Potassium Channels in Epilepsy

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This review attempts to give a concise and up-to-date overview on the role of potassium channels in epilepsies. Their role can be defined from a genetic perspective, focusing on variants and de novo mutations identified in genetic studies or animal models with targeted, specific mutations in genes coding for a member of the large potassium channel family. In these genetic studies, a demonstrated functional link to hyperexcitability often remains elusive. However, their role can also be defined from a functional perspective, based on dynamic, aggravating, or adaptive transcriptional and posttranslational alterations. In these cases, it often remains elusive whether the alteration is causal or merely incidental. With ~80 potassium channel types, of which ~10% are known to be associated with epilepsies (in humans) or a seizure phenotype (in animals), if genetically mutated, a comprehensive review is a challenging endeavor. This goal may seem all the more ambitious once the data on posttranslational alterations, found both in human tissue from epilepsy patients and in chronic or acute animal models, are included. We therefore summarize the literature, and expand only on key findings, particularly regarding functional alterations found in patient brain tissue and chronic animal models.

INTRODUCTION TO POTASSIUM CHANNELS

Potassium (K) channels are related to epilepsy syndromes on many different levels, ranging from direct control of neuronal excitability and homeostasis of ion milieu to indirect effects via metabolism. We discuss K channels and their relevance to epilepsy (1), in particular, with respect to genetic alterations in humans (2) and animal models (3), as well as acquired in humans (4) and animal models (5), and we highlight recent mechanisms on K channels in antiepileptic drug (AED) research (6).

Probably, all biological cells have K channels; they are crucial for all transmembrane transport mechanisms. In addition, since the

evolutionary appearance of voltage-gated sodium (Na_v) and calcium (Ca_v) channels, K channels are further diversified in relation to their newer function, namely, keeping neuronal excitation within limits (Anderson and Greenberg 2001; Hille 2001). Structurally, K channels consist of transmembrane (TM) protein elements similar to the Ca_v and Na_v channels and the cyclic nucleotide-regulated channels, with which the K channels can be grouped into a superfamily of “voltage-gated-like” ion channels (Yu et al. 2005; Alexander et al. 2013). The K-channel family is by far the largest: <70 human genes encoding for different α subunits have been discovered since the beginning of K-channel cloning (Fig. 1) (Coetzee et al. 1999; Goldstein et al. 2005; Gutman et al. 2005; Kubo et al. 2005; Wei

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et al. 2005; Trimmer 2015). With the formation of heteromers, modulating β subunits, and differential expression, thousands of different K channels are possible. Four α subunits are necessary to build a functional K channel (Fig. 1). The α subunits are differentiated according to whether they consist of 2, 4, or 6 TM domains. More common are functionally defined names such as “inward rectifier” K (K_{ir}) channels for 2 TM channels, “leak two pore domain” K (K_{2P}) channels for 4 TM, and “voltage-gated” K (K_v) channels for 6 TM (Fig. 1).

Inward Rectifier Potassium Channels

As the name suggests, K_{ir} channels conduct inward current better than outward current; responsible for this is a magnesium or polyamine block at depolarized potentials (Kubo et al. 2005). However, under physiological conditions, the resting membrane potential (V_{rest}) of neurons is unlikely to become more negative than the equilibrium potential of K ions (E_K); the functional importance of K_{ir} channels, such as the “classic leak K_{ir} ” channels of the $K_{ir}2$ group, is to provide the basic K current maintaining V_{rest} (Stanfield et al. 2002). Some of the K_{ir} channels are coupled to and modulated by G-proteins, among them, $K_{ir}3$ (Girk) channels. In glial cells, V_{rest} can become more negative than E_K during and because of spatial buffering of extracellular potassium concentrations ($[K]_o$), in particular via $K_{ir}4$ channels (Butt and Kalsi 2006). Thus, $K_{ir}4.1$ channels are found exclusively in glial cells (Higashi et al. 2001). The $K_{ir}6$ (K_{ATP}) channels are coupled to the intracellular energy supply; when ATP levels are high, $K_{ir}6$ channels are closed, whereas during prolonged action potential (AP) firing $K_{ir}6$ channels will eventually contribute to resetting V_{rest} (Isomoto et al. 1997).

Two Pore Domain Potassium Channels

Also K_{2P} channels contribute to leak current important for V_{rest} (Lesage and Lazdunski 2000; Goldstein et al. 2001). Hence, functionally, some of these, for example, the “tandem of P domains in weak inward rectifier (TWIK)” K

channels, behave similarly to K_{ir} channels with high $[K]_o$. Under physiological conditions, most of the K_{2P} channels are open rectifiers—they conduct mainly outward K currents (Goldstein et al. 2001). In addition, K_{2P} channels integrate other signals, as in the case of TWIK-related acid-sensitive (TASK) channels, which are sensitive to external pH changes (Lesage and Lazdunski 2000; Goldstein et al. 2001). From the human genetics point of view, there is little association between K_{2P} channels and epilepsy, but there are data on K_{2P} channels in seizure models (see below). Note that there is no simple correlation between the functional (historical) naming and the later classification according to a sequence relationship (TWIK1, $K_{2P}1.1$; TWIK2, $K_{2P}6.1$; TASK1, $K_{2P}3.1$; TASK2, $K_{2P}5.1$).

Voltage-Gated Potassium Channels

The largest ion channel group is the K_v channel family, which consists of 12 K_v (sub-) families. The founding group, the *shaker*-related K_v1 channel family was named after the muscle seizure phenotype of the corresponding fly mutant (Pongs et al. 1988). Subsequently discovered groups were classified as *shab*-related (K_v2), *shaw*-related (K_v3), and *shal*-related (K_v4) (Coetzee et al. 1999; Gutman et al. 2005). From the functional point of view, all K_v channels are activated by depolarization and deactivated by repolarization, both relatively fast. Inactivation occurs when the open channel is occluded via intracellular “ball domains” during prolonged depolarization. When inactivation is fast (i.e., visible within tens of milliseconds), it is called “A-type current” after the initial description in the gastropod *Anisodoris* (Connor and Stevens 1971). Such ball domains can be part of the channel like in the case of the A-type subunits $K_v1.4$, $K_v3.4$, and K_v4 , or they are part of an accessory unit, as in the case of the $K_v\beta1.1$ (KCNMB1), which confers the A-type phenotype on the K_v1 subunits it assembles with (Rettig et al. 1992, 1994). The term “delayed rectifier” outward current (I_K) describes the delayed activation relative to the ultrafast (μ sec range) activation of Na_v currents (Hodgkin and

Figure 1. Tree of mammalian potassium channel subunits and epilepsy research hot spots. The figure shows the known potassium (K) channel α subunits families and epilepsy research hot spots. Their relation is grouped according to sequence similarities in three major groups: two, four, and six transmembrane (TM) domain channels (2TM, 4TM, and 6TM, respectively), which are synonymously named according to gross functional differences as: inward rectifier K (K_{ir}), two-pore domain leak K (K_{2P}), and voltage-gated K (K_v) channels, respectively. Hypothetical (not realistic for individual members) main characteristics of the respective current/voltage relationships are plotted in *insets* as blue lines. Following the functional name, is the human genome organization (HUGO) name. Numbers in parenthesis are PubMed search results for “(HUGO AND epilepsy) AND Humans[Filter] NOT Review[Filter].” Marked in red are those subunits that yielded more than 10 results in this PubMed search.

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Huxley 1952). K_v4 channels typically have a tendency to reside in dendrites (Rhodes et al. 2004), whereas most K_v1 proteins are axonal (Monaghan et al. 2001), similar to $K_v3.4$ (Riazanski et al. 2001). There are also slower forms of inactivation like the “delay” current, which inactivates within hundreds of milliseconds up to seconds; this current is mediated by $K_v1.1$, $K_v1.2$, and/or $K_v1.6$ subunits (Storm 1988; Kirchheim et al. 2013). Although many groups have defined A-type currents as those blocked by millimolar concentrations of 4-aminopyridine (4-AP), it should be noted that all K_v1 channels containing the subunits, which mediate the delay current, are also sensitive to 4-AP, even in the micromolar range (as well as to nM dendrotoxin, DTX) (Storm 1988; Stuhmer et al. 1989; Grupe et al. 1990; Grissmer et al. 1994). Thus, within K_v families, α subunits form heteromultimeric tetramers with mixed biophysical and pharmacological properties (Ruppersberg et al. 1990; Hatton et al. 2001), such that precise and unambiguous identification of native functional K_v channels remains difficult. The location and properties of K_v1 channels suggests that their function in the central nervous system (CNS) is mainly to shape the duration and delay of axonal action potentials (Sheng et al. 1994; Wang et al. 1994; Rhodes et al. 1997; Monaghan et al. 2001; Wenzel et al. 2007; Kirchheim et al. 2013).

A particular epilepsy hot spot is in the K_v7 family of which the founding members dominate the repolarization of the heart AP and thereby the interval between the Q peak and T wave of the electrocardiogram (EKG). Therefore, mutations in the cardiac $K_v7.1$ (KCNQ1/ K_vLQT1) channel lead to the long QT (LQT) syndrome (Barhanin et al. 1996; Wang et al. 1996) and its expression in brain has been linked to epilepsy and sudden unexpected death (Goldman et al. 2009). The $K_v7.2$ and $K_v7.3$ subunits are widely expressed in the brain where they mediate the neuronal M-current (I_M), which is muscarine-modulated and contributes to sub-AP-threshold excitability, whereas the $K_v7.4$ channel has an important function in the inner ear (Jentsch 2000). The $K_v11.1$ or “human ether à go-go-related gene type 1” (HERG1) K channels conduct a very slowly ac-

tivating I_K in the heart (Gutman et al. 2005). This channel is mutated in the LQT2 syndrome. However, as HERG1 is also widely expressed in the brain, its mutation could also be involved in certain forms of epilepsies (Sanguinetti 2010).

Calcium-Dependent Potassium Channels

From the structural perspective, the calcium-dependent K (K_{Ca}) channels belong to the K_v channels (Fig. 1), although functionally only some are dependent on voltage in addition to calcium (Wei et al. 2005). In a strict sense, calcium-dependent K channels are those named after their small, intermediate, and big conductance, that is, the SK1-3 ($K_{Ca2.1}$, $K_{Ca2.2}$, $K_{Ca2.3}$), IK ($K_{Ca3.1}$), and BK ($K_{Ca1.1}$) channels, respectively (Sah and Faber 2002). Because the K_{Ca} nomenclature appears not well accepted, we continue to use the common SK and BK naming. These channels mediate different parts of the AP after-hyperpolarization (AHP), in particular the fast ($< \text{msec}$) AHP (fAHP, BK), and the medium duration ($\sim 100 \text{ msec}$) AHP (mAHP, SK). The channels mediating the slow AHP (sAHP) lasting seconds are heterogeneous. As with the K_v channels, accessory β subunits can strongly influence K_{Ca} channel function. One example is the BK channel $\beta 4$ (KCNMB4) subunit, which functionally reduces BK currents (Brenner et al. 2000; Lippiat et al. 2003). Further complicating the nomenclature, the channels classified K_{Ca4} , are actually sodium dependent (not calcium dependent); one example is the “sequence like a slowpoke calcium-activated” (SLACK, Slo2.2, or $K_{Ca4.1}$) channel (Bhattacharjee and Kaczmarek 2005).

GENETIC ALTERATIONS ASSOCIATED WITH EPILEPSIES: PATIENT DATA

Here, we briefly summarize the known genetic mutations associated with epilepsies in humans (for more detailed accounts, see Jentsch 2000; Kullmann 2002; Mulley et al. 2003; George 2004; Steinlein 2004; Brenner and Wilcox 2012; D’Adamo et al. 2013; Lerche et al. 2013). We will follow the broad K-channel classification defined above.

Voltage-Gated Potassium Channels

In 1998, four different groups reported that mutations in $K_v7.2$ or $K_v7.3$ channels are associated with a specific neonatal type of epilepsy, benign familial nocturnal convulsions (BNFCs), inherited in an autosomal dominant fashion (Biervert et al. 1998; Charlier et al. 1998; Schroeder et al. 1998; Singh et al. 1998). By the year 2000, >10 mutations of the proteins (mainly $K_v7.2$, two in $K_v7.3$) were identified, all leading to a reduction of I_M and increased AP rates (Jentsch 2000). Another 12 years later, the numbers increased to >60 known mutations in $K_v7.2$ and four in $K_v7.3$ (Brenner and Wilcox 2012), and they continue to increase (Soldovieri et al. 2014; Miceli et al. 2015), again mainly causing infantile epilepsies (i.e., BNFC and rolandic epilepsies) (Neubauer et al. 2008). Although a reduction in I_M provided a mechanistic link to hyperexcitability (Fig. 2), the transient phenotype of BNFC, at least in most patients, still cannot be explained on the grounds of these mutations, or why in some cases they are associated with not-so-benign epilepsies. Thus, some of these mutations (among them de novo) are linked to quite different and more severe epilepsy syndromes, such as Ohtahara syndrome (drug-resistant seizures, psychomotor retardation, burst-suppression EEG) (Weckhuysen et al. 2012, 2013; Soldovieri et al. 2014). This “case history” of one key K-channel type whose genetic mutations are connected to epilepsies exemplifies the general dilemma of genetic/phenotypic correlations. Mutations may generate small or even seemingly paradoxical functional changes, they may result in very different syndromes, or they may lack penetrance, with carriers of these mutations being totally asymptomatic. Conversely, patients with similar, clinically well-defined syndromes may not display any mutation in the relevant K channel. Despite these dilemmata, such genetic findings help to explain the neurobiological basis of epilepsies and, in some cases, directly lead to therapeutic translation.

A recent article by Syrbe et al. (2015) serves as a good example of the mentioned dilemma. Six mutations in the $K_v1.2$ channel genes were

associated with different types of juvenile epilepsies and mild to moderate intellectual disability (focal, focal dyscognitive, myoclonic, absences, and mainly secondary generalized tonic clonic). The $K_v1.2$ mutations associated with epileptic encephalopathies described in this study were found to result in both a gain or, alternatively, a loss of current function. Even if at present the findings fail to unveil a functionally unifying concept (i.e., cannot explain why a gain or a loss of function both result in the same syndrome; Fig. 2), the fact that 4-AP as an approved drug for human use can reduce these currents is currently triggering clinical studies for patients with the gain-of-function mutation. In addition, a mutation in a gene favoring inactivation of K_v1 channels, leucine-rich glioma inactivated 1 gene (LGI1), which in its mutated form does not prevent inactivation, is associated with a rare epilepsy, autosomal dominant partial epilepsy with auditory features, a form of idiopathic lateral temporal lobe epilepsy characterized by partial seizures with auditory disturbances (Kalachikov et al. 2002).

Mutations in $K_v1.1$ subunits were first described to be associated mainly with episodic ataxia type 1, that is, a cerebellar phenotype, and only sometimes (in two different mutations) additionally with partial epilepsy with secondary generalization (Zuberi et al. 1999) or generalized seizures (VanDyke et al. 1975). Functionally, the mutations described by the latter investigation result in a graded and expression-dose-dependent reduction of the K currents in oocyte expression systems, arguably supporting a reduction-of-repolarization hypothesis. Recently a de novo mutation in the $K_v3.1$ channel was described, which is associated with another rare epilepsy type, progressive myoclonus epilepsy of the Unverricht–Lundborg type, consisting of action myoclonus, tonic–clonic seizures, and ataxia (Muona et al. 2015). This channel type has been described to mediate fast firing in cerebellar neurons (Pedroarena 2011), but is also widely expressed in hippocampal and neocortical interneurons (Ozaita et al. 2002; Gutman et al. 2005), suggesting that a loss of function should be associated with reduced inhibitory cell firing (Fig. 2).

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Figure 2. Possible mechanisms of the main genetic potassium channel defects found in epilepsy patients. The cartoon illustrates the localization and effect of loss-of-function ($\downarrow$) or gain-of-function ($\uparrow$) mutations of $K_v7.2/7.3$ (KCNQ channels), $K_v1.2$, BK ($K_{Ca1.1}$), $K_v3.1$, and $K_v4.1$. Normal conditions are symbolized by black traces, functional changes caused by mutations in red. $K_v7.2/7.3$ channels are mainly located on axons and axon-initial segments of neurons, and are usually active at resting membrane potential, thereby governing excitability at the axon hillock. A loss-of-function mutation should result in both accentuated excitatory postsynaptic potentials (EPSPs) as well as in increased action potential firing, which would readily explain hyperexcitability—however, does not explain the association with either relatively benign syndromes like benign familial nocturnal convulsion (BNFC), or relatively severe syndromes like Ohthara syndrome. In a similar way, a loss-of-function mutation of $K_v1.2$, also expressed on the axon hillock, but constituting a delayed rectifier channel not constitutively open at rest, will likely increase action potential firing frequency, again accounting for increased hyperexcitability. The gain-of-function mutations also described in patients, however, remain difficult to explain mechanistically (?). This also applies for BK ($K_{Ca1.1}$) channel defects, in which gain-of-function alterations do not readily conjure a mechanism (?). Mutations of $K_v3.1$, in turn, could elicit an overall increase in excitability, as these channels are expressed mainly on interneurons and convey, by virtue of their fast hyperpolarizing action, fast-firing properties to them. Should these fail, interneurons are expected to fire less intensively. Last, mutations of $K_v4.1$ have been described. As these are expressed on astrocytes and are responsible for uptake of potassium (spatial buffering), a loss of function should result in decreased spatial buffering and, hence, activity-dependent pathological accumulation of K^+ with an overall excitatory effect by depolarizing neighboring cells.

Although the K_v2 channels have not yet been much implicated in epilepsies, two mutations in a $K_v2.1$ -channel modifier ($K_v8.2$) were found to be associated with a mild form of febrile seizures or a severe form of encephalopathy with seizures, respectively (Jorge et al. 2011). Consis-

tently, the respective mutation reduced $K_v2.1$ currents in a coexpression system. Last, another rare form of multisystem developmental disorder associated with epilepsy and intellectual disability, Temple–Baraitser syndrome, appears to be linked to a gain-of-function mutation in the

gene for $K_v10.1$ (*eag1*) channels (Simons et al. 2015). This mosaic mutation (in two mothers of affected children) apparently results in epilepsy. Thus, interfering with I_K appears to increase the risk for mainly severe epilepsies, and perhaps encephalopathy. The examples given are rare—perhaps reflecting the possibility that other mutations simply are not viable and lead to death in utero, something that might be expected if a major repolarizing current is reduced or fails altogether. Another factor may be that fast firing in interneurons could be affected, for example, in the case of mutations of $K_v3.1$ (Muona et al. 2015). Inactivating K_v channels, which mediate A-type currents, shape presynaptic calcium transients and repetitive AP firing both orthodromically as well as backpropagating into the dendrites. An association of this functional group has been found in only one patient so far, and it involves a mutation of $K_v4.2$, leading to current reduction (Singh et al. 2006). In cardiology, the $K_v11.1$ channels are long known to cause severe repolarization problems (similar to K_v7 mutations); these K_v11 channels are also increasingly considered to contribute to combined reflex epilepsy and arrhythmia, as well as to increased risk for sudden unexpected death in epilepsy (SUDEP) (cf. Zamorano-Leon et al. 2012; D’Adamo et al. 2013).

Calcium-Activated Potassium Currents

The K_{Ca} channels are interesting functionally, as their activation is linked to the amount of previous neuronal activity via the accumulated calcium influx at various time scales. Although BK channels, and in some cases the SK channels, activate the SK currents particularly increase with pathological hyperexcitation. In the context of human epilepsies, the BK channels have been at the focus of attention. Du et al. (2005) described a gain-of-function mutation in the $\alpha1$ subunit of this channel with absence epilepsy presenting in $\sim 50\%$ of the affected patients (with the other cardinal symptom being paroxysmal dyskinesia); this effect was ascribed to more effective Ca^{2+} coupling of this channel (Yang et al. 2010). In a set-association analysis trying to link single nucleotide polymorphisms

(SNPs) to epilepsies in different populations, a faint association between a mutation of the negative regulatory $\beta4$ subunit of BK channels and temporal lobe epilepsy (TLE) was found in a population-specific manner (in the Irish subset of the sample only). It would probably be stretching the evidence to ascribe gain-of-function disturbances to cortico-thalamic-circuitry-associated epilepsies (such as absence epilepsy) and loss-of-function types (presumably this SNP, although not functionally evaluated) to TLE, but such speculations have been raised (N’Gouemo 2011). To complete this list, a sporadic case of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) was reported to carry a mutation in the SLACK ($K_{Ca4.1}$) gene (Heron et al. 2012).

Inward Rectifier Potassium Channels

In epilepsy patients, mainly mutations of the astrocytic $K_{ir4.1}$ channel have been reported (Ferraro et al. 2004; Olsen and Sontheimer 2008). The symptoms resulting from these mutations can range from increased seizure susceptibility (missense variation) (Buono et al. 2004), or TLE (significant single nucleotide polymorphism association in Norwegian patient sample) (Heuser et al. 2010, 2012) to a severe combined syndrome of epilepsy, ataxia, sensorineural deafness, and tubulopathy (EAST) syndrome with $K_{ir4.1}$ loss of function (Bockenhauer et al. 2009; Scholl et al. 2009). A loss of function of 4.1 channels, located in astrocytes, could be associated with infringed astrocytic spatial buffering and consecutive activity-dependent pathological accumulation of K^+ and neuronal depolarization (Fig. 2). A speculative link to epilepsy arises also with $K_{ir2.1}$ loss-of-function mutations. These are associated with Andersen–Tawil syndrome (periodic paralysis, cardiac arrhythmias, dysmorphic features, and slight cognitive limitations) in a fraction of these patients ($\sim 1/5$), there is a history of febrile seizures as infants (Haruna et al. 2007). The investigators discussed this as a possible effect of impaired astrocytic spatial buffering; however, the latter is thought to be carried by $K_{ir4.1}$ and not $K_{ir2.1}$ (Jabs et al.

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2008), so the link to epilepsy remains elusive at the moment. The association of $K_{ir}6.2$ channels and epilepsy in the literature is mainly caused by KCNJ11 mutation-related subtypes of diabetes with epilepsy as comorbidity (Slingerland and Hattersley 2005; Shah et al. 2014). For example, a mutation in $K_{ir}6.2$ results in a syndrome (DEND) of developmental delay, infantile diabetes, and epilepsy (Hattersley and Ashcroft 2005). All in all, cases of K_{ir} mutations in epilepsy are rare. They can influence neuronal excitability as an epiphenomenon of an underlying disease, or, if mainly cerebral symptoms are present, different alterations in one channel type are associated with very different syndromes, sometimes multisystemic. This suggests that, as in some K_v channels, a severe functional infringement in such an important current is probably often lethal, which would explain why human mutations are found only rarely.

In summary, it is safe to say that mutations in $K_v7.2$ and $K_v7.3$ are solidly validated as being causal for some forms of epilepsy, although such causality is less clearly established for the other mutations described.

GENETIC ALTERATIONS ASSOCIATED WITH EPILEPSIES: ANIMAL DATA

In the following section, the link between K channels and epilepsies is addressed from the other direction—not by searching for possible mutations in individuals affected by epilepsies, but by inducing genetic variation, usually in mice, and testing whether this results in some kind of epilepsy. Whenever possible, we indicate matches to the mutations of patients.

Congenital Epilepsy Models

Before discussing genetically modified animals, some underlying genetic causes of congenital epilepsies in animals should be mentioned; in a way, the approach of the former section now mirrored in seizure-prone animal strains. The most prominent human mutation, that is, affecting the $K_v7.2$ channel, can also be found in an animal model with increased seizure susceptibility, the *sztl* mouse, albeit in combination

with a heterozygous mutation of the nicotinic acetylcholine receptor (Yang et al. 2003; Otto et al. 2004). Seizure-sensitive gerbils at least share a down-regulation (not mutation) of $K_v3.1$ (and additionally $K_v3.2$) with some patients of Unverricht–Lundborg epilepsy (Lee et al. 2009). Another similarity is the seizure susceptibility of DBA/2 mice, or Noda epileptic rats, which share features with TLE or EAST syndrome patients in that the $K_{ir}4.1$ channels are less active, reducing astrocytic buffering capacity (Inyushin et al. 2010; Harada et al. 2013). The $K_{ir}3$ channel gene is also involved in a prominent congenital model, the *weaver* mouse; in these animals, a mutation of the resulting in ion selectivity loss and reduced currents has been described (Patil et al. 1995; Slesinger et al. 1996). Genetically epilepsy-prone rats (Verma-Ahuja et al. 1995), in turn, link reductions of AHP to conditions in patients in which calcium-activated channels are mutated (a cautionary note: in the animal model, the slow AHP is down-regulated; in the human condition, with absences, it is a gain-of-function mutation [Du et al. 2005]). Other congenital channel mutations of animals associated to seizure phenotypes include the down-regulation of $K_{2p6.1}$ (TASK) channels in seizure-sensitive gerbils (Kim et al. 2007). The same TASK channel is mutated in a widespread model of absence epilepsy, the “genetic absence epilepsy rats from Strasbourg” (GAERS) (Holter et al. 2005). A complete ablation of TREK channels in mice, however, does not lead to any symptoms, which speaks against a direct causal role in epileptogenesis (Mirkovic et al. 2012).

Voltage-Gated Potassium Channels

The main epilepsy-associated human mutation, revolving around $K_v7.2$ and $K_v7.3$ channels and BNFC, is also effective in animal models. A moderate loss of these channels suffices to induce a seizure phenotype (Schroeder et al. 1998). Proving this concept, conditional deletion of $K_v7.2$ using a dominant negative mutation (Peters et al. 2005), or even $K_v7.1$ (Goldman et al. 2009), induces discrete seizures and behavioral abnormalities (increased fear), or, in

the latter case, seizures and SUDEP. This latter condition can also be mimicked by hyper-SUMOylation of K_v7 channels (Qi et al. 2014) and partly prevented by retigabine (see below). The combined homozygous $K_v7.2/K_v7.3$ mutant mouse also displays recurrent seizures, this time with a milder phenotype and no histopathological sequelae (at least in the hippocampus) (Singh et al. 2008). Deleting $K_v7.2$, while simultaneously increasing the persistent sodium current, in a compound mutant with deleted $Na_v1.2$ channels generates double trouble, as expected: a severe epilepsy with animals dying within 60 days (Kearney et al. 2006). In summary, these animal data seem to reasonably match the clinical situation (although not exactly reflecting the BNFC phenotype), with perhaps another grain of salt added that conditional cortical $K_v7.2$ knockout induces severe epilepsy and early death, but not $K_v7.3$ (however, in humans, $K_v7.3$ mutations are much rarer) (Soh et al. 2014).

Regarding some of the transgenic and knockout models in the K_v1 family, there is an incomplete overlap between human and animal data. Human epilepsies are only rarely associated with mutations of $K_v1.1$. In mouse genetic models, deletion of $K_v1.1$ (Robbins and Tempel 2012) leads to spontaneous seizure of a limbic phenotype (Smart et al. 1998), which is accompanied by electrophysiological and histopathological features of hippocampal hyperexcitability and sclerosis, respectively (Wenzel et al. 2007; Leonard et al. 2013; Simeone et al. 2013), or, in another mutation with premature stop codon, megalencephaly in addition to a seizure phenotype (Donahue et al. 1996; Petersson et al. 2003). Using a less targeted mutagenesis approach (*N*-ethyl-*N*-nitrosourea mutagenization in rats), resulting in a missense mutation in $K_v1.1$, also leads to epilepsy, in this case, tonic-clonic generalized, but also muscle symptoms (myokymia, neuromyotonia) (Ishida et al. 2012). Even interfering with K_v1 trafficking by knocking out the $\beta 2$ subunit induces hyperexcitability, but only occasionally seizures (Perkowski and Murphy 2011). The $K_v1.1$ deletion is also discussed as a possible candidate mechanism for SUDEP, because it predisposes

to brain driven cardiac arrhythmia during seizures (Glasscock et al. 2010; Moore et al. 2014). Curiously, these symptoms can be reduced by additional deletion of the $Ca_v2.1$ channel (Glasscock et al. 2007), which illustrates how a mutant gene that increases transmitter release (K_v1) can be modified by one that depresses release at synaptic terminals (the P/Q type calcium channel). This model raises the possibility that balancing excitation and inhibition on the cellular level could be an antiepileptic strategy. However, the sum effect of such channel alterations are difficult to test in vivo as overexpression of the same $K_v1.1$ channel leads to seizures, probably caused by multiple compensatory changes in other K_v channels resulting from the genetic intervention (Sutherland et al. 1999). The intervention seems to work; however, when introduced into a chronic model of epilepsy, a neocortical tetanus toxin model, lentiviral overexpression of $K_v1.1$ abolished electrographic seizures (Wykes et al. 2012). Although $K_v1.2$ subunits colocalize with $K_v1.1$, $K_v1.2$ knockout leads to rather different symptoms with brain stem seizures and early death (Brew et al. 2007). Thus, functionally, these channels do not appear to fully compensate for each other.

Similar to the human conditions, mutating the $K_v2.1$ channel modifier $K_v8.2$ in mice also results in severe, and prematurely lethal, epilepsy, but paradoxically with increased currents rather than decreased currents as in the human mutation (Jorge et al. 2011). Hence, the link of this study to the human condition is unclear. The investigators argue that the current deactivation is larger than in wild type, but once the irritating detail is spotted, the finding remains counterintuitive and definitively different from the human situation. There is only one study addressing mutations in the human $K_v3.1$ channel, resulting in very severe epilepsy (Muona et al. 2015). A knockout in a sibling channel, $K_v3.2$, leads to seizures in only a minority of affected animals, but has the electrophysiological markers of cortical hyperexcitability (Lau et al. 2000). To complete the list, a knockout of $K_v12.2$, a channel that in the context of human epilepsy has not yet been described, also leads to seizures and/or increased seizure susceptibility

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(Zhang et al. 2010). Knockout of $K_v4.2$ itself does not lead to epilepsy (Hu et al. 2006), but increases susceptibility for experimental seizure induction (Barnwell et al. 2009). A similar result is obtained when KChip2, a modulating subunit of K_v4 channels, is knocked out, which leads to reduced current density and slowed recovery from inactivation—thus, altogether a lower fast current availability (Wang et al. 2013).

Calcium-Activated Potassium Channels

The main focus in K_{Ca} -related animal models was on BK channels or more precisely its negative modulator, the $\beta 4$ subunit. In a regional (Irish) patient sample, the $\beta 4$ gene was associated with TLE in an association study (see above). Introducing this gain-of-function mutation via dysfunctional $\beta 4$ subunits leads to limbic seizures in mice (Brenner et al. 2005; Wang et al. 2009), establishing at least a loose match between human and animal data.

Inward Rectifier Potassium Channels

Inward rectifying currents in patients are affected mainly in EAST syndrome, and perhaps relevant in regional populations regarding TLE. Reports of mutations in these channel types evoking seizures are equally rare. Knockout of astrocytic $K_{ir4.1}$ channels leads to a lower threshold for stress-induced seizures (Neusch et al. 2006; Djukic et al. 2007). This deletion is also able to evoke pathologically altered EEG in zebrafish (Zdebik et al. 2013). Targeted introduction of $K_{ir6.1}$ into presynaptic terminals of the hippocampus increases seizure susceptibility, although no outright spontaneous seizures emerge (Soundarapandian et al. 2007). Expanding the deletion to a general knockout, spontaneous sharp waves occur in the EEG (Yamada et al. 2001). This channel is a vascular sibling of the β -cell ATP-sensitive $K_{ir6.2}$, whose deletion causes diabetes, whereas $K_{ir6.1}$ deletion does not. Thus, the K_{ir6} family has been implicated in epilepsy but only in the context of infantile diabetes—of which the seizures may be an epiphenomenon. In the kainate model, the link to genuine hyperexcitability is novel. Last,

knockout of the K_{ir3} channel results in convulsions on handling or stress—a mutation that has not been found in patients so far (Signorini et al. 1997).

ACQUIRED CHANGES ASSOCIATED WITH EPILEPSIES: DATA FROM HUMAN TISSUE

Acquired Channelopathy—Definition of Terms

Unlike in animal models, with patients it is usually not known whether the channel abnormalities observed in resected tissue are already present since birth or whether they were acquired during epilepsy. Acquired channel modifications could be viewed as mechanisms confirming the old hypotheses of “seizures beget seizures” (Gower 1881) and “acquired epilepsy” (Smith et al. 1954). The term “channelopathy” (Wang et al. 1993) can be used for any disease-causing channel alteration, whereas “acquired channelopathy” was coined for transcriptional ion channel modification developing postnatally (Waxman 2001). Finally, a standard nomenclature for all channelopathies was proposed by D’Adamo and colleagues combining the channel name and the disease phenotype (e.g., “ $K_v1.1$ -channelepsy” for epilepsy caused by $K_v1.1$ channel defect) (D’Adamo et al. 2013). Here, we concentrate on the K-channel abnormalities observed in tissue of epilepsy patients, which can be both adaptive and maladaptive (Wolfart and Laker 2015).

Properties of Human Brain Tissue from Epilepsy Surgery

Obviously, brain tissue of epilepsy patients can only be obtained from those disease forms that are treatable via surgical resection of an epileptogenic focus (Duncan 2011; Jobst and Cascino 2015). Furthermore, only those specimens that are resected en bloc are appropriate, and considerable tissue is destroyed during epilepsy surgery via ultrasonic aspiration (Zentner et al. 1995). The overwhelming majority of surgical tissue stems from anterior temporal lobe resections

for the treatment of TLE; extratemporal excision of neocortical tissue is less frequent (de Tisi et al. 2011; Jobst and Cascino 2015). If neocortex is resected, it often contains brain tumors such as gliomas, or maldeveloped tissue as in cortical dysplasia (Crino et al. 2002; de Tisi et al. 2011; Giulioni et al. 2014). It should be noted that many human tissue studies pool heterogeneous patient data. Here, we roughly group the studies into hippocampal and neocortical tissue.

About 90% of the hippocampi resected for treatment of epilepsy show hippocampal sclerosis (HS). This lesion, also called Ammon's horn sclerosis, is associated with the degeneration of CA1 pyramidal cells and other cell types especially in the hilus, as well as gliosis, sprouting of dentate gyrus (DG) granule cells and their dispersion (GCD) (Margerison and Corsellis 1966; Houser 1990; Wyler et al. 1992; Blümcke et al. 2012, 2013; Thom 2014). However, these sclerotic hippocampi are not entirely representative of TLE patients, because hippocampal atrophy itself positively influences the decision for surgery (Jobst and Cascino 2015). About 50% of all TLE patients show HS (Thom et al. 2010). To cope with the lack of control tissue, many studies compare severe versus mild HS specimens (Williamson and Patrylo 2007). However, the decision of whether no HS, mild HS, or severe HS exists is necessarily based on vague classification schemes (Wyler et al. 1992). Morphological studies can use autopsy samples as controls but this tissue harbors other hitches such as unequal immunogenicity and age matching. Thus, in view of the many studies concluding that epileptiform hyperexcitability results from CA1 cells in TLE animal models, it should be kept in mind that this region is depleted in about half of the TLE patients and consequently not very excitable (Cohen et al. 2002). In other words, dead cells are unlikely to seize (Delorenzo et al. 2005).

Voltage-Gated Potassium Channels

The most notorious example of an acquired K-channelopathy, the down-regulation of $K_v4.2$ A-type channels in dendrites of CA1 pyramidal cells in an animal model of TLE (Bernard

et al. 2004; but see Monaghan et al. 2008; Su et al. 2008) has not yet been confirmed in tissue of TLE patients. In contrast, the CA pyramidal cells of TLE patients express ample $K_v4.2$ protein, and quantification did not confirm lower amounts, despite the loss of pyramidal cells in this area. A Western blot analysis of human HS tissue even shows an increase of $K_v4.2$ protein in TLE patients with HS compared with those without HS (Aronica et al. 2009). From this, it appears unlikely that TLE patients suffer from a $K_v4.2$ channelopathy. Little data exists on other K_v channels. No changes in $K_v7.5$ immunostaining were detected in the temporal cortex of TLE patients versus autopsy samples (Yus-Najera et al. 2003). In neocortical tissue of five patients with TLE versus brain trauma, a regulatory protein that increases the influence of $K_v1.1$ channels was found reduced; however, this effect was ascribed to interneurons (Li et al. 2012).

Because of the above-described cell degeneration, the surviving DG granule cells have become the most frequently studied human cell type. The passive physiological properties of granule cells from TLE patients have been considered relatively similar to those of rodent granule cells (Williamson et al. 1993; Beck et al. 1996; Isokawa 1996b; Dietrich et al. 1999). On the other hand, abnormal properties of human granule cells have also been reported (Isokawa 1996a; Magloczky et al. 1997; de Lanerolle et al. 2003; Selke et al. 2006; Stegen et al. 2009, 2012). For example, it was described that a subpopulation of granule cells from HS tissue displays a hyperexcitable electrophysiology caused by faster AHPs and ensuing reduced spike frequency adaptation (Dietrich et al. 1999). K_{Ca} channels could be responsible for this difference, but this remains undetermined. In another current-clamp study of human granule cells, pharmacological block of K_v7 channels caused spike frequency acceleration, but it was concluded that K_v7 channels do not contribute to the medium AHP of granule cells (Selke et al. 2006).

Inward Rectifier Potassium Channels

A reduced input resistance of human DG granule cells, caused by increased K_{ir} resting con-

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ductances in severe versus mild HS specimen, suggested that these cells are rather hypo- than hyperexcitable (Stegen et al. 2009). Others failed to detect such currents in human granule cells altogether (Beck et al. 1997). This difference could be because of the fact that the latter study used cells dissociated from their dendrites, whereas the former study used intact neurons. Later recordings confirmed the decreased excitability of HS granule cells and revealed that it was caused by enhanced expression of $K_{ir}2$ channels and hyperpolarization-activated cation (HCN1) channels (Stegen et al. 2012). Also a relative decrease in K_{ir} currents in the astrocytes of the CA1 stratum radiatum of TLE patients with severe versus mild HS was determined (Hinterkeuser et al. 2000). The responsible channels are most likely $K_{ir}4.1$ channels because they appeared down-regulated in respective samples at the protein level (Heuser et al. 2012). This impairment of glial K buffering capacity is the last thing needed in seizure-affected tissue, in which accumulation of $[K]_o$ is exceedingly high (Bordey and Sontheimer 1998; Kivi et al. 2000). Worse, the E_K shift could depolarize V_{rest} of neighboring neurons. Therefore, glial K_{ir} -channelopathy is a potential mechanism for the seizure susceptibility in TLE (Jabs et al. 2008). On the other hand, too much $K_{ir}4.1$ could also have proconvulsive effects (Sicca et al. 2011).

ACQUIRED CHANGES IN SEIZURE/EPILEPSY MODELS

Models of Epilepsy

There are two entirely different goals for the study of animal models of epilepsy. In industrial AED testing, the goal is to screen novel molecules for their antiseizure potential; examples are maximal electroshock and i.p. pentylenetetrazol, which are proven successful, in particular with respect to AEDs against generalized epilepsies (Löscher et al. 2013). In academic research, the goal is to simulate the anatomical and physiological symptoms of human epilepsy as precisely as possible (Coulter et al. 2002; Morimoto et al. 2004). Because one hypothesis for TLE is

an initial precipitating injury (Mathern et al. 2002), many TLE models induce a status epilepticus (SE), which is then followed by chronic epilepsy. Examples are i.p. injection of kainate (Ben-Ari 1985) or pilocarpine (Turski et al. 1989), both of which produce generalized seizures but little HS (Curia et al. 2014). In contrast, SE, followed by focal seizures and HS, are induced by intrahippocampal kainate injections (Fritschy 2004). Perforant path stimulation-induced SE produces chronic bilateral seizures and HS (Bumanglag and Sloviter 2008), whereas electrical “kindling” of amygdala or hippocampus triggers seizures primarily during the stimulation without a chronic epilepsy and HS (Morimoto et al. 2004). It is also possible to acutely trigger seizure-like activity in vitro via pharmacological manipulations (Avoli et al. 2002). Finally, computational models can simulate seizure activity (Case and Soltesz 2011), but obviously the parameters have to be experimentally constrained as much as possible, because many things can produce runaway excitation in neuronal networks. Thus, all epilepsy models have advantages and disadvantages; the choice depends on the study aim.

In contrast to human epilepsy, it is clear that in animals that become epileptic after an epileptogenic insult, channel modifications are acquired; it is not clear whether the changes are causal or consequential to seizures, and whether observed channel changes are adaptive (counteracting hyperexcitability) or maladaptive (supporting hyperexcitability). Obviously, these scenarios may occur simultaneously. The most attractive changes may be the maladaptive ones, as they are considered to be, at least partly, causal to the seizures or even the disease development.

Voltage-Gated Potassium Channels

A computational model with features of the TLE network (Thomas et al. 2009) found that shifting the voltage-dependence of $K_v1.1$ channels was the second-most potent (after Na_v channels) in reducing high-frequency sustained firing in the network. The question is whether

the AP frequency has a real link to the epilepsy of patients. Taking an alternative perspective and asking which type of activity A-type channels could perturb best, another computational study concluded that it is a highly synchronized activity (Fransen and Tigerholm 2010)—again, the link to epilepsy is vague. Adding another twist to this story, desynchronization by K_v channel blockade might foster high-frequency oscillations/fast ripples that are a hallmark of seizure-like activity (Köhling and Staley 2011). There is also a strong case for adaptive K_v1 channel changes occurring after SE (Meier et al. 2015; Wolfart and Laker 2015). In the intrahippocampal kainate model of TLE, the delay current, mediated by K_v1 channels, is elevated (Kirchheim et al. 2013). Single-cell polymerase chain reaction (PCR) revealed that transcriptional up-regulation of $K_v1.1$ subunits is responsible for this reversible adaptive reaction (Kirchheim et al. 2013). Another study showed that in a systemic kainate model, $K_v1.1$ becomes less sensitive to blockade (by 4-AP) because of differential RNA editing—a change that protects against 4-AP-induced seizure-like events (in vitro, in the entorhinal cortex) (Streit et al. 2011).

Regarding A-type channels, one study suggested a $K_v3.4$ protein down-regulation in hippocampi of pilocarpine-injected rats (Pacheco Otalora et al. 2011). Many epilepsy studies addressed alterations of $K_v4.2$ channels. After systemic kainate injection, $K_v4.2$ channels were decreased for a day in some regions (DG, CA3, CA4), but unchanged in other regions (CA1) (Francis et al. 1997). In pilocarpine-injected rats, the AP backpropagating into the dendrite is increased and less sensitive to 5 mM 4-AP in CA1 pyramidal cells and this corresponds to a decrease of $K_v4.2$ (and $K_v1.4$) mRNA in microdissected hippocampi (Bernard et al. 2004). Immunohistochemical studies confirmed some of these results but also showed conflicting data (Monaghan et al. 2008; Su et al. 2008). Again, the $K_v4.2$ levels were either only transiently decreased or appeared even increased (Francis et al. 1997; Su et al. 2008). In the systemic kainate model, a decrease of $K_v4.2$ in synaptosomes was described and also inter-

preted as proepileptic mechanism (Lugo et al. 2008). However, this presynaptic effect could actually dampen fast firing and reduce transmitter release. On the other hand, down-regulation of hippocampal $K_v4.2$ was also found to occur chronically after severe traumatic brain injury and in hypoxia epilepsy models (Lei et al. 2012; Peng et al. 2013). In addition to quantitative changes of K channels, pilocarpine SE may also induce a rapid (in 2 h) redistribution of $K_v4.2$ channels, as has been shown for thalamocortical neurons (Smith et al. 2012). Importantly, cardiac $K_v4.2$ channels are also down-regulated in the pilocarpine model (Bealer et al. 2010). As these are critical for cardiomyocyte repolarization, arrhythmias arise within 2-wk post-SE.

Concerning K_v7 channels, the channels that carry the most prominent mutations among patients, it is interesting to note that in the pilocarpine model, a decreased expression in dendrites (of the subiculum) has been shown for $K_v7.2$ and $K_v7.3$ (Maslarova et al. 2013). In the amygdala, $K_v7.2$ channels appear down-regulated after kindling-induced seizures (Penschuck et al. 2005).

Calcium- and Sodium-Activated Potassium Channels

Another maladaptive channelopathy scenario associated with TLE models appears in recent publications regarding K_{Ca} channels. Thus, BK- channel expression is down-regulated particularly in the CA3 region of pilocarpine-injected rats as determined by immunohistochemistry (Pacheco Otalora et al. 2008). This phenomenon is perhaps linked to the fact that the splice variant STREX is up-regulated, which leads to lower channel expression (Ermolinsky et al. 2011). Although this would confer increased calcium sensitivity to the remaining channels, the functional outcome seems to be that action potential firing is increased (Mehranfard et al. 2015). The contrary can be the case as well. In juvenile tissue of a picrotoxin epilepsy model, BK currents appear up-regulated—and associated with increased firing (Shruti et al. 2008). Another interesting group of K_{Ca} channels are the SK channels that

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mediate part of the mAHP in many cell types; these channels can thus control excitability for hundreds of milliseconds and shape synchronization and timing of epileptiform activity (Fernandez de Sevilla et al. 2006). Both at the protein and the transcript level, SK2 (and SK3) channels were reduced after pilocarpine SE for up to 2 mo (Oliveira et al. 2010; Schulz et al. 2012). This has functional consequences. Inhibiting SK channels leads to massive exacerbation of epileptiform activity in hippocampal slices of chronically epileptic rats but not in control tissue (Schulz et al. 2012). Not only is the mAHP reduced in this tissue, but also the sAHP (Brehme et al. 2014). The mAHP reduction can be restored by blocking casein-kinase 2 (CK2), a major kinase for calmodulin phosphorylation. Because the phosphorylation of calmodulin in turn reduces SK calcium sensitivity, and because these channels are candidates for the sAHP, the restoration and normalization of the sAHP could be mediated by a normalization of SK-channel function. Intriguingly, chronic CK2 blockade renders hippocampal tissue resistant to induction of epileptiform activity in vitro (Brehme et al. 2014), opening up a novel therapeutic strategy. Even when epileptiform activity is induced in vitro via GABA-receptor blocker gabazine (within 2 h), a reduction of the AHP can be observed, which can be reverted by protein kinase A (PKA) block (Kernig et al. 2012). Because SK channels (in particular SK2) are subject to PKA-induced ubiquitination and contribute to the AHP, it is plausible that the AHP reduction is caused by activity-dependent SK-channel phosphorylation and, possibly, internalization/ubiquitination (Kernig et al. 2012). On a more speculative basis, using a network model with neuronal properties from dorsal root ganglion cells, seizure termination was brought about by modulating SLACK ($K_{Ca4.1}$) currents (Krishnan and Bazhenov 2011; Igelstrom 2013).

Inward Rectifier and Two Pore Domain Potassium Channels

An acquired K-channel pattern that is highly likely to be adaptive and that matches the hu-

man condition concerns K_{ir2} channels. In the intrahippocampal kainate model of TLE, K_{ir2} currents are strongly increased in HS-affected DG granule cells, thus stabilizing V_{rest} and reducing the input resistance and intrinsic excitability significantly (Young et al. 2009). Concomitantly, the entire K_{ir2} family ($K_{ir2.1}$, $K_{ir2.2}$, $K_{ir2.3}$, and $K_{ir2.4}$) as well as the K_{2P} channels TWIK1 ($K_{2P1.1}$) and TWIK2 ($K_{2P6.1}$, but not $K_{ir3.2}$ channels) were found to be chronically up-regulated in these cells (Young et al. 2009). Immunohistochemical studies, using the pilocarpine model, detect enhanced TASK channel signals in hippocampal tissue (Kim et al. 2009), which could be because of astrocytes (Kim et al. 2011). The $K_{ir6.2}$ channels were found reduced in the DG and the frontal cortex in a less frequently used model of limbic picrotoxin kindling; however, this expression change lasts only 12 h and its functional implications are still unclear (Jiang et al. 2007).

Apart from neuronal channels, astrocytic K channels deserve a close analysis—after all, not only do mutations in astrocytic $K_{ir4.1}$ channels occur in humans, but, also in genetic models, alterations in expression lead to epilepsy (see above). In the pilocarpine model of TLE, up-regulation of $K_{ir4.1}$ was reported, arguing for an adaptive change (Nagao et al. 2013). However, this is in strong contrast to human TLE, in which there is also functional evidence of reduced spatial buffering (Kivi et al. 2000). A study on the traumatic brain injury model in rats supports the maladaptive hypothesis, and perhaps also helps to clarify the discrepancies found between the TLE model and human TLE. In traumatic brain injury, a loss of K_{ir} current occurs predominantly in the processes of astrocytes and not in their somata (Stewart et al. 2010). Hence, the functional aspect of spatial buffering warrants further investigation—A global expression change may mask a critical change on the functionally relevant processes.

A counterintuitive mechanism that has to be mentioned in the context of K buffering is depolarization block (of Na_v and Ca_v channels) by rising $[K]_o$. Although medium to high levels of depolarization can bring neurons closer

to the AP threshold—perhaps the reason why aquaporin knockout animals have seizures, because this also alters their extracellular potassium handling (Binder et al. 2006)—too much depolarization could also drive excitatory channels in inactivation and thereby stop seizures. However, contesting views hold that it may not be so relevant (Bikson et al. 2003). Thus, the effect of K-channel activation depends on the actual $[K]_o$ level (Köhling and Staley 2011). Glial K buffering via $K_{ir}4.1$ channels may thus be instrumental in controlling seizures. All in all, from these theoretical considerations, neuronal K_v1 , K_v4 , and K_{Ca} , as well as glial K_{ir} channels, should be attractive modulation candidates.

INSIGHTS FROM ANTIEPILEPTIC DRUG RESEARCH

Epilepsy is a threshold phenomenon. Most of the time seizures do not occur. Therefore, the best AED is one that only slightly shifts the seizure threshold. Targeting specific K channels could be a strategy to achieve just that (Wolfart and Laker 2015).

Voltage-Activated Potassium Channels

In many in vitro situations, a K-channel opening can stop seizure-like activity. This is particularly expected when this activity was itself evoked via a K-channel block (Gandolfo et al. 1989). However, in contrast to Na_v and Ca_v channels (Köhling 2002; Löscher et al. 2013), only one K-channel opener (retigabine) is approved as an AED mechanism of action (Faulkner and Burke 2013). This drug shifts the availability of $K_v7.2$ and $K_v7.3$ channels to more hyperpolarized potentials, such that they are active already at V_{rest} (Main et al. 2000; Rundfeldt and Netzer 2000; Wickenden et al. 2000). Coincidentally, retigabine fulfills a major criterion for AEDs. It is specific for the neuronal forms of K_v7 ($K_v7.2$, $K_v7.3$, $K_v7.5$) and does not affect the cardiac $K_v7.1$ channel (Tatulian et al. 2001; Schenzer et al. 2005). Subsequently, many K_v7 openers have been synthesized (Peretz et al. 2005; Wu and Dworetzky 2005; Roeloffs et al. 2008; Wick-

enden et al. 2008; Raol et al. 2009), but future research needs to determine whether and how patients could benefit from such AEDs (Splinter 2013).

Other K_v channels have also been considered as targets not only for AEDs but also for gene therapy approaches. For example, in an animal model of focal (neocortical) epilepsy, viral overexpression of neocortical pyramidal cells with $K_v1.1$ channels reduced epileptic seizures (Wykes et al. 2012). Also, a pharmacological block of regulatory protein target of rapamycin (mTOR), which maintains elevated levels of $K_v1.1$ channels, is effective against experimental seizures (Sosanya et al. 2014). Another promising antiseizure strategy is to prolong the inactivation of K_v1 channels conferred by $K_v\beta1.1$ via “disinactivator” substances (Lu et al. 2008).

The activation of K_{Ca} channels, although in principle successful against experimental seizures, had considerable side effects in standard AED testing models, ruling out clinical use so far (Anderson et al. 2006).

Inward Rectifier Potassium Channels

Several K_{ir} channels have been tested as potential AEDs, and some of the already approved AEDs have retrospectively been shown to additionally open K_{ir} channels. For example, the AED pregabalin opens $K_{ir}6.2$ (K_{ATP}) channels (Huang et al. 2006). However, in conventional AED screening models, $K_{ir}6$ -targeting AEDs have proven ineffective (Wickenden 2002). In this context, it is also worth noting that the approved AED pregabalin also activates $K_{ir}1.1$ channels, which may be responsible for heart-related side effects (Lee and Liou 2014). The proposal that $K_{ir}2$ channels could function as antiepileptic channels (Young et al. 2009; Wolfart and Laker 2015) is supported by the finding that the anti-inflammatory drug tenidap, which was found to open $K_{ir}2.3$ channels (Liu et al. 2002), is also quite effective in abolishing epileptic seizures in standard AED testing models (Xu et al. 2013). Also, $K_{ir}3$ channel activation may be an AED strategy as suggested by a barium-sensitive component of the effect of AED

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gabapentin (Bertrand et al. 2003) and by a synthetic $K_{ir}3$ ($K_{ir}3.1$, $K_v3.2$ and $K_{ir}3.1$, $K_v3.4$) channel activator that yielded an antiseizure result comparable to approved AEDs (Kaufmann et al. 2013).

Potassium Channel–Inhibiting Antiepileptic Drugs

Certainly, AEDs were not designed to inhibit K channels, and unless one is able to specifically target K channels in inhibitory neurons, this effect will likely not be a goal of AED research. Nevertheless, certain effective AEDs do block K channels, and thus may indeed be preferentially acting on GABAergic interneurons, or could contribute to unwanted side effects (Danielsson et al. 2003, 2005; but see Meldrum and Rogawski 2007). Examples are lamotrigine inhibiting various K_v currents (Grunze et al. 1998; Huang et al. 2004), ethosuximide blocking BK channels (Crunelli and Leresche 2002), and levetiracetam reducing delayed rectifier K currents (Madeja et al. 2003).

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