muscle cells, these channels also participate in maintaining resting membrane potential.[185] Although BK channels are present in rat bronchial smooth muscle cells, they do not seem to contribute to resting membrane potentials or participate in excitation responses.[186]

Gastrointestinal motility is another physiological function involving BK channels, for which they appear to be particularly important in the regulation of colonic motility. In the colonic longitudinal layer, these channels are involved in setting membrane potential and determining excitability. In the circular layer, on the other hand, they do not underlie basal electrical activity, but limit the responses to excitatory agonists.[187]

In urinary bladder smooth muscle cells, BK channels play a critical role in regulating their excitability and contractility. In these cells, BK currents are activated by Ca^{2+} sparks originating from Ca^{2+} release mediated by ryanodine receptors (RyRs) that are present in the sarcoplasmic reticulum.[188] A similar mechanism has been observed in cerebral arteries.[189] The modulation of BK channel activity by spontaneous Ca^{2+} sparks is known as spontaneous transient outward current (STOC).[190]

Membrane potential profoundly alters the coupling strength of Ca^{2+} sparks in BK channels. As an explanation for this, it has been proposed that calcium and voltage dependence of the sparking BK currents is modulated.[191] Furthermore, a similar coupling mechanism between Ca^{2+} sparks and BK channel activity was demonstrated in gallbladder myocytes.[192] Thus, inhibition and/or downregulation of BK channels could be the

cause of smooth muscle cell contractility alteration, as found in urinary bladder overactivity.[193]

In brief, despite tissue and interspecies diversity, a general behavior can be observed as a common factor for BK contribution to cell physiology. This has profound implications in many tissues and organs where smooth muscle activity plays an important role in regulating pressure, volume and flow. Finally, changes in the activity or expression of BK channels are related to cardiovascular pathological states, as will be discussed below.

BK Channels in Hair Cells

In the cochlea the sound sensitive region resides in the basilar membrane in the organ of Corti. Is in this membrane where the hair cells, the sound sensitive cells, reside. In frog, chick, and turtle, used as models of this sense, frequency tuning is performed almost exclusively in these cells. Hair cells are arranged tonotopically and show a gradual change in oscillation frequency that correspond to the cell's tonotopic location.[194-196] The oscillation in membrane potential appears as a consequence of the interplay of an inward Ca^{2+} current and an outward K^+ current. In hair cells BK currents are activated by an increase in internal Ca^{2+} concentration brought about by the opening of L-type voltage-dependent Ca^{2+} channels (VDCC) that colocalize with BK channels (**Fig. 3A**).[36,37] Activation of BK channels hyperpolarizes the cell, closing VDCC, thus promoting the membrane potential oscillation. Subsequent membrane voltage oscillations are damped, because as VDCC channels close, fewer BK channels are recruited in each cycle. The combination between the number and type of BK channel in each sensory cell, control the resonant frequency of a particular hair cell. The origin of the wide range of BK gating kinetics along the tonotopic map is still under debate. The presence of many different BK splice variants changing along the tonopic axis led to the hypothesis that this was the origin of the changes in gating kinetic properties of the channel.[197-199] However, due to their limited range of relaxation time constants of the BK splice variants found in hair cells, the splice variant hypothesis appear to be part of but not all the story.[200,201] As discussed earlier in this review, other means of altering BK function is the co-expression of α and β subunits. The presence of different alternative splice variants, together with a differential expression of β1 subunit has been proposed to be the main mechanism that generates the cochlear tonotopic gradient.[201,202] Actually, a gradient in the expression of the β1 subunit slows BK channel kinetics toward the low-frequency apex of the cochlea.[203] More recently, it was found that the β4 subunit is also expressed in a gradient along the tonopic axis of the basilar membrane. β4 is preferentially expressed in the apical end of the basilar papilla suggesting that this subunit may also play an important role in the hair cell electrical behavior.[102]

BK Channels and Diseases, Pathophysiological and Genetic Involvement

In humans, alterations in BK channels are known to be important in the pathophysiology of hypertension,[204,205] asthma,[206] diabetes, and vascular insulin secretion,[123,207] epilepsy,[208-210] and cancer.[211,212] In this section we will briefly discuss some of these findings that link BK channels with the diseases in which they play a major role.

BK channels and hypertension

BK channels are known to be essential regulators of blood pressure and tissue perfusion.[213] An important observation supporting this view is that knocking-out the β1 subunit gene yields an increment in arterial tone and blood pressure.[214] Since the β1 subunit increases the apparent calcium sensitivity of BK channels, its absence would reduce functional coupling to calcium sparks for BK channel activation, thus increasing muscle tone and blood pressure.[214]

Moreover, BK channel polymorphisms may be related to genetic forms of hypertension and cardiovascular diseases. Single-nucleotide polymorphisms (SNPs) that promote either "gain-of-function" or "loss-of-function" have been identified in both the α and β1 subunits.[215-217] AE65K polymorphism in the β1 subunit diminishes the prevalence of severe hypertension as well as myocardial infarction.[204,218]

BK channels and diabetes

In diabetes mellitus there are several metabolic changes, some of which are reflected in BK channel function. Vessels in diabetics are a common target, and some of the effects described previously for vascular smooth muscles tend to increase or are modified due to the development of diabetes. The β1 subunit of BK channels is downregulated under diabetic conditions in several cells where BK is expressed, leading to alterations in intracellular Ca^{2+} sensitivity.[219] Furthermore, there is an increment of coronary heart disease in diabetics compared with normal subjects or to those that have other vascular diseases. It has been reported that one of the factors contributing to coronary dysfunction leading to coronary heart disease is related to the downstream regulation of β1 subunit channel expression in coronary arteries induced by diabetes.[220] β1 expression is also impaired in other alterations promoted by diabetes in the microvasculature, such as in diabetic retinopathy.[207] Other vessels affected by the downregulation of β1 expression in diabetes are those found in the brain, hence creating greater susceptibility to strokes.[221]

BK channels may also play a role in insulin secretion during diabetes, since they regulate action potential firing in pancreatic β-cells.[222] Splice variants of β2 subunits (i.e., β2a and β2b) have been observed to be expressed in the pancreas in experimental models as well as in patients with diabetes.[123] The predominant splice variant is β2b, and the functional characteristics of α subunit and β2b complexes expressed in heterologous systems are almost identical to those of the α subunit alone, lacking inactivation. This fact may explain alterations of insulin secretion by pancreas islets during diabetes.

BK channels and asthma

In the airway pathway, the β1 subunit seems to play a major role regulating BK channel sensitivity to intracellular Ca^{2+}.[223] Genetic studies in high-prevalence asthma populations are consistent with these findings.[206] Additionally, evidence that BK channels are sensitive to estrogen may explain gender susceptibility to asthma.[224]

BK channels and kidney disease

In the kidney epithelia, BK impairment by different β subunits leads to hydrosaline retention an hypertension.[225,226] A common allelic variant for SNPs in hypertension is the E65K mutation in the β1 subunit, which increases basal glomerular filtration rate. It has been anticipated that profiling this SNP can contribute to the prognosis of progressive renal disease.[227] Besides the β1 subunits, β2 and β4 are also expressed in the kidney epithelial cells.[140] In podocytes, nephrin seems to organize BK channel expression at the surfaces of nearby cells.[228]

BK channels and nervous system diseases

The activation of BK channels in the nervous system is related to the modulation of a number of physiological processes, like action potential firing and transmitter release,[229,230] and are the main effectors for the modulation of a wide range of neurotransmitters, including those that are involved in the pathogenesis of several neurological and psychiatric disorders. Genetic analyses of a human syndrome in which generalized epilepsy coexists with paroxysmal dyskinesia has uncovered a disease that causes mutations in the RCK domain of the α subunit.[208,210] A highly conserved aspartate at position 434 appears to be replaced by a glycine mutation that leads to higher intracellular Ca^{2+} sensitivity and to the enhancement of BK currents in heterologous expression systems. These changes may lead to an overall increase in neuronal excitability as a consequence of faster repolarization of action potentials, allowing neurons to fire at faster rates to the point of producing generalized epilepsy and paroxysmal dyskinesia. At the single channel level, the missense mutation D434G increases BK channel open probability by spending less time in the long-lived closed state.[231] This mutation has also been important in understanding basic questions and issues, such as the link between Ca^{2+} sensitivity and BK channel opening enhancement. This is because this mutation is located in a cytosolic motif immediately following the activation gate in the S6 helix (known as AC region), which is thought to mediate allosteric coupling between Ca^{2+} binding and channel aperture. Other epileptogenic mutations are related to changes in the expression of the α subunit. More specifically, these changes have been observed in the medial temporal lobe in epilepsy.[232] β3 subunit deletions have also been implicated in the genesis of epilepsy, particularly in the absence of seizures. It has been shown that a single base pair deletion in exon 4 of the *KCNMB3* gene (delA750) eliminates the last 21 amino acids of this subunit, thus altering BK channel inactivation.[209] Likewise, deletion of β4 subunits has also been linked to epilepsy, based on evidence of temporal lobe epilepsy in mice when such subunits are deleted. It is interesting to note that α/β4 channels activate and deactivate slower than those composed by the α subunit alone, allowing for better control of the firing processes in neurons.[233] Psychiatric diseases such as autism and mental retardation have also been linked to BK channel deficits.[234] Finally, BK channels are also major players for many sensory responses such as hearing. It has been shown that α subunit deficiency can lead to progressive deafness in a similar way as it has been observed for KCNQ4.[235]

BK channels and cancer

BK channels have been found to be one of the most frequent channels in tumor cell lines, such as prostate cancer, ovary cancer, osteosarcoma, breast cancer, gliomas, meningiomas, and other brain tumors.[236,237] In non-excitable cells, BK channels are important in functions such as cell proliferation, migration, and volume regulation.[238] BK channels act as effective transducers of changes in intracellular Ca^{2+} to signal proliferation and migration, which lead to invasive proliferations of the transformed cells (**Fig. 3B** and **C**).[238] In some cases, BK channels have also been found in the inner membrane of mitochondria, such as in some glioma culture cells.[239] Overexpression of BK channels, in particular of BK isoforms with enhanced Ca^{2+}-sensitivity, strongly correlate with the degree of malignancy observed in gliomas.[211,240] In breast cancer cells, BK channel expression has been shown to be related to cell cycle and division, correlating with high proliferation rates and malignant tumors.[241,242] BK channel expression has also been correlated with the production of metastasis in the brain (see **Fig. 3C**).[212] Amplifications of the BK channel gene have also been observed in many types of prostate cancers.[243] The study of BK channels in prostate cancer has shown that BK channels open at resting potentials and low intracellular Ca^{2+},[244] thus paving the way to find γ subunits.[149] **Figure 3B** and **C** shows a scheme of the role of BK channels in cell proliferation and migration that can be related to cancer malignancy.

Conclusions and Future Perspectives

Since their discovery, BK channels have emerged as key players in many physiological and pathophysiological conditions, also posing exciting biophysical questions relating to the convergence of voltage and free intracellular Ca^{2+} in the opening of K^+ channels during evolution. In essence, BK channels are unique molecular transducers that link intracellular signals with extracellular stimuli through the interplay of multiple tuning knobs that control signaling gain and timing, thus allowing for the correct physiological activity of cells, organs and tissues. Although the key components related to Ca^{2+} sensitivity and voltage-dependent gating have been amply explored, many questions remain unanswered from the molecular biophysics standpoint, as well as regarding the many pathophysiological issues where this channel is a relevant actor. Finally, it is it is worth noting that changes in the activity or expression of BK channels are linked to several pathophysiological disorders, such as cardiovascular illness states, cancer, diabetes and neurological diseases. This highlights the importance of accurately understanding how conduction may take place and how it can be modulated in order to find possible therapeutic interventions for these diseases.

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