Calcium-Activated Potassium Channels and the Regulation of Vascular Tone

Different calcium signals in the endothelium and smooth muscle target different types of Ca\(^{2+}\)-sensitive K\(^+\) channels to modulate vascular function. These differential calcium signals and targets represent multilayered opportunities for prevention and/or treatment of vascular dysfunctions.

Quintessence of Vascular Ca\(^{2+}\) and K\(^+\) channels

Vascular tone and hence blood pressure are determined by the contractile state of vascular smooth muscle cells (VSMCs) within the blood vessel wall, which is regulated by intracellular calcium concentration ([Ca\(^{2+}\)]\(_i\)). Vasoconstrictors act through increasing [Ca\(^{2+}\)]\(_i\), as well as on the apparent calcium sensitivity of the contractile process in VSMCs, whereas relaxing factors have the opposite effect. In contrast, an elevation in endothelial [Ca\(^{2+}\)]\(_i\), induces relaxation of the adjacent VSMCs. Therefore, fine tuning of [Ca\(^{2+}\)]\(_i\), in both cell types is imperative for precise regulation of organ and tissue perfusion.

The major pathways for an increase in myocyte [Ca\(^{2+}\)]\(_i\), are voltage-dependent Ca\(^{2+}\) channels (VDCC) and nonselective cation channels at the plasmalemmal membrane or the internal store release channels, i.e., the ryanodine (RyR) and the inositol trisphosphate (IP\(_3\)) receptors found in the sarcoplasmic reticulum (SR) membrane (FIGURE 1). Global [Ca\(^{2+}\)]\(_i\), is mainly dictated by the open state probability of L-type VDCC, which are finely controlled by the membrane potential. Activity of different ion channels present at the plasma membrane such as K\(^+\), Cl\(^-\), and cation channels govern the membrane potential and therefore affect the VDCC activity and calcium entry. Opening of K\(^+\) channels such as the large-conductance Ca\(^{2+}\)-activated K\(^+\) channel (BK) hyperpolarizes the membrane, promoting closure of VDCC and thus opposing vasoconstriction.

In contrast to the VSMCs, an increase in endothelial [Ca\(^{2+}\)]\(_i\), results in vascular relaxation through endothelium-derived relaxing factors such as nitric oxide (NO), prostacyclin (PGI\(_2\)), and endothelium-derived hyperpolarizing factor (EDHF) (FIGURE 1). Furthermore, due to the absence of VDCC, hyperpolarization of the endothelial membrane by activation of Ca\(^{2+}\)-sensitive K\(^+\) channels does not reduce calcium influx. In fact, membrane potential hyperpolarization would promote calcium entry possibly involving transient receptor potential channels (TRPC1, TRPC3, TRPC4, TRPC6, TRPV4, etc.) through an elevation of the electrochemical driving force for Ca\(^{2+}\) (14, 129).

Ca\(^{2+}\): The Genesis of All Signals

An increase in [Ca\(^{2+}\)]\(_i\), in endothelium or in VSMCs exerts opposing influences on blood vessel diameter. The nature of calcium signals in endothelium and smooth muscle are also fundamentally different. Endothelium-dependent vasodilators such as acetylcholine appear to act in part through the elevation of endothelial [Ca\(^{2+}\)]\(_i\), followed by the generation of endothelium-derived relaxing factors. However, the nature of the intracellular calcium dynamics at rest in the endothelium remains unclear. Endothelial calcium waves and “puffs” (small punctate and local increases of calcium) have been reported, but the role and the sources of such local and spontaneous calcium dynamics remain to be clearly determined.

Although relatively little is known about calcium signaling in the native endothelium, the calcium dynamics in vascular myocytes have been well studied. Three different forms of calcium signaling have been identified in smooth muscle. First, global cytosolic [Ca\(^{2+}\)], represents averaged calcium levels throughout the entire cytoplasm and controls smooth muscle contractility through the activation of the myosin light-chain kinase (46). Global calcium can also influence gene expression via a calmodulin (CaM) kinase activation of the transcription factor CAMP response element binding protein (25, 130) or via the nuclear factor of activated T-cells (42, 49). A second form of calcium signaling reported in vascular smooth muscle consists of propagating waves (“calcium waves”). Calcium waves can be induced by extracellular alkalization or exposure to caffeine (48) as well as by endogenous vasoconstrictors such as UTP (57) or norepinephrine (14, 53, 82, 89). These calcium waves or oscillations result from intracellular calcium release through IP\(_3\)R and/or RyR (14, 57). Whereas calcium waves are thought to be responsible for smooth muscle contraction (14, 60), they can also paradoxically activate BK channels, promoting membrane hyperpolarization and thereby opposing smooth muscle contraction (139). Thus, although information regarding calcium waves in vascular smooth muscle is rapidly emerging, their physiological function remains only partly resolved.

The general view of a necessary homogeneous elevation of calcium throughout the entire cell for effective calcium signaling has been altered by the discovery of highly spatially and temporally localized calci-
nM (58, 85) (FIGURE 1). A calcium spark, by virtue of its massive local calcium elevation, has the potential to modulate Ca^{2+}-dependent processes that are not responsive to global increases in [Ca^{2+}]_{i}. Early reports linking local calcium release to membrane currents came from recordings of spontaneous transient cur-

FIGURE 1. Roles of BK, SK, and IK channels in the regulation of vascular function
The small-conductance SK3 channel and intermediate-conductance IK channels are expressed in the vascular smooth muscle (SM), and activation of these channels can lead to vasodilation. These channels regulate the membrane potential of endothelial cells and are activated by a rise in intracellular calcium ([Ca^{2+}]_{i}). Membrane potential hyperpolarization of endothelial cells elevates the driving force for calcium entry, possibly through transient receptor potential (TRP) channels. An increase in [Ca^{2+}]_{i} would elevate nitric oxide (NO) and production of arachidonic acid metabolites [prostacyclin (PGI2), epoxyeicosatrienoic acids (EETs)], which can hyperpolarize the adjacent SM. Endothelial membrane potential hyperpolarization could also be transmitted through myoendothelial gap junctions to hyperpolarize the SM, which by decreasing calcium entry through voltage-dependent calcium channels (VDCCs) leads to vasodilation. Elevation of intravascular pressure leads to membrane potential depolarization, activation of VDCCs, an elevation of [Ca^{2+}]_{i}, and vasoconstriction. This vasoconstriction process is opposed by stimulation of calcium sparks, which activate BK channels in vascular SM. Consistent with this, suppression of the expression of SK3 channel in the endothelium or ablation of the genes for the β1- or α-subunits of the BK channels leads to SM membrane potential depolarization, increased vascular tone, and hypertension.
rents through Ca\(^{2+}\)-sensitive K\(^+\) channels in neurons from frog sympathetic ganglia (19, 76, 77). Later, transient outward currents through BK channels were measured in VSMCs and in non-VSMCs and were referred to as spontaneous transient outward currents (12).

**BKKing**

**The mammoth’s skeleton**

The native BK channel is composed of four α- and four β-subunits (62, 115). The α-subunit, encoded by the Slo gene, is the pore-forming portion of the channel and consists of 11 hydrophobic domains (S0–S10) (FIGURE 2A). Current opinion suggests that the transmembrane-spanning domains (S0–S6) constitute the so-called “core” region with an extracellular NH\(_2\) terminus. The four remaining domains (S7–S10) are thought to be located in the cytoplasm and form the COOH-terminal “tail” of the protein. Similar to other voltage-gated channels (such as K\(_v\)), the S4 domain contains several positively charged amino acids and most likely represents the voltage sensor of the channel. The pore-forming region is located in the S5-S6 linker, and four α-subunits form a functional channel pore even in the absence of β-subunits (122). Recent studies suggest that the α-subunit also contains an intrinsic sensitivity to [Ca\(^{2+}\)]\(_i\). This might be conferred by a “Ca\(^{2+}\) bowl” located in the tail region of the protein (7, 100, 101). However, other groups associated the calcium sensitivity of the α-subunit not only with a calcium bowl but also with a regulator of conductance located in the RCK (RCK) domain located between the core and the tail region of the protein (68, 138). Nonetheless, the presence of another Ca\(^{2+}\)-binding or -sensing site was inferred by the channel’s responsiveness to increasing levels of [Ca\(^{2+}\)], even in the absence of the entire intracellular tail—including the calcium bowl and the RCK domain (95). Slo is the only gene encoding for the α-subunit, but many splice variants with different properties have been identified. These splice variants might explain various BK channel properties reported in different tissues, e.g., voltage sensitivity, phosphorylation by cAMP-dependent protein kinase (PKA) or cGMP-dependent protein kinase (PKG), or membrane trafficking (26, 120, 140). This variability is expanded through the association of BK with different β-subunits. The β-subunit of the BK channel is composed of two transmembrane domains with a long extracellular linker, whereas the NH\(_2\) and the COOH terminals are located in the cytoplasm (FIGURE 2). So far, four β-subunit genes and up to eight β-subunit proteins have been identified, each providing different modulatory effects on the pharmacology and activation gating of the channel (62, 124, 135, 136). The predominant subunit in VSMCs is the β1 isoform (62, 115). The β1-subunit interacts with the S0 domain and the extracellular NH\(_2\) terminus of the α-subunit, thereby increasing the apparent voltage and calcium sensitivity of the channel (18, 63, 88, 94).

**The king’s motivation**

The activation of BK channels by membrane potential is not fixed but rather depends on [Ca\(^{2+}\)]\(_i\) (78). Under low-calcium conditions, the BK channel behaves as a pure voltage-dependent K\(^+\) channel (51, 114). The voltage-sensing mechanism of the BK channel is independent of Ca\(^{2+}\) binding. However, calcium shifts many of the voltage-dependent parameters to more negative voltages and allows the channel to function under a physiological range of membrane potentials (9, 28). Due to a very close proximity to SR Ca\(^{2+}\)-release sites, the BK channel can be exposed to relatively high levels of calcium ions (>10 μM Ca\(^{2+}\)) (93). Although the α-subunit determines the basic calcium sensitivity of the BK channel, the β1-subunit appears to be responsible for the translation of physiological calcium signals to regulate vascular function. Indeed, genetic deletion of the β1-subunit leads to a decreased calcium sensitivity of the BK channel, resulting in an uncoupling of BK channels from calcium sparks. Furthermore, deletion of the β1-subunit leads to a more depolarized membrane potential, an elevation of [Ca\(^{2+}\)], followed by vasoconstriction, and ultimately an elevation of arterial blood pressure (18, 73, 96). Consistent with these results, a gain-of-function mutation of the β1-subunit was reported to protect against human diastolic hypertension by increasing the apparent calcium and voltage sensitivity of the BK channel (37, 84).

**The enzymatic sway**

The BK channel can be phosphorylated by several kinases, including PKA, PKG-I, and protein kinase C (PKC) (69, 102). Although endogenous vasodilators act through elevation of cAMP or cGMP, vasoconstrictors lead to the activation of PKC. Phosphorylation of the channel serves to modulate its apparent calcium and voltage sensitivity. In most cases, PKA and PKG-I activate the BK channel by increasing its open probability, thereby shifting its voltage-activation curve toward more negative membrane potentials but without affecting the single-channel conductance or the voltage sensitivity, represented by the slope of the voltage-activation curve (4, 81, 92, 97). PKA or PKG-I can also indirectly activate BK channels by phosphorylation of phospholamban, which increases the SR calcium load by disinhibiting the SR calcium ATPase, resulting in an elevated calcium spark frequency and amplitude (58, 131). On the other hand, PKC phosphorylation inhibits the BK channel in smooth muscle (80, 103, 113). It has also been reported that phosphorylation by PKC determines the susceptibility of the channel to be stimulated by either PKG-I or PKA (141). This is consistent with the finding that PKC activates BK channels via PKG-I in rat pulmonary arterial
myocytes (8). Taken together, the current knowledge about enzymatic regulation of BK suggests that both PKG-I and PKA activate BK channels, whereas the role of PKC remains uncertain.

**Pharmacology**

The pharmacology for BK channels (Table 1) is restricted to a potent blockade by external tetraethylammonium ions (a general K⁺ channel blocker) and a series of tremorgenic alkaloids, including paxilline (71), as well as a more effective and specific inhibition by several scorpion toxin peptides such as iberiotoxin and charybdotoxin (38, 45). Although these compounds do not have clear therapeutic potential, they (particularly iberiotoxin) are very useful tools to study BK channel function. Several small-molecule BK channel openers have been reported for both native and cloned BK channels (44). For example, the benzimidazolone NS-1619 has been shown to activate BK channels (90), but its functional effect also involves inhibition of Ca²⁺ currents and voltage-activated K⁺ channels (50). In addition to these drugs, other substances can also influence BK channel activity. It has been demonstrated that estrogen at high concentrations (micromolar) binds to BK channels, primarily to the β1-subunit, and directly regulates channel expression and function (30, 67, 126). Heme proteins and reactive oxygen species were also reported as modulators of BK activity (116, 117), as they both inhibit vascular smooth muscle BK channels by targeting the α-subunit, thereby eliminating physiological activity of the channel. Finally, ethanol has been shown to inhibit BK channels in vascular smooth muscle, leading to an increased vasoconstriction (31, 72, 128).

**SK Channels**

A **symbiotic scaffold**

Another class of Ca²⁺-activated K⁺ channels with a smaller unitary conductance (10–40 pS) was first identified in brain, referred to as small-conductance Ca²⁺-activated K⁺ channels (SK channels). Up to four members of that highly conserved family are now identified (SK1–SK4, encoded by KCNN1–KCNN4 genes) including a Ca²⁺-activated K⁺ channel that was previously identified in erythrocytes and lymphocytes as an intermediate-conductance (IK) channel based on single channel conductance and a distinct pharmacology.
sensitivity to cytoplasmic calcium within the submolar range (36, 104, 105, 137). It has been suggested that CaM binding also regulates trafficking and assembly of SK channels (59, 70). No other subunits have been identified yet. The expression pattern of SK channels is quite different from the BK channel. In fact, SK channels are expressed in neurons, endothelium, epithelium, and several types of smooth muscles (e.g., urinary bladder) but not in VSMCs. However, SK4 was shown to be expressed in VSMCs, but only when the myocytes were in a proliferative state (87).

The mandatory element
Opening of the SK pore is independent of the membrane potential but strictly depends on \([\text{Ca}^{2+}]_i\). The calcium sensitivity of SK channels depends on CaM. The binding of calcium ions to the coupled CaM induces a conformational change of the complex involving an interlacing of cytoplasmic loops that leads to the channel pore opening (FIGURE 1D). A Hill coefficient of 4 for the dose-response curve of SK channels was observed (73). However, IK is now referred to as SK4 due to a high degree of similarity with the other SK channels. A functional SK channel results from the coassembly of four subunits, each of them consisting of six transmembrane domains (S1–S6) with intracellular NH2 and COOH terminals (FIGURE 2C). The pore region (S5–S6) is the only homologous region to other families of K+ channels. It has been suggested that different subunits (SK1–SK3) could interact to form heteromultimers (54, 83). Moreover, native occurrence of such heteromeric association was suggested by the coimmunoprecipitation of SK2 and SK3 from mouse brain (109). Interestingly, this channel family lacks voltage sensitivity even with the presence of several charged amino acids in the fourth membrane-spanning domain. It is worth noting that the absence of a Ca2+-binding motif or sequence (Ca2+ bowl, EF-hand) would suggest insensitivity to [Ca2+]. However, recent work showed that CaM, a ubiquitous Ca2+-binding protein, is tethered to the proximal COOH terminus of each subunit (FIGURE 2D) and confers the channel's sensitivity to cytoplasmic calcium within the submicromolar range (36, 104, 105, 137). It has been suggested that CaM binding also regulates trafficking and assembly of SK channels (59, 70). No other subunits have been identified yet. The expression pattern of SK channels is quite different from the BK channel. In fact, SK channels are expressed in neurons, endothelium, epithelium, and several types of smooth muscles (e.g., urinary bladder) but not in VSMCs. However, SK4 was shown to be expressed in VSMCs, but only when the myocytes were in a proliferative state (87).

### Table 1. The pharmacology of BK channels

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<td>Auxiliary (\beta) (4)</td>
<td>Calmodulin (4)</td>
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<td>KCNN4</td>
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<td>Four (\beta) genes ((\beta_1\–\beta_4))</td>
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<td>Adrenal gland</td>
<td>Nonvascular SM</td>
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BK, large-conductance Ca2+-sensitive K+ channel; SK, small-conductance Ca2+-sensitive K+ channel; IK, intermediate-conductance Ca2+-sensitive K+ channel; SM, smooth muscle; CKII, casein kinase II; 1-EBIO, 1-ethyl-2-benzimidazolinone; DC-EBIO, 5,6-Dichloro-1-ethyl-1,3-dihydro-2H-benzimidazole-2-one; TEA+, tetraethylammonium ions; TRAM-34, 1-[(2-chlorophenyl)diphenylmethyl]-1H-pyrazole.
channel for Ca\(^{2+}\) suggests a highly cooperative binding of calcium ions. As expected, the half-maximal activation value (EC\(_{50}\)) of SK is \(\approx\) 300–500 nM [Ca\(^{2+}\)]\(_i\), similar to the EC\(_{50}\) values for CaM (15, 55). Note that a somewhat higher EC\(_{50}\) of 740 nM has been reported for SK4 in cultured mouse aortic endothelial cells (3). However, caution should be exercised when comparing data from cultured cells with native endothelium. Furthermore, high concentrations of Ca\(^{2+}\) and other divalent cations have been suggested to block the pore of cloned SK2 channels, but this remains to be demonstrated under physiological conditions (108).

The shadows

To our knowledge, there is no report of regulation (other than by calcium) of the SK channel family in the endothelium. The only studies reporting enzymatic regulation of SK channel activity originate either from heterologous expression systems or from tissues other than endothelial cells. Stimulation of the human cloned SK4 by PKA has been reported but does not involve a direct phosphorylation of the channel (39, 40). Similar results were reported for rat acinar cells and human erythrocytes (47). The widely expressed PKC was also shown to stimulate SK currents in erythrocytes and cultured cells (29, 133). In 2004, Bildl et al. (13) showed that a phosphorylation by the colocalized casein kinase II (CKII) reduces the calcium sensitivity and accelerates SK2 channel deactivation in brain. Interestingly, CKII seems to phosphorylate the associated CaM instead of the pore-forming protein itself (13). These authors suggested that the SK2 channel is part of a complex including CKII and protein phosphatase 2A. Moreover, the same phosphatase has been suggested to regulate SK3 in human brain (119).

Estrogen treatment has been shown to increase SK3 expression in guinea pig brain (16) and an estrogen-stimulated genomic determinant for rat SK3 expression has been identified (56), supporting the idea that estrogen may regulate SK channel expression in endothelium as well. However, additional studies on the endothelium are required to generalize the concept that estrogen status modulates SK expression.

Pharmacology

From a pharmacological perspective, the SK family can be divided into two groups: the SK1–SK3 subfamily and SK4. The first subgroup is highly sensitive to the bee venom toxin apamin with distinct affinity for all three isoforms, SK2 being the most sensitive and SK1 the least. Scyllatoxin and other compounds such as biccuculline, dequinalium, and its more potent derivative UCL 1684 are also potent inhibitors of this group (33, 110). Although SK4 is insensitive to those peptides and molecules, other compounds inhibit this channel without affecting the SK1–SK3 subfamily. For instance, SK4 current is decreased by the scorpion toxin charybdotoxin, which also inhibits BK channels. Other compounds like clotrimazole and 1-[2-chlorophenyl)diphenylmethyl]-1H-pyrazole (TRAM-34) are more specific inhibitors of SK4 channels (112, 134). On the other hand, all SK channels are stimulated by chlorzoxazone, zoxazolamine, the neuroprotective drug riluzole, 1-ethyl-2-benzimidazolone (1-EBIO), its derivative 5,6-dichloro-1-ethyl-1,3-dihydro-2H-benzimidazole-2-one (DC-EBIO), and, as more recently reported, NS-309 (1, 23, 111, 112). However, these stimulators cannot substitute for the absolute requirement of calcium for SK channel activation. Moreover, an increase in apparent channel sensitivity to calcium was suggested as mechanism of action of 1-EBIO and riluzole (24, 91).

Smooth Muscle BK Channels Regulate Vascular Tone and Blood Pressure

Resistance arteries exist physiologically in a partially constricted state, from which they constrict further or dilate, to respond to the perfusion needs of the tissue or organ. A major physiological stimulus for constriction is intravascular pressure (referred to as “myogenic tone”) (11). Resistance arteries respond to an elevation in intravascular pressure by a graded membrane depolarization, elevation in [Ca\(^{2+}\)]\(_i\), and constriction, which is dependent on the increased calcium entry through VDCC (86). A number of negative feedback mechanisms are linked to the increase in VSMC [Ca\(^{2+}\)]\(_i\), including the activation of BK channels (17). For example, in cerebral artery myocytes, calcium sparks activate BK channels and therefore play an important role as a negative feedback element in the regulation of pressure-induced constrictions (64, 85).

Block of BK channels by iberiotoxin induces a membrane depolarization, followed by an elevation of [Ca\(^{2+}\)]\(_i\), and vasoconstriction (17, 18, 64).

Moreover, evidence suggests that BK channels also play a role in vasoconstriction as they are inhibited by the potent vasoconstrictors angiotensin II (121) and thromboxane A2 (106) in bilayers. Later reports have shown that an agonist-induced contraction may involve tyrosine phosphorylation of BK leading to inhibition of the channel (52). Furthermore, Alioua et al. (5) further demonstrated that 5-HT and angiotensin II contractions involve BK channel inhibition by the tyrosine kinase c-Src.

Endothelial SK Channels Regulate Vascular Tone and Blood Pressure

The vascular endothelium plays a key role in the regulation of vasoconstrictor tone through the release of vasoconstrictors (endothelin) and through the tonic production and release of NO, PGI2, and EDHF. The identity of EDHF has been a matter of debate for many years, but it seems now that EDHF is an amalgam of...
mechanisms and compounds that differ depending on vascular beds and species. However, several lines of evidence suggest Ca\(^{2+}\)-activated K\(^+\) channels as an important component of the EDHF response in various vascular beds (21). The increase of [Ca\(^{2+}\)]\(_i\) in endothelium induced by acetylcholine or other vasodilators is generally followed by relaxation of the artery even when NO and PGI\(_2\) production is inhibited. SK and IK channels are clearly involved in the EDHF-induced vasodilation. Membrane potential hyperpolarization induced by SK channels opening would further increase calcium influx in endothelial cells by increasing the electrochemical gradient for calcium. The combination of charybdoxin and apamin has been reported to inhibit vasodilation of arteries induced by acetylcholine, substance P, and other endothelial-mediated vasodilators (20, 22, 34, 35, 41). Furthermore, selective intraluminal application of SK channel inhibitors is able to inhibit EDHF (32, 125). Also, application of 1-EBIO induces an hyperpolarization of the endothelium that is associated with a relaxation of the arteries (34, 75, 127). Recently, suppression of SK3 channel expression has been demonstrated to increase arterial tone and blood pressure in a reversible manner (118). Furthermore, SK3 channels appear to be expressed by vascular endothelium but not in smooth muscle (118). Collectively, these findings indicate that endothelial SK channels play a key role in the regulation of vascular tone and may represent an important pharmacological target, particularly since their vascular expression is exclusive to the endothelium.

**Conclusions: Role in Disease and Therapeutic Potential**

The critical influence of Ca\(^{2+}\)-activated K\(^+\) channels in both endothelium and smooth muscle cells suggests an involvement in cardiovascular diseases. Indeed, the prevalence of hypertension increases with age, and this is correlated with a reduction of BK channel expression (74, 88). A number of recent findings support the importance of the smooth muscle BK channel in the regulation of vascular tone and blood pressure. Ablation of the gene for the smooth muscle specific \(\beta_1\)-subunit of the BK channel leads to an increase in vascular tone and hypertension, accompanied by left-ventricular hypertrophy in mice (73). In 2004, Fernández-Fernández et al. (37) reported a mutation of the human \(\beta_1\) gene leading to a gain of function of the BK channel associated with a low incidence of human diastolic hypertension. Moreover, \(\beta_1\) relative to the \(\alpha\)-subunit expression is downregulated in chronically hypertensive rats (6). Consistent with the effects of the \(\beta_1\) subunit knockout, ablation of the \(Slo\) gene leads to an increase in vascular tone and hypertension (98) as well as other pathologies such as ataxia (99), urinary incontinence (79), and erectile dysfunction (132). In addition, reactive oxygen species were shown to inhibit BK channel activity, revealing a molecular basis for a vascular dysfunction involving oxidative stress (116). These findings provide a solid rationale for a potential use of selective BK channel openers in the prevention and treatment of cardiovascular disorders.

Drugs promoting SK channel opening or expression might represent a novel and important therapeutic strategy for hypertension. SK3 and IK channels are expressed in vascular endothelium, and suppression of expression of SK3 channels leads to an elevation of blood pressure (118). Attenuated vasoconstrictor responses in rats with cirrhosis are associated with elevated endothelial SK channel expression (65), and blunted endothelium-dependent vasodilation of carotid arteries after balloon catheter injury appear to be linked to decreased SK3 and IK expression in regenerated endothelial cells (10). As recently reported, SK4 blockers suppress proliferation of endothelial cells and angiogenesis, and SK4 channels are expressed in proliferative smooth muscle cells (43, 87); these findings suggest SK channels as a potential therapeutic target for restenosis (66). The presence and crucial functions of SK4 channels in erythrocytes and lymphocytes and SK1–SK3 channels in the brain support the impetus for the development of specific cardiovascular drugs for vascular BK channels and for endothelial SK3 and IK channels (107, 134). Development of such drugs could have significant impact on future approaches aimed at prevention and treatment of cardiovascular disease.

**References**

REVIEWS


