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Targeting BK (big potassium) Channels in Epilepsy

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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).

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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, Ca²⁺-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 Ca²⁺-activated K⁺ (BK_{Ca}) channels, which are gated by membrane depolarization and rise in intracellular Ca²⁺ ([Ca²⁺]_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 Ca²⁺ provides an important negative-feedback system for controlling Ca²⁺ entry into neurons, either by deactivating voltage-gated Ca²⁺ (Ca_v) channels or increasing the activity of the Na⁺/Ca²⁺ exchangers, thus regulating Ca²⁺-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 Ca²⁺ 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 Ca²⁺ 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 Ca²⁺-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 [Ca²⁺]_i and membrane depolarization. The mechanisms of Ca²⁺ 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 Ca²⁺ such that >10 μM [Ca²⁺]_i is required for channel activation [7]. This sensitivity of BK_{Ca} channels to Ca²⁺ is an important negative feedback mechanism for controlling Ca²⁺ entry and subsequent Ca²⁺-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 Ca²⁺-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 Ca²⁺ and other intracellular stimuli [13,14,15]. The distal region (S9-S10 segments) or tail domain of the C-terminus contains the Ca²⁺ bowl, an aspartate-rich region that is a structural element of the RCK2 domain [13,15]. Each BK_{Ca} channel α -subunit contains two tandem RCK1-RCK2 domains [14], and the channel sensitivity to Ca²⁺ 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 Ca²⁺-dependent in the C-terminus.

BK_{Ca} channels have at least one low-affinity and two high-affinity Ca²⁺-recognition sites. The high-affinity Ca²⁺ recognition sites are located in RCK1 domain [17,18] and in the Ca²⁺ bowl of RCK2 domain [13,15,19]. The low-affinity Ca²⁺ 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 [Ca²⁺]_i is in the range of a few hundred nanomolar to tens of micromolar), the low-affinity Ca²⁺-recognition site(s) is not occupied by Ca²⁺ [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 [Ca²⁺]_i.

In addition to membrane depolarization and increased [Ca²⁺]_i, BK_{Ca} channels are also activated by intracellular Mg²⁺ [20,21] and the low-affinity Ca²⁺-recognition site in RCK1 also mediates the channel's sensitivity to Mg²⁺ [20,21,22]. In addition, the Ca²⁺ bowl in RCK2 also binds Mg²⁺, 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 Ca²⁺ 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 Ca²⁺ 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 β 1 through β 4) have been identified thus far, each encoded by a specific gene *KCNMB1-4* (human) or *Kcnmb1-4* (mouse) [30]. In non-excitabile cells, a novel BK_{Ca} channel auxiliary subunit, leucine-rich repeat containing protein (LRRC26) that is unrelated to the neuronal β 1–4 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 β 1 subunit enhances Ca²⁺ sensitivity of BK_{Ca} channels and slows the rate of channel opening, whereas β 2 subunit confers fast inactivation kinetics [35,36]. The β 3 subunit increases BK_{Ca} channel activity [7,36] and alternative splicing of this gene's RNA produces four distinct isoforms (β 3a-d), each of which has four sequence variants (V1-V4) [37,38]. The (β 3a through (β 3c subunits cause partial inactivation of BK_{Ca} channels [38], whereas the β 3d subunit has no obvious effect on channel gating [38]. Of the four variants in the β 3 subunit family, only the V4 variant of the β 3 subunit markedly alters the channel's gating properties, including its fast inactivation kinetics [37]. Finally, the brain-specific BK_{Ca} channel regulatory β 4 subunit increases and decreases channel activity in high and low [Ca²⁺]_i, respectively [7]. The β 4 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 β 4 subunit inhibits STREX variant channels via a Ca²⁺-dependent mechanism [40]. Thus, at low [Ca²⁺]_i, the β 4 subunit reduces the open probability of the STREX variant channel by slowing its activation. At intermediate and high [Ca²⁺]_i (i.e., >5.3 μ M), the β 4 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, β 4 subunit slows both the activation and deactivation kinetics of ZERO variant channels. Thus, it has been suggested that local Ca²⁺ environment in combination with ZERO or STREX variant BK_{Ca} channels will determine whether β 4 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 Ca²⁺ 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 mitoBK_{Ca} 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 β 1 and β 4 subunit expression seems focused to non-CNS and CNS tissues, respectively [50]. In the CNS, the expression of BK_{Ca} channel β 2, β 3, and β 4 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 β 1 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 β 4 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 β 4-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 Ca²⁺ and pH, regulate BK_{Ca} channel activity [52,53]. For instance, BK_{Ca} channels are activated by micromolar increases in [Ca²⁺]_i levels. Such increases in [Ca²⁺]_i levels are restricted to “Ca²⁺-nano/microdomains” in the immediate vicinity of the Ca²⁺ source. In the CNS, the Ca²⁺ 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 Ca²⁺ 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 β 2 or β 4 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 Ca²⁺ influx, BK_{Ca} channels also are activated by Ca²⁺ that is released from intracellular ryanodine-gated Ca²⁺ pools [57]. Whether Ca²⁺ released from inositol triphosphate-gated Ca²⁺ 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 Ca²⁺ release from intracellular Ca²⁺-gated stores and Ca²⁺ 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 [Ca²⁺]_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 (Zn²⁺) is an important intracellular molecule that may play an essential role in the control of neuronal excitability, as intracellular Zn²⁺ ([Zn²⁺]_i) activates BK_{Ca} channels [62]. Conversely, reduced [Zn²⁺]_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 Zn²⁺ is abundant in mossy fibers. In a model of TLE, Zn²⁺ 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 [Zn²⁺]_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 tetraethylammonium (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 venom 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 Ca²⁺-dependent chloride channels [66]. Paxilline blocks BK_{Ca} channels-containing β 4 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 (α KTX 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/β 1 and α/β 4 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 as NS11021, biaryl amines (mefenamic and flufenamide acid), diaryl ureas (NS 1609), pyridyl amines, 3-aryloxin-oles, 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, 17 β -estradiol increases BK_{Ca} channel currents by enhancing both channel opening and the expression of both α and β 4 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 Ca²⁺-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 Ca²⁺ 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 β 4 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 [Ca²⁺]_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 [Ca²⁺]_i increases by repolarizing the membrane, deactivating Ca_v channels and increasing activity of the Na⁺/Ca²⁺ exchanger.

Neuronal mitochondria are an important system for sequestering [Ca²⁺]_i. Physiologically, mitoBK_{Ca} 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 Ca²⁺ 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 [Ca²⁺]_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 Ca²⁺ 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 [Ca²⁺]_i following Ca²⁺ release from intracellular Ca²⁺-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 α-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 Ca²⁺, enhanced voltage- and Ca²⁺-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 Ca²⁺-dependent activation initiated at the Ca²⁺ 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 properties 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 β 2 subunits, and increases the channel function (i.e., opening rate) of BK_{Ca} channels containing β 1 and β 4 subunits but slows rates of both channel opening and closing of BK_{Ca} channels that contain β 3b subunits [35]. Interestingly, a polymorphism in the gene encoding the BK_{Ca} channel β 4 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} β 3 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 β 3 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 β 3b-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 β 4 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 β 4 subunits triggers seizures may include i) enhanced Ca²⁺ 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 β 4 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 $\beta 4$ 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 $\beta 4$ subunits may provide a molecular basis for both seizure resistance and neuroprotection.

The BK_{Ca} channel regulatory $\beta 4$ subunit in the inner mitochondrial membrane may also contribute to neuroprotection, 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 Ca²⁺ levels and changes in mitochondrial membrane potential [91]. Neuronal mitoBK_{Ca} channels would then, be activated due to rising [Ca²⁺] in the matrix in response to an increase in cytosolic Ca²⁺, 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 downregulation 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 pentylenetetrazole-induced generalized tonic-clonic seizures in animals that were not pre-sensitized [94]. These findings suggest the convulsant pre-sensitization may contribute 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 Ca²⁺ 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 β 4 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 Ca²⁺ 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 secondary 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 role in the management of seizure-induced lesions underlying the development of pharmacoresistant TLE.

To date, only the model of picrotoxin- and pentylentetrazole-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 β 4 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 β 3 and β 4 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.

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Highlights Box

- BK_{Ca} channels are activated by both membrane depolarization and increased intracellular Ca²⁺.
- 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 β 4 subunit triggers temporal lobe seizures.
- Mutation in the KCNMB3 gene encoding for the regulatory BK_{Ca} channels β 3 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.