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PERSPECTIVES | *Translational Physiology*

Molecular structure and function of big calcium-activated potassium channels in skeletal muscle: pharmacological perspectives

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Maqoud F, Cetrone M, Mele A, Tricarico D. Molecular structure and function of big calcium-activated potassium channels in skeletal muscle: pharmacological perspectives. *Physiol Genomics* 49: 306–317, 2017. First published April 28, 2017; doi:10.1152/physiolgenomics.00121.2016.—The large-conductance Ca^{2+}-activated K^+ (BK) channel is broadly expressed in various mammalian cells and tissues such as neurons, skeletal muscles (sarco-BK), and smooth muscles. These channels are activated by changes in membrane electrical potential and by increases in the concentration of intracellular calcium ion (Ca^{2+}). The BK channel is subjected to many mechanisms that add diversity to the BK channel α-subunit gene. These channels are indeed subject to alternative splicing, auxiliary subunits modulation, post-translational modifications, and protein-protein interactions. BK channels can be modulated by diverse molecules that may induce either an increase or decrease in channel activity. The linkage of these channels to many intracellular metabolites and pathways, as well as their modulation by extracellular natural agents, have been found to be relevant in many physiological processes. BK channel diversity is obtained by means of alternative splicing and modulatory β- and γ-subunits. The association of the α-subunit with β- or with γ-subunits can change the BK channel phenotype, functional diversity, and pharmacological properties in different tissues. In the case of the skeletal muscle BK channel (sarco-BK channel), we established that the main mechanism regulating BK channel diversity is the alternative splicing of the *KCNMA1/slo1* gene encoding for the α-subunit generating different splicing isoform in the muscle phenotypes. This finding helps to design molecules selectively targeting the skeletal muscle subtypes. The use of drugs selectively targeting the skeletal muscle BK channels is a promising strategy in the treatment of familial disorders affecting muscular skeletal apparatus including hyperkalemia and hypokalemia periodic paralysis.

sarcolemma BK channel; splicing mechanism; potassium channel openers; neuromuscular disorders

LARGE-CONDUCTANCE Ca^{2+}-activated K^+ (BK) channels are members of a family of Ca^{2+} and voltage-dependent potassium channels. BK channels are considered channel complexes composed of either homotetramers of the pore-forming calcium and voltage-sensing α-subunit encoded by the *slo1* gene (*KCNMA1*) (51) alone or in association with regulatory tissue-specific auxiliary β- or γ-subunits (Fig. 1, *A–C*). In several tissues, BK channels have been reported to be modulated by auxiliary subunits and alternative splicing of the *slo1* gene, which confer important physiological role to the channels. BK channels are ubiquitously expressed in cell membranes of mammalian tissues (neurons, smooth and skeletal muscles, exocrine cells) (19), 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 nonnervous cells (55, 68). The BK α-subunit consists of seven transmembrane spanning domains (S0–S6) including the extracellular NH_2 terminus, the P-loop between S5 and S6 domains, and a large intracellular COOH terminus containing a number of regulatory sites, including the regulators of conductance for K^+ ions (RCK 1 and 2) and two or three Ca^{2+} binding sites (32) (Fig. 1*A*). BK channels play a pivotal role in the functioning of many cells in the animal as well as in the plant kingdom; they are not only in charge of the membrane repolarization of the action potentials and transmitter/hormone release but also control cell proliferation. These channels regulate a number of physiological events, like blood pressure, smooth muscle relaxation, or electrical tuning and have a leading role in many pathophysiological conditions such as epilepsy or the behavioral response to alcohol, to give only a few examples (32).

Four β-subunits (Fig. 1*B*, Table 1) have currently been identified (β_1, β_2, β_3, and β_4), and despite the fact that they all share the same topology (28), it has been shown that every β-subunit has a specific tissue distribution and that they modify channel kinetics as well as their pharmacological properties and the apparent Ca^{2+} sensitivity of the α-subunit in different ways. Additionally, different studies have shown that natural, endogenous, and synthetic compounds can modulate BK channels through β-subunits. In addition, a splicing mechanism of the *KCNMB3* gene (Fig. 2) may play a role in the functional diversity of BK channels (15, 28, 34, 111). The β_3-subunit thus identified four splice variants (a–d) (Table 1). Unlike β_1 and β_2, the β_3-subunits were observed to alter the calcium sensitivity or voltage dependence of the α-subunit. Of the four splicing variants, only a, b, and c induced partial inactivation.

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 (Fig. 1*C*) (Table 1). The first γ-subunit described was LRRC26 (γ_1), which induces a Ca^{2+}-independent leftward shift of ~140 mV in the opening probability vs. voltage curve, with ~18 mV (116, 117).

The BK channel is subject to posttranslational modification such as the addition of phosphate (PO_4^{3-}) groups to functionally

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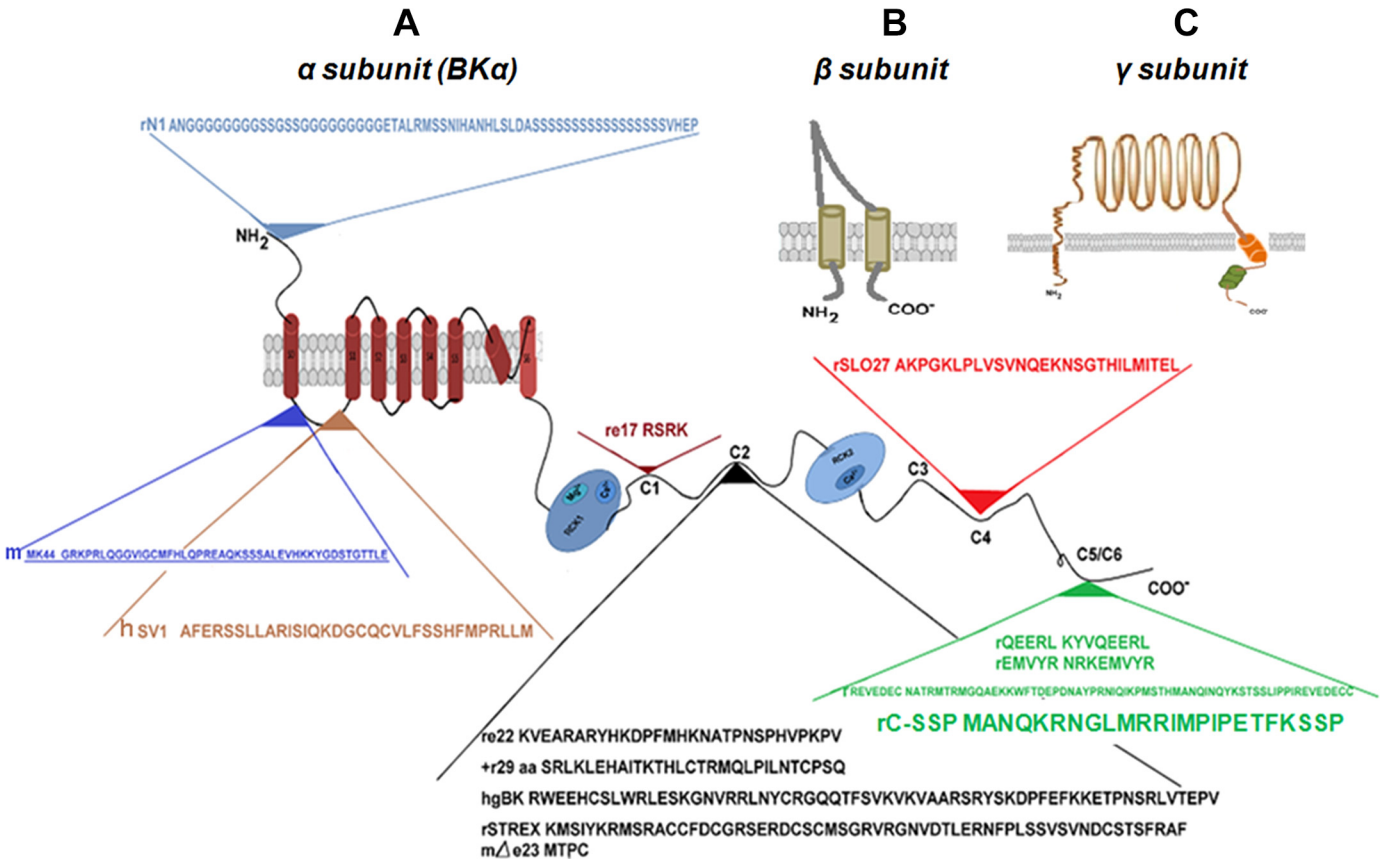

Fig. 1. Schematic structure and membrane topology of large-conductance Ca^{2+}-activated K^+ (BK) channel subunits α (*A*), β (*B*), and γ (*C*). α-Subunit and alternative splicing of the *KCNMA*1 gene. The length of each segment is represented in approximate scale. S0–S6 are transmembrane domains and intracellular domains. For sites 1–6, arrows show the sites of alternative splicing within the sequence of the α-subunit. Site 7 indicates the site of alternative carboxyl-terminal exon choice. The Ca^{2+}-regulated domains RCK1 and RCK2 are shown in blue outline, and the calcium bowl is represented as a yellow circle. At each site of alternative splicing the amino acid sequences of mammalian species (h, human; r, rat; m, mouse) are shown. RCK1/2, regulator of K^+ conductance; NH_2, amino terminus; COO^-, carboxy terminus; LRRD, leucine-rich repeat domain; TM, transmembrane segment.

important residues (Ser/Thr/Tyr) (35) present within the channel pore-forming α-subunit and regulation of endogenous molecules such as stimulation of CO, H^+, and Zn^{2+}, steroids, Heme, and fatty acids (79, 88) (Fig. 2).

In addition, the BK channel is also subject to a diverse array of posttranslational modifications (Fig. 2) including protein lipidation, glycosylation, and ubiquitination to control the number and regulation of BK channels in specific cell types (88).

BK Channel Structure and Function

BK channels are assembled and positioned on membrane surfaces including the plasma membrane, of the nucleus and other intracellular organelles (90, 122), among these the inner membranes of the mitochondrial BK (mito-BK). There is a single gene, encoding the α-subunit of BK channels, in contrast to 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 (53, 70), the *slo1* splicing can produce the α-subunit of the BK channel with different functional properties and tissue distribution (1, 121). Despite the existing large number of variants of the *KCNMA1*, only about 11 alternative splicing sites have been functionally characterized for the vertebrate BK α-subunit. Most variation occurs in the NH_2-terminal part, in the linker region between S0 and S1, and in intracellular COOH-terminal part in the linker region between domains RCK1 and RCK2 (Fig. 1*A*). Alternative splicing can modify the functional properties of BK channels, including Ca^{2+} and voltage sensitivity, cell surface expression, and regulation by diverse intracellular signaling pathways (27, 70). 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 (38, 54).

Abnormal expression/activity of BK channels is implicated in an array of human diseases involving many organs mostly smooth muscle and neuronal tissues such as the nervous, pulmonary, cardiovascular, renal, and urinary systems, among these the overactive bladder (36), hypertension, obesity (19), autism, and adult onset of neuronal ceroid lipofuscinosis (37). In skeletal muscle, different types of BK channels have been found (60, 86, 105). Slow-twitch rat fibers indeed showed an elevated expression/activity of BK channel, which is characterized by a low sensitivity to Ca^{2+} ions and lack of response to the BK channel opener acetazolamide (61, 105). In contrast, the BK channel found in the fast-twitch rat fibers showed a low expression/activity, high sensitivity to Ca^{2+} ions, and activat-

Table 1. *Alternative splicing variants of BK channel subunits and tissue distribution*

Channel or Subunit		Gene Symbol (human)	Location	Alternative Splicing and Synonyms	Number of Insertions of the Amino Acids	Tissue Expression
Hslo		*KCNMA1*	10q22.3	*Zero* Slo*1* maxi-K, KCa1.1	0	brain, kidney, thymus, stomach, muscle, small intestine, testis, adrenal gland, uterus, prostate, pituitary, breast virgin, breast pregnant, breast lactating, embryo (15)
				SV1 insertion site: S0–S1 linker longer	33	myometrium, brain (38)
				Mk44 insertion site: S0–S1 linker longer	44	myometrial, aortic smooth muscle (49)
				Slo27 *Ca27 ALCOREX* insertion site: 4(C_4)	27	human trabecular meshwork cells (119), brain, cerebellum, brain regions (30)
				STREX *e21* insertion site: 2(C_2)	58	brain, heart, kidney, spleen, thymus, stomach, muscle, skeletal muscle (18), small intestine, lung, testis, adrenal gland, pancreas, uterus, prostate, pituitary, breast virgin, breast pregnant, breast lactating, breast involuting, embryo (15)
				Δ*e23* insertion site: 2(C_2)	4	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 (15)
				+29aa *hbr5* *e22* insertion site: 2(C_2)	29	human brain (110), skeletal muscle (8). spleen, liver, muscle, small intestine, skeletal muscle (18). uterus, prostate, breast virgin, breast pregnant, breast lactating, breast involuting, embryo (15)
				Gbk insertion site: 2(C_2)	63	human gliomas (120), astrocytes (67) Müller glial cells (17)
				e17 SRKR insertion site: 1(C_1)	4	hypothalamus, brain, SCN (87), skeletal muscle (18)
				REVEDEC *VEDED* *C-DEC* insertion site: COOH terminus	61	
				QEERL C-ERL insertion site: COOH terminus	8	
				EMVYR C-YVR insertion site: COOH terminus	8	
				C-SSP insertion site: COOH terminus	24	
β-Subunit	β_1	*KCNMB1*	5q34			smooth muscle, aorta, trachea, kidney, urinary bladder, brain (15)
	β_2	*KCNMB2*	3q26.32			spleen, placenta, pancreas, heart, kidney, uterus, brain, dorsal root ganglia (15)
	β_3	*KCNMB3*	3q26.3-q27	β*3a*		spleen, placenta, pancreas, heart, kidney
				β*3b*		spleen, pancreas, kidney, heart, brain, placenta, lung, liver, testes (15)
				B3*c*		spleen, prostate, placenta, liver, kidney, pancreas, ovary, brain, lung (15)
				β*3d*		spleen, testes, placenta, kidney, pancreas, brain, lung (15)
	β_4	*KCNMB4*	12q			brain, neuronal tissue, kidney, bladder smooth muscle (15)
γ-Subunit	γ_1	*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 (15)
	γ_2	*LRRC52*	1q24.1			testis, skeletal muscle, placenta, sperm cells, kidney, lung, prostate, thyroid gland, salivary gland (15)

Continued

Table 1.—*Continued*

Channel or Subunit	Gene Symbol (human)	Location	Alternative Splicing and Synonyms	Number of Insertions of the Amino Acids	Tissue Expression
γ_3	*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 (15)
γ_4	*LRRC38*	p36.21			cerebellum, brain (whole), fetal brain, placenta, uterus, testis, skeletal muscle, aorta, spleen, trachea, prostate, thyroid gland, thymus, salivary gland, adrenal gland (15)

ing response to the drugs (97, 105). The different types of BK channel play fiber-specific roles contributing to the calcium-dependent phenotype determination and adaptation/remodeling to physiological and pathological stimuli potentially affecting drug response. For instance, a BK channel subtype characterized by a low channel activity and enhanced acetazolamide response is observed in slow-twitch fibers in parallel with the slow-to-fast twitch fibers transition following muscle disuse in adult rat (105), while an abnormally enhanced BK channel current is observed during aging in fast-twitch rat fibers, which are characterized by muscle disuse and fast-to-slow twitch fibers transition (71, 108).

The BK channel sense extracellular K^+ ion concentration regulating fiber remodeling during hyperkalemia as observed in cell line and in a rat model of ischemia-reperfusion associated with hyperkalemia (99, 101). The abnormal activation of BK channel observed during hyperkalemia is consistent with biophysical property of the channel whose single channel conductance is enhanced in response to elevated external K^+ ion concentration. BK channel protein levels were significantly lower in the membrane fraction and higher in the cytosolic fraction of hypokalemic periodic paralysis (hypoPP) patient muscle cells than normal cells, even after cell depolarization suggesting an the altered subcellular distribution of BK channels in this disorder (46).

In neurons, under physiological conditions, activation of BK channels contributes to action potential (AP) repolarization, gives rise to the fast after-hyperpolarization (fAHP) that follows the AP, shapes dendritic Ca^{2+} spikes, and influences neurotransmitter release (65). Thus, activation of BK channels is an intrinsic inhibitory mechanism to counter membrane depolarization and the excessive accumulation of cytosolic Ca^{2+} that occurs during seizures. Accordingly, putative loss-of-function mechanisms of BK channels have been associated with temporal lobe epilepsy (TLE), as fAHP conductance mediated by BK channels was reduced in epileptic patients. Paradoxically, gain-of-function mutations in BK channel α-subunit gene actually contribute to the development of certain forms of idiopathic generalized epilepsy in humans (20). Thus, both gain of function and loss of function of BK channels are potentially important molecular targets for developing drugs to prevent epileptogenesis and suppress both temporal lobe seizures and absence seizures.

Polymorphisms of the β_1- and α-subunits are associated with hypertension and asthma. The vascular smooth muscle BK channel is a key element in the control of vascular tone and

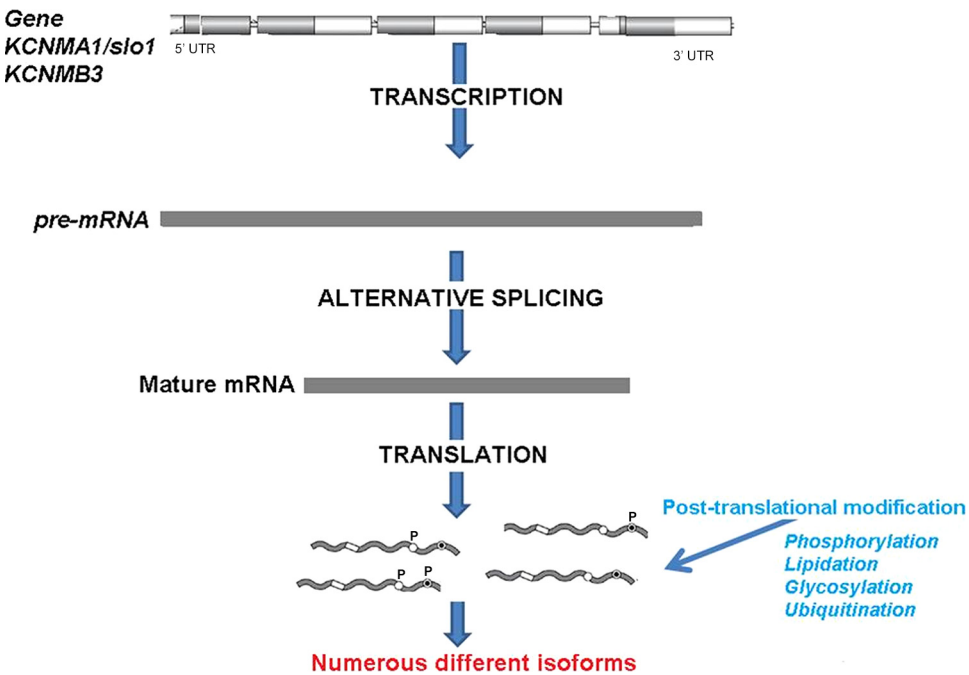

Fig. 2. Posttranscriptional and posttranslational modifications that control the *KCNMA1* and *KCNMB3* genes. UTR, untranslated region.

is formed by an ion-conducting α-subunit and a regulatory β_1-subunit, which couples local increases in intracellular Ca^{2+} to augmented channel activity and vascular relaxation. A gain-of-function polymorphism (E65K) in the β_1-subunit gene *KCNMB1* is associated with low prevalence of moderate-to-severe diastolic hypertension particularly in woman (85). Polymorphisms in the *KCNMB1* gene have also been associated with the baroreflex function in humans (26). Polymorphisms of the α-subunit are also associated with an enhanced risk of systolic and general hypertension and myocardial infarction (94). The *KCNMB1* Glu65Lys polymorphism is associated with reduced systolic and diastolic blood pressure in middle-aged men (66). A loss-of-function variant of the *KCNMB1* gene is associated with severe asthma in African American male (83).

The role of BK channels in the proliferation process in tumor cells is controversial. Some studies have suggested that BK channels contributed to the high proliferative or invasive potential in a number of malignant cell lines, such as nonmetastatic (MCF-7) breast cancer cells (69), brain-specific metastatic (MDA-MB-361) breast cancer cells (42), human prostate cancer cells PC3 (6), colorectal carcinogenesis (47), glioma (91, 112), and in neuroblastoma SH-SY5Y cells (16). Some others concluded that BK channels are not required for the proliferation in glioma (1) or breast cancer cells because the BK channel blockers charybdotoxin or iberiotoxin did not affect cell proliferation (77). In contrast, BK channels have been reported to exhibit antiproliferative and antitumorogenic properties in osteosarcoma cells, ovarian cancer cells, glioma cells, and in human MDA-MB-231 breast cancer cells. The bisphosonate zoledronic acid used in the osteoporosis associated with bone metastasis and the BK channel opener NS1619 induced apoptosis through the opening of BK channels, while *hslo* gene silencing or channel blockers induced cell proliferation (9, 17, 31, 57).

These controversial results may be ascribed to various factors related, for instance, to the expression level of the BK channel α-subunit, as in the case of the PC3 cells and in the SH-SY5Y cells, the splicing mechanism involved as in the case of the glioma cells, the phosphorylation state of the BK channel α-subunit that may affect the interaction with the death signaling protein.

KCNMA1 Gene Variants in the Tissues

STREX/ZERO splice variant of the KCNMA1 gene. The STREX exon is an insertion of 58 amino acids in the COOH-terminal splice site 2 (C_2) (Fig. 1*A*, Table 1) (118) of the α-subunit protein confers distinct functional phenotypes to BK channels, such as altered Ca^{2+} sensitivity and changing responsiveness of the channels to cAMP signaling from stimulatory to inhibitory, compared with the ZERO variant, lacking this insert. It has also been shown that BK channels containing the SS4 splice variant [an insertion of a 27 amino acid segment upstream to the COOH-terminal Ca^{2+}−bowl in splice site 4 (C_4) of the α-subunit] were activated more rapidly than the ZERO variant in the presence of the same voltage stimulus, and the difference in these activation kinetics was dependent on the concentration of intracellular Ca^{2+} (93, 118).

Studies of cloned mouse BK variants, expressed in HEK293 cells, demonstrated that cAMP-dependent protein kinase (PKA)-mediated phosphorylation activates BK ZERO variant but inhibits the STREX variant, which could thus impact channel function including Ca^{2+} sensitivity. The level of STREX expression also has important modulatory consequences as it has been previously shown that only one subunit within the tetrameric Slo channel needs to be of the STREX type to alter channel function. It has also been shown that protein palmitoylation (a posttranslational modification affecting multiple ion channels) can regulate the activity and surface expression of BK channel α-subunits in native tissues and cultured cells (93). The STREX exon is dynamically regulated during development, and its expression is under hormonal control (114). The exposure to adrenal glucocorticoids suppresses STREX inclusion, while adrenal androgens promote STREX inclusion (39). The STREX inclusion reduces the stimulatory effects of alcohol on BK channel activity in neurons (72). The STREX-increased sensitivity of BK channels to inhibition by oxidation this effect is consistent with the high cysteine content of the STREX exon (79, 115).

Despite the evidence implicating a role of the polymorphism of the β_4-subunit in epilepsy, the upregulation of the STREX variant channels (and downregulation of ZERO variant channels) in dentate gyrus DG granule cells are associated with TLE, while upregulation of the STREX variant may contribute to gain-of-function BK channels that give rise to temporal lobe seizures, as this variant exhibits faster activation and slower deactivation kinetic (65).

SV1 Splice Variant of the KCNMA1 gene. The BK-α subunit splice variant SV1 was found in rat myometrium and in the brain. SV1 has a 33-amino acid insert in the S1 transmembrane domain that does not alter S1 (Fig. 1*A*, Table 1) overall hydrophobicity, but makes the S0–S1 linker longer (122). The BK channel splice variant (SV1) acts as a dominant-negative regulator of BK channel α- and β_1-subunit expression. It is likely that SV1 induces differential surface expression of BK channels and thus may contribute to plastic changes necessary for the proper function of excitable and nonexcitable tissues (122). The role of SV1 as a dominant-negative regulator of BK channel expression under physiological or pathological conditions needs to be determined. At present, we know that SV1 transcripts are present in the myometrium and the brain, and it is possible that their levels may change during the estrous cycle, pregnancy, and neurodevelopment or neurodegenerative conditions modifying BK channel expression (89).

BK0/BK-SRKR (e17) variant splice of the KCNMA1 gene. The BK0/BK-SRKR variants were identical except for the presence of a four-amino acid insert (SRKR) for the splicing site 1 (C_1) (Fig. 1*A*, Table 1) (110). Inclusion of the SRKR exon (BKSRKR) resulted in a large reduction of BK channel activity, demonstrated by a rightward shift in G/V relationships, slower activation rates, and faster deactivation rates. These effects were abrogated by dephosphorylation only when SRKR was present (87).

Glioma BK channel variant splice of the KCNMA1 gene. BK ion channels have several spliced variants. One spliced variant initially described within human glioma cells, this isoform consists of 34 amino acids inserted into the intracellular region of the basic BK ion channel at splicing site 2 (C_2) of *hSlo* and was named glioma BK (gBK) (Fig. 1*A*, Table 1) (8, 74); this variant form was only seen when an additional 29-amino acid insert called the hbr5 region was simultaneously coexpressed

within the BKα-channel (25, 92). These variants of the *hslo* gene are characterized by enhanced sensitivity to $[Ca^{2+}]_i$ and are the target of modulation by growth factors (34). The gBK channels enhance glioma cell survival under stress conditions; the inhibition of the gBK channel cause arrest of cells in S phase, followed by apoptosis (25). PCR primers specific for this inserted region confirm that human glioma cell lines and freshly resected surgical tissues from glioblastoma multiforme patients strongly expressed gBK mRNA. Normal human brain tissue weakly expressed this transcript (7, 25, 92).

Mk44 variant splice of the KCNMA1 gene. In human myometrial smooth muscle cells the *KCNMA1* gene generates isoforms with different responses to contractile stimuli. The human myometrium expresses high levels of the splice variant of the BK channel containing a 44-amino acid insertion (mK44) (Fig. 1*A*, Table 1) (49) in the first intracellular loop and is less sensitive to Ca^{2+} and voltage compared with BK channels lacking these 44 amino acids (4, 40). Recent studies in human myometrial cells have shown that mK44 is proteolytically cleaved, resulting in membrane localization of the NH_2 terminus with retention of the COOH terminus in the endoplasmic reticulum (48). This isoform is expressed predominantly in myometrial and aortic smooth muscle and demonstrates decreased sensitivity to intracellular Ca^{2+} (49). The addition of 44 amino acids into the mK44 isoform introduces several putative consensus motifs for endoproteolytic digest and one putative site for N-myristoylation (49).

Delta e23 splice of the KCNMA1 gene. The Δe23 splice variant was largely expressed in a diffuse perinuclear distribution and colocalized with an endoplasmic reticulum. The Δe23 splice variant shows a dominant negative effect of plasma membrane expression (13, 50). A conserved motif within the intracellular COOH terminus of mammalian BK channels is required for efficient export of the channels from the endoplasmic reticulum (13), although the precise role of the intracellular COOH terminus in plasma membrane targeting is controversial (13). The COOH-terminal truncation of the Δe23 splice variant would result in the loss of this motif. Thus, Δe23 channels would be predicted to reside largely in the endoplasmic reticulum.

REVEDEC and alternative splicing in the extreme COOH terminus of Slo1 gene. Alternative splicing in the extreme COOH terminus of *Slo1* gives rise to channels with markedly different patterns of trafficking to the plasma membrane (44, 56). The variant, known as VEDEC (Slo1VEDEC), after the last five residues at the COOH terminus, tends to be retained in intracellular compartments but can be translocated to the plasma membrane by treating cells with appropriate growth factors (44, 56). Two other COOH-terminal splice variants, referred to as Slo1QEERL, Slo1EMVYR, and C-SSP (Fig. 1*A*, Table 1) (118), show much higher levels of steady-state expression in the plasma membrane (44, 45, 56, 80). Coexpression of BK β-subunits also can stimulate trafficking of Slo1 to the plasma membrane (121). The Slo1_DEC isoform is the longest with 61 residues distinct from the other two isoforms (123). The Slo1_ERL and Slo1_VYR isoforms have identical length but differ at the last eight residues (Fig. 1*A*) (56).

The mito-BK variant has been proposed to be coupled to the respiratory chain complex, potentially affecting mito-dehydrogenases activity (3). The mito-BK channel is composed by the assembly of hslo-subunit encoded by the *KCNMA1* gene, a splice variant BK-DEC harboring an amino acid sequence of 50/61 amino acid at the COOH-terminus of the protein (DEC), the β_4-subunit with a minor contribution of the β_2 (88). The mito-BK activation of drugs is believed to exert cytoprotective action in cardiomyocytes and neurons (3). No specific mito-BK drugs are available, and the mechanism by the DEC-specific amino-acid residues at the extreme COOH terminus promotes retention of the channel in ER is not entirely clear.

Finally, the COOH-terminal exons so far appear to regulate trafficking and cell surface localization for the channel rather than significantly affecting current properties; the presence of the VEDEC motif at the COOH terminus of Slo1 channels (Fig. 1*A*) is sufficient to confer a dominant-negative effect on cell surface expression of itself or other types of Slo1 subunit. Treating cells with short peptides containing the VEDEC motif increased surface expression of $Slo1_{VEDEC}$ channels transiently expressed in HEK293 cells and increased current through endogenous BK channels in mouse podocytes (43, 50).

The steady-state surface expression of a membrane protein is determined by the rates and balance of movements into and out of the plasma membrane. Whereas the presence of the VEDEC motif in Slo1 reduces constitutive steady-state expression on the cell surface, the available data do not indicate how the VEDEC motif produces (43).

The DEC COOH terminus is capable of intimately interacting with actin, tubulin, and PP2A-A. The isoform-specific association of the PP2A with Slo1_DEC raises the intriguing possibility that the enzymatic activity in one subunit in a tetrameric channel may regulate its own state of phosphorylation as well as those of the neighboring subunits. This intra- and intersubunit regulation may then contribute to the isoform specificity including the channel surface expression. Phosphorylation-dependent surface expression of proteins represents a new emerging concept in the cell biology of ion channel regulation. Recent examples include activity-dependent surface expression mediated by 14-3-3 (14). Whether PP2A-mediated reduction of phosphorylation causes the lower surface expression of the Slo1_DEC is an interesting subject of future investigation.

Slo27 splice of the KCNMA1 gene. This variant includes a sequence of 27 amino acids in the COOH terminus at the C4 site (29) (Fig. 1*A*, Table 1). The open probability of the variant containing the 27 amino acids is significantly increased by arachidonic acid, while the variant lacking the 27 amino acids is insensitive to arachidonic acid. In addition, sensitivity of BK channels to arachidonic acid depends on cytosolic phospholipase A_2, and the splice variant are sensitive to unoprostone a structural analog of arachidonic acid (21, 29). Unoprostone increased BK channel currents, making the channel more sensitive to calcium (119).

e20-e20fwd (hbr5) variant splice of the KCNMA1 gene. The e20 variant resulted in a 29-amino acid (IYF) insert from inclusion of SITE 2 (c2) (23, 84). The e20 splice variant displayed a calcium and voltage sensitivity similar to that previously reported for the murine ZERO variant. This variant had considerably slower deactivation kinetics compared with ZERO or e20. The e20 splice variant had a significantly increased single channel conductance (6, 13, 50). Splice variant e22 mRNA was predominantly expressed in embryonic tissue (13, 73), and the e22 splice variant also displayed a

significant left shift in the conductance-voltage relationship, compared with ZERO (13).

N.1 and alternative splicing in the extreme NH_2 terminus of the KCNMA1 gene. Both variants contained an alternate translation start encoded by additional sequence in the extracellular NH_2 terminus of the channel N.1 splice (MANG) (84, 118). This variant of the BK channel contains a 61-amino acid insertion in the first extracellular region, and there is evidence of the presence of an MSS splice containing a 36-amino acid insertion in the NH_2 terminus (84).

KCNMA1 Gene Variants in Skeletal Muscle

In skeletal muscle, using molecular cloning and patch-clamp technique in excised patch mode, we established that the alternative splicing of the *KCNMA1/slo1* gene is the main mechanism regulating the sarcolemma BK (sarco-BK channel) diversity in the muscle phenotypes (18, 96). Slow-twitch rat fibers indeed showed an elevated expression/activity of BK channel, which is characterized by a low sensitivity to Ca^{2+} ions and lack of response to the BK channel opener acetazolamide (59, 96, 105). In contrast, the BK channel found in the fast-twitch rat fibers showed a low expression/activity, high sensitivity to Ca^{2+} ions, and activating response to the drugs (97, 105). The analysis of rat *KCNMA1/slo1* gene at N1 and C1–C6 splice sites found the presence of five different variants in both fast-twitch and slow-twitch muscles, such as e17 in C1, e22 and +29 amino acids in C2, and rSlo27 and rSlo0 in C4. Real time-PCR experiment showed that e22 and rSlo0 variants were markedly expressed in fast-twitch muscle sustaining the BK channel activity in this muscle phenotype; the rSlo27 was found in the slow-twitch muscle, giving rise to different molecular BK channel (18).

BK Channel Openers

BK channel openers are represented by a large variety of synthetic compounds such as benzimidazolones, biarylthioureas, anthraquinone analogs, tetrahydroquinolines, terpenes, and benzofuroindoles; marketed drugs such as carbonic anhydrase inhibitors, nonsteroidal anti-inflammatory drugs, biphosphonates, and estrogen receptor modulators; endogenous modulators such as estrogen hormone, fatty acids, CO and Heme; and natural exogenous modulators such as anthraquinones, dehydrosoyasaponin-1, docosahexaenoic acid (DHA), the polyphenol (mallotoxin/rottrelin), and flavonoids (resveratrol and quercetin) (5, 33, 57, 75, 79, 96, 97).

These compounds were extensively investigated for their effects as smooth muscle relaxants and more recently for their cardioprotective and neuroprotective effects. The drug action is dependent on the functional state of the α-subunit and on the internal calcium concentration. In addition, the drug action in these tissues is dependent on the presence of auxiliary subunits such as the β_1 in smooth muscle and β_2 and β_4 in neurons; the recently cloned γ-subunits seem to have a pharmacological role (5, 22). The benzimidazolone NS1619 was the most investigated compounds in smooth muscle disorders such as pulmonary hypertension, erectile dysfunction, and bladder instability (53, 76), as well as in inflammation and cytoprotection (24, 52). The activating action of NS1619 and Cym04 was found to be dependent on the S6/RCK (regulator of conductance for K^+) linker of the Slo1; indeed, the response to both drugs was lost in hslo1-9a, an exon 9 variant with a distinct S6/RCK1 linker sequence having two deletion mutations, which is expressed in the brain (24). Site-directed mutagenesis identified a K330 as an important residue for drug action. The use of NS1619 is however limited by a relatively poor potency and many off-target effects. Several compounds were investigated such as a biarylthiourea NS11021, which works by shifting the voltage-activation curve of the channel to more negative potentials increasing open probability as many other activators (5). This compound showed cardioprotective and smooth muscle relaxant effects with arterial vasodilation and reduction of the contractility of urinary bladder as well as neuroprotective effects. The novel GoSlo-SR group of compounds are synthetic anthraquinone analogs that are capable of shifting the voltage dependence of BK activation by more than −100 mV in the submicromolar concentration range, and their effects are not dependent on β-subunits or calcium ions and are effective at negative membrane potentials (78, 113). The drug response is reduced in Slo1_9a, suggesting that the S4/S5 linker, the cytosolic end of S6, and the S6/RCK1 linker are involved in the action of these compounds.

Compounds with novel chemical structures include the voltage-sensitive dye bis-(1, 3-dibutylbarbituric acid) trimethine oxonol [DiBAC4 (3)], N-arylbenzamide analogs, and NS19504, which are potent smooth muscle relaxant compounds investigated for their ability to resolve bladder hyperactivity (10, 64, 82). A fluoro-oxindole analog, BMS204352, activates BK channel in the nanomolar concentration range and was developed as an antistroke drug in a preclinical animal model of ischemia and stroke but failed in phase III clinical trials for the lack of selectivity action (5); benzofuroindoles were investigated mostly for the treatment of urinary incontinence, overactive bladder, erectile dysfunction, and stroke, and some of them entered phase I and II clinical trials but failed (5). To date the only BK channel opener in clinical development is andolast, which showed clinical efficacy and an acceptable safety profile in mild/moderate asthma (63). None of these compounds were investigated for their selectivity against α- or β-subunit splicing. Within the BK channel openers, the carbonic anhydrase (CA) inhibitors, such as acetazolamide and dichlorphenamide, and their structural analogs were investigated in our laboratories for their capability to modulate the skeletal muscle BK channels (10, 59). Acetazolamide and dichlorphenamide are capable to activate at micromolar concentrations the BK channels in excised patches from fast-twitching rat fibers and are capable to prevent the insulin-induced paralysis in the K^+-depleted rat, not a genetic animal model of hypoPP (95, 104). HypoPP is a familial disorder associated with gain-of-function mutations of the genes encoding for the α-subunits of the voltage-dependent sodium channel and L-type calcium channel and downregulation of the sarcolemma inwardly rectifying K^+ channels and the ATP-sensitive K^+ channels (KATP) (98, 106, 109). Drugs targeting ATP-sensitive K^+ channels and/or BK channels are effective in restoring the depolarized skeletal muscle fibers in humans and animals affected by hypoPP and in preventing paralysis (41, 98, 102, 107). These drugs are also able to prevent the skeletal muscle atrophy associated with downregulation or pharmacological block of KATP and BK channels (11, 12, 61, 62, 102, 103). At therapeutic concentrations, acetazolamide and dichlorphenamide also inhibit the membrane-bound CA enzymes

CAIV/XIV and the CAII cytosolic form with changes in the intra-/extracellular [H^+]. This may indirectly affect the activity of extra-/intracellular proton exchange mechanisms. In our experiments acetazolamide inhibited the monocarboxylate transporter, reducing the efflux of lactate, thereby preventing myopathy (100). The activity of ion channels showing pH-sensitive gating may be also affected by acetazolamide and dichlorphenamide with therapeutic effects (58). This work was the pharmacological basis for the use of acetazolamide and dichlorphenamide in periodic paralysis. Dichlorphenamide (2010) obtained the orphan drug designation in the treatment of the hyperPP and hypoPP in the USA. More recently, clinical trial investigations showed that dichlorphenamide is effective in reducing the average number of attacks per week in hypoPP patients (81). Therefore, dichlorphenamide can be a preferred drug in hypoPP patients, including those not responsive to acetazolamide, while acetazolamide is also effective in hyperPP and myotonia (98). The BK channel-opening action of acetazolamide and dichlorphenamide and of their structure-related analogs is muscle phenotype dependent. The elevated expression/activity of the rSlo27 variant found in slow-twitch rat skeletal rat fibers affected the pharmacological response of the functional BK channels (18). We found that bendroflumethiazide (BFT), acetazolamide (ACTZ), NS1619, quercetin (QUERC), ethoxzolamide (ETX), and dichlorphenamide (DCP) were more effective on fast-twitch muscle BK channel than on slow-twitch muscle BK channel subtypes. The drug actions correlated with the expression level of the e22 and rSlo0 variants markedly expressed in this tissue, suggesting that these isoforms can be the molecular targets for these drugs. Resveratrol (RESV) and ETX were effective in either BK channels subtypes, while hydrochlorthiazide (HCT) was not effective. The action of RESV correlated with the expression level of the rSlo27 variant in this tissue, suggesting that it may be the molecular target of this drug (18). The rSlo27 variant expressed in the HEK293 cells is selectively activated by unoprostone, which failed to activate the rSlo0 variant lacking the 27-amino acid sequence (119). The rSlo27 is the ethanol-sensitive variant known as alcohol-regulated exon ALCOREX, which is expressed in pituitary GH3 cell line and in neurons, and it is activated by arachidonic acid. BFT, ACTZ, and DCP were the most effective BK channel openers in fast-twitch rat fibers and were equally effective at positive and negative membrane potentials in the presence of Ca^{2+} ions (Table 2). ACTZ and DCP were more potent at negative membrane potential, showing an EC_{50} in the submicromolar concentration range. ETX and REV were instead the most effective drugs in slow-twitch rat fibers. BFT was the most potent BK channel activator on a recombinant hslo channel showing a biphasic concentration-response relationship with an EC_{50} of 1.2×10^{-9} M and 5.1×10^{-6} M (98, 101). In our experiments, NS1619 was capable to activate the BK channels of native rat fast-twitch rat fibers and, to a minor extent, the BK channels of slow-twitch rat fibers in excised patch-clamp mode in the micromolar concentration range (Table 2). This compound was able to fully enhance the current from the recombinant hslo subunit at +30 mV (V_m) but was much less effective at negative membrane potentials (69, 98). The observed effects of ACTZ and DCP as BK channel openers on fast-twitch and recombinant channels at different voltage membranes and their enhanced potency at rest may explain the efficacy of these drugs in periodic paralysis.

Summary and Perspectives

Altering the splice variant composition of BK channels can alter their activity and apparent sensitivity to calcium, regulation by protein phosphorylation, and other intracellular signaling cascades, as well as in cell surface expression. This posttranscriptional mechanism is operative in skeletal muscle and contributes to the formation of muscle phenotype-dependent functional BK channels.

The sarco-BK channels are relevant drug targets in the hypoPP and may be involved in mediating the actions of acetazolamide and dichlorphenamide in the hyperkalemic periodic paralysis and myotonia. The combination of BK channel openers such as acetazolamide and dichlorphenamide with Na^+ channel blockers such as mexiletine and flecainide may help to resolve the weakness and myotonia discharge, respectively, in myotonic patients. However, clinical-specific protocols need to be investigated to address this issue. In conclusion, the presence of different types of BK channel in skeletal muscle may have implications for drug-based therapy of neuromuscular disorders, including hyper-/hypokalemic periodic paralysis. A particular combination of BK subunits that includes the slo27 may lead to the formation of BK channel

Table 2. *Pharmacological properties of BK channel in skeletal muscle*

Drugs	BK Channel Subunits	Pharmacological Effects in Skeletal Muscle
Acetazolamide (ACTZ), dichlorphenamide (DCP), ethoxzolamide (ETX), bendroflumethiazide (BFT), resveratrol (RESV), NS1619, quercetin (QUERC)	low expression/activity of BK channel of fast-twitch rat fibers: e22 = rSlo27 > rSlo0 = +29aa > e17	rank order of efficacy at +30 mV (V_m) in excised patches: BFT≥ACTZ = DCP = NS1619 = QUERC = ETX = RESV; activation of sarco-BK channels by all drugs in K^+-depleted rat and activation of sarco-BK channels by acetazolamide and dichlorphenamide in human affected by hypokalemic periodic paralysis; therapeutic use in periodic paralysis and myotonia
Hydrochlorthiazide, methazolamide		no actions
Acetazolamide, dichlorphenamide, ethoxzolamide bendroflumethiazide, resveratrol, NS1619.	elevated expression/activity of BK channel of slow-twitch rat fibers: rSlo27 > +29aa = e22> e53 ≥ rSlo0	rank order of efficacy at +30 mV (V_m) in excised patches: ETX ≥ REV > NS1619 = DCP = BFT = ACTZ
Hydrochlorthiazide, methazolamide, quercetin		no actions
Acetazolamide, dichlorphenamide, ethoxzolamide bendroflumethiazide, resveratrol, NS1619	hSlo subunit expressed in Hek293	rank order of efficacy at +30 mV (V_m) in whole cell mode: BFT = NS1619 > ACTZ = DCP>ETX = RESV = QUERC > MTZ
Hydrochlorthiazide		no actions

unresponsive to the drugs. Drugs targeting the slow-type BK channel or the fast-twitch type may be helpful in disorders affecting specific muscle phenotypes.

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No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

F.M. performed experiments; F.M. analyzed data; F.M. prepared figures; M.C. and D.T. edited and revised manuscript; A.M. and D.T. conceived and designed research; A.M. and D.T. approved final version of manuscript; D.T. drafted manuscript.

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