Chapter 53

Potassium Channelopathies of Epilepsy

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INTRODUCTION

Channelopathies are inherited genetic changes in ion channel genes that generate a disease. Given the pivotal role of voltage-dependent potassium channels in moderating neuronal excitability, it is not surprising that these channels are well represented among the channelopathies contributing to epilepsy. Voltage-dependent potassium channels are regarded as the “initial responders” that shape and moderate depolarization of excitability cells. However, this oversimplification belies a heterogeneous mix of diverse voltage-dependent potassium channels in the nervous system that are specialized for function in different subcellular compartments, in different neuronal types, and, indeed, even at different voltages. Consistent with this, the uncovering of epilepsy channelopathies during the past two decades has revealed a number of potassium channels that contribute to epilepsy in distinct ways when genetically altered. This chapter provides a brief overview of the various potassium channelopathies that have so far been identified to contribute to epilepsy. In so doing, it also highlights the distinct functions that different potassium channels serve in regulating excitability and how they contribute to epilepsy when such functions are altered.

WHAT ARE POTASSIUM CHANNELS?

The minimal structures that comprise potassium channels are best represented by the
inward rectifier potassium channels (KCNJ family, Fig. 53–1). These channels include two transmembrane segments that flank a pore-loop domain. The transmembrane segments form an aqueous channel, and the pore-loop domain filters ions to selectively allow potassium flux. These components are conserved in all potassium channels. Binding of magnesium and polyamines at the intracellular vestibule of the channel is a property unique to the inward rectifier class of potassium channels that controls ion flux. Binding and occlusion of the pore occur at relatively positive but not negative voltages, therefore giving these channels the property of inward rectification (larger inward than outward conductance). Conduction through the channel is also regulated by conformational changes in the channel, either near the selectivity filter or at the second transmembrane segment that allows some inward rectifiers, such as the adenosine triphosphate (ATP)-sensitive potassium channels, to gate channel opening in response to intracellular signals such as ATP concentration.

Evolution and gene duplication have diversified the potassium channel family to include the twin pore channels (Fig. 53–1), which are thought to contribute to the “leak” resting potassium current and therefore affect resting membrane potentials. As well, an additional 4-transmembrane segment (S1–S4 segment) has been appended to the channel pore (S5–S6 segment) to create the 6-transmembrane channel family (Fig. 53–1). The 6-transmembrane family has diversified extensively, both to maintain potassium-selective channels and evolve members of nonselective cation channels not shown here. Among the 6-transmembrane potassium channels, some have evolved an intracellular domain that mediates the response to intracellular ion fluxes such as calcium-activated (KCNN) and sodium-activated (KCNT) potassium channels. The voltage-activated potassium channel family has charged transmembrane residues, located in the S4 segment, but additional residues may occur in the S1–S3 segment, which senses the membrane electric field and allosterically couples to the channel gate to promote channel opening. The voltage sensor domain not only affects the voltage sensitivity of channels (the relative change in open probability per change in voltage) but also determines the voltage ranges at which channels open. For example, voltage sensors may

**Figure 53–1.** The potassium channel gene family and epilepsy channelopathies. Family members are organized according to transmembrane structure. Genes within each family that are known to occur with epilepsy channelopathy mutations are boxed below in red. shaker-related channel genes that encode nonconducting subunits (KCNF, KCNG, KCNS, and KCNV channel genes) are not included in the diagram.
be tuned to activate at voltages below threshold to affect the resting membrane potential, near threshold to affect the action potential firing frequency, or at high voltages to contribute only to spike repolarization.

A subset of voltage-dependent potassium channels can undergo inactivation. This includes some members of the shaker and eag families of potassium channels. Inactivation is a transition from channel opening to closing despite continued depolarization. Inactivation is often mediated by an amino-terminal sequence (ball-and-chain sequence) that plugs the pore following channel opening and is called N-type inactivation. N-type inactivation is often relatively quick (in the tens to hundreds of milliseconds) and is mediated by amino terminal sequences intrinsic to the channel pore-forming subunit, or it can be conferred by accessory subunits that contain a ball-and-chain sequence. Inactivation can also be of a slow type (occurring over hundreds of milliseconds to seconds), called P- or C-type inactivation, that occurs by conformational changes at the pore. Fast inactivation of potassium channels is seen as A-type potassium currents. These currents repolarize membrane voltages during one or the first few action potentials but inactivate over multiple spikes. This may lead to a broadening of action potentials or higher action potential frequency during the late components of a spike train.

Members of the voltage-dependent potassium channels include a very large family, perhaps encompassing 32 channel genes in humans (see the HUGO list at http://www.genenames.org/genefamily/kcn.php) and outside the scope of this introduction. Figure 53–1 highlights those genes that have human epilepsy mutations. From this chart, we can see that the inward rectifiers potassium channel family contain two members, KCNJ10 and KCNJ11, that contribute to inherited epilepsies as part of more complex disorders (ataxia, sensorineural deafness, and kidney tubulopathy [EAST] and developmental delay, epilepsy, and neonatal diabetes [DEND] syndromes, respectively). The remaining and majority of the epilepsy potassium channelopathies reside among the voltage-dependent potassium family members. These include two members of the shaker-related family (KCNA1 and KCND2), two members of the KvLQT family (KCNO2 and KCNO3), and one member of the Slo-related family, KCNMA1. Below, we will provide a review of these various channel genes that contribute to epilepsy when mutated and attempt to describe what is known regarding the physiological basis for increased excitability.

**KCNA1**

Historically, human KCNA1 (Kv1.1) mutations were first identified as an autosomal dominant ataxia channelopathy that has subsequently been classified as episodic ataxia type 1 (EA1). Episodic ataxia type 1 occurs as brief episodes of discoordination induced by startle, stress, or heavy exertion. Patients may also experience continuous muscle movement (myokymia) either during or between attacks of ataxia. It was later found that a subset of individuals with KCNA1 mutations, T226R and A242P, also experience partial seizures. The T226R mutation causes EA1, myokymia, and partial-onset epilepsy. The A242P mutation does not cause ataxia, but does cause partial epilepsy and myokymia. An interesting observation was that the T226R mutation is penetrant for epilepsy only in some families or family members, suggesting that the KCNA1 epilepsy phenotype is sensitive to secondary environmental or genetic influences. As well, KCNA1 mutations have been identified that exhibit different comorbidities, such as partial epilepsy and myokymia but no ataxia, or mutations that exhibit myokymia alone. Thus, the different nature of KCNA1 mutations appears to also confer phenotypic variability.

**Effect of KCNA1 Epilepsy Mutations on Potassium Currents**

KCNA1 encodes potassium channels related to the Drosophila shaker family of voltage-gated potassium channels. KCNA1 currents differ from the shaker A-type currents due to a lack of intrinsic fast inactivation. However, in some cells, coassembly with the Kvbeta1 accessory subunits or heteromeric assembly with KCNA4 subunits confers fast inactivation. KCNA1 channels are often assigned to a low-voltage-threshold, fast-activated delayed rectifier potassium current that inactivates over a slow time period (hundreds of milliseconds). The two KCNA1 mutations causing epilepsy, T226R and A242P, are located in the
S2 transmembrane domain\textsuperscript{10,11} The common feature is that both mutations are likely to be hypomorphs since they dramatically reduce expression or trafficking of channels in expression systems.\textsuperscript{10,12,17,18} The T226R mutation also reduces channel function by shifting the conductance voltage relationship to positive potentials and dramatically slowing the activation time.\textsuperscript{17}

The correlation between KCNA1 hypomorphic mutations and epilepsy is also strengthened by knockout studies of the KCNA1 gene in mice.\textsuperscript{19} KCNA1 knockout mice have frequent spontaneous seizures, although ataxia is not apparent. Electrophysiological studies suggest normal intrinsic excitability but enhanced excitability related to axonal repolarization and propagation. These results are consistent with KCNA1 channel preferential expression in axons and presynaptic terminals.\textsuperscript{20,22} Studies of KCNA1 mutations expressed in neurons also suggest that epilepsy mutations (T226R) perturb presynaptic function rather than intrinsic excitability.\textsuperscript{22}

**KCNA1 and Sudden Unexplained Death in Epilepsy**

Recently, work on Kv1.1 channels has significantly advanced the understanding of the potential mechanisms of sudden unexplained death in epilepsy (SUDEP), which refers to death of unknown cause in individuals who have epilepsy. Death in these individuals is approximately 40-fold higher than in individuals without epilepsy.\textsuperscript{23} The work of Glasscock and colleagues indicates that increased excitability at parasympathetic nerves may contribute to SUDEP.\textsuperscript{24} This was revealed using KCNA1 knockout mice that are predisposed to SUDEP and have cardiac arrhythmias, including atrioventricular conduction block that is increased during seizures. The authors used the parasympathetic antagonist atropine to correct the arrhythmias, suggesting that KCNA1 channel defects may increase vagus nerve activity sufficiently to cause SUDEP.

**KCNA1 Channelopathy as a Consequence of LGI1 Mutations**

Voltage-dependent potassium channels are heavily regulated to alter their properties or expression, depending on the needs of the neuron. Mutation of the LGI1 protein presents one example of a situation in which genetic alteration of a potassium channel regulatory protein may contribute indirectly to epilepsy. The LGI1 protein was first identified as a candidate gene that is absent or downregulated in malignant brain tumors.\textsuperscript{25} Its acronym is based on the finding that it is a leucine-rich gene that is 	extit{inactive}d in gliomas. The LGI1 gene encodes a single transmembrane protein with leucine-rich repeats in the extracellular amino terminus that is similar to a family (F-20) of cell adhesion proteins and receptors.\textsuperscript{25} Linkage analysis and cloning have identified mutations in this gene as a cause of the inherited disorder autosomal dominant lateral temporal lobe epilepsy (ADLTE), also named 	extit{autosomal dominant partial epilepsy with auditory features} (ADPEAF).\textsuperscript{26–28} ADLTE occurs as simple partial seizures, of temporal lobe origin, with acoustic and sensory hallucinations. Some individuals also have a less frequent, secondarily generalized seizure. The LGI1 locus carries mutations in about 50% of all ADLTE families.\textsuperscript{25,26}

A connection between LGI1 and KCNA1 channels was discovered using biochemical purification of KCNA1 complexes that revealed coassembly of LGII1 protein.\textsuperscript{30} The KCNA1 channel also copurified a number of other proteins, including KCNA4 (Kv1.4) channels and KCNB1 (Kvbeta1), both of which assemble with and confer fast N-type inactivation properties on KCNA1 channels. A pivotal finding was that LGI1 occludes KCNB1-mediated increases in inactivation rates. This presumably creates a more sustained A-type current and may reduce excitability in neurons. The finding that ADLTE LGI1 mutants do not have antagonistic effects on KCNB1 inactivation suggests that LGI1 mutations may increase excitability in ADLTE patients through increase inactivation of KCNA1-containing, A-type currents.\textsuperscript{30}

A more thorough understanding of LGI1 mutation on the neurophysiology of ADLTE was provided using genetic mouse models of the disease. Knockout of the LGI1 gene causes severe myoclonic seizures in early life (12–20 days), and mice die shortly thereafter.\textsuperscript{31} Interestingly, heterozygous LGI1 null mice do not show a seizure phenotype, whereas ADLTE LGI1 individuals are heterozygous for a mutant allele.\textsuperscript{29} A transgenic study suggests that this can be explained by the mutant LGI1
protein in ADLTE patients acting in a dominant negative manner on wild-type protein.\textsuperscript{32}

Consistent with LGI1 protein action on KCNA1 channels, LGI1 knockout had no effect on intrinsic properties of neurons, but it increased spontaneous glutamate-mediated excitatory postsynaptic potentials.\textsuperscript{33} In addition, transgenic expression of the ADLTE truncation mutant of LGI1 in mice also increased excitatory synaptic transmission.\textsuperscript{34} However, studies suggest that LGI1 has multiple interacting protein targets and that the mechanism for increased excitability is complex. Besides producing mutant LGI1 effects on presynaptic KCNA1 channels,\textsuperscript{35} LGI1 interacts with the postsynaptic protein ADAM22\textsuperscript{36} and has effects on synapse maturation\textsuperscript{37} that may also contribute to seizures when mutated.

**KCND2**

**KCND2 AND A-TYPE CURRENTS**

The KCND2 channel contributes to voltage-gated potassium currents that undergo fast inactivation and are broadly classified as A-type currents (I\textsubscript{A}). Among the genes contributing to A-type current, KCND2 and its family members (KCND1–3, also called Kv4.1-Kv4.3) are activated at subthreshold voltages and enriched in somato-dendritic compartments, and therefore have the more specialized designation of the I\textsubscript{A} current.\textsuperscript{38} One of these family members (KCND3) also underlies the transient outward (I\textsubscript{TO}) current of the cardiac action potential in humans.\textsuperscript{39}

**KCND2 Channelopathy Mutation**

The KCND2 potassium channel is an ion channel that has been heavily studied for its role in acquired epilepsy, whereas its role as a potassium channelopathy gene requires further study. Evidence of KCND2 channels as a channelopathy mutation is limited to a report of a single individual identified in a genetic screen of individuals with temporal lobe epilepsy.\textsuperscript{40} Sequencing of the KCND2 locus identified a carboxyl terminal 5 nucleotide deletion that leads to a premature stop codon and truncation of the last 44 amino acids of the protein.\textsuperscript{41} Electrophysiology studies in transfected HEK293 cells did not detect discernible effects on channel gating. However, the average current density of transfected cells is reduced by approximately half, suggesting that the mutation is a hypomorph due to reduced current density. Whether this mutation is responsible for, or coincident with, epilepsy in this single patient is uncertain, particularly since genetic ablation of KCND2 is insufficient to cause spontaneous seizures in mice.

**Acquired Changes in KCND2 and Seizures**

Our understanding of I\textsubscript{A} current and KCND channels in epilepsy mainly concerns their role in the control of dendritic excitability. These currents have often been studied in CA1 dendrites that are sufficiently large at distances from the soma at which they can be detected by sophisticated patch-clamp recording techniques. The I\textsubscript{A} current is expressed as a gradient, being more enriched at distal versus proximal dendrites.\textsuperscript{42} The contribution of this current by KCND2 is confirmed by immunohistochemistry\textsuperscript{43} and also by gene knockout of KCND2 that largely eliminates the dendritic I\textsubscript{A} current.\textsuperscript{44} An important function of this I\textsubscript{A} gradient is to limit the amplitude of backpropagating action potentials to distal dendrites.\textsuperscript{45} This provides a repolarizing current that limits excitability and activation of N-methyl-D-aspartate (NMDA) receptors that otherwise enhance the long-term potentiation of synapses. Importantly, the I\textsubscript{A} current is inhibited by both protein kinase A and protein kinase C phosphorylation that is upstream of ERK kinase phosphorylation of channels. The sensitivity of KCND2 to these kinases makes dendrites particularly prone to enhanced excitability following changes in any number of signaling cascades that alter these kinases. With regard to epilepsy, ERK inhibition of Kv4.2, coupled with transcriptional downregulation, appears to mediate enhanced dendritic excitability and seizures following pilocarpine-induced status epilepticus.\textsuperscript{46} In addition models of cortical and hippocampal malformations that are prone to seizures also show a correlative reduction in Kv4.2 expression and current in heterotopic cell regions.\textsuperscript{47} Finally, knockout of Kv4.2 also demonstrates increases susceptibility to seizures following convulsant stimulation.\textsuperscript{48}
**KCNMA1**

**KCNMA1 AND THE BK CHANNEL**

The KCNMA1 gene encodes large-conductance potassium channels that are dually activated by calcium and voltage. In accordance with their name (BK channel, “big K conductance”), these channels tower over most voltage-gated channels in single-channel conductance (~250 pS, more than 20-fold larger than shaker-type potassium channels) and can potentially have dramatic effects on membrane voltage.\(^{42}\)

Interestingly, only the single KCNMA1 gene encodes this class of potassium channel. Their large conductance combined with their broad distribution means that these channels are relatively easy to detect and have been characterized in many cell types. BK channels are observed in skeletal and smooth muscle cells, central nervous system (CNS) and peripheral nervous system (PNS) neurons, endothelial and kidney epithelial cells, and other cell types. Gene identification was made possible by cloning of the *Drosophila* Slowpoke gene locus and cDNA.\(^{43}\) Therefore, these channels are also called slo channels or muslo or hsklo for their mouse or human orthologues, respectively. Although they have structural homology to other voltage-dependent potassium channels, BK channels have an additional amino-terminal transmembrane domain (designated S0) and a large carboxyl terminal domain that has structural domains for two calcium-binding sites per subunit.\(^{44}\) Finally, a family of four tissue-specific accessory \(\beta\) subunits modulates the biophysical properties and pharmacology of BK channels.\(^{35}\)

**KCNMA1 Gating Properties**

Understanding the biophysical properties of BK channels allows us to infer some principles of channel function that are borne out by studies in native cells. The first is that BK channels are effectively activated by calcium concentrations (micromolar) not normally occurring at global concentrations (hundreds of nanomolars). The BK current evoked by action potential-shaped voltage waveforms provides an estimate of 14 \(\mu\)M calcium required to evoke half-maximal current.\(^{46}\) Thus, BK channels often require colocalization with a calcium source for significant activation.\(^{47}\) Second, there are examples of BK regulation by numerous mechanisms, including alternative splicing, accessory subunits, phosphorylation status, and redox state. Therefore, BK channel gating properties appear to be tightly regulated for their local calcium environment. Finally, BK channel opening is sensitive in a roughly additive fashion to both calcium and voltage.\(^{48}\)

Thus, BK channels are well tailored for repolarization of action potentials that are coincident with calcium transients, such as occur during action potentials in the soma or in presynaptic nerve terminals. The combined voltage and calcium sensitivity also means that BK channels deactivate following repolarization of action potentials, which restrict their contribution to the fast component of the afterhyperpolarization. Other purely calcium-sensitive potassium channels, such as SK channels, are not deactivated by repolarization and usually contribute to a more sustained (medium) afterhyperpolarization.\(^{49}\)

**BK Channel Function in Neurons**

Owing to their broad tissue distribution, the physiological roles of BK channels are quite diverse. Indeed, limiting the focus of this review on epilepsy overlooks a large body of knowledge concerning BK channels outside the nervous system. These include control of tonic and phasic smooth muscle constriction, in renal control of potassium secretion, and control of hormone release of many secretory cells. However, even in the nervous system, BK channels have been studied within many different neuronal compartments and within many neuronal types.

BK channel effects are often uncovered with the highly specific scorpion toxin iberotoxin, or with charybdoxin, which also blocks intermediate-conductance potassium channels (IK channels).\(^{42}\) Worth noting is that the affinity for scorpion toxin is reduced by some beta accessory subunits and shows little block with the accessory beta4 subunit.\(^{50}\) However, organic blockers, such as paxilline, which have more recently come into use, block BK channels independently of beta subunit composition.\(^{51}\)

Blocking BK channels causes broadening of the action potential and, in some neurons, eliminates the fast component of the afterhyperpolarization.\(^{49}\) In CA1 and lateral amygdala...
BK Channels and Acquired Epilepsy

The first evidence that BK channels may enhance the excitability related to seizures was obtained in cultured cortical neurons. The gamma-aminobutyric acid (GABA) antagonist and convulsant pentyleneetetrazol (PTZ) causes bursting activity in cultured cortical neurons. Treatment of cells with the BK channel blocker iberiotoxin inhibited bursting activity in PTZ-treated and pro-epileptic L mouse cortical neurons. In a picrotoxin seizure model, it was also observed that increased firing rates in cortical neurons could be attenuated by BK channel block. Interestingly, the effectiveness of BK channel block occurs during the second but not the first picrotoxin treatment. This suggests that BK channels are part of a maladaptive upregulation in cortical neurons following seizures. Further, it was shown that systemic injection of the BK channel blocker paxilline was effective in protecting against subsequent picrotoxin-induced seizures.

Human BK Channel Epilepsy Channelopathy

The BK channel pore-forming subunit knockout mice have a plethora of defects, including slowed growth rates, cerebellar dysfunction and ataxia, defects in circadian rhythms, and a number of defects due to smooth muscle hypercontractility. Interestingly, seizures have not been reported in KCNM1 knockout mice. Rather, it is a gain-of-function mutation that causes nonconvulsive seizures in humans. The effect is partially penetrant, showing apparent absence type seizures in 9 of 16 affected family members. The polymorphism also causes 12 of the 16 family members to have a paroxysmal nonkinesigenic dyskinesia. The single aspartate-to-glycine (D434G) amino acid change resides in one of the calcium activation domains (RCK domain, regulator of conductance of potassium) in the pore-forming alpha subunit. Interestingly, expression of the mutant channels in Xenopus oocytes or cultured cells demonstrates an increased current due to faster activation and an increased open probability. More detailed biophysical studies suggest that the mutation affects calcium-dependent gating and may also directly reduce the energetic barrier to opening.

The mechanisms by which the BK channel D434G gain-of-function mutation causes epilepsy in humans will require a transgenic animal model for greater understanding. Reduced excitability in inhibitory neurons may explain the seizures; however, BK channel expression predominates in excitatory principal neurons of most brain regions, including the cortex and hippocampus. An exception is brainstem vestibular neurons, where BK channels moderate high-frequency action potential firing. Alternatively, it may be that the human BK channel gain of function acts in a manner similar to that seen in CA1 pyramidal neurons, where BK channels sharpening of action potentials secondarily increases excitability. A similar effect is also seen in the BK channel β4 knockout mice. The β4 accessory subunit inhibits BK channel opening through a slowing of activation, and therefore the β4 knockout mice may also be considered a gain-of-function model. In these animals, epilepsy is also observed, although because of the strong localization of β4 in the hippocampus, the seizures appear to be secondarily generalized with a temporal lobe origin. Thus, there are at least two genetic models and one acquired seizure model to support the paradoxical findings that BK potassium channels increase excitability and can lead to seizures.
KCNQ Channelopathy Mutations

The M-type potassium current (I\(_M\)) regulates the resting membrane potential and spike frequency adaptation and can contribute to slow afterhyperpolarization following action potentials. In addition, a large number of mutations in two genes encoding the subunits that comprise the M-channel, KCNQ2 (Kv7.2) and KCNQ3 (Kv7.3), result in the seizure disorder benign familial neonatal convulsions (BFNC). In BFNC, seizures typically begin within the first 3 days of life and can be partial or generalized. Importantly, the seizures remit spontaneously and normal development follows in the majority of cases, although the incidence of later seizures is higher than in the general population in some families. The initial findings implicating the Kv7.2 and Kv7.3 channelopathies in BFNC were the first to link mutations in potassium channels to a familial epilepsy. While different mutations in KCNQ3 have been identified to date, at least 63 different mutations in KCNQ2 have been observed in families with BFNC. In addition, de novo KCNQ2 mutations have been identified in patients with benign neonatal seizures whose seizures also remit. Many of these mutations result in a haploinsufficiency of these channels, while other mutations, such as those that occur in the pore region of the channels, result in a reduction of function. In addition, a number of mutations in KCNQ2 are located in transmembrane regions of channels and can alter gating properties. Therefore, it is thought that the newborn seizures that occur as a consequence of these mutations are due to a reduction of function of the M-type channels and a concomitant increase in excitability of neurons. Mutations in KCNQ2 that cause BFNC have also been associated with other disorders as well, such as rolandic epilepsy, drug-resistant epilepsy, and/or mental retardation. Therefore, mutations in these channels have attracted considerable attention over the last decade, especially as a novel anticonvulsant, retigabine (RGB), has as its primary mechanism of action a shift in the activation curve for I\(_M\) to a more hyperpolarized potential. This finding, coupled with the genetic findings described above, has garnered enthusiasm for consideration of the M-channel as a potential and novel therapeutic target for the treatment of seizures.

KCNQ Mutations and Animal Models

To study the contribution of mutations in the M-channel to seizure disorders, a number of animal models have been developed. These include the Kcnq2 knockout mouse, the dominant-negative Kcnq2 G279S mutation, the Szt1 spontaneous deletion mouse strain, the Kcnq2 A306T knockin mouse, and the Kcnq3 G311V knockin mouse. Mice homozygous for both the Kcnq2 knockout and Szt1 mutations are lethal, dying soon after birth due to a lung defect. However, mice heterozygous for the Kcnq2 knockout and the Szt1 mutation, are viable. In addition, all of the knockin mice that have been generated to date are viable, even when homozygous for the mutations. Electrophysiology experiments performed on CA1 neurons in the in vitro hippocampal brain slices obtained from these mouse models have uniformly found decreased I\(_M\) amplitude, decreased current density, and, when examined, a reduction in action potential accommodation compared to their wild-type C57BL/6 littermates. In addition to the observed alterations found in the membrane currents, significant differences in I\(_M\) pharmacology in CA1 neurons recorded from Szt1 mice have been observed. These differences have intriguing parallels to the results of in vivo experiments in the Szt1 mice, including a highly significant decrease in sensitivity to RBG. These results have profound implications for pharmacotherapy, as they suggest that antiepileptic drugs that target the M-channel, such as retigabine and flupirtine, may be less effective in patients with underlying KCNQ2 mutations that result in a haploinsufficiency.

KCNQ1

A member of the Kv7 family of potassium channels, Kv7.1, is encoded by the KCNQ1 gene and forms the \(\alpha\) subunit of this potassium channel. Kv7.1 is expressed in cardiac tissue, and mutations in this gene have been linked to the long QT syndrome (LQTS) and fatal cardiac arrhythmias. Over 300 mutations have been identified in this gene, and many of those mutations result in a prolongation of the cardiac action potential and sudden death.
been thought that this gene was not expressed in the CNS, but recent work has convincingly demonstrated that in fact KCNQ1 is expressed in brain.\textsuperscript{94} In two mouse lines with LQT\textsubscript{3} mutations, Kcnq1 A340E and T311I, mice heterozygous and homozygous for the mutations have cardiac abnormalities, as well as exhibiting both partial and generalized seizures.\textsuperscript{94} In addition, at least one mouse in the study was observed to die following a prolonged period of seizure activity, bradycardia, cardiac depression, and ultimately cardiac arrest.\textsuperscript{94} As SUDEP may be responsible for a large percentage of deaths in patients with epilepsy, these findings provide support for evaluating the LQT\textsubscript{3} genes in patients with epilepsy and concomitant cardiac irregularities.

**KCNJ10**

The inward-rectifying potassium channel (Kir\textsubscript{4.1}) is highly expressed in glial cells in the CNS, as well as in cochlear, cardiac, kidney, and other tissues, and is encoded by the KCNJ10 gene. Kir channels expressed by glial cells buffer extracellular potassium in the CNS following neuronal action potentials and are primarily responsible for maintaining low extracellular levels of potassium in the CNS. Quantitative trait loci mapping experiments first identified a mutation in the mouse Kcnj10 gene that was correlated with a reduction in seizure susceptibility in the DBA/2 mouse,\textsuperscript{85} and a variation in the human KCNJ10 has also been found to be associated with common forms of human epilepsy.\textsuperscript{96–98} Furthermore, coding region mutations in the KCNJ10 gene that are linked to a familial form of epilepsy with ataxia, sensorineural deafness, and kidney tubulopathy (EAST syndrome) have recently been identified.\textsuperscript{99,100} When KCNJ10 is expressed in CHO cells, these mutations are found to result in a loss of (or greatly reduced) function.\textsuperscript{101} In addition, recent work has demonstrated that astrocytes from DBA/2 mice, which harbor the initially described variant, have a decreased Kir current and also exhibit a reduction in glutamate transport compared to the more seizure-resistant strain of mice, C57Bl/6.\textsuperscript{102} Therefore, variants of KCNJ10 may be associated with common forms of human epilepsy by reducing seizure thresholds. However, there are also rare mutations in this gene that can underlie familial types of epilepsy that are part of a more complex phenotype.

**KCNJ11**

The KCNJ11 gene encodes the Kir 6.2 protein that comprises the pore region of the ATP-sensitive potassium channel (K\textsubscript{ATP}).\textsuperscript{103} Not only is Kir 6.2 highly expressed in brain, but it is also found in pancreatic β cells. When the intracellular levels of ATP are high, the ion channel in both neurons and β cells is closed, allowing for depolarization, action potential generation, and the release of neurotransmitters and insulin, respectively.\textsuperscript{104} However, to conserve energy, when intracellular levels of ATP are low, the ion channel opens and causes a hyperpolarization of both neurons and β cells, thus inhibiting action potential generation, calcium influx, and the release of either neurotransmitters or insulin, respectively. Mutations in the KCNJ11 gene that reduce the affinity for ATP and increase the probability of channel opening result in a syndrome characterized by developmental delay, epilepsy, and neonatal diabetes (DEND).\textsuperscript{105,106} The diabetes results from a reduced ability to release insulin due to membrane hyperpolarization that occurs as the ion channel remains open. It is hypothesized that increased expression of K\textsubscript{ATP} channels in inhibitory neurons may underlie the epilepsy that occurs in DEND. Such a gain-of-function mutation in a potassium channel is paradoxical and resembles that observed in the BK channels described above. In a recently published case study of a DEND patient, treatment with a sulfonylurea drug, glibenclamide, successfully treated the diabetes and permitted insulin therapy to be halted, most likely as a consequence of blocking the K\textsubscript{ATP} channel.\textsuperscript{106,107} This block aids in the depolarization of the β cells of the pancreas and allows insulin release to resume. Interestingly, following treatment with glibenclamide, the seizures were substantially diminished and the arrhythmia observed on the patient’s sleep electroencephalogram was resolved.\textsuperscript{106} While generalized sharp-wave activity was still observed during sleep, this patient demonstrated substantial psychomotor improvement. This suggests that early diagnosis and treatment of DEND could result in preventing seizures and concomitant psychomotor impairments.\textsuperscript{105}
CONCLUSIONS

An exceedingly large number of familial and de novo channelopathies in several different types of potassium channels have already been found to underlie, or be associated with, many types of epilepsy. Given that the role of most potassium channels is to contribute to the maintenance of membrane hyperpolarization and repolarization, it is not surprising that loss-of-function mutations contribute to epilepsy. However, recently described potassium channelopathies resulting in gain of function can also, paradoxically, result in epilepsy. Furthermore, as many LQTS mutations arise in potassium channels, a link between epilepsy, SUDEP, and LQTS, as has now been observed for KCNQ1, may begin to inform prevention strategies for patients at risk for SUDEP. Finally, animal models harboring human mutations found in potassium channels have contributed greatly to our understanding of the mechanisms whereby specific channelopathies contribute to epilepsy, and it is anticipated that as this field continues to develop, advances in treatment strategies for patients will also be elucidated from such animal models.

DISCLOSURE STATEMENT

The authors have nothing to disclose.

REFERENCES


53. Potassium Channelopathies of Epilepsy 697


698 Jasper’s Basic Mechanisms of the Epilepsies, 4th Ed.


