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REVIEW

BK_{Ca} channels as physiological regulators: a focused review

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Abstract: Large-conductance Ca^{2+}- and voltage-gated big K^+ (BK_{Ca}, MaxiK, or Slo1) channels are expressed in almost every cell of mammalian tissues and participate in a multitude of physiological processes such as vascular tone regulation, neuronal excitability, neurotransmitter release, neurovascular coupling, bladder tone regulation, urinary K^+ excretion, and retinal circulation. BK_{Ca} channel is a tetramer of the pore-forming α-subunit encoded by a single gene, *Slo*. The BK_{Ca}-α-subunits are associated with the modulatory β-subunits, which contribute to the functional diversity of the channel. BK_{Ca} channels sense and regulate membrane voltage and intracellular Ca^{2+}, which then modulates several cell signaling and metabolic pathways. This review focuses on the main physiologic roles of BK_{Ca} channels and the pathogenesis of diseases associated with their loss or malfunction. The mechanistic information highlighted in this review is aimed to enhance the understanding of the unique and diverse roles of BK_{Ca} channels in various physiological and pathophysiological phenomena.

Keywords: neurovascular coupling, large conductance calcium, Ca^{2+}-activated potassium channels, BK_{Ca} channel physiology

Introduction

Calcium (Ca^{2+})-activated potassium channels (K_{Ca}) or the channels possessing large conductance (BK_{Ca}, MaxiK, $K_{Ca}1.1$) are mainly characterized by a high unitary conductance of ~100–300 pS.[1] Unlike other subfamilies of K_V, BK_{Ca} channels are both voltage- and Ca^{2+}-regulated potassium channels. The native BK_{Ca} channel is formed by four pore-forming subunits (α) that are encoded by the *Slo1* gene.[1–3] Splicing of the *Slo1* messenger (m)RNA has been shown to contribute to differences in the regulatory properties of the channel as a result of variability in the responses to steroids and the availability of the phosphorylation sites. Furthermore, studies have demonstrated the contributory role of different splice variants between tissues in voltage sensitivity of the channels.[4] Importantly, the splice variation of an α-subunit may significantly alter the localization of BK_{Ca} channels to endoplasmic reticulum.[2–7]

BK_{Ca} channels belong to the family of voltage-gated potassium channels.[5–7] However, BK_{Ca} channels are also known to be activated solely by a stimulus-evoked increase in intracellular Ca^{2+} concentrations ($[Ca^{2+}]_i$). Interestingly, the resultant large efflux of K^+ ions through the activation or opening of BK_{Ca} channels repolarizes the membrane, closes the voltage-gated calcium channels (VGCC), and reduces Ca^{2+} influx into the cells.[8–12] The properties of BK_{Ca} channels therefore integrate various cellular and molecular signaling events via modulation of membrane excitability and Ca^{2+} homeostasis.

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BK_{Ca} channels have also been outlined as negative feedback regulators of membrane potential and Ca^{2+} homeostasis in numerous physiological processes (Figure 1). These include modulating neurotransmitter release,[8] neurovascular coupling,[13] regulating vascular and respiratory tone,[14,15] endocrine secretion,[16,17] interspike interval and spike frequency adaptation,[8] and urinary bladder tone.[18] Given their relevance in essential physiological processes, these channels are encoded by a substantial number of genes in higher organisms. BK_{Ca} channels are implicated in several disease conditions including epilepsy,[19] diabetes,[20] Alzheimer's disease,[21] subarachnoid hemorrhage,[22] neuromuscular abnormalities,[23] motor impairment,[24] hypertension,[14,25] urinary incontinence,[26] overactive urinary bladder,[27,28] and noise-induced hearing loss.[29] This review discusses the scientific know-how on BK_{Ca} channels serving as a key regulator in various physiologic and pathophysiologic processes.

BK_{Ca} channel structure and properties

The native BK_{Ca} channel is composed of four α- and four β-subunits, present in a 1:1 ratio (Figure 2).[30,31] The α-subunit contains seven putative transmembrane-spanning α helical segments and is accountable for the ion conduction, for selectivity, and for sensing the voltage alteration.[32] The cytoplasmic carboxy tail contains two intrinsic high-affinity Ca^{2+} binding sites and phosphorylation sites and has been implicated in the direct gating of the channel. The β-subunit is composed of two transmembrane domains with a long extracellular linker, whereas the amino- and carboxy-terminals are located in the cytoplasm. BK_{Ca}-β-subunits have been shown to influence the Ca^{2+} sensitivity of channel gating[33–36] and trafficking of channels to the plasma membrane.[13,37,38] Evidence clearly shows that although BK_{Ca} channels exist in differing subunit stoichiometries, a full complement of four β1-subunits is crucial for the optimal effect of the channel.[39] Differences in subunit stoichiometry, isoform expression, degree of phosphorylation, or the expression of splice variants may result in channels of varying voltage, Ca^{2+}, and stress sensitivity and selectivity (Figure 2). Furthermore the spatial localization of BK_{Ca} channels has also been reported to influence its function within a given tissue. Interestingly, an efficient activation of BK_{Ca} channels (by locally produced Ca^{2+} transients or sparks) requires a

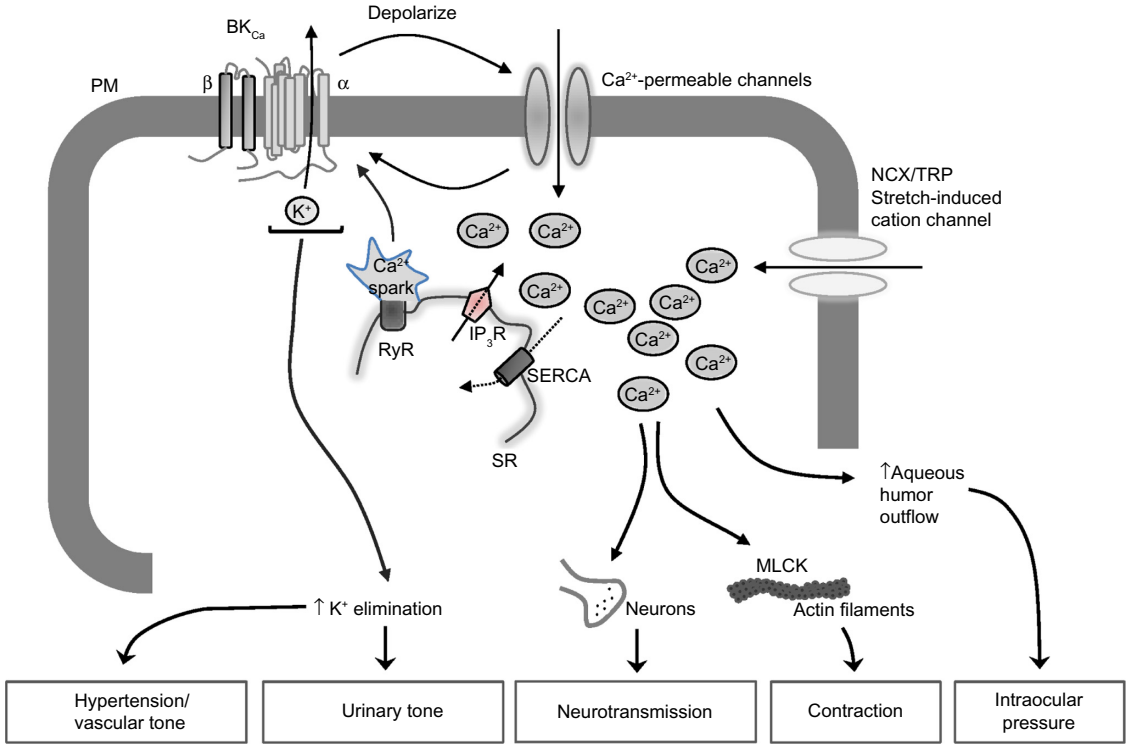

Figure 1 Signaling pathway downstream of BK_{Ca} channels involved in the regulation of various physiological processes.
Notes: BK_{Ca} channels mediate membrane potential changes that regulate Ca^{2+} channels. Intracellular stores of Ca^{2+} released to the cytosol via the ryanodine receptor of the sarcoplasmic reticulum activate BK_{Ca} channels. An increase in the intracellular Ca^{2+} levels and an increase in the elimination of K^+ regulate several physiological processes, including vascular tone, neurotransmission, intraocular pressure, and urinary bladder tone.
Abbreviations: BKCa, large conductance calcium-activated potassium channels; PM, plasma membrane; RyR, ryanodine receptor; IP_3R, inositol 1,4,5 triphosphate receptor; SERCA, sarcoendoplasmic reticulum ATPase; SR, sarcoplasmic reticulum; NCX, sodium–calcium exchanger; TRP, transient receptor potential channel; MLCK, myosin light chain kinase.

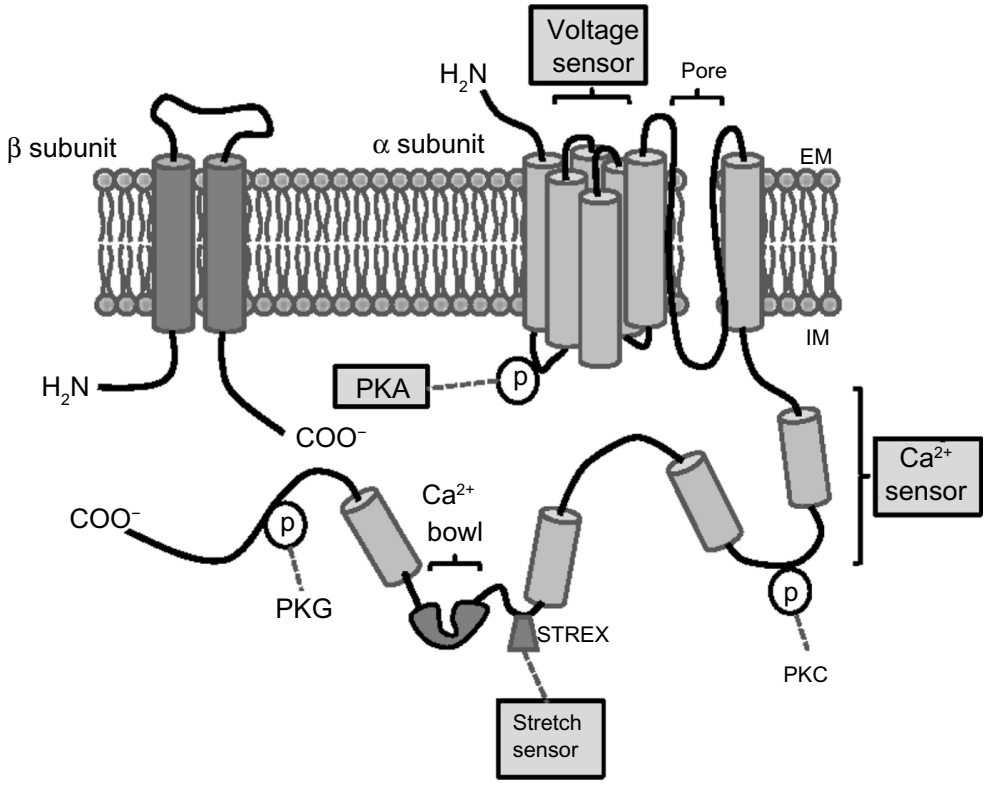

Figure 2 Structure and regulation of BK$_{Ca}$ channel.
Notes: Schematic diagram representing the threading of BK$_{Ca}$ channel subunits (α and β) through the plasma membrane. Agonist-mediated stimulation leads to the activation of PKA, PKC, and PKG and to the phosphorylation of the subunits, an important mechanism through which BK$_{Ca}$ channel modulates physiological process. Cytoplasmic C-terminal domain consists of four primary Ca^{2+} binding sites, called the "Ca^{2+} bowl". The domains sensitive to voltage, Ca^{2+}, and stretch are also depicted.
Abbreviations: BKCa, large conductance calcium-activated potassium channels; PKA, protein kinase A; PKG, protein kinase G; EM, extracellular side of plasma membrane; IM, intracellular side of plasma membrane; STREX, hormonal stress axis exon; PKC, protein kinase C; p, phosphate binding site.

close proximal arrangement between sarcoplasmic reticulum (SR) and plasma membrane (PM). It is interesting to note that this spatial arrangement is usually observed in smooth muscle and endothelial cells where the SR/endoplasmic reticulum (ER) is close to PM invaginations.[40] In fact, the α-subunit of BK$_{Ca}$ is known to contain two Caveolin (Cav) binding domains and is associated with Cav-1 and Cav-2 in endothelial cells.[41] It is likely that the binding of BK$_{Ca}$ channels to Cav-1/2 proteins or its localization in caveolae may facilitate its association with other signaling partners, either directly or indirectly, such as c-Src tyrosine kinase,[42] nonselective cation channels, the *Trp* family of proteins,[43] the G-protein-coupled receptor-mediated signaling cascade,[44] and actin filaments,[41,45] to mention a few.

The association of BK$_{Ca}$ channels with specific membrane domains has also been implicated in the functional coupling of this channel to other ion channels, including nonselective cation channels, transient receptor potential and VGCC.[46,47] Thus, the BK$_{Ca}$ channel serves as a physiological regulator in association with other proteins. Proteomic analysis of BK$_{Ca}$ channel binding partners in mouse cochlea revealed that 50% of the proteins have affiliations with K^+ and Ca^{2+} channels, whereas almost 20% of the proteins are related to mitochondria,[26] suggesting a potential role of BK$_{Ca}$ channels in many aspects of cellular and molecular dynamics. Therefore, it is imperative to delineate the structure, localization, and function of these channels to develop new and effective treatment strategies.

BK$_{Ca}$ channels regulation of vascular tone

Vascular tone in small arteries and arterioles is the major determinant of vascular resistance in response to several stimuli, including myogenic (pressure) components and vasoactive agents.[14] Myogenic constriction is a characteristic of resistance blood vessels and plays an essential role in regulating microcirculation blood flow, providing the basal tone in resistance arteries. Increased myogenic constriction has been reported in several hypertensive models and is associated with vascular diseases.

The organs that have a higher vascular tone (eg, myocardium, skeletal muscle, skin, splanchnic circulation) exhibit

large vasodilatory capacity, whereas those having relatively low vascular tone (eg, cerebral and renal circulation) have low capacity. A noticeable exception to this rule is cerebral vasospasm occurring after subarachnoid hemorrhage. The blood vessels, both arterial and venous, exhibit some degree of vascular smooth muscle contraction under basal conditions, which determines the tone, and hence the diameter, of the vessel.[48] Baseline $[Ca^{2+}]_i$, vasoconstrictor-mediated increase in $[Ca^{2+}]_i$, and Ca^{2+} sensitivity significantly contribute to the contractile state of the blood vessel wall. These processes are orchestrated via different ion channels (K^+, Cl^-, and nonselective cation channels), which govern the membrane potential and affect the Ca^{2+} influx and VGCC activity. The Ca^{2+} flux that activates K^+ channels (mainly BK_{Ca}) indirectly hyperpolarizes the membrane, promoting the closure of VGCC. The Ca entry occurring in the vicinity of ryanodine receptors on sub-plasma membrane endoplasmic reticulum is key because the Ca^{2+} sparks generated by the ryanodine receptor "event" are linked to plasma membrane BKCa opening and the extrusion of K^+ (Figure1). Thus, BK_{Ca} channels serve as a counter-regulatory mechanism by reverting vasoconstriction, particularly in the intense myogenic constriction of resistance vessels exposed to high intraluminal pressures.[14,15] Therefore, BK_{Ca} channels are the key regulators in protecting excessive vasoconstriction through a Ca^{2+}-dependent relaxation mechanism.

The function of BK_{Ca} channels, especially in vascular smooth muscle cells, is finely tuned by its regulatory β1-subunit through enhancing the channel for its Ca^{2+} sensitivity. Using BK_{Ca}-$\beta1^{-/-}$ mice[49] and insulin-resistant hypertensive rat models,[50–52] studies have revealed an increase in arterial blood pressure and left ventricular hypertrophy. Interestingly, the lack of functional β1-subunit altered the coupling between Ca^{2+} signaling and membrane potential changes. Furthermore, pharmacological studies blocking BK_{Ca} channels have demonstrated an increase in the decaying conduction of a local depolarization, which basically represents the junctional and plasma membrane resistance.[50] A decrease in expression of β1-subunit of the BK_{Ca} channel has also been reported in coronary artery aging in humans and rats.[53,54]

BK_{Ca} channels are also present in endothelial cells,[14,41,55–58] where they contribute to hyperpolarization,[59] participate in endothelial-dependent vasodilation,[60] and improve endothelial dysfunction.[61–63] Interestingly, studies specifically designed to target endothelial BK_{Ca} channels with luminal administration of the specific blocker iberiotoxin in arteries demonstrated the restoration of vasoconstrictor responsiveness and the normalization of the membrane potential to control levels,[64] suggesting an involvement of endothelial BK_{Ca} channels in vessel reactivity. Furthermore, recent studies have shown a cholesterol-dependent activation of BK_{Ca}, suggesting the role of Cav-1 in the regulation of its activity.[65] However, the exact mechanisms by which Cav-1 proteins or the caveolae invaginations may affect either the localization of BK_{Ca} channels to the plasma membrane or the downstream signaling molecules, such as nitric oxide synthase, are still not clear.

BK_{Ca} channels have also been involved in coronary artery vasodilation,[66–69] mainly through the endothelium-mediated stimulation-dependent responses of coronary artery smooth muscle cells (CASMCs).[70–74] The mediators, termed endothelium-derived hyperpolarizing factor, released from endothelial cells activate BK_{Ca} channels in CASMCs.[75,76] Typically, substances that constrict coronary vessels inhibit BK_{Ca} channels in CASMCs, including angiotensin II,[77,78] endothelin 1,[75,79] and thromboxane A2.[80] Inhibition of BK_{Ca} channels by these G-protein-coupled receptors may alter several of the downstream signaling cascade, mainly protein kinase C[44], c-Src kinase,[42] and so on. However, studies designed to explore the role of BK_{Ca} channels in ischemic[81] and metabolic vasodilation[82] showed no or little effect. Nevertheless, alterations in the activity of BK_{Ca} channels were demonstrated in several vascular pathologies, including diabetes,[20,83,84] atherosclerosis and ischemia,[85] hypertension,[25,51,76] cardiac hypertrophy,[15] and cardiomyopathy.

BK_{Ca} channels in neuronal excitability and neurotransmitter release

BK_{Ca} channels are ubiquitously expressed in the central nervous system, and their expression is highly variable within different brain regions. BK_{Ca} channels play an important role in regulating neurotransmitter release at central nervous system nerve terminals, controlling action potential duration, firing frequency, and spike frequency adaptation, resulting in fast after-hyperpolarization.[8] Studies intended to explore the regional distribution and the level of expression have revealed that BK_{Ca} channels are preferentially located at the axon terminals[11,86] and dendrites.[87,88] In neurons, the main functions of BK_{Ca} channels are to generate the fast and prolonged after-hyperpolarization (lasting from hundreds of milliseconds to seconds) after an action potential. Prominently, the generation of after-hyperpolarization contributes significantly to the maintenance of the shape and duration of the action potential.[89]

BK_{Ca} channels are primarily activated in response to elevations in $[Ca^{2+}]_i$ through the opening of voltage-dependent[87] or neurotransmitter-gated[90] Ca^{2+} channels, as well as by release of Ca^{2+} stores.[91] The activation of BK_{Ca} channels by rise in $[Ca^{2+}]_i$ shifts the activation voltage concentration dependently into a physiological range by limiting the depolarization-induced bursting activity. In contrast, in Purkinje cells, which lack BK_{Ca} channels, the net result is a less-negative resting membrane potential and decreased amplitude of the after-hyperpolarization.[92]

Several studies point to a possible functional coupling between BK_{Ca} channels and voltage-gated Ca^{2+} channels in the central nervous system. It is clear that in several types of neurons, BK_{Ca} channels are physically associated with voltage-gated Ca^{2+} channels and that this complex invariably provides a mechanism by which micromolar concentrations of $[Ca^{2+}]_i$ (calcium sparks) are delivered to BK_{Ca} channels and tightly control their activity without affecting other Ca^{2+}-dependent signaling processes. Moreover, the characteristics of BK_{Ca} channels are largely determined by the specific subunit of voltage-gated Ca^{2+} channels to which they are associated and adapt BK_{Ca} channel function to the requirement of particular neurons or neuronal subcompartments. Interestingly, blocking voltage-gated Ca^{2+} channels correspondingly inhibits BK_{Ca} channels, as observed in conditions in which extracellular Ca^{2+} was removed. In lieu of voltage-gated Ca^{2+} channels bound to BK_{Ca}, these channels have also shown to be operated by more distant Ca^{2+} sources or by a global increase in $[Ca^{2+}]_i$. This functionality of BK_{Ca} channels has originated the term free BK_{Ca}. Free BK_{Ca} channels are well demonstrated in chromaffin cells[93,94] and in CA3 pyramidal cells,[11] where submillimolar concentrations of ethylene glycol tetraacetic acid inhibit the activity of BK_{Ca} channels. The free BK_{Ca} channels are believed to serve as an emergency brake in situations where extraordinarily large Ca^{2+} transients lead to cellular damage or apoptosis.[11]

Given their role in controlling neuronal excitability, BK_{Ca} channels have been increasingly implicated in several neurological disorders, including epilepsy, cerebellar ataxia, and paroxysmal movement disorders.[95–97] In epilepsy, studies have indicated a missense mutation ($^{D}434^{G}$) in the α-subunit BK_{Ca} gene, which is characterized by an increase in the BK_{Ca} channel's sensitivity to Ca^{2+} and increased membrane currents, resulting in a gain-of-function effect.[98,99] Furthermore, this mutation, also observed in the pathophysiology of idiopathic absence epilepsy, confers specific changes in the regulatory properties of the BK_{Ca} channel subunits. However, a loss-of-function BK_{Ca} channel phenotype was demonstrated to be associated with temporal lobe epilepsy, where a polymorphism in the BK_{Ca}-β4-subunit was revealed.[101] Moreover, loss-of-function BK_{Ca} channel has been implicated in tonic-clonic seizures and alcohol withdrawal seizures. Thus, both loss-of-function and gain-of-function BK_{Ca} channels might serve as molecular targets for drugs to suppress certain seizure phenotypes, including temporal lobe seizures and absence seizures, respectively.

BK_{Ca} channels in mitochondria

Channel activity similar to that of plasma membrane BK_{Ca} channels have been reported in the inner membrane of mitochondria (mitoBK_{Ca}). The mitoBK_{Ca} was initially found in the glioma cells[102] and later in cardiac myocyte[103] and rat brain neurons.[100] Several observations confirmed the existence of BK_{Ca} channel β4-subunit in the inner membrane of neuronal mitochondria.[104] The changes in the cytosolic Ca^{2+} concentration greatly affect neuronal cell metabolism via modulating mitochondrial response. Skalska et al[105] have clearly demonstrated a Ca^{2+}-induced dissipation of mitochondrial membrane potential, an underlying process for mitochondrial respiration, metabolism, and viability. Thus, the studies delineating the presence of mitoBK_{Ca} in neurons, its contribution to mitochondrial Ca^{2+} signaling, and mitochondrial membrane potential changes support the neuroprotective role of mitoBK_{Ca} in specific brain structure.

BK_{Ca} channels in neurovascular coupling

Neuronal activity is thought to communicate to arterioles in the brain to promote an adequate blood supply. This phenomenon is known as neurovascular coupling and employs multiple mechanisms, including, but not limited to, purinergic signaling, cytochrome P450 products, cyclooxygenase products, and K^+. One of these mechanisms is through astrocytic Ca^{2+} signaling to cause local vasodilation in the activated brain area. In particular, K^+ released from astrocytic end feet via BK_{Ca} channels is thought to interact with K^+ inward rectifier channels on pial arteriolar smooth muscle cells, inducing hyperpolarization and relaxation.[13,106]

Paradoxically, this communication may cause vasoconstriction in some cases. Modest increases in Ca^{2+} induce dilation, whereas larger increases switch dilation to constriction.[107] BK_{Ca} channels in astrocytic end feet are believed to mediate the majority of the dilation and the entire vasoconstriction, implicating local extracellular K^+ as a vasoactive signal for both dilation and constriction. Therefore, BK_{Ca} channels at the astrocytic end foot are able

to determine both arteriolar dilation and constriction based on the $[Ca^{2+}]_i$ changes.

Interestingly, BK_{Ca} channel dysfunction has been recently associated with pathophysiologic changes occurring during type 1 diabetes mellitus.[20] In particular, a significant decrease in the pial arteriolar dilations evoked by somatosensory activation, via sciatic nerve stimulation, was found in streptozotocin-treated diabetic rats. This depressed neurovascular coupling response is likely linked to PKC-mediated changes in BK_{Ca} and K^+ inward rectifier channel activity, as normal dilating responses of pial arterioles to sciatic nerve stimulation and applications of K^+-channel openers were readily restored by acute PKC inhibition. Interestingly, in a model of type 2 diabetes mellitus, whole-cell currents of BK_{Ca} channels were significantly decreased in cerebral artery smooth muscle cells, compared with control, and the sensitivities of BK_{Ca} channels to voltage, paxilline, and NS1619 were all diminished in diabetic rats.[108]

BK_{Ca} channels in regulating retinal circulation

Vertebrate retinas share the same fundamental neuronal organization, comprising various cell classes such as photoreceptors, bipolar cells, amacrine cells, and ganglion cells. The retina receives oxygen and nutrients diffused from the choriocapillaries to the rods, cones, and nerve layers in the inner retina. Therefore, to preserve the delicate balance between the flow of blood and the needs of the retinal nerve layers, the vasculature of the retina is designed to maximize the control of capillary perfusion.

Several lines of evidence have demonstrated the existence and functional role of BK_{Ca} channels in rod signaling.[109] In addition, BK_{Ca} channels have been shown to be located at the synaptic terminal, contributing to the amplification of glutamate release at the rod photoreceptor synapse.[110] The signaling of BK_{Ca} channels in the cone pathway is poorly studied compared with the rod pathways. Work by Yagi and Macleish[111] has hinted at the absence of BK_{Ca} channels in the cones of the primate retina. However, blocking BK_{Ca} channels induced a reduction in light-evoked input from bipolar cells and amacrine cells to ganglions in mouse retina,[112] thus suggesting a possible existence of BK_{Ca} channels in the cone pathway in rodents. Furthermore, genetic deletion of BK_{Ca} channels has been shown to affect the photoreceptor and bipolar cell responses in mouse retina.

Moreover, recent studies have shown the contributions of BK_{Ca} channels in the regulation of retinal blood flow via the action of several vasodilators in endothelium and vascular smooth muscle.[113] Administration of a BK_{Ca} channel opener (BMS-191011) to male Wistar rats specifically improved retinal circulation without affecting cardiovascular functions.[114] Studies in diabetic retinal models demonstrate a decreased Ca^{2+} sensitivity of BK_{Ca} channels and an uncoupling of BK_{Ca} channel activation from Ca^{2+} release in diabetic retinal vascular smooth muscle cells.[115] The drastic reduction in spontaneous Ca^{2+} sparks results in delayed activation of BK_{Ca} channel-mediated K^+ outward currents, an underlying process for arteriolar vasoconstriction, as commonly observed in retinal diseases, mainly diabetic retinopathy.[115–117] Hitherto, studies delineating the roles of BK_{Ca} channels in retinal circulation and physiology have been unclear. More detailed investigations are warranted to enhance the understanding of the significance of BK_{Ca} channels in retinal circulation physiology.

BK_{Ca} channels in the urinary system

Maintenance of K^+ concentration within the physiological range is vital for various cellular functions, including cell volume regulation and regulation of membrane electrical properties. The kidney is the primary site where balancing K^+ concentration and K^+ secretion in the distal convoluted tubules of nephron is critical for determining the amount of K^+ excretion. Several segments of the distal convoluted tubules of nephron have been shown to express BK_{Ca} and renal outer medullary K^+ channels. Although renal outer medullary K^+ channels are considered the primary channels involved in K^+ secretion because of their open probability, BK_{Ca} channels are suggested to contribute to the volume regulation in the distal convoluted tubules of nephron.

BK_{Ca} channels have been reported in a variety of renal cell types, including urinary bladder smooth muscle cells,[118] afferent arterioles,[119] glomerular mesangial cells,[120,121] and visceral epithelial cells (podocytes) in the Bowman's capsule.[3] BK_{Ca} channels have been demonstrated to be negative feedback, counteracting agonist-induced contraction, mainly in mesangial cells.[120,121] BK_{Ca} channels act as a conduit of K^+ secretion in the distal convoluted tubules, medullary, and cortical thick ascending limbs,[122] distal connecting tubules,[123] and cortical collecting ducts.[124] Investigations on BK_{Ca}-$\beta1^{-/-}$-subunit knockout models failed to demonstrate an increase in flow-mediated K^+ secretion, whereas BK_{Ca}-$\alpha1^{-/-}$ mice showed diminished capacity to secrete K^+,[125] suggesting the significance of the β1-subunit in maintaining a proper renal kaliuretic function via regulating flow-mediated K^+ secretion.[19,126] This may also be explained by the activation of BK_{Ca} channel activation in response to cyclic guanosine

monophosphate and nitric oxide synthase through the protein kinase G (PKG) pathway. Activation of BK$_{Ca}$ by PKG via its β1-subunit[127] synergistically increases BK$_{Ca}$ currents under conditions of increased flow via enhancing the Ca^{2+} sensitivity of the channel.[35]

In addition to mediating flow-induced K^+ secretion, BK$_{Ca}$ channels in the distal nephron have been demonstrated to respond to arginine vasopressin via the PLC/Ca^{2+}/PKC signaling pathway. Furthermore, BK$_{Ca}$ channels have also been shown to play a role in the renal response to aldosterone and/or a high-K^+ diet. Studies using iberiotoxin, a specific BK$_{Ca}$ channel blocker, confirmed the inhibition of renal K^+ secretion associated with a high-K^+ diet.[128] Interestingly, a study by Najjar et al[129] using the isolated, perfused cortical collecting duct from rabbits administered a high-K^+ diet showed an increase in the expression of BK$_{Ca}$ channels in the apical membrane. However, it is not clear whether an accelerated K^+ secretion on high K^+ diet is a result of an effect of aldosterone on BK$_{Ca}$ channel activity or its localization to the cell membrane.

BK$_{Ca}$ channels have also been shown to play an important role in regulating urinary bladder smooth muscle function, which is associated with urinary frequency and overactive bladder. Overactive bladder is a common pathologic condition resulting from the alteration of detrusor muscle excitability linked to several myogenic and neurological factors.[130] BK$_{Ca}$ channels are predominantly involved in the relaxation of bladder smooth muscle.[131] Therefore, decreased expression of BK$_{Ca}$ channels, mainly in the bladder outlet, may result in alteration of sensory afferent activity leading to enhanced detrusor tone during urine storage.[130]

Physiological regulators of BK$_{Ca}$ channels

Studies in recent years have identified an enormous list of regulatory physiological mechanisms, which may serve as potential drug targets for interfering with BK$_{Ca}$ channel activity. Mechanisms modulating channel function include subunit composition,[132] phosphorylation,[132] palmitoylation,[133] and alternative splicing.[134,135] However, channel function may be affected at different levels, such as protein synthesis, cellular localization, and trafficking. Furthermore, several upstream signaling molecules participating in orchestrating the above mentioned regulatory mechanisms are the object of research. In general, any mechanisms that alter the presence or function of BK$_{Ca}$ channels in the plasma membrane may profoundly influence the magnitude of whole-cell BK$_{Ca}$ channel currents and, consequently, cell and tissue physiology.

In addition, investigations aimed to understand the molecular aspects of BK$_{Ca}$ channel activity have revealed various target sites of the channel protein. Several allosteric inhibitors were identified and developed to inhibit its activity and functions. Few of the inhibitors, namely, tetraethylammonium, the peptide inhibitors charybdotoxin and iberiotoxin, and the fungal alkaloids paxilline and lolitrem B are widely used in both in vitro and in vivo models. Among these, iberiotoxin is the best characterized inhibitor of BK$_{Ca}$ channel activity.[64,128,136] However, iberiotoxin was identified to have several limitations on its use in whole-animal experiments because of its low-activity against channels containing the β4-subunit,[137,138] as well as its impermeable nature across the cell membrane. The membrane-permeable fungal alkaloid paxilline has become widely used as a BK$_{Ca}$ channel inhibitor in molecular physiology because of its ability to block BK$_{Ca}$ channels complexes with β4-subunits.[139] More recently, however, another fungal alkaloid, lolitrem B, has been shown to be five times more potent at inhibiting BK channels in comparison with paxilline.[140,141] Seven lolitrem compounds have also been shown to be BK channel inhibitors.[142] Lolitrem B is the causative agent of ryegrass staggers, a nervous disorder of animals that graze perennial ryegrass infected with the endophytic fungi *Neotyphodium lolii*. Using a mouse model of ryegrass staggers, it has been shown that lolitrem B produces ataxia and tremors by inhibiting BK channels.[141] In addition to lolitrem B, this endophyte-grass symbiosis also produces other structurally related lolitrem analogues in which only minor structural changes have a dramatic effect on tremorgenicity.[143–145]

Summary

This review highlights the potential roles of BK$_{Ca}$ channels in regulating various physiological processes. Furthermore, the functional versatility of BK$_{Ca}$ channels conferred by the assembly of auxiliary subunits and alternative splicing of the pore-forming subunits has been addressed. The information provided in this review strongly suggests that the BK$_{Ca}$ channel, its subunits, and its associated proteins are promising targets for the regulation of various biological and physiological processes, and hence for the treatment of several diseases. This review addressed how the understanding of BK$_{Ca}$ channel-mediated mechanisms can be used therapeutically to treat or prevent several pathologies. More studies to understand the allosteric modulations of these channels or upstream mediators, which may result in both gain- and loss-of-function, will likely result in clinically relevant compounds. In addition, the identification of

BK_{Ca} channel subunit variants and their unique contribution to physiological processes is crucial to selectively target pathophysiological cascades.

Disclosure

The authors report no conflicts of interest in this work.

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