Published in final edited form as:
Expert Opin Ther Targets. 2011 November ; 15(11): 1283–1295. doi:10.1517/14728222.2011.620607.

Targeting BK (big potassium) Channels in Epilepsy

Prosper N'Gouemo
Interdisciplinary Program in Neuroscience and Department of Pediatrics, Georgetown, University Medical Center, Washington, DC 20057

Abstract

Introduction—Epilepsies are disorders of neuronal excitability characterized by spontaneous and recurrent seizures. Ion channels are critical for regulating neuronal excitability and, therefore, can contribute significantly to epilepsy pathophysiology. In particular, large conductance, Ca^{2+}-activated K^+ (BK_{Ca}) channels play an important role in seizure etiology. These channels are activated by both membrane depolarization and increased intracellular Ca^{2+}. This unique coupling of Ca^{2+} signaling to membrane depolarization is important in controlling neuronal hyperexcitability, as outward K^+ current through BK_{Ca} channels hyperpolarizes neurons.

Areas covered—This review focuses on BK_{Ca} channel structure-function and discusses the role of these channels in epilepsy pathophysiology.

Expert opinion—Loss-of-function BK_{Ca} channels contribute neuronal hyperexcitability that can lead to temporal lobe epilepsy, tonic-clonic seizures and alcohol withdrawal seizures. Similarly, BK_{Ca} channel blockade can trigger seizures and status epilepticus. Paradoxically, some mutations in BK_{Ca} channel subunit can give rise to the channel gain-of-function that leads to development of idiopathic epilepsy (primarily absence epilepsy). Seizures themselves also enhance BK_{Ca} channel currents associated with neuronal hyperexcitability, and blocking BK_{Ca} channels suppresses generalized tonic-clonic 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.

Keywords

Anticonvulsant; Epileptogenesis; Gain-of-function; Gene mutation; Loss-of-function; Seizures

1. Introduction

Epilepsies are disorders of neuronal hyperexcitability that are characterized by spontaneous and recurrent seizures. Seizure disorder etiologies are usually divided into idiopathic, cryptogenic and symptomatic forms. Idiopathic epilepsies are characterized by focal or generalized seizures that do not result from brain lesion or metabolic abnormality. Seizure predisposition is common in idiopathic epilepsies, and genetic defects including mutations in genes encoding for Ca^{2+}-dependent ion channels are important in the etiology of this neurological disease. Dysregulation of Ca^{2+} homeostasis and Ca^{2+} signaling are also important factors that contribute to epileptogenesis in acquired epilepsy including temporal lobe epilepsy (TLE).

Address correspondence to: Prosper N'Gouemo, PhD, Assistant Professor, Tel: 202-687-8464, Fax: 202-444-7161, pn@georgetown.edu.

Declaration of interest: The author declares no conflict of interest.

Potassium channels control the resting membrane potential and therefore play a critical role in regulating neuronal excitability. Based on their structure, biophysical characteristics, pharmacological sensitivities and physiology, K^+ channels are classified as voltage-gated (K_v), inwardly rectifying, Ca^{2+}-activated and tandem-pore K^+ channels. Potassium channels contribute to the pathophysiology of a broad range of neurological disorders. In particular, inherited dysfunctions of K_v channels, KQT-like subfamily, member 2 and 3, caused by gene mutations are known to contribute to the development of common idiopathic epilepsy syndromes in humans [1]. Also important to epilepsy causation is the large conductance, voltage- and Ca^{2+}-activated K^+ (BK_{Ca}) channels, which are gated by membrane depolarization and rise in intracellular Ca^{2+} ($[Ca^{2+}]_i$) levels. This unique feature of BK_{Ca} channels signaling to membrane depolarization is important for controlling neuronal hyperexcitability as the resulting outward K^+ current through these channels serves to repolarise or hyperpolarize the membrane. In addition, the exquisite sensitivity of BK_{Ca} channels to Ca^{2+} provides an important negative-feedback system for controlling Ca^{2+} entry into neurons, either by deactivating voltage-gated Ca^{2+} (Ca_v) channels or increasing the activity of the Na^+/Ca^{2+} exchangers, thus regulating Ca^{2+}-dependent processes.

Under physiological conditions, activation of neuronal BK_{Ca} channels contributes to action potential (AP) repolarization, gives rise to the fast afterhyperpolarization (fAHP) that follows the AP, shapes dendritic Ca^{2+} spikes and influences neurotransmitter release [2, for review]. Thus, activation of BK_{Ca} channels is an intrinsic inhibitory mechanism to counter membrane depolarization and the excessive accumulation of cytosolic Ca^{2+} that occurs during seizures. Accordingly, putative *loss-of-function* mechanisms of BK_{Ca} channels have been associated with TLE, as fAHP conductances (mainly mediated by BK_{Ca} channels) were reduced in epileptic patients [3]. Paradoxically, *gain-of-function* mutations in BK_{Ca} channel subunit genes actually contribute to the development of certain forms of idiopathic generalized epilepsy in humans [4]. Thus, both gain-of-function and loss-of-function BK_{Ca} channels are potentially important molecular targets for developing drugs to prevent epileptogenesis and suppress both temporal lobe seizures (TLS) and absence seizures.

This review summarizes our current knowledge of BK_{Ca} channel structure-function and discusses the contribution of BK_{Ca} channels gain-of-function and loss-of-function mechanisms to epileptogenic neuronal hyperexcitability, and their potential as therapeutic targets for epilepsy.

2. BK_{Ca} channels

2.1 Structure and biophysical characteristics of BK_{Ca} channels

When unitary conductance is determined from current-voltage plots in symmetrical $[K^+]$ (>100 mM), three groups of Ca^{2+}-activated K^+ channels can be distinguished: large conductance (100-300 pS; BK_{Ca}), intermediate conductance (25-100 pS; IK_{Ca}), and small conductance (2-25 pS; SK_{Ca}) channels [5, for review]. Unlike SK_{Ca} and IK_{Ca} channels, BK_{Ca} (also known as BK, Slo1, Big K^+, MaxiK or KCNMA1) channels are activated by both elevated $[Ca^{2+}]_i$ and membrane depolarization. The mechanisms of Ca^{2+} and voltage dependency of BK_{Ca} channels are independent, with each mechanism being able to increase the open-channel probability [6]. Under physiological conditions, BK_{Ca} channels have a low affinity for Ca^{2+} such that >10 μM $[Ca^{2+}]$i is required for channel activation [7]. This sensitivity of BK_{Ca} channels to Ca^{2+} is an important negative feedback mechanism for controlling Ca^{2+} entry and subsequent Ca^{2+}-dependent processes. Structurally, a minimal functional BK_{Ca} channel consists of four identical pore-forming α subunits, which determine the basic properties of unitary conductance, voltage- and Ca^{2+}-sensitivity, and channel opening probability. In most tissues, however, the BK_{Ca} channel α subunits are associated with up to three regulatory β subunits, whose expression are rather tissue-specific.

2.1.1 Pore-forming α subunit—The BK_{Ca} channel pore-forming α-subunit is encoded by the *KCNMA1* (human) or *Kcnma1* (mouse) gene [8]. Like Ca_v channels, voltage-gated Na^+ (Na_v) channels and other K_v channels, BK_{Ca} channel α subunits have six transmembrane segments (S1-S6) at the short extracellular N-terminus [5]. In addition, BK_{Ca} channels have a unique hydrophobic segment (S0) that leads to an exoplasmic N-terminus and additional four hydrophobic segments (S7-S10) in the large intracellular C-terminus [9]. The K^+-selective pore is located at the center of four α subunits and is surrounded by the voltage-sensing domain (S1-S4 segments) [10]. The acidic residues in S2 and S3 segments, together with basic (positively charged) residues in the S4 segment, confer voltage sensitivity to BK_{Ca} channels [10,11], and membrane depolarization causes movement of these charged residues, resulting in the opening (gating) of the K^+-selective pore [6,9,11]. The pore-forming motif is a loop between S5 and S6 segments that controls channel permeation and the S6 segment is believed to serve as the major structural determinant for the channel gate [12].

The intracellular C-terminal domain contains two regulators of conductance for K^+ (RCK1 and RCK2) domains and contributes to the physiological regulation of BK_{Ca} channels by Ca^{2+} and other intracellular stimuli [13,14,15]. The distal region (S9-S10 segments) or tail domain of the C-terminus contains the Ca^{2+} bowl, an aspartate-rich region that is a structural element of the RCK2 domain [13,15]. Each BK_{Ca} channel α-subunit contains two tandems RCK1-RCK2 domains [14], and the channel sensitivity to Ca^{2+} is determined by a “gating ring” of eight RCK domains from four assembled α subunits [13,15,16]. The BK_{Ca} gating ring has a wide central hole that allows ions to move freely between the conduction pore and the intracellular side [15]. Thus, BK_{Ca} channel gating occurs via two independent sensing mechanisms, one that is voltage-dependent in the N-terminus and the other one that is Ca^{2+}-dependent in the C-terminus.

BK_{Ca} channels have at least one low-affinity and two high-affinity Ca^{2+}-recognition sites. The high-affinity Ca^{2+} recognition sites are located in RCK1 domain [17,18] and in the Ca^{2+} bowl of RCK2 domain [13,15,19]. The low-affinity Ca^{2+} recognition site is located in the RCK1 domain, but its function has not been clearly established [17]; it is known, however, that under physiological conditions (in which $[Ca^{2+}]_i$ is in the range of a few hundred nanomolar to tens of micromolar), the low-affinity Ca^{2+}-recognition site(s) is not occupied by Ca^{2+} [20]. This observation suggests that this site could exert only a small effect (if any) in increasing the open-channel probability following an increase in $[Ca^{2+}]_i$.

In addition to membrane depolarization and increased $[Ca^{2+}]_i$, BK_{Ca} channels are also activated by intracellular Mg^{2+} [20,21] and the low-affinity Ca^{2+}-recognition site in RCK1 also mediates the channel's sensitivity to Mg^{2+} [20,21,22]. In addition, the Ca^{2+} bowl in RCK2 also binds Mg^{2+}, albeit with low-affinity [23]. BK_{Ca} channels are further regulated by intracellular H^+. Although some reports have conflicted, evidence shows that unlike other K_v channels, lowering [24] or increasing [25] intracellular pH, under defined conditions, enhances or decreases BK_{Ca} channel conductances, respectively. The RCK1 domain of BK_{Ca} channel also serves as the proton sensor [26], suggesting a common sensing domain for Ca^{2+} and protons. Other regulatory domains sites located in the C-terminus include phosphorylation sites for c-AMP-dependent protein kinase (PKA) and protein kinase C (PKC). Phosphorylation by PKA and PKC activates and inhibits BK_{Ca} channels, respectively [27]. Thus, metabolic factors can play an important role in controlling BK_{Ca} channel activity.

The BK_{Ca} channel *KCNMA1*gene is subjected to alternative splicing that results in number of transcription variants. Alternatively spliced BK_{Ca} channel variants exhibit both Ca^{2+} and voltage sensitivity [28]. Multiple sites of alternative splicing in the *KCNMA1* gene have

been identified, with the majority being located within the C-terminus. Interestingly, two splice isoforms of the *KCNMA1* gene are expressed in the brain including the so-called stress axis hormone-regulated exon (STREX) and ZERO variant [28,29]. Thus, STREX-containing BK_{Ca} channel splice variant has a cysteine-rich insertion that the ZERO variant lacks [28,29]. Compared to the ZERO variant, the STREX variant accelerates and slows the channel's activation and deactivation kinetics, respectively, resulting in a dramatic enhancement of BK_{Ca} channel open time [29]. Thus, STREX-containing BK_{Ca} channel splice variant exhibits biophysical characteristics that may have functional relevance, as *KCNMA1* mutation that enhances BK_{Ca} conductances (gain-of-function) give rise to idiopathic generalized epilepsy [4].

2.1.2 Regulatory β subunits—Four different types of BK_{Ca} channel β subunit (called β1 trough β4) have been identified thus far, each encoded by a specific gene *KCNMB1-4* (human) or *Kcnmb1-4* (mouse) [30]. In non-excitable cells, a novel BK_{Ca} channel auxiliary subunit, leucine-rich repeat containing protein (LRRC26) that is unrelated to the neuronal β1–4 subunits has been identified and characterized [31]. Structurally, the BK_{Ca} channel β subunit has two membrane-spanning domains and each subunit is interposed between two adjacent α subunits [32]. Functionally, β subunits alter the gating and pharmacological sensitivity of BK_{Ca} channels, as well as their regulation by phosphorylation [33,34]. In particular, the regulatory β1 subunit enhances Ca^{2+} sensitivity of BK_{Ca} channels and slows the rate of channel opening, whereas β2 subunit confers fast inactivation kinetics [35,36]. The β3 subunit increases BK_{Ca} channel activity [7,36] and alternative splicing of this gene's RNA produces four distinct isoforms (β3a-d), each of which has four sequence variants (V1-V4) [37,38]. The (β3a through (β3c subunits cause partial inactivation of BK_{Ca} channels [38], whereas the β3d subunit has no obvious effect on channel gating [38]. Of the four variants in the β3 subunit family, only the V4 variant of the β3 subunit markedly alters the channel's gating properties, including its fast inactivation kinetics [37]. Finally, the brain-specific BK_{Ca} channel regulatory β4 subunit increases and decreases channel activity in high and low $[Ca^{2+}]_i$, respectively [7]. The β4 subunit also slows the activation and deactivation kinetics of BK_{Ca} channels [7] and decreases the channel's sensitivity to pore blockers such as charybdotoxin and iberiotoxin [34,39]. Moreover, the BK_{Ca} channel β4 subunit inhibits STREX variant channels via a Ca^{2+}-dependent mechanism [40]. Thus, at low $[Ca^{2+}]_i$, the β4 subunit reduces the open probability of the STREX variant channel by slowing its activation. At intermediate and high $[Ca^{2+}]_i$ (i.e., >5.3 μM), the β4 subunit reduces BK_{Ca} channel open probability by opposing the slow deactivation conferred by the STREX exon. In contrast to its effect on STREX variant channels, β4 subunit slows both the activation and deactivation kinetics of ZERO variant channels. Thus, it has been suggested that local Ca^{2+} environment in combination with ZERO or STREX variant BK_{Ca} channels will determine whether β4 subunit containing BK_{Ca} channels can contribute to shaping the AP or regulating neurotransmitter release [40].

2.2 Localization of BK_{Ca} channels in the central nervous system

2.2.1 BK_{Ca} channel α subunit—BK_{Ca} channel α subunits are ubiquitously expressed in the central nervous system (CNS), yet they are preferentially located at the terminal areas of primary projection tracts [41], which is consistent with the role of these channels in regulating neurotransmitter release. Accordingly, in the cortex and hippocampus, BK_{Ca} channel α subunits are more abundantly expressed in glutamatergic nerve terminals than in GABAergic nerve terminals [42]. BK_{Ca} channel α subunits are also present in neuronal post-synaptic compartments [43], where they contribute to AP repolarization at the soma and generate the fAHP [44]. High expression levels of α subunit protein and mRNA are present in the neocortex, olfactory system, piriform cortex and hippocampus [41,45]. BK_{Ca} channel α subunit proteins are also found in mossy fibers, the axons of dentate gyrus (DG) granule

cells that innervate CA3 pyramidal neurons, and within the perforant pathway, which is the principal excitatory projection innervating the hippocampus [41]. The presence of BK_{Ca} channel α subunit proteins in CA3 and CA1 pyramidal neurons and in hippocampal projections [46] may be of pathophysiological relevance because these limbic networks contribute to TLE epileptogenesis. The BK_{Ca} channel α subunit is also moderately expressed in the cortical and basolateral nuclei of the amygdala [45,46], a limbic structure that is also implicated in the pathogenesis of TLE.

In the basal ganglia, BK_{Ca} channel α subunit proteins are highly concentrated in globus pallidus, substantia nigra pars reticulata and entopeduncular nucleus [41,45,46], where this channel may play a role in the pathophysiology of ataxia and tremors. The BK_{Ca} channels α subunit proteins are also expressed in the thalamus, hypothalamus and habenula [45,46]. Interestingly, the thalamus plays a critical role in the pathophysiology of absence epilepsy in humans. Mesencephalic nuclei, including the periaqueductal gray, which plays an important role in the networks for pain and seizures, express BK_{Ca} channel α subunit proteins, at low to moderate levels [46]. The inferior colliculus (IC), which is critical in initiating acoustically evoked generalized tonic-clonic seizures, has moderate expression of BK_{Ca} channel α subunit proteins in the central nucleus and external cortex and high expression in the dorsal cortex [46]. Finally, in the cerebellum, the Purkinje cells, molecular layers and deep nuclei as well as the interpeduncular nucleus, all express BK_{Ca} channel α subunit mRNA at high levels [46].

ZERO variant BK_{Ca} channels are abundant in the brain, whereas STREX variant channels are only weakly expressed [28]. STREX-containing BK channels are primarily present in the pituitary gland, neocortex, hippocampus and cerebellum [40]. In the hippocampus, STREX variant channels are present in the DG granule cells and in CA3 pyramidal neurons, whereas these channels exhibit a weak expression in CA1 neurons [40]. Thus, STREX variant channels may play an important role in controlling excitability of DG granule cells and CA3 pyramidal neurons.

In CNS neurons, BK_{Ca} channel α subunits are also present in the mitochondria [47]. These channels are localized in the inner membrane and found in a limited subset of mitochondria in several brain structures, including the cerebral cortex, hippocampus and cerebellum [47]. The mitochondrial BK_{Ca} (called mitoBK_{Ca}) channel is also selective for K^+ and activated by both Ca^{2+} and voltage, and has a conductance of 260-320 pS [48]. The structure of brain mitoBK_{Ca} channels remains unknown. Nevertheless, it is possible that both neuronal membrane and mitoBKCa channels are splice variants of the same *KCNMA1* gene, as this gene may undergo extensive pre-mRNA splicing [49].

2.2.2 BK_{Ca} channel β subunits—In contrast to the widely distributed BK_{Ca} channel α subunit, the four regulatory β subunits display a restricted pattern of expression [37,38]. BK_{Ca} channel β1 and β4 subunit expression seems focused to non-CNS and CNS tissues, respectively [50]. In the CNS, the expression of BK_{Ca} channel β2, β3, and β4 subunit mRNA ranges from very weak to high in various structures including the neocortex, hippocampus, amygdala, substantia nigra, thalamus, and spinal cord [7,50,51].

Co-expression of BK_{Ca} channel α and β1 subunit mRNA has been clearly demonstrated in Purkinje cells, in some brainstem nuclei and in the hypothalamus [45]. Surprisingly, no co-expression of BK_{Ca} channel α and β subunits was found in the hippocampal formation (DG, CA1-3 areas), the amygdala, and all thalamic areas except zona incerta [45]. This apparent lack of BK_{Ca} channel β subunit expression in these areas might be due to weak expression that could not be detected using *in situ* hybridization methods. Interestingly, both the STREX variant and the β4 subunit are present in CA3 pyramidal cells and in DG granule

cells [40], and this may be of relevance in TLE pathophysiology. Of the four regulatory BK_{Ca} channel β-subunits, only β4-subunit are expressed in the inner membrane of neuronal mitochondria [51], which suggests an important role for this subunit in the mechanisms of neuroprotection or neurodegeneration.

Significant splicing of the α subunit-encoding *KCNMA1* (see 2.1.1) or β subunit-encoding *KCNMB3* (see 2.1.2) gene, differential tissue-specific expression of the various BK_{Ca} channel β subunits, and post-translational modification of channel subunits, all contribute to the particular BK_{Ca} channel phenotype that is expressed in a given tissue or brain region.

2.3 Regulation of BK_{Ca} channel activity

Given their role in controlling neuronal excitability, modulating BK_{Ca} channels may have clinical relevance. Many factors important to epilepsy pathophysiology, including Ca^{2+} and pH, regulate BK_{Ca} channel activity [52,53]. For instance, BK_{Ca} channels are activated by micromolar increases in $[Ca^{2+}]_i$ levels. Such increases in $[Ca^{2+}]_i$ levels are restricted to "Ca^{2+}-nano/microdomains" in the immediate vicinity of the Ca^{2+} source. In the CNS, the Ca^{2+} that activates BK_{Ca} channels is provided primarily by Ca_v channels and N-methyl-D-aspartate (NMDA) receptors [45,54,55]. Indeed, BK_{Ca} channels co-localize with Ca_v channels, such that Ca^{2+} diffuse only ~13 nanometers after entering the neuron before binding to BK_{Ca} channels [56]. The specific Ca_v type that interacts with BK_{Ca} channels varies from neuron to neuron and includes $Ca_v1.2$ (L-type), $Ca_v2.1$ (P/Q-type), $Ca_v2.2$ (N-type) and Ca_v3 (T-type), but not $Ca_v2.3$ (R-type) channels [55]. In some CNS neurons, BK_{Ca} channels that contain β2 or β4 subunits can associate with $Ca_v1.2$, $Ca_v2.1$ and $Ca_v2.2$ channels [55]. Co-localization of BK_{Ca} channels with NMDA receptors in CNS neurons [54] suggests that BK_{Ca} channels may an important role in shaping the action of glutamate and controlling its release in various brain regions. In addition to depolarization-dependent Ca^{2+} influx, BK_{Ca} channels also are activated by Ca^{2+} that is released from intracellular ryanodine-gated Ca^{2+} pools [57]. Whether Ca^{2+} released from inositol triphosphate-gated Ca^{2+} pools can also activate neuronal BK_{Ca} channels remains unknown. Based on their distribution, BK_{Ca} channels in the plasma membrane belong to two distinct pools, namely clustered and scattered channels, which are activated by Ca^{2+} release from intracellular Ca^{2+}-gated stores and Ca^{2+} entry through Ca_v channels, respectively [58].

Membrane depolarization often leads to intracellular acidification, and many types of ion channels, including BK_{Ca} channels are sensitive to H^+ exposure. Interestingly, acidification reduces the activity of BK_{Ca} channels, under high $[Ca^{2+}]_i$ conditions [26,59,60]. This sensitivity of BK_{Ca} channels to protons may play an important role in the pathophysiology of epilepsy, as intracellular acidification in some CNS neurons is tightly coupled to seizure termination [61]. Zinc (Zn^{2+}) is an important intracellular molecule that may play an essential role in the control of neuronal excitability, as intracellular Zn^{2+} ($[Zn^{2+}]_i$) activates BK_{Ca} channels [62]. Conversely, reduced $[Zn^{2+}]_i$ can contribute to neuronal hyperexcitability. In TLE, recurrent mossy fibers (which project from the DG granule cells to CA3 pyramidal neurons) synapse the DG, thus facilitating the synchronous firing of the granule cells. Interestingly, vesicular Zn^{2+} is abundant in mossy fibers. In a model of TLE, Zn^{2+} released from recurrent mossy fibers is thought to contribute to DG granule cells bursting [63]. Such epileptiform activity may be due to altered sensitivity of BK_{Ca} channels to $[Zn^{2+}]_i$.

Numerous BK_{Ca} channel blockers and activators (i.e., openers) are used to identify these channels and study their functions. Several potent and commonly used BK_{Ca} channel blockers include tetraethylamonium (TEA), paxilline, penitrem A, charybdotoxin, iberiotoxin and quinoline. TEA has poor selectivity for BK_{Ca} channels, as it also blocks other K_v channels, including $K_v7.2$ and $K_v7.4$ channels [64]. Charybdotoxin, a peptide

isolated from the venom of the scorpion *Leiurus quinquestriatus*, is a nonselective BK_{Ca} blocker that also blocks $K_v1.2$ and IK_{Ca} channels [65]. Iberiotoxin, a peptide isolated from the venon of the scorpion *Buthus tamulus*, the tremorgenic fungal toxins paxilline and penitrem A, and the quinoline alkaloid tetrandrine are all fairly selective for BK_{Ca} channels, but also suppress Ca^{2+}-dependent chloride channels [66]. Paxilline blocks BK_{Ca} channels-containing β4 subunits whereas iberiotoxin exhibits low activity for these channels [34]. Interestingly, mitoBK_{Ca} channels are sensitive to both charybdotoxin and iberiotoxin [67]. Another BK_{Ca} channel blocker of interest include Slotoxin (αKTX 1.11), that was isolated from the venom of scorpion *Centruroides noxius* Hoffman. Slotoxin appears to selectively block the BK_{Ca} channels and can pharmacologically distinguish BK_{Ca} channel complexes containing α, α/β1 and α/β4 subunits [68]. Finally, cholesterol, an endogenous compound, inhibits BK_{Ca} channels activity by decreasing both the mean open and closed times [69].

BK_{Ca} channel activators are predicted to stabilize the neuron's resting membrane potential by increasing K^+ efflux, which lead to membrane hyperpolarization and subsequently dampens neuronal excitability. Many compounds activate BK_{Ca} channels including synthetic benzimidazolone derivatives such has NS11021, biaryl amines (mefenamic and flufenamide acid), diaryl ureas (NS 1609), pyridyl amines, 3-aryloxin-doles, benzopyrans, dihydropyridines, and natural modulators such as dehydrosoyasaponin-1 and flavonoids. Among the commonly used BK_{Ca} channel activators, NS11021 is a compound of interest, as it increases the open probability of BK_{Ca} channels but does not affect Ca_v, K_v, or Na_v channels [70].

Several endogenous factors that have been implicated in the pathophysiology of epilepsy including nitric oxide, arachidonic acid metabolites, and estradiol also modulate BK_{Ca} channel activity through G-proteins, phosphorylation or dephosphorylation. Both arachidonic acid and nitric oxide potentiate BK channel activity by slowing inactivation kinetics and enhancing channel opening, respectively [71,72]. Similarly, 17β-estradiol increases BK_{Ca} channel currents by enhancing both channel opening and the expression of both α and β4 subunits [73]. Finally, ethanol, an exogenous compound that contributes to the etiology of alcohol withdrawal seizures, activates BK_{Ca} channels by increasing their mean open time and promoting Ca^{2+}-driven channel gating [74].

2.4 The physiological role of BK_{Ca} channels

The primarily function of BK_{Ca} channels is to generate a fAHP after contributing to AP repolarization. The BK_{Ca} channel-mediated fAHP that follows an AP controls the shape and duration of that AP, thus determining the amount of Ca^{2+} that enters the neuron. Following a fAHP, many neurons exhibit a prolonged AHP that is comprised of medium (mAHP) and slow (sAHP) both of which are generated by SK_{Ca} channels; moreover, the sAHP is thought to play an important role in controlling spike frequency [75]. Based on their biophysical characteristics, two functionally groups of BK_{Ca} channels have been identified, namely inactivating and non-inactivating BK_{Ca} channels. The non-inactivating BK_{Ca} channels are further classified into two types including type I and type II channels. The type I non-inactivating BK_{Ca} channels contribute to AP repolarization and the induction of the fAHP and are sensitive to charybdotoxin and iberiotoxin, whereas the type II non-inactivating BK_{Ca} channels are slowly gated, iberiotoxin-resistant channels [34,76]. The molecular correlates of type I and type II non-inactivating BK_{Ca} channels are poorly understood. Nevertheless, BK_{Ca} channels that contain β4 subunits contribute to type II non-inactivating channels [34].

BK_{Ca} channels also play an important role in regulating neurotransmitter release at CNS nerve terminals. Calcium influx into presynaptic terminal via Ca_v channels initiates neurotransmitter release and activates BK_{Ca} channels, which in turn inhibit the release of

neurotransmitter. It has been suggested that presynaptic BK_{Ca} channels are recruited only following conditions associated with a massive $[Ca^{2+}]_i$ accumulation in presynaptic terminals, for example during seizures [77]. Under such conditions, BK_{Ca} channels would limit depolarization-induced bursting activity by hyperpolarizing the presynaptic membrane, leading to deactivation of Na_v and Ca_v channels, and thereby inhibiting subsequent APs. This mechanism provides a rapid inhibitory response at the presynaptic terminals that is consistent with their role as an “emergency brake” that protects against neuronal hyperexcitability and prevents seizure-related neurodegeneration [78]. Another important role for BK_{Ca} channels is to prevent excessive $[Ca^{2+}]_i$ increases by repolarizing the membrane, deactivating Ca_v channels and increasing activity of the Na^+/Ca^{2+} exchanger.

Neuronal mitochondria are an important system for sequestering $[Ca^{2+}]_i$. Physiologically, mitoBKCa channels are important for the K^+ transport. Unlike BK_{Ca} channels in the plasma membrane, opening of mitoBK_{Ca} channels results in depolarization of the inner mitochondrial membrane, which in turn modulates the mitochondria function. MitoBK_{Ca} channels may constitute a link between cytosolic and intramitochondrial Ca^{2+} and mitochondrial membrane potential dependent reactions. The functional role of mitoBK_{Ca} channels is poorly understood. Nevertheless, these channels may play an important role in both buffering $[Ca^{2+}]_i$ and neuroprotection or neurodegeneration.

In general, the activation of BK_{Ca} channel reduces neuronal excitability, an action that should dampen epileptiform bursts. However, in some neurons BK_{Ca} channel activation *enhances* neuronal excitability. For instance, in hippocampal CA1 pyramidal cells, BK_{Ca} channels-containing β2 subunits promote frequency-dependent AP broadening during repetitive firing, an effect that is reduced by BK_{Ca} channel blockers [76,78,79]. This effect is mediated through rapid spike repolarization and the fAHP, which may limit the inactivation of Na_v channels and the activation of other slower K_v channels (such as delayed rectifier K^+ channels) during interspike interval [80]. Similarly, in DG granule cells, β4 subunits are believed to prevent BK_{Ca} channels from contributing to membrane repolarization, as genetically deleting of these subunits promotes both high frequency firing and AP sharpening (or narrowing), thus reducing AHP duration [81].

2.5 The role of BK_{Ca} channels in epilepsy pathophysiology

Complex spike bursts caused by enhanced inward currents through Ca_v channels constitute a critical epileptogenic mechanism [52]. BK_{Ca} channel currents, which are Ca^{2+} dependent, oppose neuronal activity and reduce neuronal hyperexcitability that could otherwise lead to seizures. Surprisingly, blocking BK_{Ca} channels inhibits epileptiform bursting in models of acute seizures and inherited epilepsy [82]. BK_{Ca} channel blockade also inhibits bursting activity induced by elevated $[Ca^{2+}]_i$ following Ca^{2+} release from intracellular Ca^{2+}-gated pools [82]. Because BK_{Ca} channels are important in controlling neuronal excitability under normal physiological conditions, it may seem counterintuitive to postulate that BK_{Ca} channel activation might contribute to neuronal hyperexcitability. Nevertheless, such effects can occur in the presence of BK_{Ca} channels that carry a gain-of-function mutation in their a-subunits [4].

2.5.1 Clinical studies—BK_{Ca} channels were first implicated in seizure-inducing neuronal hyperexcitability when it was reported that fAHP conductances were reduced in DG granule cells obtained from surgical samples from TLE patients [3]. At the time, the mechanism(s) by which altered BK_{Ca} channels contributed to seizures include downregulation of channel expression, altered channel trafficking and insertion to the plasma membrane or a loss-of-function mutation that gives rise to nonfunctional or hypo-functional channel. However, recent evidence indicates that some mutations in the genes encoding BK_{Ca} channels give

rise to a gain-of-function mechanism that is associated with human idiopathic generalized epilepsy and absence epilepsy in particular [4].

Evidence indicates that the D434G missense mutation in the α subunit *KCNMA1* gene may contribute to inherited generalized epilepsy (manifesting primarily as absence epilepsy, although generalized tonic-seizures occur in some patients), which is associated with paroxysmal dyskinesia [4]. This mutation is characterized by an increase in BK_{Ca} channel's sensitivity to Ca^{2+}, enhanced voltage- and Ca^{2+}-dependent channel activation, increased membrane currents, and an increased channel mean open time, all of which are consistent with BK_{Ca} channels gain-of-function effect [4,36,83]. This mutation specifically alters Ca^{2+}-dependent activation initiated at the Ca^{2+} binding site within the RCK1 domain [84]. Several mechanisms for how D434G mutation causes BK_{Ca} channel gain-of-function effect (and the subsequent contribution to neuronal hyperexcitability and seizures) have been suggested and include rapid repolarization of APs and relief of Na_v channels inactivation, up-regulation of hyperpolarization-activated channels or inhibition of GABAergic interneurons with subsequent disinhibition of thalamocortical circuits [4]. The D434G mutation may also confer specific changes to the proprieties of the regulatory BK_{Ca} channel β subunits, thus contributing to the pathophysiology of idiopathic epilepsy. Indeed, this mutation enhances the availability of BK_{Ca} channels that contain β2 subunits, and increases the channel function (i.e., opening rate) of BK_{Ca} channels containing β1 and β4 subunits but slows rates of both channel opening and closing of BK_{Ca} channels that contain β3b subunits [35]. Interestingly, a polymorphism in the gene encoding the BK_{Ca} channel β4 subunit is associated with human TLE [85]. Thus, some BK_{Ca} channel variants that have a gain-of-function phenotype may contribute to certain forms of inherited generalized epilepsy in humans when the thalamus and thalamo-cortical circuits are involved in the pathophysiology of seizures, whereas a loss-of-function BK_{Ca} channels phenotype may be associated with TLE.

The gene encoding the regulatory BK_{Ca} β3 subunit *(KCNMB3)* has also been implicated in the pathophysiology of epilepsy. The *KCNMB3* gene maps a region in the human chromosome 3 (3q26.3-q27) [86]. This segment is duplicated in the dup(3q) syndrome, which is characterized by congenital and neurological abnormalities, including seizures [86]. Because dup(3q) syndrome has early onset during development, the duplication of the *KCNMB3* gene suggests that overexpression of this gene and the resulting increase in the β3 subunit protein levels may contribute to seizure etiology. Similarly, a susceptibility locus for idiopathic generalized epilepsy maps to the 3q26 chromosome region [87]. In humans, mutations in the *KCNMB3* gene may also contribute to both neuronal hyperexcitability and seizures as a single nucleotide deletion in exon 4 (delA750) is associated with idiopathic generalized epilepsy (mostly in the form of typical absence epilepsy) [88]. Interestingly, BK_{Ca} channels containing the β3b-V4 (delA750 mutation) variant exhibit fast inactivation kinetics [38], suggesting a reduced ability of these channels to repolarize the membrane during an AP, and thus leading to neuronal hyperexcitability.

2.5.2 Experimental studies—In sharp contrast to clinical studies that suggest gain-of-function BK_{Ca} channels essentially contribute to the pathophysiology of absence epilepsy, experimental studies indicate BK_{Ca} channels gain-of-function mechanisms can also trigger TLE. Thus, BK_{Ca} channel β4 subunit knockout mice exhibit TLS associated with a gain-of-function phenotype in their BK_{Ca} channels that sharpens (narrows) APs and supports higher firing frequency in DG granule cells [81]. The mechanisms by which a gain-of-function of BK_{Ca} channels without β4 subunits triggers seizures may include i) enhanced Ca^{2+} sensitivity of BK_{Ca} channels, ii) reduced AHP size, iii) *de novo* generation of type I, fast-gated BK_{Ca} channels, or iv) limited recruitment of SK_{Ca} channels between spikes [81]. A loss of β4 subunits may also remove their inhibitory effect on STREX variant BK_{Ca}

channels, leading to an increase in BK_{Ca} channel function. Interestingly, DG granule cells have the strongest expression of β4 subunits in the hippocampal formation, and upregulation of the STREX variant channels (and downregulation of ZERO variant channels) in DG granule cells are associated with TLE [89]. Thus, upregulation of STREX variant may contribute to gain-of-function BK_{Ca} channels that give rise to TLS, as this variant exhibit faster activation and slower deactivation kinetics. The DG has a very high threshold for seizure initiation and is resistant to seizure-induced neurodegeneration. Thus, neuronal BK_{Ca} channel β4 subunits may provide a molecular basis for both seizure resistance and neuroprotection.

The BK_{Ca} channel regulatory β4 subunit in the inner mitochondrial membrane may also contribute to neurprotection, as the functional role of mitoBK_{Ca} channel is in part associated with this subunit. Mitochondrial dysfunction is associated with several multiple epileptic phenotypes, including TLE [90]. The mechanisms of how neuronal mitochondrial dysfunction contributes to epileptogenesis are not fully understood. Evidence indicates that seizures can elicit both significant increases in mitochondrial Ca^{2+} levels and changes in mitochondrial membrane potential [91]. Neuronal mitoBK_{Ca} channels would then, be activated due to rising [Ca^{2+}] in the matrix in response to an increase in cytosolic Ca^{2+}, and the consequence of these channels opening is K^+ efflux into mitochondria matrix, resulting in depolarization of mitochondrial inner membrane, which would then stimulate respiration. Mitochondria are a major source of reactive oxygen species (ROS), and the mitochondria-mediated catalytic removal of ROS prevents status epilepticus-induced neuronal cell loss [92]. Thus, activation of mitoBK_{Ca} channels would contribute to seizure suppression and confer neuroprotection via inhibition of ROS synthesis. Alternatively, downregulation of mitoBK_{Ca} channels would contribute to (i.e., facilitate) seizure-induced neuronal cell loss.

Seizures themselves also can confer a gain-of-function effect to BK_{Ca} channels. Accordingly, picrotoxin-induced generalized tonic-clonic seizures give rise to a BK_{Ca} channel gain-of-function that is characterized by enhanced BK_{Ca} currents and increased neuronal firing in the somatosensory (barrel) cortex [93]. Interestingly, BK_{Ca} channel blockers suppressed generalized tonic-clonic seizures in pre-sensitized animals and reversed the elevated neuronal firing that follows tonic-clonic seizures [93,94]. These findings suggest that blocking gain-of-function BK_{Ca} channels may be a potential mechanism for suppressing seizures. The extent to which seizure-induced gain-of-function BK_{Ca} channels contribute to seizure generation and the development of chronic epilepsy remains unknown.

Loss-of-function or downregulated BK_{Ca} channels may also contribute to the pathophysiology of seizures in models of inherited generalized tonic-clonic epilepsy and TLE. For instance, the severe seizure strain of genetically epilepsy-prone rats (GEPR-9), which exhibit enhanced susceptibility to acoustically evoked seizures, have reduced fAHP conductances in hippocampal CA3 neurons [95]. In line with these studies, BK_{Ca} channel current density is significantly reduced in IC neurons of the moderate seizure strain (GEPR-3) [N'Gouemo, unpublished results]. However, the reduced BK_{Ca} current density was not associated with downegulation of BK_{Ca} channel α-subunit in IC neurons of GEPR-3s [96]; thus, other mechanisms (such as phosphorylation or dephosphorylation of the channel) may account for the reduced current density. In a model of TLE, however, a downregulation of the BK_{Ca} channel α subunits was reported in the cortex and hippocampus (specifically in the mossy fibers), during the active (or chronic) phase of epilepsy [97,98]. Interestingly, BK_{Ca} channels are abundantly expressed at glutamatergic presynaptic terminals including at the mossy fibers where they can control glutamate release under conditions of excessive neuronal activity. Thus, downregulation of presynaptic BK_{Ca} channels may contribute to mossy fibers hyperexcitability and aberrant glutamate release during epileptogenesis. Finally, penitrem A, a potent blocker of BK_{Ca} channels triggers

seizures and status epilepticus [99]; thus providing direct evidence that these channels are critical for controlling neuronal hyperexcitability that leads to seizures.

Acute alcohol exposure potentiates BK_{Ca} channel activity [74] that should reduce neuronal excitability and provide a basis for the neurodepressive effect of alcohol. Interestingly, an abrupt reduction or cessation of chronic alcohol consumption leads to the development of alcohol withdrawal syndrome characterized by neuronal hyperexcitability and seizures (primarily generalized tonic-clonic seizures). Because of the role that BK_{Ca} channels play in controlling neuronal excitability, these channels may contribute to the etiology of alcohol withdrawal seizures. Consistent with this hypothesis, alcohol withdrawal seizures are associated with a reduction in both BK_{Ca} channel current density and BK_{Ca} channel α-subunit expression in IC neurons (N'Gouemo, unpublished data).

Thus, the aforementioned studies provide evidence to support the notion that both gain-of-function and loss-of-function BK_{Ca} channels play important roles in the pathophysiology of epilepsy. The specific role of these BK_{Ca} channels may ultimately depend, at least, in their cellular localization, anatomical distribution, variant channel expression and seizure type.

2.5.3 BK_{Ca} channel activators and blockers as antiepileptic drugs—In humans, mutations in the BK_{Ca} channels that result in a gain-of-function phenotype have been implicated in the pathophysiology of idiopathic generalized seizures [4]. Accordingly, blocking these BK_{Ca} channels should suppress seizures. In support of this hypothesis, ethosuximide, a drug of choice for human absence epilepsy inhibits neuronal BK_{Ca} channels, in addition to its primary effect of blocking Ca_v3 channels [100]. Furthermore, paxilline, a BK_{Ca} channel blocker, has anticonvulsant effects in models of picrotoxin- and pentylenetetrazole-induced generalized seizures in pre-sensitized animals [94]. Interestingly, at the tested dose, paxilline did not suppress acute picrotoxin- or pentlylenetetrazole-induced generalized tonic-clonic seizures in animals that were not pre-sensitized [94]. These findings suggest the convulsant pre-sensitization may contributes to the gain-of-function effect on BK_{Ca} channels, which may serve as molecular target for the anticonvulsant effect of paxilline. Loss-of-function of BK_{Ca} channels are also associated with inherited and acquired susceptibility to generalized tonic-clonic seizures and TLE, suggesting that activating BK_{Ca} channels can provide an elegant mechanism for seizure suppression. Accordingly, zonisamide, a clinically used antiepileptic drug, activates BK_{Ca} channels in addition to other mechanisms suggesting that this pharmacological activity may contribute to some extent to its anticonvulsant effect.

3. Concluding remarks

BK_{Ca} channels are important regulators of neuronal activity and represent an intrinsic inhibitory mechanism for critically restoring normal neuronal excitability. Thus, BK_{Ca} channel activators may serve as potential anticonvulsants. However, enhanced BK_{Ca} channel function may lead to increased excitability by modifying the refractory period of the associated conductances. Furthermore, mutations in the genes encoding the BK_{Ca} subunits can give rise to BK_{Ca} channel gain-of-function phenotype resulting in neuronal hyperexcitability and seizures. Seizures themselves also can induce a gain-of-function effect in BK_{Ca} channels, as a consequence of seizure activity. Blocking BK_{Ca} channels suppresses the channel gain-of-function effect and seizures, which strongly suggest these channels, are also of therapeutic interest as drug targets. Understanding the molecular basis of how both BK_{Ca} channels gain-of-function and loss-of-function BK_{Ca} channels contribute to epileptogenesis and seizure generation may lead to developing rational therapies for certain inherited and acquired epilepsy syndrome.

4. Expert opinion (1,000 words; actual:999)

The role of BK_{Ca} channels in epilepsy pathophysiology is complex as activation of these channels can lead to both anti- and pro-epileptic activities. This dual action of BK_{Ca} channels depends on many factors including the seizure type. Emerging evidence suggests that loss-of-function mechanisms of BK_{Ca} channels are associated with inherited seizure susceptibility, alcohol withdrawal seizures, and TLE, while gain-of-function effects on BK_{Ca} channels are thought to contribute to the etiology of absence epilepsy.

Despite significant progress in managing epilepsy syndromes, approximately one-third of patients with epilepsy live with uncontrolled seizures, and unwanted side effects from antiepileptic drugs are common. One of the major challenges in the management of seizures is drug resistance, the causes of which are both multiple and complex and include a failure of the antiepileptic drugs to block inward Ca^{2+} and Na^{+} currents through Ca_v and Na_v channels, respectively, or to enhance GABA-mediated inhibition. There is an urgent need to develop novel antiepileptic drugs based on the underlying mechanisms of neuronal hyperexcitability that may lead to both epileptogenesis and seizure generation. Thus, there is intense and growing interest in the BK_{Ca} channel loss-of-function mechanisms associated with epilepsy and the novel BK_{Ca} channel gain-of-function mechanisms that give rise to seizures, both of which can result from mutations in the gene that encodes for the channel's pore-forming α subunit. Likewise, there is intense interest in gain-of-function effect on BK_{Ca} channels that is caused by seizures themselves, as this may serve as putative mechanism in epileptogenesis.

Although the phenotype of human epilepsy that is caused by gain-of function BK_{Ca} channels seems limited to absence epilepsy, there is evidence implicating a polymorphism β4 subunit polymorphism in TLE (likely with secondary generalization), which is the most common form of refractory epilepsy in adults. All of this suggests that inhibiting gain-of-function BK_{Ca} channels is a promising means to treat some epilepsy syndromes. Interestingly, BK_{Ca} channel blockers suppress both gene mutation- and seizure-induced gain-of-function effect and these blockers exert anticonvulsant effects in models of picrotoxin- and pentylenetetrazole-induced seizures in pre-sensitized young animals. The BK_{Ca} channel gain-of-function mechanisms that lead to seizures may also include elevated extracellular $[K^{+}]$, which is tightly associated with neuronal hyperexcitability and seizures. Blocking BK_{Ca} channels may therefore stabilize extracellular $[K^{+}]$ at physiological levels and suppress seizures. Thus, gain-of-function BK_{Ca} channels along with the GABAergic system and T-type Ca^{2+} channels are important molecular targets underlying epileptogenesis in absence epilepsy.

Because gain-of-function BK_{Ca} channels can contribute to the pathogenesis of absence epilepsy, this raises the concern that clinically effective antiepileptic drugs which enhance BK_{Ca} channel conductances, for example zonisamide, may inappropriately affects thalamic networks activity, thereby leading to absence seizures (despite suppressing other seizure phenotypes). Thus, there is an urgent need for studies to investigate the extent to which *i*) selective activation of BK_{Ca} channels can suppress seizures and *ii*) activating BK_{Ca} channels worsens absence seizures and/or trigger additional seizure phenotypes in absence epilepsy.

There is also interest in BK_{Ca} channel loss-of-function mechanisms as downregulated BK_{Ca} channels and/or decreased channel activity are associated with neuronal hyperexcitability that can lead to seizures and epileptogenesis. To date, downregulation of BK_{Ca} channels has been associated with inherited seizure susceptibility (tonic-clonic seizures), alcohol withdrawal seizures (primarily tonic-clonic seizures) and TLE (likely with secondarily generalization). Thus, compounds that open and activate BK_{Ca} channels can be used to

prevent and treat these seizures. Furthermore, presynaptic BK_{Ca} channels openers, by suppressing glutamate release and contributing neuroprotection, may have a promising in role in the management of seizure-induced lesions underlying the development of pharmacoresistant TLE.

To date, only the model of picrotoxin- and pentylenetetrazole-induced seizures in pre-sensitized young animals has sufficiently demonstrated that blocking BK_{Ca} channels suppresses seizures. Other models that would be useful for confirming this result include: animal models of acute generalized seizures (maximal electroshock) and epileptogenesis (chemical or electrical kindling; post-status epilepticus models of TLE). Future studies in relevant animal models of absence epilepsy (e.i., Genetic Absence Epilepsy Rat from Strasbourg, the Wistar Absence Glaxo from Rijwik, and the γ-hydroxybutyrate spike-and-wave model) and suitable clinical populations are needed to validate the anticonvulsant profile and potential clinical application of BK_{Ca} channel blockers. The BK_{Ca} channel β4 subunit knockout mouse is a useful model to determine the role of this subunit (and its dysfunction) in TLE. However, caution should be exercised when interpreting the relevance of this model, as knocking down the channel subunit results in a protein loss but not a production of dysfunctional protein that is the case for BK_{Ca} channel mutations that lead to inherited epilepsy in humans.

Our understanding of how BK_{Ca} channels activators and inhibitors can be used therapeutically to treat or prevent seizures and epilepsy is still in the early stages. A comprehensive structure-function analysis of gain-of-function and loss-of-function BK_{Ca} channels that leads to epileptogenesis and seizures may be helpful in designing new therapeutic strategies. Developing BK_{Ca} channel blockers (and activators) that are selective for channels containing β3 and β4 subunits would certainly help determine the extent to which these subunits might mediate antiepileptic/antiepileptogenic effects. In addition, it also would be interesting to determine whether certain BK_{Ca} channel openers that were originally developed to treat various diseases such as erectile dysfunction (3-thio-quinolines, 4-aryl-3-aminoquinolones), ischemic stroke (fluoro-oxindole,4-aryl-3-aminoquinolones) exhibit antiepileptic/antiepileptogenic effects.

This review raises the hypothesis that both gain-of-function and loss-of-function BK_{Ca} channels may contribute to epileptogenesis and seizure generation. Identification of altered BK_{Ca} channel mechanisms that lead to neuronal hyperexcitability will contribute to a better understanding of the molecular substrates for epileptogenesis and seizure generation and eventually lead to more effective strategies for treating seizures and epilepsy. Targeting BK_{Ca} channels to suppress seizures and treat epilepsy can be challenging because of both anti- and pro-epileptic activity following activation of these channels. Nevertheless, identification of diverse BK_{Ca} channel α and β subunit variants may enhance the possibility of targeting selective brain areas with selective BK_{Ca} channel openers and blockers, and therefore leading to better strategies for epileptogenesis prevention and treatment of certain seizure types and epilepsy syndromes.

Acknowledgments

This work was supported by an NIH grants (NS047193 and AA020073). The author would like to thank Drs. Carl L. Faingold and Alejandro M. Dopico for advice and editorial assistance.

References

1. Neubauer BA, Waldeggers S, Heinzinger J, et al. KCNQ2 and KCNQ3 mutation contribute to different idiopathic epilepsy syndromes. Neurology. 2008; 71:177–183. [PubMed: 18625963]

2. Berkefeld H, Falker B, Schulte U. Ca^{2+}-activated K^+ channels: from protein complex to function. Physiol Rev. 2010; 90:1437–1459. [PubMed: 20959620]
3. Williamson A, Spencer DD, Shepherd GN. Comparison between membrane and synaptic properties of the human and rodent granule cells. Brain Res. 1993; 622:194–202. [PubMed: 8242356]
4**. Du W, Bautista JF, Yang H, et al. Calcium-sensitive potassium channelopathy in human epilepsy and paroxysmal movement disorder. Nat Genet. 2005; 37:733–738. The D434G mutation in the BK_{Ca} channel α subunit KCNMA1 gene contributes to the development of idiopathic epilepsy in humans and gives rise to the channel gain-of-function mechanisms. [PubMed: 15937479]
5. Salkoff L, Butler A, Ferreira G, et al. High-conductance potassium channels of the SLO family. Nat Rev Neurosci. 2006; 7:921–931. [PubMed: 17115074]
6. Horrigan FT, Aldrich RW. Coupling between voltage sensor activation, Ca^{2+} binding and channel opening in large conductance (BK) potassium channel. J Gen Physiol. 2002; 120:267–305. [PubMed: 12198087]
7. Brenner R, Jegla TJ, Wickenden A, et al. Cloning and functional characterization of novel large conductance calcium-activated potassium channel β-subunits, hKCNMB3 and hKCNMB4. J Biol Chem. 2000; 275:6453–6461. [PubMed: 10692449]
8. Pallanek L, Genetzky B. Cloning and characterization of human and mouse homologs of the *Drosophila* calcium-activated potassium channels gene *slowpoke*. Hum Mol Genet. 1994; 3:1239–1243. [PubMed: 7987297]
9. Wallner M, Meera P, Toro L. Determinant for beta-subunit regulation in high-conductance voltage-activated and Ca^{2+}-sensitive K^+ channels: an additional transmembrane region at the N-terminus. Proc Natl Acad Sci USA. 1996; 93:14922–14927. [PubMed: 8962157]
10. Ma Z, Lou XJ, Horrigan FT. Role of charged residues in the S1-S4 voltage sensor of BK channels. J Gen Physiol. 2006; 127:309–28. [PubMed: 16505150]
11. Díaz L, Meera P, Amigo J, et al. Role of the S4 segment in a voltage-dependent calcium sensitive potassium (hSlo) channel. J Biol Chem. 1998; 273:32430–32436. [PubMed: 9829973]
12. Wu Y, Xiong Y, Wang S, et al. Intersubunit coupling in the pore of BK channels. J Biol Chem. 2009; 284:23353–23363. [PubMed: 19561088]
13**. Yuan P, Leonetti MD, Pico AR, et al. Structure of the human BK channel Ca^{2+}-activated apparatus at 3.0 A resolution. Science. 2010; 329:182–187. The authors describe the crystal structure of the human BK_{Ca} channel C-terminus. The BK_{Ca} channel has a gating ring that is formed by four pairs of RCK1 and RCK2 domains. [PubMed: 20508092]
14. Schreiber M, Salkoff I. A novel calcium-sensing domain of the BK channel. Biophys J. 1997; 73:1355–1363. [PubMed: 9284303]
15. Wu Y, Yang Y, Ye S, et al. Structure of the gating ring from the human large-conductance Ca^{2+}-activated K^+ channel. Nature. 2010; 466:393–397. [PubMed: 20574420]
16. Wang L, Sigworth FJ. Structure of the BK potassium channel in a lipid membrane from electron cryomicroscopy. Nature. 2009; 461:292–295. [PubMed: 19718020]
17. Xia XM, Zeng X, Lingle CJ. Multiple regulatory sites in large-conductance calcium-activated potassium channels. Nature. 2002; 418:880–884. [PubMed: 12192411]
18. Zhang G, Huang SY, Yang J, et al. Ion sensing in the RCK1 domain of BK channels. Proc Natl Acad Sci USA. 2010; 107:18700–18705. [PubMed: 20937866]
19. Yusifov T, Savalli N, Gandhi CS, et al. The RCK2 domain of the human BKCa channel is a calcium sensor. Proc Natl Acad Sci USA. 2008; 105:376–381. [PubMed: 18162557]
20. Zhang X, Solaro CR, Lingle CJ. Allosteric regulation of BK channel gating by Ca^{2+} and Mg^{2+} through a nonselective, low affinity divalent cation site. J Gen Physiol. 2001; 118:607–636. [PubMed: 11696615]
21. Shi J, Krishnamoorthy G, Yang Y, et al. Mechanism of magnesium activation of calcium-activated potassium channels. Nature. 2002; 418:876–880. [PubMed: 12192410]
22. Yang H, Shi J, Zhang G, et al. Activation of Slo1 BK channels by Mg^{2+} coordination between the voltage sensor and RCK1 domains. Nat Struct Mol Biol. 2008; 15:1152–1159. [PubMed: 18931675]

23. Javaherian AD, Yusifov T, Pantazis A, et al. Metal-driven operation of the human large-conductance voltage- and Ca^{2+}-dependent potassium channel (BK) gating ring apparatus. J Biol Chem. 2011; 286:20701–20709. [PubMed: 21471215]
24. Avdonin V, Tang XD, Hoshi T. Stimulatory action of internal proton on Slo1 BK channels. Biophys J. 2003; 84:2969–2980. [PubMed: 12719228]
25. Brelidze TI, Magleby KL. Protons block BK channels by competitive inhibition with K^+ and contribute to the limits of unitary currents at high voltages. J Gen Physiol. 2004; 123:305–319. [PubMed: 14981139]
26. Hou S, Xu R, Heinemann SH, et al. Reciprocal regulation of the Ca^{2+} and H^+ sensitivity in the SLO1 BK channel conferred by the RCK1 domain. Nat Struct Mol Biol. 2008; 15:403–410. [PubMed: 18345016]
27. Zhou XB, Wulfsen I, Utku E, et al. Dual role of protein kinase C on BK channels regulation. Proc Natl Acad Sci USA. 2011; 107:8005–8010. [PubMed: 20385812]
28. Chen L, Tian L, MacDonald SHF, et al. Functionally diverse complement of large conductance calcium and voltage-activated potassium channel (BK) α-subunits generated from a single site of splicing. J Biol Chem. 2005; 280:33599–33609. [PubMed: 16081418]
29. Xie J, McCobb DP. Control of alternative splicing of potassium channels by stress hormones. Science. 1998; 280:443–446. [PubMed: 9545224]
30. Jiang Z, Wallner M, Meera P, et al. Human and rodent maxiK channel b-subunit genes: cloning and characterization. Genomics. 1999; 55:57–67. [PubMed: 9888999]
31. Yan J, Aldrich RW. LRRC26 auxiliary protein allows BK channel activation at resting voltage without calcium. Nature. 2010; 466:513–516. [PubMed: 20613726]
32. Lui G, Niu X, Wu RS, et al. Location of modulatory β subunits in BK potassium channels. J Gen Physiol. 2010; 135:449–459. [PubMed: 20385746]
33. Dworetzky SI, Boissard CG, Lum-Ragan JT, et al. Phenotypic alteration of a human BK (hSlo) channel by hSlobeta subunit coexpression: changes in blocker sensitivity, activation/relaxation and inactivation kinetics, and protein kinase A modulation. J Neurosci. 1996; 16:4543–4550. [PubMed: 8764643]
34. Meera P, Wallner M, Toro L. A neuronal beta subunit (KCNMB4) makes the large conductance, voltage- and Ca^{2+}-activated K^+ channel resistant to charybdotoxin and iberiotoxin. Proc Natl Acad Sci USA. 2000; 97:5562–5567. [PubMed: 10792058]
35. Lee US, Cui J. β-subunit-specific modulations of BK channels function by a mutation associated with epilepsy and dyskinesia. J Physiol. 2009; 587:1481–1498. [PubMed: 19204046]
36. Wallner M, Meera P, Toro L. Molecular basis of fast inactivation in voltage and Ca^{2+}-activated K^+ channels: a transmembrane beta-subunit homolog. Proc Natl Acad Sci USA. 1999; 96:4137–4142. [PubMed: 10097176]
37. Hu S, Labuda MZ, Pandolfo M, et al. Variants of the KCNMB3 regulatory subunit of maxi BK channels affects channel inactivation. Physiol Genomics. 2003; 15:191–198. [PubMed: 14612589]
38. Uebele VN, Laggrutta A, Wade T, et al. Cloning and functional expression of two families of β-subunits of the large conductance calcium-activated K^+ channels. J Biol Chem. 2000; 275:23211–23218. [PubMed: 10766764]
39. Wang B, Rothberg BS, Brenner R. Mechanism of β4 subunit modulation of BK channels. J Gen Physiol. 2006; 127:449–465. [PubMed: 16567466]
40. Petrick D, Brenner R. Regulation of STREX exon large conductance, calcium-activated potassium channels by the β4 accessory subunit. Neuroscience. 2007; 149:789–803. [PubMed: 17945424]
41. Knaus HG, Schwarzer C, Koch RO, et al. Distribution of high-conductance Ca^{2+}-activated K^+ channels in rat brain: targeting to axons and nerve terminals. J Neurosci. 1996; 16:955–963. [PubMed: 8558264]
42. Matire M, Barrese V, D'Amico M, et al. Presynaptic BK channels selectively control glutamate versus GABA release from cortical and hippocampal nerve terminals. J Neurochem. 2010; 115:411–422. [PubMed: 20681950]
43. Sailer CA, Kaufmann WA, Kogler M, et al. Immunolocalization of BK channels in hippocampal pyramidal neurons. Eur J Neurosci. 2006; 24:442–454. [PubMed: 16903852]

44. Poolos NP, Johnston D. Calcium-activated potassium conductances contribute to action potential repolarization at the soma but not the dendrites of hippocampal CA1 pyramidal neurons. J Neurosci. 1999; 19:5205–5212. [PubMed: 10377332]
45. Chang CP, Dworetzky SI, Wang J, et al. Differential expression of the alpha and beta subunits of the large-conductance calcium-activated potassium channel: implication for channel diversity. Brain Res Mol Brain Res. 1997; 45:33–40. [PubMed: 9105668]
46. Sausbier U, Sausbier M, Sailer CA, et al. Ca^{2+} -activated K^+ channels of the BK-type in the mouse brain. Histochem Cell Biol. 2006; 125:725–741. [PubMed: 16362320]
47. Douglas RM, Lai JC, Bian S, et al. The calcium-sensitive large-conductance potassium channel (BK/MAXI K) is present in the inner mitochondrial membrane of rat brain. Neuroscience. 2006; 139:1249–1261. [PubMed: 16567053]
48. Kulawiak B, Bednarczyk P. Reconstitution of brain mitochondria inner membrane into planar lipid bilayer. Acta Neurobiol Exp (Wars). 2005; 65:271–276. [PubMed: 16130801]
49. Soom M, Gessner G, Heuer H, et al. A mutually exclusive alternative exon of *slo*1 codes for a neuronal BK channel with altered function. Channels. 2008; 2:278–282. [PubMed: 18719396]
50. Behrens R, Nolting A, Reimann F, et al. hKCNMB3 and hKCNMB4, cloning and characterization of two members of the large-conductance calcium-activated potassium channel beta subunit family. FEBS Lett. 2000; 474:99–106. [PubMed: 10828459]
51. Piwonska M, Wilczek E, Szewczyk A, et al. Differential distribution of Ca^{2+}-activated potassium channel beta4 subunit in rat brain: immunolocalization in neuronal mitochondria. Neuroscience. 2008; 153:446–60. [PubMed: 18359571]
52**. Sanabria ERG, Su H, Yaari Y. Initiation of network bursts by Ca^{2+}-dependent intrinsic bursting in the rat pilocarpine model of temporal lobe epilepsy. J Physiol. 2001; 532:205–216. The authors report a dramatic de novo appearance of Ca^{2+}-dependent bursting that contribute to epileptogenesis in a model of temporal lobe epilepsy. Thus, targeting Ca^{2+}-dependent mechanisms may have therapeutic potentials. [PubMed: 11283235]
53. Xion ZQ, Saggau P, Stringer JL. Activity-dependent intracellular acidification correlates with the duration of seizure activity. J Neurosci. 2000; 20:1290–1296. [PubMed: 10662818]
54. Isaacson JS, Murphy GJ. Glutamate-mediated extrasynaptic inhibition: direct coupling of NMDA receptors to Ca^{2+}-activated K^+ channels. Neuron. 2001; 31:1027–1034. [PubMed: 11580901]
55. Berkefeld H, Sailer CA, Bildl W, et al. BKCa-Ca_V channel complexes mediate rapid and localized Ca^{2+}-activated K^+ signaling. Science. 2006; 314:615–620. [PubMed: 17068255]
56. Müller A, Kukley M, Uebachs M, et al. Nanodomains of single Ca^{2+} channels contribute to action potential repolarization in cortical neurons. J Neurosci. 2007; 27:483–495. [PubMed: 17234581]
57. Chavis P, Ango F, Michel JM, et al. Modulation of big K^+ channels activity by ryanodine receptors and L-type Ca^{2+} channels in neurons. Eur J Neurosci. 1998; 10:2322–2327. [PubMed: 9749760]
58. Kaufmann WA, Kasugai Y, Ferraguti F, et al. Two distinct pools of large-conductance calcium-activated potassium channels in the somatic plasma membrane of central principal neurons. Neuroscience. 2010; 169:974–86. [PubMed: 20595025]
59. Song X, Su W, Chen L, et al. Functional expression of large-conductance Ca^{2+}-activated potassium channels in lateral globus pallidus neurons. Neuroscience. 2010; 169:1548–1556. [PubMed: 20600663]
60. Su W, Song X, Ji JJ. Functional expression of a large-conductance Ca^{2+}-activated K^+ channel in mouse substantia nigra pars compacta dopaminergic neurons. Neurosci Lett. 2010; 471:1–5. [PubMed: 20036716]
61. Xion ZQ, Saggau P, Stringer JL. Activity-dependent intracellular acidification correlates with the duration of seizure activity. J Neurosci. 2000; 20:1290–1296. [PubMed: 10662818]
62. Hou S, Vigeland LE, Zhang G, et al. Zn^{2+} activates large conductance Ca^{2+}-activated K^+ channel via an intracellular domain. J Biol Chem. 2010; 285:6434–6442. [PubMed: 20037152]
63. Timofeeva O, Nadler JV. Facilitation of granule cell epileptiform activity by mossy fiber-released zinc in the pilocarpine model of temporal lobe epilepsy. Brain Res. 2006; 1078:227–234. [PubMed: 16490181]
64. Hermann A, Gorman AJ. Effects of tetraethylammonium on potassium currents in a molluscan neuron. J Gen Physiol. 1981; 78:87–110. [PubMed: 6265594]

65. Guillemare E, Honore E, Pradier L, et al. Effects of the level of mRNA expression on biophysical properties, sensitivity to neurotoxins, and regulation of the brain delayed-rectifier K^+ channel Kv1.2. Biochemistry. 1992; 31:12463–12468. [PubMed: 1281425]

66. Sones WR, Leblanc N, Greenwood IA. Inhibition of vascular calcium-gated chloride currents by blockers of KCa1.1, but not by modulators of KCa2.1 or KCa2.3 channels. Br J Pharmacol. 2009; 158:521–531. [PubMed: 19645713]

67. Skalska J, Bednarczyk P, Piwońska M, et al. Calcium ions regulate K^+ uptake into brain mitochondria: The evidence for a novel potassium channel. Int J Mol Sci. 2009; 10:1104–1120. [PubMed: 19399240]

68. Garcia-Valdes J, Zamudio FZ, Toro L, et al. Slotoxin, alphaKT×1.11, a new scorpion peptide blocker of MaxiK channels that differentiates between a and a+P (β1 or β4) complexes. FEBS Lett. 2001; 505:369–373. [PubMed: 11576530]

69. Crowley JJ, Treistman SN, Dopico AM. Cholesterol antagonizes ethanol potentiation of human brain BK channels reconstituted into phospholipid bilayers. Mol Pharmacol. 2003; 64:365–373. [PubMed: 12869641]

70. Bentzen BH, Nardi A, Calloe K, et al. The small molecule NS11021 is a potent specific activator of Ca^{2+}-activated big conductance K^+ channels. Mol Pharmacol. 2007; 72:1033–1044. [PubMed: 17636045]

71. Sun X, Yao H, Zhou D, et al. Modulation of *hslo* BK current inactivation by fatty acid esters of CoA. J Neurochem. 2008; 104:1394–1403. [PubMed: 18005338]

72. Lee JE, Kwak J, Suh C, et al. Dual effects of nitric oxide on the large conductance calcium-activated potassium channels of rat brain. J Biochem Mol Biol. 2006; 39:91–96. [PubMed: 16466643]

73. Nishimura I, Ui-Tei K, Saigo K, et al. 17β-estradiol at physiological concentration augments Ca^{2+}-activated K^+ currents via estrogen receptor β in the gonadotropin-releasing hormone neuronal cell line GT1-7. Endocrinology. 2008; 149:774–782. [PubMed: 17962348]

74. Liu J, Vaithianathan T, Manivannan K, et al. Ethanol modulates BK_{Ca} channels by acting as an adjuvant of calcium. Mol Pharmacol. 2008; 74:628–640. [PubMed: 18552122]

75. Bond CT, Herson PS, Strassmaier T, et al. Small conductance Ca^{2+}-activated K^+ channel knock-out mice reveal the identity of calcium-dependent afterhyperpolarization currents. J Neurosci. 2004; 24:5301–5306. [PubMed: 15190101]

76. Faber ES, Sah P. Ca^{2+}-activated K^+ (BK) channel inactivation contributes to spike broadening during repetitive firing in the rat lateral amygdala. J Physiol. 2003; 2:552. 483–497.

77. Hu H, Shao LR, Chavoshy S, et al. Presynaptic Ca^{2+}-activated K^+ channels in glutamatergic hippocampal terminals and their role in spike repolarization and regulation of transmitter release. J Neurosci. 2001; 21:9585–9597. [PubMed: 11739569]

78. Rundén-Pran E, Haug FM, Storm JF, et al. BK channel activity determines the extent of cell degeneration after oxygen and glucose deprivation: a study in organotypical hippocampal slice cultures. Neuroscience. 2002; 112:277–288.

79. Shao LR, Halvorsrud R, Borg-Graham L, et al. The role of BK-type Ca^{2+}-dependent K^+ channels in spike broadening during repetitive firing in rat hippocampal pyramidal cells. J Physiol. 1999; 521:135–146. [PubMed: 10562340]

80**. Gu N, Vervaeke K, Storm JF. BK potassium channels facilitate high-frequency firing and cause early frequency adaptation in rat CA1 hippocampal pyramidal cells. J Physiol. 2007; 580:859–882. Extracellular field recordings show that BK_{Ca} channels contribute to high frequency burst firing in response to strong depolarizing current. [PubMed: 17303637]

81**. Brenner R, Chen QH, Vilaythong A, et al. BK channel β4 subunit reduces dentate gyrus excitability and protects against temporal lobe seizures. Nat Neurosci. 2005; 8:1752–1759. Genetic deletion of BK_{Ca} channel β4 subunit gives rise to the channel gain-of-function mechanisms associated with temporal lobe seizures. [PubMed: 16261134]

82**. Jin W, Sugaya A, Tsuda T, et al. Relationship between large conductance calcium-activated potassium channel and bursting activity. Brain Res. 2000; 860:21–28. The authors report that BK_{Ca} channels contribute to bursting activity. Interestingly, blockade these channels suppresses epileptiform bursting in various models of acute seizures. [PubMed: 10727620]

83. Wang B, Rothberg BS, Brenner R. Mechanism of increased BK channel activation from channel mutation that causes epilepsy. J Gen Physiol. 2009; 133:283–294. [PubMed: 19204188]

84. Yang J, Krishnamoorthy G, Saxena A, et al. An epilepsy/dyskinesia-associated mutation enhances BK channel activation by potentiating Ca^{2+} sensing. Neuron. 2010; 66:871–883. [PubMed: 20620873]

85. Cavalleri GL, Weale ME, Shianna KV, et al. Multicentre search for genetic susceptibility loci in sporadic epilepsy syndrome and seizure types: a case-control study. Lancet Neurol. 2007; 6:970–980. [PubMed: 17913586]

86. Riazi MA, Brinkman-Mills P, Jonhson A, et al. Identification of a putative regulatory subunit of a calcium-activated potassium channel in the dup(3q) syndrome region and a related sequence on 22q11. 2 Genomics. 1999; 62:90–94. [PubMed: 10585773]

87. Sander T, Schulz H, Saar K, et al. Genome search for susceptibility loci of common idiopathic generalized epilepsies. Hum Mol Genet. 2000; 9:1465–1472. [PubMed: 10888596]

88**. Lorenz S, Heils A, Kasper JM, et al. Allelic association of a truncation mutation of the KCNMB3 gene with idiopathic generalized epilepsy. Am J Med Genetics. 2007; 144B:10–13. This study reveals an allelic association with of the KCNMB3 delA750 mutation with common idiopathic generalized epilepsy, particularly absence epilepsy. [PubMed: 16958040]

89. Ermolinsky B, Skinner F, Garcia I, et al. Upregulation of STREX splice variant of the large conductance Ca^{2+}-activated potassium (BK) channel in a rat model of mesial temporal lobe epilepsy. Neurosci Res. 2011; 69:73–80. [PubMed: 20933547]

90. Kudin AP, Zsurka G, Elger CE, Kunz WS. Mitochondrial involvement in temporal lobe epilepsy. Exp Neurol. 2009; 218:326–332. [PubMed: 19268667]

91. Bindokas VP, Lee CC, Colmers WF, et al. Changes in mitochondrial function resulting from synaptic activity in the rat hippocampal slice. J Neurosci. 1998; 18:4570–4587. [PubMed: 9614233]

92. Rong Y, Doctrow SR, Tocco G, et al. EUK-134, a synthetic superoxide dismutase and catalase mimetic, prevents oxidative stress and attenuates kainate-induced neuropathology. Proc Natl Acad Sci USA. 1999; 96:9897–9902. [PubMed: 10449791]

93*. Shruti S, Clem LR, Barth AL. A seizure-induced gain-of-function in BK channels is associated with elevated firing activity in neocortical pyramidal neurons. Neurobiol Dis. 2008; 30:323–330. Picrotoxin-induced generalized tonic-clonic seizures give rise to BK_{Ca} channels gain-of-function mechanisms in pyramidal neurons of primary somatosensory (barrel) cortex. [PubMed: 18387812]

94. Sheehan JJ, Benedetti BL, Barth AL. Anticonvulsant effects of the BK-channel antagonist paxilline. Epilepsia. 2009; 50:711–720. [PubMed: 19054419]

95*. Verma-Ahuja S, Evans MS, Espinosa JA. Evidence of increased excitability in GEPR hippocampus preceding development of seizure susceptibility. Epilepsy Res. 1995; 31:161–173. Inherited loss-of-function BK_{Ca} channels may contribute to the pathophysiology of inherited seizure susceptibility in the genetically epilepsy-prone rats. [PubMed: 9722027]

96. N'Gouemo P, Yasuda RP, Faingold CL. Protein expression of small conductance calcium-activated potassium channels is altered in inferior colliculus neurons of the genetically epilepsy-prone rat. Brain Res. 2009; 1270:107–111. [PubMed: 19254702]

97**. Pacheco Otalora LF, Hernandez EF, Arshadmansab MF, et al. Down-regulation of BK channel expression in the pilocarpine model of temporal lobe epilepsy. Brain Res. 2008; 1200:116–131. Downregulation of BK_{Ca} channel proteins is associated with the development of temporal lobe epilepsy. [PubMed: 18295190]

98**. Ermolinsky B, Arshadmansab MF, Patcheco Otalora LF, et al. Deficit of Kcnma1 mRNA expression in the dentate gyrus of epileptic rats. Neuro Report. 2008; 18:1291–1294. Downregulation of the gene encoding for BK_{Ca} channel **α** subunit is associated with the development of temporal lobe epilepsy.

99**. Young KL, Villar D, Carson TL, et al. Tremorgenic mycotoxin intoxication with penitrem A and roquefortine in two dogs. J Am Vet Med Assoc. 2003; 222:52–53. The authors report that BK_{Ca} channels blockade triggers seizures and status epilepticus, providing a compelling evidence of the role of these channels in seizure etiology. [PubMed: 12523480]

100. Crunelli V, Leresche N. Block of thalamic T-type Ca^{2+} channels by ethosuximide is not the whole story. Epilepsy Curr. 2002; 2:53–56. [PubMed: 15309166]

Highlights Box

- BK_{Ca} channels are activated by both membrane depolarization and increased intracellular Ca^{2+}.
- Outward K^+ currents through BK_{Ca} channels hyperpolarize neurons.
- Blockage of BK_{Ca} channels can trigger seizures and status epilepticus.
- Genetic deletion of the regulatory BK_{Ca} channel β4 subunit triggers temporal lobe seizures.
- Mutation in the KCNMB3 gene encoding for the regulatory BK_{Ca} channels β3 subunit is associated with idiopathic generalized epilepsy.
- Loss-of-function mechanisms of BK_{Ca} channels have been associated with temporal lobe seizures, tonic-clonic seizures and alcohol withdrawal seizures.
- Gain-of-function mutations in BK_{Ca} channel pore-forming α subunit contribute to the development of absence epilepsy.
- Generalized tonic-clonic seizures can confer a gain-of-function effect to BK_{Ca} channels
- Both loss-of-function and gain-of-function BK_{Ca} channels may be potential therapeutic targets for certain epilepsy syndromes.