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Calcium- and voltage-gated BK channels in vascular smooth muscle

Alex M. Dopico[1], **Anna N. Bukiya**[1], and **Jonathan H. Jaggar**[2]

[1]Department of Pharmacology, College of Medicine, The University of Tennessee Health Science Center, Memphis, TN, USA

[2]Department of Physiology, College of Medicine, The University of Tennessee Health Science Center, Memphis, TN, USA

Abstract

Ion channels in vascular smooth muscle regulate myogenic tone and vessel contractility. In particular, activation of calcium- and voltage-gated potassium channels of large conductance (BK channels) results in outward current that shifts the membrane potential towards more negative values, triggering a negative feed-back loop on depolarization-induced calcium influx and SM contraction. In this short review, we first present the molecular basis of vascular smooth muscle BK channels and the role of subunit composition and trafficking in the regulation of myogenic tone and vascular contractility. BK channel modulation by endogenous signaling molecules, and paracrine and endocrine mediators follows. Lastly, we describe the functional changes in smooth muscle BK channels that contribute to, or are triggered by, common physiological conditions and pathologies, including obesity, diabetes and systemic hypertension.

Keywords

Slo1 gene; *KCNMB1* gene; MaxiK channel; calcium signaling; vascular smooth muscle; vascular pathophysiology

Basic phenotype of the vascular smooth muscle BK channel and its structural basis

Voltage- (V) and Ca^{2+}-gated currents carried by K^+ channels of large unitary conductance (Maxi-K or BK channels) were first reported in rabbit portal vein [81] and guinea pig mesenteric artery [10] myocytes. Since then, BK channels have been ubiquitously found in smooth muscle (SM) across vascular territories and species, as reviewed in [79,93,99]. The basic ionic current phenotype mediated by BK channel activity in SM is an intracellular (IC) Ca^{2+}-activated, outwardly rectifying K^+ current with fast activation and almost negligible inactivation. In addition to dual gating by transmembrane (TM) voltage and Ca^{2+}_{ic}, SM BK channels may be mechano-gated. Negative pressure applied to the back of the patch-pipette

Correspondence: Alex Dopico, MD, PhD, Dept. Pharmacology, College of Medicine, UTHSC, 71 South Manassas St., Memphis, TN, 38163, adopico@uthsc.edu.

evokes an increase in the activity of BK channels expressed in cell-free, SM membrane patches. This phenomenon was observed in arterial myocytes from the pulmonary [90] and systemic, i.e., mesenteric [49] and coronary [189] circulations. BK channels in human coronary artery myocytes, however, increased activity after a sinusoidal stretch stimulus is stopped [189]. Mechano-gating of SM BK channels is sensitive to phalloidin, an actin filament stabilizer [149], indicating that mechano-gating may involve structures additional to the BK channel subunits themselves.

The basic BK channel phenotype described above results from the tetrameric association of BK "α subunits", also termed slo1 proteins (Fig. 1), as this protein is the product of the *Slo1* or *KCNMA1* gene in mammals. Slo1 channels belong to the superfamily of TM6 V-gated ion channels. As such, slo1 proteins include a S1-S6 "core" highly conserved with that of K_V channels. However, slo1 proteins distinctly add: 1) an S0 segment, which renders an extracellular (EC) N-end [133], and 2) a cytosolic "tail domain" (CTD) of >800 amino acids, which provides a variety of regulatory sites for *divalent-induced activation* and for posttranslational modification, mainly via de/phosphorylation [97,163,167]. Thus, the Ca^{2+}-gated slo1 channel is a member of the subfamily of *ion*-gated K^+ channels [87]. The channel-forming slo1 monomer is a modular protein that combines pore-gating, V-sensing, and ion (Ca^{2+} and Mg^{2+})-sensing domains [61,181,192,205] (Fig. 1). The CTD includes two Regulator of Conductance for K^+ structures (RCK1 & 2) where two high affinity Ca^{2+}-binding sites have been mapped, in addition to a low affinity site that primarily binds $Mg^{2+}{}_{ic}$ at physiological concentrations [100,193]. Data from *Aplysia* slo1 show that Ca^{2+} is coordinated by seven oxygen atoms in both high affinity sites: Asp356, Asp525, Glut591 and Arg503 are critical for interacting with the ion in the "RCK1" high affinity site while Asp902, Asp905, Asp906, Asp907, Gln899 and Asn438 are critical in the second high affinity site [174], which includes an Asp-enriched region termed "Calcium-Bowl" [162]. In turn, the RCK1 low affinity site, also known as the "Mg^{2+} site", requires Glut328, Glut363, Glut388, Arg161 and Thr385 to interact with the metal. Cooperative binding of $Ca^{2+}{}_{ic}$ to both high affinity sites expands an elastic gating ring formed by a total of eight RCKs (two/slo1 monomer), which is coupled to the V-sensing domain through a rigid linker [174] (Fig. 1).

Although slo1 proteins are products of a single gene, Slo1 pre-mRNA is processed by alternative splicing, editing, and regulation by miRNA. These processes, together with major post-translational regulation mechanisms such as phosphorylation, glycosylation, lipidation and ubiquitination, render a wide variety of BK protein isoforms and their corresponding BK channel functional phenotypes, as reviewed elsewhere [100,167]. In rat cerebral artery SM, in situ hybridization revealed two splice variants [154]: SS4 (+81 amino acids) and SS2 (+174). The latter, also known as "STREX" splice variant, has also been found in pig pulmonary artery and vein SM [51]. STREX expression is tightly regulated by steroidal hormones [99,194]. The STREX sequence, inserted between both RCK domains, is associated with a leftward shift in the macroscopic conductance/maximal macroscopic conductance (G/G_{max})-V plot and slower current activation [34,194], increased sensitivity to suppression of current by acute hypoxia and oxidation [53,129], mechano-sensitivity [183] and, albeit in neurons, reduced sensitivity to potentiation of current by acute ethanol exposure [150].

In addition, alternative splicing often reveals unique sites for some of the major post-translational modifications mentioned in the previous paragraph, rendering further pleiotropy at slo1 channel expression, trafficking and ion current phenotype; for a comprehensive review, see [167]. These processes, phosphorylation in particular, also target the constitutive domains/regions (i.e., not resulting from alternatively spliced exons) of the slo1 channel; thus, protein kinase A (PKA)- and protein kinase G (PKG)-mediated phosphorylation usually result in channel activation while protein kinase C (PKC)-mediated phosphorylation usually leads to channel inhibition [98,163,167]. However, some slo1 isoforms appear to be species-specific: Ca^{2+}/calmodulin-dependent kinase II (CamKII) targeting of slo1 Thr107 leads to activation of BK channels in bovine aorta [114], yet Thr107 is non-conserved in most species.

In most mammalian tissues, including SM, slo1 channels are tightly associated with small, two-TM proteins termed BK β subunits (Fig. 1), adding a major level of diversity to BK channel phenotypes, in addition to posttranscriptional and posttranslational modification of slo1. Four β types have been identified, each encoded by a different gene (*KCNMB1-4*). Remarkably, SM highly expresses β1, with expression levels of β2–4 being negligible [9,17,110,121]. Beta1 subunit co-expression slows down the macroscopic current activation and deactivation kinetics, and introduces a significant leftward shift in the G/G_{max}-V relationship [110,121]. This increase in apparent Ca^{2+}-sensitivity allows BK channels to effectively sense nearby increases in Ca^{2+} from submicromolar (≥0.1) to low micromolar (≤30) at the physiological negative voltages found in vascular SM [86,88,147]. Thus, BK channel-generated outward K^+ currents shift the membrane potential towards more negative values and thus, exert a negative feed-back on depolarization-induced Ca^{2+} influx and SM contraction, favoring SM relaxation. Therefore, vascular SM BK channel activators are effective vasodilators, as reviewed in [93] while genetic ablation of the BK β1 subunit (e.g., in the $KCNMB^{-/-}$ mouse) is associated with increased myogenic tone [18]. Finally, β1 subunits embolden BK channels with distinct pharmacology, including channel activation by 17β-estradiol [180], micromolar levels of hydrophobic cholanes and their nonsteroidal analogs [22,23,29,132], leukotriene B4 [24], dehydrosoyasaponin-I [131], hydroclorothiazide [127], equol [203], tungstate [57], increased sensitivity to PIP_2 [179] and DHA [74,75], and ethanol-induced reduction of channel activity at low μM Ca^{2+}_{ic} [94,95]. The role of SM BK channels as pharmaco-therapeutic targets has been recently reviewed elsewhere [93,219].

Since the discovery of LRRC26 protein's functional association with slo1 channels in prostate cancer cells [196], several proteins, globally termed BK "γ" subunits (1, 2, 3 and 4, encoded by *LRRC26, -52, -55* and *-38*, respectively) have been found to associate and modulate slo1 channel activity in several tissues [110,196,197]. In particular, LRRC26 has been reported to be associated with slo1 in cerebral SM cells. This association leads to an increase in the apparent Ca^{2+}-sensitivity of the channel whereas LRRC26 knockdown increases myogenic tone and attenuates the vasoconstriction induced by iberiotoxin (Ibtx) and the vasodilation induced by NS1619, which are BK channel inhibitors and activators, respectively [54].

Finally, in addition to the plasmalemma, BK have been found in mitochondria and nuclear envelope, yet to our knowledge, no studies were conducted in vascular SM cells [6,55,109]. Trafficking of BK channel subunits between the plasmalemma and internal organelles, and the contribution of such trafficking to control of myogenic tone are discussed below.

Subunit localization and trafficking

Slo1 proteins and β1 subunits are trafficked to the plasma membrane through distinct mechanisms in arterial SM cells (Fig. 2). A slo1 variant with a 33-amino acid insert in the S1 domain that was identified in rat myometrium contains an endoplasmic reticulum (ER) retention sequence which prevents it from trafficking to the plasma membrane when expressed in HEK293 cells [206]. In heterologous expression systems, the presence of STREX [194] increases surface expression over the ZERO variant [143]. None, or only a small proportion, of mRNA contains the STREX insert in rat cerebral and cremaster arteries, and colonic SM BK channels lack STREX [83,143,183,215]. Thus, STREX appears to have little to no effect on BK channel surface abundance in SM cells.

Virtually all slo1 proteins are localized at the plasma membrane of cerebral and mesenteric artery SM cells [104–106,207]. Anterograde and retrograde protein trafficking steps are regulated by low molecular mass Rab GTPases, of which ~60 members have been identified in mammals [80]. Rab proteins are physically associated with certain types of trafficking vesicles, where they act as molecular switches to control transport [80]. Slo1 proteins traffic to the plasma membrane through a Rab4A-dependent pathway, suggesting early endosomes transport the channel to the surface in cerebral artery SM cells [105]. In contrast, knockdown of Rab11A or Rab11B does not alter surface or total slo1 protein, indicating that recycling endosomes do not control the cellular localization of this BK subunit [104] (Fig. 2). Angiotensin II (ang II), a vasoconstrictor, stimulates PKC-dependent internalization and degradation of surface slo1 protein, which reduces BK current density in arterial SM cells, increases myogenic tone and attenuates responses to BK channel modulators. In contrast, $NO^{\bullet}$, a vasodilator, does not alter surface slo1 protein [105] (Fig. 2). These studies suggest that physiological stimuli can regulate surface levels of slo1 protein to control contractility in arterial SM.

In contrast to slo1 proteins, most β1 subunits are located intracellularly, with only a small proportion of total protein present at the plasma membrane in unstimulated cerebral artery SM cells [104]. Experiments performed using FRET and RNAi indicate that a large proportion of IC β1 is stored within Rab11A-positive recycling endosomes [104]. $NO^{\bullet}$, through the activation of PKG, increases Rab11A activity and the rapid surface trafficking (within seconds) of β1 subunits [104,207] (Fig. 2). These β1 subunits associate with surface-resident slo1 channels, increasing their apparent Ca^{2+}-sensitivity and single channel open probability (Po) [104,207]. Intravascular pressure and membrane potential also stimulate an increase in the plasma membrane abundance of auxiliary β1 subunits in arterial SM cells. Membrane depolarization stimulates voltage-dependent Ca^{2+} channels leading to Ca^{2+} influx, which activates Rho kinase 1 (ROCK1) and ROCK2 [106]. In turn, ROCK phosphorylates Rab11A, which stimulates anterograde trafficking of IC β1 subunits to the plasma membrane (Fig. 2). As found with $NO^{\bullet}$, these β1 subunits associate with plasma

membrane-resident BK channels, increasing their apparent Ca^{2+}-sensitivity. This leads to BK channel activation and vasodilation [106]. Although $NO^{\bullet}$ and depolarization act through distinct signaling mechanisms, both stimuli mobilize the same IC β1 subunit pool [106]. Thus, $NO^{\bullet}$/PKG and depolarization/Ca^{2+} activate BK channels both by directly increasing P_o and indirectly by stimulating an increase in the abundance of surface β1 subunits in arterial SM cells [73,104,106,158] (Fig. 2). Endothelin-1, a vasoconstrictor, stimulates PKC-mediated phosphorylation of Rab11A at Ser177, which reduces Rab11A activity. This effect rapidly reduces surface β1 abundance, leading to a decrease in BK channel Ca^{2+}-sensitivity, a reduction in transient BK currents and vasoconstriction [207]. In contrast to regulation by ET-1, ang II does not alter surface levels of β1 subunits [105] (Fig. 2).

These findings regarding physiological control of surface β1 protein are consistent with observations made using recombinant proteins which suggest that BK channels can contain one to four β1 subunits and that an increase in the β1:α ratio causes an incremental shift in voltage-dependence [184]. Endocytosis inhibitors increase surface β1 protein in arterial SM cells, suggesting that β1 constantly recycles between the plasma membrane and recycling endosomes. Thus, physiological vasoregulatory stimuli can differentially regulate Rab11A activity to alter surface levels of surface β1 subunits and BK channel activity. Conceivably, stimuli that alter surface levels of β1 may not only control anterograde trafficking, but also modulate β1 internalization, although this remains to be determined [104]. These studies provide the first evidence that the multisubunit composition of a native ion channel is not set from a rigid stoichiometry but is dynamic, and can be rapidly modulated by physiological vasoregulatory stimuli to control activity in arterial SM cells.

Regulation by Ca^{2+}

Global Ca^{2+}_{ic} in arterial SM cells ranges between ~100 and 300 nM, these concentrations being too low to significantly increase BK P_o [85]. A large body of evidence indicates that *localized* IC Ca^{2+} transients, termed *Ca^{2+} sparks*, activate BK channels in arterial SM cells [84,85,141]. Ca^{2+} sparks occur due to the opening of ryanodine-sensitive Ca^{2+} release (RyR) channels located on the sarcoplasmic reticulum (SR) membrane [84] (Fig. 3). In vascular SM cells, the peripheral SR membrane and the plasma membrane locate in very close spatial proximity (~20 nm) [41,107]. RyR channels present in this region of peripheral SR generate Ca^{2+} sparks in arterial SM cells [141,155,199]. The simultaneous opening of several RyR channels generates a subplasmalemmal Ca^{2+} transient that increases the local $[Ca^{2+}]_i$ within the vicinity of nearby surface BK channels to 4–30 μM [147] (Fig. 3). A single Ca^{2+} spark activates multiple plasma membrane BK channels, generating a macroscopic BK transient [85,141]. Ca^{2+} spark frequency is the primary determinant of transient BK current frequency, although the percentage of Ca^{2+} sparks that activate a transient BK current is dependent upon several factors, including arterial bed, animal species and age [82,108,148,215]. The amount of macroscopic BK current generated during a transient is regulated by the effective coupling of BK channels to a Ca^{2+} spark. BK channel apparent Ca^{2+} sensitivity is a major determinant of effective coupling and can be modulated by many factors, including voltage, protein kinases and the abundance of surface β1 subunits [18,82,108,148,207,214,215]. Ca^{2+} sparks occur at a frequency of ~1 Hz and spread for ~1–2 μm (full width at half-maximal amplitude). Thus, the Ca^{2+} released into the cytosol during

a spark does not significantly contribute to global $[Ca^{2+}]_i$ in arterial SM cells [85]. Rather, repetitive transient BK currents cause membrane repolarization, which reduces the activity of voltage-dependent Ca^{2+} channels, causing a decrease in global $[Ca^{2+}]_i$ [85] (Fig. 3).

Arterial SM cells also generate propagating IC Ca^{2+} transients, termed *Ca^{2+} waves*, which occur due to sarcoplasmic reticulum Ca^{2+} release through RyR and/or IP_3 receptors. The frequency of Ca^{2+} waves is increased by stimuli, including intravascular pressure and vasoconstrictor ligands that bind to Gq-coupled receptors [84,89,128]. In contrast, vasodilator stimuli, such as acidic pH, convert Ca^{2+} waves to Ca^{2+} sparks [38]. Evidence from these studies suggests that Ca^{2+} waves do not activate BK channels in arterial SM cells.

Major physiological role

Intravascular pressure stimulates arterial depolarization, with the full working range of arterial SM membrane potential between ~−60 and −20 mV [65,66,91]. Pressure-induced depolarization activates voltage-dependent Ca^{2+} channels, leading to an increase in $[Ca^{2+}]_i$ and vasoconstriction [69]. Pioneering work indicated that pressure-induced membrane depolarization also stimulated BK channels in arterial SM cells [16]. A large body of evidence now supports this negative-feedback mechanism which partially opposes myogenic vasoconstriction, as previously reviewed in [69,85]. Vasodilators, including those acting through the stimulation of PKA and PKG, activate BK channels, leading to membrane hyperpolarization and vasodilation [104]. PKG and PKA stimulate BK channels by both increasing Ca^{2+} spark frequency and by elevating BK channel sensitivity to Ca^{2+} sparks [153]. TRPV4 channel activation leads to Ca^{2+} influx that stimulates Ca^{2+} sparks and thus, BK channels, resulting in vasodilation [52]. Vasodilators can also act through direct effects on BK channels. Carbon monoxide, a gaseous vasodilator produced by heme oxygenase, increases the apparent Ca^{2+}sensitivity of BK channels through mechanisms, including direct binding to reduced heme attached to the heme-binding domain of slo1 proteins [83]. Vasoconstrictors, including serotonin and thromboxane A_2, stimulate phospholipase C through the G protein G_{q11} [59,178]. PLC cleaves phosphatidylinositol 4,5-bisphosphate to diacyglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). DAG activates PKC, which reduces BK channel activity both directly and indirectly through Ca^{2+} spark inhibition, leading to membrane depolarization and vasoconstriction [107,164]. The auxiliary β1 subunit is essential for the regulation of arterial contractility by SM cell BK channels. In β1 subunit knockout (*$KCNMB1^{-/-}$*) mice, BK channels are insensitive to activation by Ca^{2+} sparks and do not oppose pressure-induced vasoconstriction, leading to an increase in systemic blood pressure [18]. The impact of BK channel activity on contractility varies in arteries of different organs. A higher ratio of β1:slo subunits in SM cells of cerebral arteries increases channel activity and functionality. In contrast, a lower β1:slo1 ratio in cremaster muscle arteries lowers activity and the impact of BK channels on changes in contractility [200].

Regulation by intracellular signals other than Ca^{2+}_{ic}

Magnesium

Magnesium exerts complex effects on BK channel activity. In rat cerebral artery myocytes, Mg^{2+}_{ic} decreases BK current unitary amplitude at concentrations ranging from 1 to 4 mM [209]. This is voltage-dependent, with outward currents being more sensitive to Mg^{2+}_{ic} block than the inward component. The voltage dependency of block is more apparent as Ca^{2+}_{ic} concentration is decreased. However, 0.5 mM Mg^{2+}_{ic} increases BK P_o when studied in presence of low (1 μM) Ca^{2+}_{ic} and membrane potentials within the physiological range. Thus, it has been proposed that under conditions in which Ca^{2+}_{ic} does not exceed a few micromolar, Mg^{2+} tonically activates BK channels in vascular SM [209]. Consistently, 5 mM Mg^{2+} increases whole-cell BK currents in rabbit basilar cerebral artery myocytes [42].

Protons

BK current recordings in inside-out patches from human internal mammary artery myocytes document an increase in current in response to increased IC pH [156]. Conceivably, protons themselves inhibit BK current, as was shown in rat tail artery myocytes [163]. However, whole-cell BK currents in rabbit basilar artery myocytes are activated by acidosis, this effect being mediated by an increased in Ca^{2+}_{ic} [145].

Redox compounds

In inside-out patches, exposure of the inner membrane leaflet to NADH inhibits BK currents in rabbit pulmonary artery myocytes, while NAD activates [102]. Glutathione inhibits BK current in the same preparation while its redox partner glutathione disulfide increases channel activity [102].

Peroxynitrite

Peroxynitrite, an oxidant formed in cells during metabolism, is a known vasoconstrictor [19,118]. Peroxynitrite decreases whole-cell K^+ current in human coronary arteriole myocytes [118]. Addition of Ibtx does not evoke further decrease in K^+ current [118], suggesting that peroxynitrite abolishes BK currents. BK current sensitivity to peroxynitrite has been confirmed in inside-out patches from rat MCA myocytes: IC peroxynitrite reduces both BK P_o and open dwell times [19].

Phosphorylation

The modulation of BK currents by phosphonucleotides and protein kinases varies from tissue to tissue and on whether cell integrity allows for intracellular signaling [60,163,170]. While many reports demonstrate that PKA activates vascular BK currents [163], drugs that inhibit PKA have been reported to reduce BK currents in rabbit coronary artery SM cells, yet this effect seems to be independent of kinase inhibition itself [146]. PKC-induced BK current inhibition has been observed in cultured porcine coronary artery myocytes [134], rat tail [164] and mesenteric artery myocytes [171]. PKC also down-regulates BK currents in pulmonary artery myocytes from pulmonary hypertension-prone (Fawn-hooded) rat. This effect is achieved by PKC inhibiting cAMP-driven activation of BK channels [7,8]. Yet,

PKC activation up-regulates BK currents in rat pulmonary artery myocytes [8]. This effect seems to involve phosphorylation of slo1 at Ser1076 [217], and is blocked by a specific PKG inhibitor [8].

PKG activates BK currents in a variety of vascular preparations, as reviewed in [163]. In human coronary artery SM, the cGMP-dependent pathway mediates BK channel activation and eventual vasodilation evoked by testosterone [40]. The same IC signaling is involved in vasonatrin peptide actions on rat mesenteric and human radial artery [202]. Likewise, PKG mediates regulation of BK currents by the D(1)-like receptor for dopamine D(5)R in human coronary artery SM [140]. cAMP-dependent pathway signaling underlies BK channel activation by calcitonin gene-related peptide (CGRP) in rat mesenteric arteries [12]. PKA pathway also mediates the potentiation BK current by beta-adrenoceptor stimulation in basilar cerebral artery myocytes from guinea pigs [169]. Several cAMP-dependent vasodilators, including isoproterenol, dopamine, and prostaglandin E2, activate BK channels in porcine coronary artery myocytes via cAMP-induced activation of PKG, but not PKA activation itself [187,218]. Thus, there is an intricate interplay between protein kinases to modulate vascular SM BK current.

Alpha5beta1 integrin activation increases SM BK currents in rat cremaster muscle arterioles [191]. Interestingly, alpha5beta1 integrin increases BK P_o in both cell-attached and excised patches [191]. This result documents that integrin-driven phosphorylation of slo1 protein does not require IC mediators or cell integrity. Further investigation a recombinant slo1 BK channel cloned from mouse and expressed in HEK 293 cells reveals that alpha5beta1 integrin-induced increase in BK current is mediated via C-src phosphorylation of Tyr766 in slo1 protein and does not require the presence of BK β1 subunits [191,201].

BK channel phosphorylation is developmentally regulated. In sheep, fetal basilar artery BK channels are phosphorylated to a greater extend when compared to adult vessels [112]. While inside-out patches of adult ovine basilar artery myocytes exhibit greater PKA activity, fetal myocytes display more prominent PKG and phosphatase activities. This differential profile and eventual degree of BK channel phosphorylation may underlie developmental changes in BK current phenotypes [113].

Phosphoinositides

Phosphatidylinositol 4,5-bisphosphate (PIP_2) directly activates BK channels in rat cerebral artery myocytes. This effect is linked to enhanced Ca^{2+}_{ic}-driving gating without alterations in voltage-gating or unitary conductance. PIP_2 activation of BK current requires the presence of an RKK sequence in the S6-S7 cytosolic linker, an effect that is drastically amplified by the presence of the β1 subunit [179]. Indeed, co-transfection of HEK 293 cells with slo1 cloned from rat cerebral SM (cbv1) and human β1 results in currents highly sensitive to PIP_2. Substitution of β1 with β4 reduces PIP_2 sensitivity. PIP_2–induced activation of native BK channels occurs in freshly isolated cerebral artery myocytes but not in skeletal myocytes, which lack β1. Pharmacological block of PIP_2 degradation, which increases endogenous PIP_2 levels, leads to MCA dilation [179].

Regulation by paracrine mediators

Carbon monoxide (CO)

Carbon monoxide dilates cerebral arterioles through BK channel binding, which increases Ca^{2+} spark-BK channel coupling [83]. In contrast, a longer exposure to CO constricts cerebral arteries through inhibition of $NO^{\bullet}$ [103].

Nitric oxide ($NO^{\bullet}$)

Nitric oxide donors activate whole-cell BK currents in rat mesenteric artery (secondary and tertiary branches) SM cells [135]. This effect is not modified by guanylyl cyclase inhibition. Moreover, $NO^{\bullet}$-mediated increase in BK current can be observed in inside-out patches [72,135]. $NO^{\bullet}$ facilitates the rate of channel reopening without delaying the open-to-closed transition [72]. However, endothelial $NO^{\bullet}$ production and $NO^{\bullet}$ supplementation of de-endothelialized arteries in porcine coronary vasculature desensitize vascular SM BK channels to cGMP and inhibit vasorelaxation by C-type natriuretic peptide and atrial natriuretic peptide [111]. *Hydrogen peroxide (H_2O_2).* Flow-induced endothelial production of H_2O_2 activates BK currents in cell-attached patches of human coronary arteriole myocytes [115]. H_2O_2-induced activation of BK currents is mediated by dimerization, activation and translocation to the plasma membrane of IC PKG Iα [208]. H_2O_2 production may also diminish BK currents. In particular, high levels of EC glucose inhibit BK currents and slow activation and deactivation kinetics of hslo1 expressed in HEK 293 cells [121]. High-glucose-driven downregulation of BK current density and alterations in macroscopic current kinetics have been also documented in cultured human coronary myocytes. The glucose-driven increase in reactive oxygen species results in H_2O_2 oxidation of hslo1 cysteine at position 911 [121].

Hypoxia

Long-term hypoxia has been shown to increase the apparent Ca^{2+} sensitivity of basilar cerebral artery SM BK channels in adults and near-term sheep [175]. This increase occurs with a decrease in the phosphorylation of the channel when compared to normoxic controls [175]. *Amino acids.* Non-proteinogenic homocysteine decreases whole-cell BK current density in human and rat mesenteric [31] and porcine coronary [5] artery myocytes. The long-term (24 hour) effect of homocysteine on BK currents can be reversed by an inhibitor of NADPH oxidase activity [31].

Apelin-13

This endogenous peptide exerts vasoconstriction via inhibition of SM BK current, as shown during whole-cell recordings rat MCA myocytes [137]. Apelin-induced BK current inhibition is absent in excised patches. Moreover, apelin-13 inhibits BK current via phosphoinositide 3-kinase-dependent pathway [137].

Adiponectin

Adiponectin is peptide originated in perivascular adipose tissue that increases BK current in myocytes from 1st and 2nd order mesenteric arteries of mouse [124]. This increase in current

reduces the mesenteric artery's contraction in response to norepinephrine [124]. *Endothelin*. The effect of endothelin-1 on BK currents depends on the peptide's concentration, as shown in cell-attached patches of porcine coronary artery myocytes. At low levels (<10 nM), endothelin-1 potentiates BK current. In contrast, higher levels render BK channel inhibition with a notable decrease in mean open time [77]. Low levels of endothelin-1 and endothelin-3 increase BK Po, with endothelin-1 being two orders of magnitude more potent (E_{max}=1 nM) than endothelin-3 [76]. In a study on rat renal artery myocytes, endothelin receptors have been implicated in the inhibitory effect of high levels of endothelin-1 on BK currents [11]. However, the downstream pathways that mediate opposite effects of low versus high doses of endothelin-1 on BK currents are unlikely to be similar. Indeed, BK current activation by lower doses of endothelin-1, but not the inhibition by higher doses, is blocked by a Ca^{2+} channel blocker [77]. *Lipopolysaccharide*. Lipopolysaccharide (LPS), a bacterial endotoxin, activates rat cerebrovascular myocyte BK channels in a dose-dependent manner only when applied at the cytosolic side of the membrane in inside-out patches [70–72]. LPS-driven BK channel activation is reduced by lowering Ca^{2+}_{ic} levels, yet remains unaltered by changes in TM voltage [70,72]. LPS-induced activation of BK channels is blunted by pre-incubation of myocytes with $NO^{\bullet}$ inhibitors [70,72]. These findings suggest that $NO^{\bullet}$ signaling "primes" BK channels to an LPS-activatable state(s).

Regulation by neuronal factors, transmitters, hormones, and circulating agents

Cholesterol

Cholesterol (CLR) modulation of vascular BK channels has been extensively reviewed elsewhere [46–48]. In general, BK channels are inhibited by elevated CLR or up-regulated upon CLR depletion. However, BK channel activity in atherosclerotic plaques (likely enriched in CLR) is higher when compared to non-atherosclerotic sections of human coronary arteries [188]. A possible role of differential BK subunit composition in the final response of BK channels to CLR is under current investigation.

CLR-induced inhibition of slo1 proteins cloned from rat cerebral artery myocytes (cbv1 channels) and incorporated into planar lipid bilayers involves seven CLR Recognition Amino acid Consensus (CRAC) motifs in the cbv1 CTD [168]. Whether CRACs provide a binding platform for CLR, or alternatively, allosterically regulate CLR binding to another site(s), remains to be determined. BK channel inhibition is not evoked by enantiomeric CLR [20]. Thus, CLR action on BK current is either mediated by a direct steroid-protein interaction or involves a membrane lipid side that recognizes chirality. In addition to regulation of channel function, CLR enrichment down-regulates BK current density via activated proteolysis of slo1 proteins in cultured human coronary artery myocytes [190]. In contrast, CLR enrichment of rat MCA myocytes during the course of a high-CLR diet up-regulates β1 subunits level at the plasma membrane [21]. Thus, CLR modulation of BK current is governed by multiple mechanisms.

Bile acids

Lithocholic acid, a naturally occurring CLR metabolite, dilates rat and mouse MCA through activation of vascular SM BK channels [22]. The magnitude of bile acid-induced increase in BK channel activity is inversely related to the number of hydroxyl groups in the bile acid molecule [50]. Subsequent studies established that the most effective bile acid activator of BK channels, lithocholic acid, increased BK currents via direct interaction with the BK β1 subunit [25,27,28]. The lithocholate-sensing site resides on TM2 of β1. This site consists of Thr169, which forms a hydrogen bond with the hydroxyl group at C3 of lithocholate, and of Leu172,Leu173, which provide hydrophobic interactions with the lithocholic acid's hydrophobic core [27]. The strict dimensional features of this site explained previous observations on the chemical requirements for effective BK channel activators from the bile acid family, i.e., cholane steroids [25,50].

Natural and synthetic estrogens

Modulation of BK channel activity by estrogens includes two components: indirect modulation through estrogen receptor signaling and direct interaction with the BK channel protein. 17beta-estradiol increases open probability of BK channels in mesenteric artery SM cells of post-menopausal women and this effect is inhibited by the estrogen receptor antagonist ICI182,780 [36]. In human coronary artery myocytes, 17-beta estradiol increases whole-cell BK currents [186]. Acute activation of BK current by estrogen has been shown to be mediated by estrogen receptor alpha [64]. In addition, in this preparation and in porcine coronary artery myocytes, estrogen-induced increase in BK current involves G protein-coupled estrogen receptor 1 (GPER). Estrogen-induced increase in BK current is apparent in cell-attached, but not in excised, membrane patches [204]. GPER activation results in dilation of de-endothelialized coronary arteries, which is attenuated in presence of Ibtx [204]. Estradiol-triggered signaling downstream of GPER remains elusive. This signaling may involve activation of neuronal-type nitric oxide synthase within coronary artery myocytes. Indeed, overexpression of nNOS within human coronary artery myocytes increases BK currents in cell-attached patches [63], while an estrogen-driven increase in whole-cell BK current is reversed in presence of $NO^{\bullet}$ synthase blocker [186]. Estrogen-triggered increase in intravascular NO is likely to depend on PI3-kinase/AKt phosphorylation signaling cascade [63] and is linked to the cGMP signaling pathway [186].

Studies on recombinant BK channels heterologously expressed in *Xenopus laevis* oocytes or following channel reconstitution into artificial phosphoglyceride bilayers underscore that a direct estrogen-BK β1 subunit is necessary for the steroid to increase channel activity [39,180]. This phenomenon requires the presence of at least two β1 subunits and low μM Ca^{2+}_{ic} [39]. Notably, 17α-estradiol lacks the ability to increase BK currents when compared to 17β-estradiol [39,180]. It remains to be determined whether these findings can be replicated in native SM cells.

The synthetic estrogen Quat-DME-oestradiol induces relaxation of pre-constricted isolated rat aortic rings, this relaxation being Ibtx-sensitive. Moreover, Quat-DME-oestradiol activates whole-cell currents following co-expression of slo1 and BK β1 subunits in HEK cells [125]. Considering the membrane-impermeable nature of this estrogen, the ability of

Quat-DME-oestradiol to activate BK channels is consistent with an EC location for the estrogen-sensing site in BK channel proteins.

Angiotensin II

Ang II reduces whole-cell BK current in rat renal arterial myocytes, and this reduction was abolished by ang II type 1 receptor (AT1R) antagonist [212]. Confocal imaging of myocytes and transfected HEK cells reveals co-localization of BK channels with AT1R. Direct interaction between slo1 protein CTD and AT1R has been established as a G-protein independent mechanism that enables ang II control over BK currents [212]. Paradoxically, AT2 receptor mediates ang II vasodilation, as demonstrated in rat mesenteric microvessels [44]. This action is abolished by Ibtx. Moreover, ang II increase in BK current in whole-cell and cell-attached patches is suppressed by AT2 receptor block [44]. Thus, BK channels represent a common downstream target of ang II receptor activators.

Ghrelin

Ghrelin reduced BK currents and thus increased contractile force of guinea-pig femoral arteries [136]. Ghrelin downregulation of BK current has been observed in whole-cell patch-clamp recordings from guinea-pig femoral artery myocytes, and requires activation of Galpha(i/o) proteins, phosphatidylinositol phospholipase C, phosphatidylcholine phospholipase C, PKC and IP_3-induced calcium mobilization from IC stores [136].

Pituitary adenylate cyclase activating polypeptide (PACAP)

Transient BK currents in rat cerebellar artery myocytes are activated by pituitary adenylate cyclase activating polypeptide (PACAP), this activation resulting in vasodilation [92]. PCAP action on BK currents is likely mediated by an increase in Ca^{2+} spark frequency [92]. A similar mechanism has been proposed to underlie the vasodilation caused by exchange protein activated by cAMP (Epac), as demonstrated in rat mesenteric arteries and isolated myocytes [157].

Interleukins

Interleukin-1 beta (IL-1 beta) exerts biphasic effects on whole-cell BK currents in cultured rat aortic myocytes. Short application (up to 30 min) of IL-1 beta increases BK currents, this effect being blunted by a H_2O_2 scavenger catalase [58]. Longer presence of IL-1 beta (up to 48 hours) down-regulates BK currents, and this action is only partially diminished by the catalase [58]. IL-1beta modulation of BK currents results in myocyte hyper- and depolarization, respectively [58].

Leukotrienes

Native BK channels in membrane patches from freshly isolated myocytes and heteromeric BK channels consisting of cbv1 and BK β1 subunits expressed in *Xenopus* oocytes are both activated by leukotriene B4 (LTB4) with a concentration causing 50% of maximal effect (EC_{50})=1 nM [24]. LTB4 action is not mimicked by LTA4, LTC4 or LTD4. LTB4 activation of BK channels is contingent upon the presence of Thr169 in the TM2 domain of β1 [24].

Thus, LTB4 shares this site with the β1 subunit-specific BK channel activator lithocholic acid.

Cannabinoids

Methanandamide has been reported to potentiate BK currents in mouse aortic myocytes [160]. Moreover, anandamide and methanandamide-driven BK current potentiation can be observed in HEK 293 cells expressing either slo1 protein alone or in combination with β1 or β4 subunits. These effects are absent in excised patches. While the influence of CaM, PKG, CB1 and CB2 receptors, and MAP kinases has been ruled out, the identity of the IC messenger responsible for cannabinoid activation of BK channels remains unknown [160].

Regulation by arachidonic acid, analogs and derivatives

Direct modulation of BK channel activity by fatty acids have been documented in several vascular trees. In rabbit coronary artery myocytes, arachidonic acid (0.5–10 microM) increases BK channel activity in cell-attached and inside-out patches [1]. The potentiation of BK current is also exerted by myristic, linoleic, palmitoleic, and palmitic acids [1]. Longer chain fatty acids are more effective than shorter chain fatty acids in increasing BK current. There is no difference between the effects of saturated versus unsaturated fatty acids on BK current [1]. A SM BK channel component likely contributes to both arachidonic acid-driven dilation of rat retinal arterioles [96], and to docosahexaenoic acid-driven attenuation of hypoxia-evoked constriction of rat pulmonary arteries [198].

Modulation of BK currents by signaling lipids extends to the omega-3 fatty acid family. Docosahexaenoic acid (DHA) activates BK channels in cell-free membrane patches of HEK cells following heterologous expression of human slo1 and β1 subunits. In contrast, DHA ethyl ester or 17-hydroxyl DHA are unable to modulate slo1+β1 currents [75]. The DHA-driven increase in BK current has been observed across a wide range of $[Ca^{2+}_{ic}]$ (10 nM-100 μM). Arg11 and Cys18 in BK β1 are critical for DHA potentiation of BK current [74].

In addition to direct BK channel activation by DHA, the latter can potentiate BK currents via the cytochrome P450 metabolite 16,17-epoxydocosapentaenoic acid [182]. The physiological importance of DHA-driven activation of BK current has been established at the organ level: DHA-mediated dilation of rat coronary arteries is diminished in presence of CYP epoxygenase inhibitors or BK channel blockers [182]. Moreover, DHA is unable to reduce blood pressure in slo1 knock-out mice [75].

Eicosapentaenoic acids are arachidonic acid metabolites that activate vascular SM BK channels and relax various vascular beds [32,101]. In human pulmonary arteries, the concentration-dependent dilation evoked by 17(18)-epoxyeicosatetraenoic acid 17(18)-EpETE is accompanied by myocyte hyperpolarization and reversed by Ibtx [139]. BK channels in cerebral artery myocytes from *KCMNB1*$^{-/-}$ mice are still sensitive to 17(18)-EpETE, pointing at slo1 protein as a lipid sensor [68].

11,12-epoxyeicosatrienoic acid (11,12-EET), an endothelium-derived hyperpolarizing factor, dilates human internal mammary arteries through SM BK channel activation [4]. 11,12-EET

and its analogs 11-nonyloxy-undec-8(Z)-enoic acid, 11-(9-hydroxy-nonyloxy)-undec-8(Z)-enoic acid and 11,12-trans-oxidoeicosa-8(Z)-enoic acid also dilate rat mesenteric arteries [43]. These compounds activate SM BK currents in whole-cell, cell-attached, and cell-free patch-clamp configurations. This effect along with vasodilation are reversed by the protein phosphatase 2A inhibitor okadaic acid [43]. The mechanism by which of 11,12-EET potentiates BK currents remains elusive. However, 11,12-EET facilitates co-immunoprecipitation of slo1 and β1 subunits in pulmonary artery SM mitochondria [119]. This effect results in the loss of mitochondria membrane potential and eventual pulmonary vasoconstriction [119]. A set of EET analogs dilates canine and porcine coronary arterioles [211]. 11,12-EET enantiomers and (6)13,14- epoxydocosatetraenoic acid also activate BK channels in inside-out patches from myocytes freshly isolated from rat coronary arteries [211].

Dihydroepoxyeicosatrienoic acids (DHETs), which are epoxyeicosatrienoic acid metabolites, are potent BK channel activators. In inside-out patches from rat coronary artery myocytes, 11,12- dihydroepoxyeicosatrienoic acid activates BK currents with EC_{50}s in the low nanoM [122]. The effect of 11,12-DHET on BK current includes modulation of voltage- and to a lesser extent, Ca^{2+}-dependent gating, being ineffective in the absence of $Ca^{2+}{}_{ic}$. Increase channel activity by 11,12-DHET results from increase in channel open time, and decreases in channel closed time and in the open-to-close transition rates [122].

Changes under physiological and pathological conditions

Given the wide distribution of SM BK channels across vessel types and vascular territories, it is not surprising that functional changes in SM BK channels contribute to the mechanisms leading to, or are reactively triggered by, physiological and pathological conditions (Table I). *Pregnancy, development and aging*. SM BK channel expression and function are increased in uterine arteries during pregnancy likely as a result of decreased oxygen levels in blood. The resulting increase in SM BK current reduces myogenic tone and facilitates BF to the fetus [78,216]. In sheep uterine arteries, pregnancy led to not only increases in β1 and slo1 protein expression but also to an expression switch among different slo1 isoforms [159]. β1 overexpression and higher BK function is also observed in aortic, mesenteric [33] and cerebral artery SM [26] during postnatal growth into adulthood. On the other hand, decreases in α and β1 expression and BK function are reported in coronary SM of aging rats [126,142]. *Oxidative stress, hypoxia and reperfusion*. SM BK channels are proposed to be modulated by redox species through “direct” activation or inhibition mechanisms. While these mechanisms do not involve freely diffusible cytosolic signals, cell integrity or organelles (with exception of the membrane where the channel resides), the channel protein site(s) involved in these direct actions usually has remained elusive in most cases. Thus, both superoxide and H_2O_2 may directly activate SM BK channels leading to artery dilation [67,176,185]. In contrast, H_2O_2 reduces the activity of heterologously expressed BK channels by oxidation of slo1 Cys residues [173]. Whether this mechanism operates in native SM or has consequences on SM tone remains to be determined.

In pulmonary arteries, hypoxia has been reported to induce both an increase and a decrease in BK channel expression in vascular SM [2]; reviewed in [14]. Whether the former plays a

pathophysiological role while the latter reflects a compensatory mechanism to hypoxia, remains to be fully established. Long-term hypoxia leads to an increase in β1 expression in basilar arteries of near-term ovine fetuses, with SM BK channels in these arteries showing an increase in Ca^{2+}-sensitivity [175]. Likewise, chronic intermittent hypoxia leads to increased vasodilation, which is mediated by SM BK channels [62]. In contrast, in adult middle cerebral arteries, chronic hypoxia reduces the ability of PKG to activate SM BK channels [177]. *Obesity and diabetes*. Inhibition of SM BK currents by direct targeting of slo1 by H_2O_2, in addition to decreased channel expression, constitutes a pathophysiological mechanism underlying the reduction of BK currents in coronary artery SM that occurs in response to high glucose [121]. Likewise, streptozotocin administration leads to reduced expression of slo1 and β1 subunits, leading to reduced BK current in SM cells [45,130]. In this model of diabetes, not only is BK channel function reduced, but also channel activation by lipid mediators, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), is impaired. Oral administration of n-3 PUFAs, however, increases β1 expression [172]. Likewise, reduced β1 expression in diabetes can be reversed by transcriptional activation induced by Nrf2, which also reduces body weight and blood glucose levels in a high fat diet-induced diabetic mouse [123]. In contrast, in the Zucker diabetic rat, reduced BK current in SM is not associated with decrease in β1 expression [30]. BK channels show a reduced sensitivity to superoxide, which has been interpreted as a compensatory response to counter the deleterious impact of diabetes on the vascular system [116]. Expression of β1 subunits is also decreased in retinal arterioles from insulin-resistant rats [130]. It has been suggested that abnormal BK channel function participates in the pathophysiology of diabetic retinopathy by increasing retinal vessel constriction with eventual reduction in local blood flow [138]. An up-regulation of BK β1 subunits has been found in coronary SM in the obese Zucker rat, with the authors speculating that an increase in SM BK channel activity may contribute to maintain proper SM tone and $NO^{\bullet}$-mediated vasodilation [37].

Hypertension and stroke

Changes in subunit expression and overall BK channel function vary according to hypertension model, vessel type and/or species under study. An increase in SM BK channel function has been reported in the Fawn hooded hypertensive rat [144], and increased slo1 expression with enhanced BK channel function has been reported in cerebral artery SM from spontaneously hypertensive rats (SHR) [117]. An increase in SM BK function is usually interpreted as a compensatory effect to counteract enhanced SM depolarization and Ca^{2+} influx associated with increased intravascular pressure. Mechanistically, it is possible that stretch itself exerts a key control on SM BK activity. Indeed, pathological stretch increases the activity of both BK and L-type Ca^{2+} channels and thus, regulates $Ca^{2+}{}_{ic}$ oscillations in vascular SM [213]. Of note, the increase in BK channel subunits and function found in SHR are normalized by aerobic exercise [166,210]. Exercise, however, increases both β1 subunit expression and channel function in normotensive rats [166]. In contrast to data from SHR, a decrease in the expression of the slo1 subunits has been reported in the SM of L-nitro-arginine hypertensive rats [15], and a decrease in both SM BK current density and expression has been reported in elderly, hypertensive humans [35]. Consistently, *Slo1*$^{-/-}$ mice exhibit arterial hypertension [161]. The latter has been attributed to the complete suppression of BK channel-generated STOCs, a reduced efficacy of the cGMP/PKG

pathway, which normally activates BK current, and, as also reported for *KCNMB1*$^{-/-}$ mice [152], to primary aldosteronism [161].

BK β1 subunit downregulation has been reported in arterial SM from both SHR and ang II-dependent hypertensive rats [3]. Consistently, *KCNMB1*$^{-/-}$ mice exhibit abnormally high blood pressure and increased contractile responses of arterial SM. The latter has been linked to disruption of the normal coupling between RyR-evoked Ca^{2+} sparks and BK-generated STOCs [18,151]. Conversely, humans who carry the SNP G352A, which leads to the gain-of-function E65K substitution in the BK β1 subunit [56], exhibit a reduced prevalence of diastolic hypertension, albeit in elderly women only, and protection against infarction and stroke [165]. Of note, genetic ablation of β1 subunits, however, favors fibrosis but does not evoke hypertension in high-fat fed obese mouse [195].

Conclusions

Since the first identification of BK channel-mediated currents in vascular SM, major progress has been made defining the biophysics, cell biology, physiology and pharmacology of these ion channels. Their widespread expression and involvement in key physiological processes, including the regulation of myogenic tone and contractility, uncover SM muscle BK channels as significant players in several vascular diseases and as possible targets of putative pharmaco-therapies. Of note, the high expression of BK β1 subunits in SM when compared with their poor expression in other tissues, renders this auxiliary protein a target of research efforts to selectively modulate SM function.

As our understanding of SM BK channels progresses, major gaps in knowledge are also unveiled. The native SM BK channel is composed of several different subunits, yet the precise composition and stoichiometry remains uncertain. Whether SM BK channel composition and thus, current phenotype, varies in vasculature of different organs remains largely understudied. Both slo1 and BK β1 proteins result from significant processing, including pre-RNA splicing, RNA editing, miRNA regulation, and post-translational modification. Many of the results documenting these phenomena, however, have been obtained in tissues other than SM, and the involvement of these processes in SM physiology or pathology deserves further evaluation.

BK channels in SM have been reported to be modulated by a plethora of intracellular signals, membrane components, paracrine messengers, neurotransmitters, hormones and other circulating agents. In many cases, such modulation seems to involve direct ligand recognition by the channel protein(s). Moreover, distinct amino acid residues have been identified as ligand sensors. In the absence of structural data, it remains unknown whether such BK regions contribute to ligand binding or behave as allosteric sites, with actual binding occurring elsewhere in the BK protein(s) and/or the local lipid microenvironment. Additional complexity exists since a ligand may be sensed by more than one site in the BK channel protein, a point in case being $Ca^{2+}{}_{ic}$.

Novel membrane and intracellular proteins that contribute to Ca^{2+} influx and/or SR Ca^{2+} release and repletion are being discovered, e.g., TRP channels, STIM and Orai proteins.

Such discoveries may require a reconsideration of the physiological functions of BK channels in vascular SM. Finally, BK channels have been mapped to organelles other than the plasmalemma, including mitochondria and the nuclear envelope, yet the structure and function of these proteins in vascular SM remain to be discovered.

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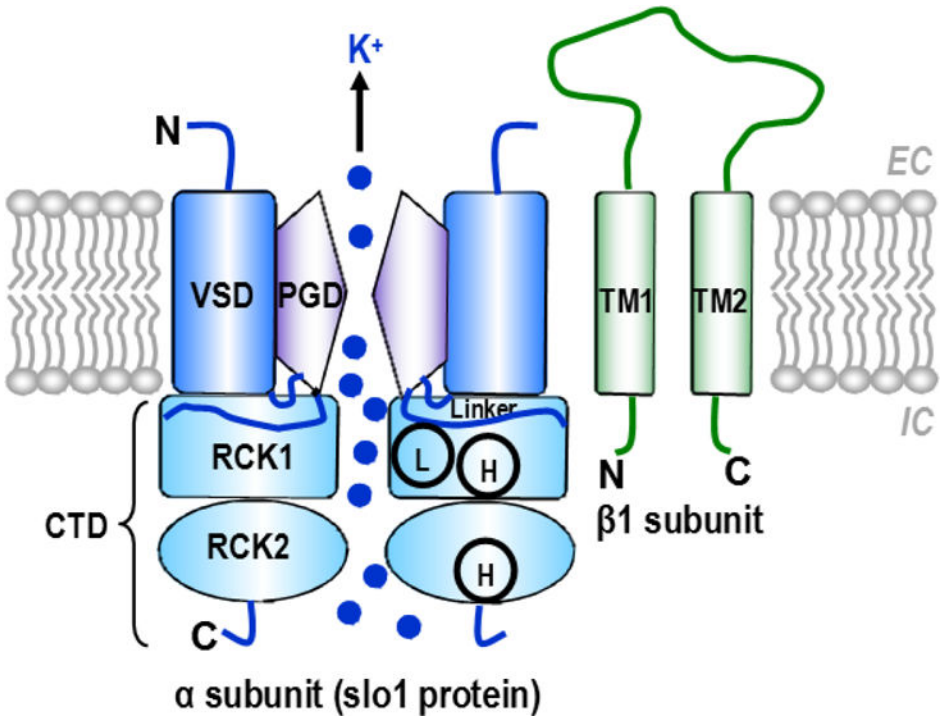

Fig. 1.

Lateral view of the plasmalemma with a cross-section through two BK channel-forming slo1 proteins, also known as BK α-subunits (in blue), that contribute to form a fully functional BK channel homotetramer. In vascular smooth muscles, these subunits are associated with small, two transmembrane proteins known as BK β1 subunits (in green) that modify the biophysical and pharmacological properties of the native channel. The modular nature of slo1 proteins is underscored: each subunit contains a voltage sensor domain (VSD, in blue), a central pore– gate domain (PGD, in violet), and a long C-terminal of intracellular location termed cytosolic tail domain (CTD). Each CTD contains two Regulators of Conductance for K^+ (RCK) domains. RCK1 includes binding sites for Ca^{2+} (labeled H for high affinity divalent recognition site) and Mg^{2+} (labeled L for low affinity divalent recognition site). RCK2 includes another H site. VSD and CTD are connected to PGD by linkers and through domain-domain interface contacts.

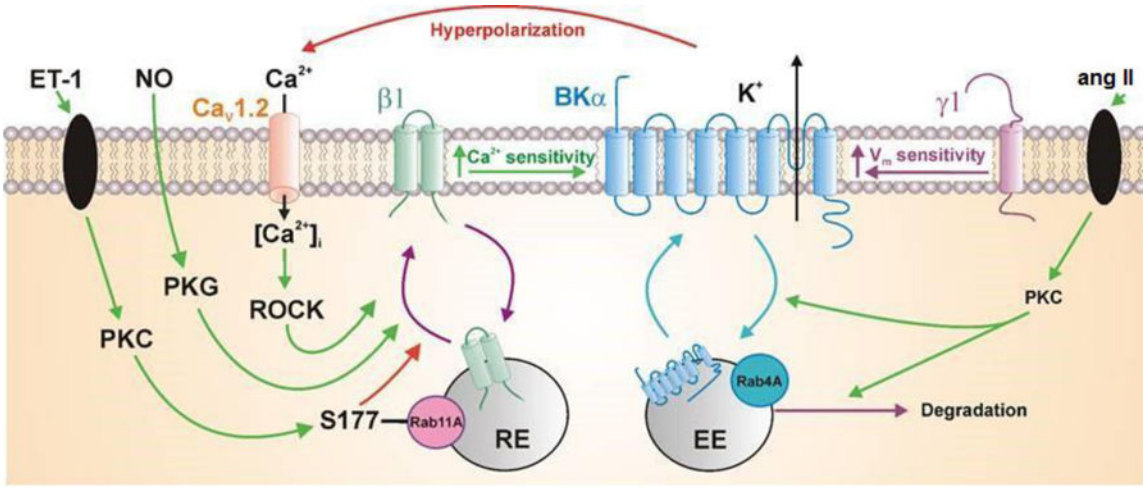

Fig. 2.

Regulation of BK channel activity and function by subunit trafficking. Slo1 proteins traffic to the plasmalemma *via* a Rab4A-dependent pathway, suggesting that early endosomes transport the channel to the plasmalemma. Angiotensin II (ang II) stimulates PKC-driven internalization and degradation of surface slo1 protein, thereby reducing BK current. A significant proportion of intracellular β1 in resting arterial SM is stored within Rab11A-positive recycling endosomes. $NO^{\bullet}$, through the activation of PKG, increases Rab11A activity, leading to the rapid surface trafficking of β1. Calcium influx through voltage-dependent calcium (Ca_V) channels activates Rho kinases, which stimulates anterograde trafficking of intracellular β1 subunits. Endothelin-1 stimulates PKC-mediated phosphorylation of Rab11A at Ser177, which reduces Rab11A activity and inhibits surface trafficking of β1. An increase in surface β1 subunits activates BK channels, whereas a decrease in surface β1 inhibits BK channels, causing corresponding changes in arterial contractility. The regulation of BK channel voltage-sensitivity by LRR26, the so-called BK γ1 subunit (in violet), is also shown.

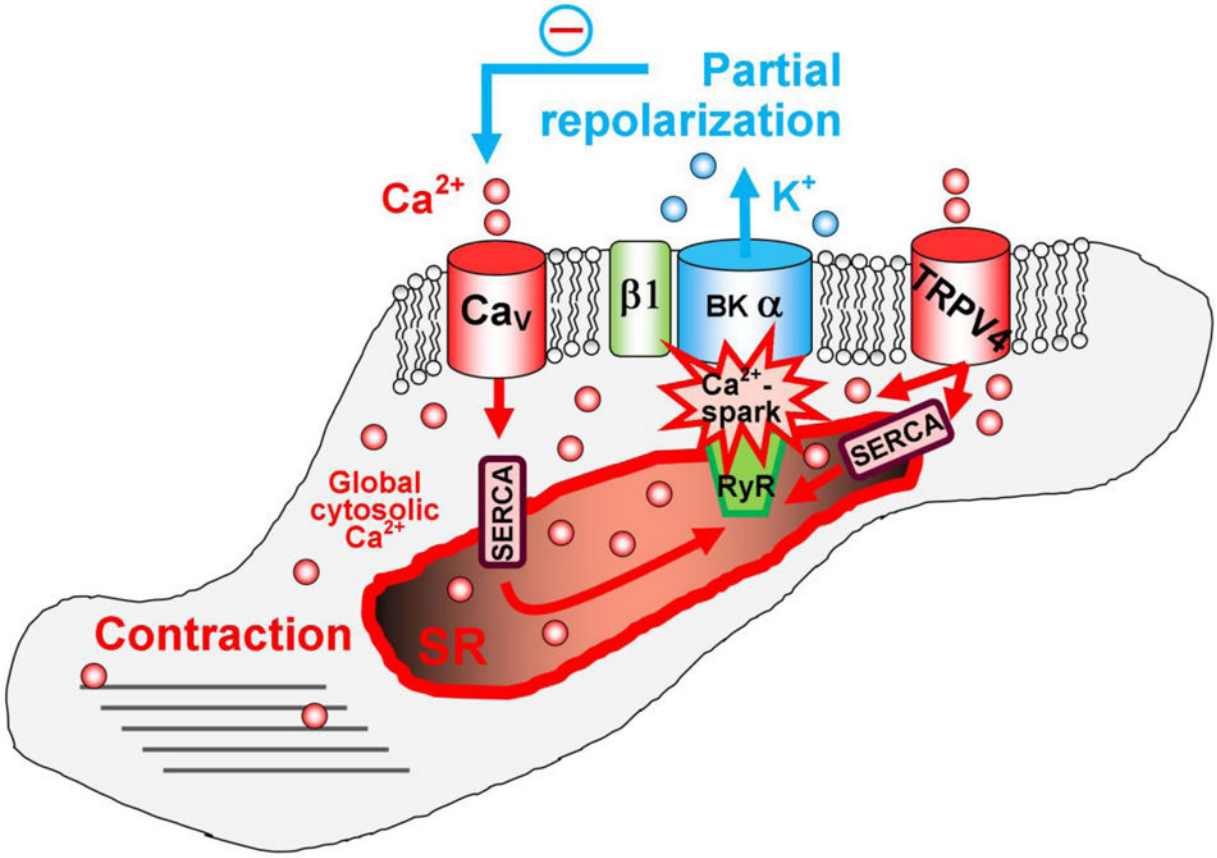

Fig. 3.

In vascular myocytes, *localized* intracellular Ca^{2+} signals (termed Ca^{2+} sparks) activate BK channels. Ca^{2+} sparks occur following the opening of ryanodine-sensitive Ca^{2+} release (RyR) channels located on the sarcoplasmic reticulum (SR) membrane. The effective coupling of BK channels to a Ca^{2+} spark controls the amount of current generated during each BK transient. Ca^{2+} released into the cytosol during a spark does not significantly contribute to global $[Ca^{2+}]_{ic}$ in arterial SM cells. Rather, repetitive transient BK currents evoke partial repolarization of the plasmalemma, which reduces the activity of voltage-dependent Ca^{2+} (Ca_V) channels. Ca^{2+} influx through Ca_v channels elevates $[Ca^{2+}]_{ic}$, which triggers vasoconstriction. Intracellular Ca^{2+} is sequestered into the SR by the SR Ca^{2+}-ATPase, which increases SR Ca^{2+} load, a major modulator of Ca^{2+} spark frequency. The repolarization caused by Ca^{2+} spark-induced BK channel activation decreases Ca_V channel activity, thereby reducing $[Ca^{2+}]_{ic}$, with consequent partial vasodilation. The activation of transient receptor potential V4 (TRPV4) channels leads to Ca^{2+} influx that stimulates Ca^{2+} sparks and transient BK currents, leading to vasodilation.

Table I

Major physiological and pathological conditions and associated changes in SM BK channels

Condition	Experimental model- species	Arterial vessel smooth muscle	Variable	Outcome	References
Development	Rat	Aortic and mesenteric	β1 protein and BK current	Increased	[33]
	Rat	Middle cerebral	β1 protein and BK current	Increased	[26]
	Sheep	Middle cerebral	slo1 protein β1 protein	DecreasedIncreased	[177]
Pregnancy	Sheep	Uterine	β1 protein and BK current	Increased	[78,159]; *reviewed in* [216]
Ageing	Rat	Coronary	BK current	Decreased	[126,142]
Redox (H_2O_2)	Cat	Cerebral	BK current	Potentiation	[185]
	Pig	Coronary			[77,176]
	Recombinant BK channels	N/A		Inhibition	[173]
Hypoxia	Human	Pulmonary	β1 protein	Increased	[2]
	Chronic hypoxia on near-term ovine fetus	Middle cerebral	Slo1 protein	Decreased	[177]
	Chronic intermittent hypoxia *on top of* renovascular hypertension in rats	Mesenteric	β1 protein and BK current	Increased	[62]
Diabetes	High glucose to recombinant slo1 channels	N/A	BK current	Reduced	[121]
	Streptozotocin to rat	Retinal arterioles	β1 protein and BK current	Decreased	[130]
	Streptozotocin to mouse	Cerebral	β1 protein and BK current	Decreased	[45]
Diabetes-obesity	Zucker rat	Mesenteric 3rd order branches	β1 protein and BK current	Unchanged,decreased	[30]
		Coronary	β1 protein and BK current	Increased	[37]
Hypertension	Fawn hooded rat	Cerebral	BK current	Increased	[144]
	SHR	Small cerebral	Slo1 protein and BK current	Increased	[117]
		Mesenteric	Slo1, β1 proteins and BK current	Increased	[210]
	L-nitro-Arg hypertensive rat	Mesenteric	Slo1 protein and BK current	Decreased	[15]
	Angiotensin II-infused rat	Basilar and other cerebral	β1 protein, STOC- spark coupling	Decreased	[3]