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MOLECULAR PLASTICITY

Dendritic ion channelopathy in acquired epilepsy

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Summary

Ion channel dysfunction or "channelopathy" is a proven cause of epilepsy in the relatively uncommon genetic epilepsies with Mendelian inheritance. But numerous examples of acquired channelopathy in experimental animal models of epilepsy following brain injury have also been demonstrated. Our understanding of channelopathy has grown due to advances in electrophysiology techniques that have allowed the study of ion channels in the dendrites of pyramidal neurons in cortex and hippocampus. The apical dendrites of pyramidal neurons comprise the vast majority of neuronal surface membrane area, and thus the majority of the neuronal ion channel population. Investigation of dendritic ion channels has demonstrated remarkable plasticity in ion channel localization and biophysical properties in epilepsy, many of which produce hyperexcitability and may contribute to the development and maintenance of the epileptic state. Herein we review recent advances in dendritic physiology and cell biology, and their relevance to epilepsy.

KEY WORDS: Dendrites, Channelopathy, K^+ channels, Na^+ channels, Ca^{2+} channels, Hyperpolarization-activated, cyclic nucleotide-gated channels, Pyramidal neurons.

Ion channel dysfunction or "channelopathy" is a proven cause of epilepsy in the relatively uncommon genetic epilepsies with Mendelian inheritance. But channelopathy has been long hypothesized to underlie epilepsy from acquired insults to the brain, which makes up the preponderance of human epilepsy cases of known cause. In recent years, numerous examples of acquired channelopathy in experimental animal models of epilepsy have been demonstrated. In part, our understanding of channelopathy has grown due to advances in electrophysiology techniques that have allowed the study of ion channels in the dendrites of pyramidal neurons in cortex and hippocampus. The apical dendrites of pyramidal neurons comprise the vast majority of neuronal surface membrane area, and thus the majority of the neuronal ion channel population. Investigation of dendritic ion channels has demonstrated remarkable plasticity in ion channel localization and biophysical properties in epilepsy, many of which produce hyperexcitability and may contribute to the development and maintenance of the epileptic state. Herein we review recent advances in dendritic physiology and cell biology, and their relevance to epilepsy.

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Ion Channel Dysfunction as a Cause of Acquired Epilepsy

The term "channelopathy" was coined by Ptáček (1997) to describe dysfunction of a Na^+ channel underlying inherited hyperkalemic periodic paralysis. Since then, the concept of channelopathy has been expanded to cover a number of syndromes with dysfunction of ion channels at their foundation, including myopathy, pain, cardiac arrhythmia, and epilepsy. In epilepsy, the channelopathy hypothesis was proven by the discovery of mutations in ion channel genes associated with inherited epilepsy syndromes, beginning with the linkage between autosomal dominant nocturnal frontal lobe epilepsy and nicotinic acetylcholine receptor mutations in 1995. In fact, the majority of epilepsy syndromes with Mendelian inheritance derive from a mutation in an ion channel gene (reviewed in Mantegazza et al., 2010 and shown in Table 1). This underscores the central role of ion channel dysfunction—both voltage-gated and ligand-gated, but especially the former—in causing at least the Mendelian inherited epilepsy syndromes.

That ion channel dysfunction is central to epilepsy has been an underlying assumption for years. Dating back at least to the "epileptic neuron" hypothesis propagated in the 1950s and beyond, neuronal hyperexcitability in

Table 1. Human epilepsy syndromes with Mendelian inheritance caused by ion channel mutations

Syndrome	Ion channels	Genes
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	Nicotinic acetylcholine receptor $\alpha 4$ and $\beta 2$	*CHRNA4, CHRNB2*
Benign familial neonatal convulsions (BFNC)	Kv7.2, Kv7.3	*KCNQ2, KCNQ3*
Generalized epilepsy with febrile seizures-plus (GEFS+)	Nav1.1, Nav $\beta 1$	*SCN1A, SCN1B*
Severe myoclonic epilepsy of infancy (SMEI)	Nav1.1	*SCN1A*
Benign familial neonatal-infantile seizures (BFNIS)	Nav1.2	*SCN2A*
Idiopathic generalized epilepsy and episodic ataxia	Cav $\beta 4$	*CACNB4*
Developmental delay, epilepsy, and neonatal diabetes (DEND)	Kir6.2	*KCNJ11*
Epilepsy, ataxia, sensorineural deafness, and tubulopathy (EAST)	Kir4.1	*KCNJ10*

epilepsy was assumed to result from alterations in intrinsic or synaptic currents (Ward, 1961). But until the elucidation of these rare genetic epilepsy syndromes beginning in 1995, no proof tied hyperexcitability at a neuronal level to the dysfunction of ion channels. Since then, there has been a great expansion of understanding of the links between ion channel dysfunction and epilepsy. As an example, consider the contents of *Jasper's Basic Mechanisms of the Epilepsies*, a comprehensive review of the state-of-the-art in epilepsy knowledge. In 1999, the table of contents of the 3rd edition listed only four chapters devoted to ion channel dysfunction in epilepsy (and two of these were specific to Rasmussen's syndrome; Delgado-Escueta et al., 1999) In 2012, the 4th edition table of contents lists 18 chapters dedicated to specific ion channelopathies (Noebels et al., 2012).

But just because a link exists between Mendelian genetic epilepsy and ion channelopathy, can we assume that the remainder of human epilepsy, inherited and acquired, is similarly caused by channelopathy? A recent large-scale study of single-nucleotide polymorphisms in human ion channel genes showed no clear association between mutations in any one gene and sporadic epilepsy, including the known human epilepsy genes (Klassen et al., 2011). This decreases the likelihood that any strong genetic associations will explain sporadic epilepsy, although studies targeting epilepsy in families with at least two affected individuals (if not necessarily demonstrating strict Mendelian inheritance) such as the Epilepsy Phenome-Genome Project may yet find some genetic links in this subset of inherited human epilepsy.

Yet the ion channelopathy hypothesis may still be relevant for acquired human epilepsy. In acquired epilepsy, even when the inciting cause is head injury or brain hemorrhage, it is likely that the final common pathway of the development and maintenance of epilepsy involves ion channel dysfunction. Supporting this view is the abundant evidence that ion channel dysfunction occurs in animal models of epilepsy and contributes to induction and maintenance of the epileptic state, as we will discuss below. Therefore we maintain that the study of ion channelopathy in acquired epilepsy is relevant and important.

Unlike the genetic epilepsies, which can be studied in humans with only a tube of blood for gene sequencing, the study of channelopathy in acquired epilepsy requires brain tissue, thus most experimentation has occurred in animal models. In some cases, investigators have replicated animal model findings in human tissue obtained during epilepsy surgery. However, a caveat to most of the findings discussed below is that they are almost exclusively based on animal model work. That said, the last 15 years has seen tremendous gains in our understanding of how ion channel properties are altered during the development of epilepsy. One of the key drivers of this growth in channelopathy research has been the expansion of neurophysiologic investigation from an exclusive focus on the cell body of the neuron to encompass the dendrites and axon initial segment—in essence, the 95% of the neuron outside the soma. This change in focus, made possible by advances in electrophysiology technique, has led to the realization that some dendritic ion channels undergo dramatic changes during epileptogenesis, and indeed may be the primary locus of altered neuronal excitability in epilepsy. Below we discuss how our conception of ion channel function in neurons has grown to include dendritic and axonal ion channel populations, and investigation of how the localization of these channels changes in epilepsy.

Nonuniform Ion Channel Distribution in Pyramidal Neurons

The neuronal soma has been the default target for cellular electrophysiology since the advent of brain slice preparations in the 1970s, especially in the hippocampus where the principal neurons lie in stratified layers. In the mid-1990s, advances in infrared differential interference contrast (IR-DIC) microscopy enabled investigators to visualize the dendritic trees and axon initial segments of pyramidal neurons in unstained brain slices. IR-DIC optics enabled patch-clamp recordings from these small caliber processes, and thus a great expansion of the frontiers of cellular electrophysiology, particularly into the apical dendrites. The dendrites of pyramidal neurons, the principal neurons of cortex and hippocampus, comprise

the great majority of the neuron's surface membrane area (Fig. 1). Thus, until the advent of dendritic patch-clamp techniques, the overall ion channel population of pyramidal neurons was essentially unknown. Although a small number of reports of blind sharp electrode recordings from dendrites had previously established that they supported action potential (AP) firing (Wong et al., 1979), the advent of visualized patch-clamp techniques offered the ability to perform cell-attached recordings that measured localized ion channel properties just within the 1 μm^2 area of the pipette tip, and allowed simultaneous recordings at two or more sites on the same neuron (Stuart et al., 1993). The first publication to use visualized patch clamp in 1994 used dual simultaneous somatic and dendritic recordings to provide stunning proof that dendritic APs in fact back-propagate from the soma (Stuart & Sakmann, 1994).

Dendritic cell-attached patch recordings, used to measure ion channel properties such as current density and voltage-dependent activation, subsequently redefined the conception of dendritic electrical properties. The study of A-type K^+ channels represented the leading edge of this technique in the investigation of ion channel localization in pyramidal neurons. Measurements along the main apical dendrites in CA1 hippocampal pyramidal neurons found that the density of I_A, the current generated by A-type K^+ channels, increases as a linear gradient from soma to dendrites, with the dendritic current density about fivefold greater than that at the soma (Hoffman et al., 1997). This current is largely mediated by the Kv4.2 isoform, with a lesser contribution from Kv4.3 and Kv1.4. The striking I_A gradient pattern dispelled the idea that ion channels were uniformly distributed throughout the neuron; rather, at least for voltage-gated ion channels, nonuniform distributions are the rule not the exception. The high dendritic density of I_A diminishes the excitability of the dendrites by decreasing the amplitudes of backpropagated APs as well as excitatory postsynaptic potentials (EPSPs) generated by dendritic excitatory synaptic activity. Other dendritic K^+ channels, such as those mediating delayed-rectifier currents, appear to be expressed in comparable densities in soma and dendrites (Chen & Johnston, 2004), whereas a Ca^{2+}-activated K^+ current may be expressed at lower density in the dendrites compared to the soma (Poolos & Johnston, 1999).

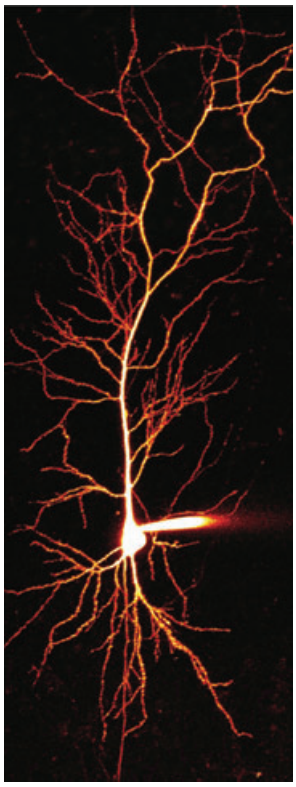

Figure 1.
Two-photon micrograph of a CA1 hippocampal pyramidal neuron showing the profusion of apical and basilar dendrites emanating from the cell soma. Micrograph courtesy of Raymond Chitwood, PhD.

Hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels constitute another voltage-gated ion channel family that is dendritically enriched to an even greater extreme than A-type K^+ channels. These channels, including the HCN1 and HCN2 subtypes, are seen at 7- to 10-fold greater density in distal CA1 pyramidal neuron dendrites compared to the soma, again showing a linear increase in density with distance from the soma (Magee, 1998). HCN channels are permeable to both Na^+ and K^+ and produce a noninactivating ''sag'' conductance that is active at typical neuronal resting potentials. Blocking these channels normally leads to hyperpolarization of resting potential, but with a net increase in excitability of the dendrites due to interactions with other ionic conductances present in the membrane (George et al., 2009). This inhibitory effect of HCN channels on pyramidal neuron excitability is particularly evident in response to repetitive excitatory synaptic input, reducing ''temporal summation'' of EPSPs (Magee, 1999). Another interesting feature of HCN channel biology is their activation by certain antiepileptic drugs, such as lamotrigine, both in cortex and hippocampus where HCN1 is predominant (Poolos et al., 2002), and in thalamus where HCN2 channels modulate rhythmic burst firing of thalamocortical neurons (Ying et al., 2007). HCN channels may thus represent therapeutic targets for antiepileptic drug action (Biel & Postea, 2011).

Both T- and R-type calcium channels (e.g., Cav3.2 and Cav2.3, respectively) exist in higher density in the dendrites than the soma (Magee & Johnston, 1995). T-type channels appear to underlie burst potentials generated in the dendrites, driving repetitive AP firing from the soma, whereas R-type Ca^{2+} channels underlie the large, slow

Ca^{2+}-mediated APs arising in distal dendrites. Both of these conductances increase the excitability of the dendrites.

It is interesting that Na^+ channels do not seem to be localized in large gradient patterns in the dendrites (Magee & Johnston, 1995). Although there is little information on the distribution patterns of Na^+ channel subtypes, fast-inactivating Na^+ current (I_{Na}) is seen in approximately constant densities throughout the somatodendritic axis of CA1 pyramidal neurons. However, electrophysiologic evidence suggests that persistent Na currents (I_{NaP}) may arise principally perisomatically; whether this represents a differential distribution of a particular Na channel subunit, or altered biophysical properties of subunits, remains unclear (Yue et al., 2005). In the apical dendrites of other neurons, such as CA3 hippocampal pyramidal neurons or parvalbumin positive interneurons, Na^+ channels are present in sufficient density to enable dendritic AP propagation, but generally are present at lower densities than at the soma (Hu et al., 2010; Kim et al., 2012).

In contrast to the voltage-gated ion channels, there is much less information on ligand-gated channels such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), *N*-methyl-D-aspartate (NMDA), and γ-aminobutyric acid (GABA) receptor-mediated currents. It appears that AMPAergic currents are enriched in the dendrites, and serve to counter the electrotonic decrement that distal synaptic events undergo in their passive propagation to the soma (Andrasfalvy & Magee, 2001). Although it is well known that inhibitory interneurons project selectively to dendritic and somatic compartments of principal neurons (e.g., the dendritic projections of oriens lacunosum-moleculare interneurons compared to the perisomatic projections of parvalbumin-positive chandelier cells), there is little known about the $GABA_A$-receptor subunit composition in these differing compartments (Klausberger, 2009). $GABA_B$ receptors are metabotropic and activate inward rectifier K^+ channels. They are expressed largely in dendritic regions (Kulik et al., 2003).

The same electrophysiologic techniques that enable study of dendritic ion channels have also been applied to the axon initial segment (AIS), the unmyelinated region of the axon that emerges from the soma. It has been long known that in pyramidal neurons, the AIS is the site of AP initiation, not the soma. This has been classically explained by a 10- to 1,000-fold higher density of Na^+ channels at the AIS than on the soma, as determined by histologic techniques (Johnston, 2010). However, patch-clamp recordings and Na^+-imaging studies of the AIS suggest that the density of functional Na^+ channels, although higher in the AIS than in the soma, may not be as high as suggested from immunohistochemistry, and that the lower threshold for AP initiation results from a hyperpolarized shift in I_{Na} voltage-dependent activation and the presence of I_{NaP} (Colbert & Johnston, 1996; Colbert & Pan, 2002; Fleidervish et al., 2010). The role of the AIS in neuronal excitability is an active area of research, and one that is highly relevant for studies of epileptogenesis (Kole & Stuart, 2012).

Another influence on AP firing, particularly sustained AP firing such as occurs during a seizure, is the Kv7.2 and 7.3 delayed rectifier channels that are also localized to the axosomatic region. These channels, encoded by the *KCNQ2* and *KCNQ3* genes, mediate the classical ''M current,'' a noninactivating, slowly activating K^+ current that is inhibited by muscarinic acetylcholine receptor activation (Shah et al., 2008). Increasing attention has been focused on the Kv7.2/7.3 channels due to their involvement in the benign familial neonatal convulsions (BFNC) epilepsy syndrome, and their targeting by a recently approved antiepileptic drug, ezogabine (retigabine outside the United States) (Gunthorpe et al., 2012).

Acquired Alterations in Ion Channel Localization in Epilepsy

The studies described above should paint a picture of the pyramidal neuron not as a featureless plain of homogeneously distributed ion channels, but rather as possessing a richly varied topography, with peaks and valleys of ion channel density spread throughout the somatodendritic axis and axon initial segment. It is also worth noting that not all pyramidal neurons are the same. There is considerable variability of neuronal properties in the longitudinal axis of the hippocampus, and this variability likely subserves the different functions of these regions (Fanselow & Dong, 2010). With this idea in mind, we can consider what recent studies tell us about the changes in that tableau of ion channel localization that occur during and after the development of epilepsy. We will focus on the three voltage-gated ion channels—A-type K^+ channels, HCN channels, and T-type Ca^{2+} channels—that have been most intensively studied in animal models. As we consider the changes in channel localization that have been described, we will also address the several key questions to establish their relevance to epileptogenesis: do changes in channel localization occur after a neural insult but before the onset of spontaneous seizures, or do they occur only in established epilepsy? Does the change in ion channel properties influence the development of epilepsy? And does evidence exist for involvement of the channelopathy in human acquired epilepsy syndromes? Considering this evidence, where it is available, aids in the interpretation of whether changes in ion channels in acquired epilepsy are cause or consequence of epileptogenesis.

A-Type K^+ Channels

The study that changed the paradigm of acquired channelopathy in neurons from one that had been considered a

purely somatic phenomenon to one localized in the dendrites was published in 2004 (Bernard et al., 2004). This study used whole-cell dendritic current clamp recordings to examine the activity of A-type K^+ channels in CA1 pyramidal neuron dendrites in chronically epileptic rats. The epilepsy model used was status epilepticus (SE) induced by pilocarpine in rats, and the time point examined was 6 months post-SE, when animals were having spontaneous convulsive seizures. It was observed that the amplitudes of backpropagating APs in the dendrites of neurons from epileptic animals were increased. It had been previously demonstrated that dendritic AP amplitude was strongly influenced by the high dendritic density of I_A; in the epileptic animals, pharmacologic blockade of I_A had a much smaller effect on dendritic excitability than the same blockade in controls. Although this study did not make voltage-clamp measurements of I_A per se, assays of Kv4.2 protein and messenger RNA (mRNA) content, the main constituent of I_A, showed decreases in Kv4.2 expression in epileptic animals, suggesting that transcriptional down-regulation underlied the loss of I_A in chronically epileptic animals.

The effects of dendritic I_A down-regulation on neuronal excitability in epilepsy are significant: increased backpropagating AP amplitude leads to enhanced activation of voltage-gated Ca^{2+} channels and NMDA receptor–mediated synaptic currents (which are partially voltage-dependent in addition to being ligand-gated). But it is unlikely that I_A down-regulation was solely responsible for the epileptic state. This study examined only the chronic epilepsy time point; therefore, it was unclear if I_A down-regulation preceded the development of epilepsy; and a subsequent study demonstrated that although Kv4.2 deletion virtually eliminates dendritic I_A (Chen et al., 2006), loss of Kv4.2 expression does not by itself cause epilepsy, although it enhances induction of epilepsy by convulsant drugs (Barnwell et al., 2009). In humans, there is a single report of a gene mutation leading to loss of functional Kv4.2 expression in an individual with epilepsy (a nonsense mutation in the *KCND2* gene leading to truncation of the Kv4.2 protein), found in a screening of 69 unrelated patients with temporal lobe epilepsy (Singh et al., 2006). (Of note, the patient's father also harbored the mutation, but did not have epilepsy.)

Although the first study to show Kv4.2 channelopathy in an animal model of chronic epilepsy did not examine the induction of channelopathy following SE, other studies have since shown that I_A is acutely down-regulated in the first several hours post-SE (Lugo et al., 2008), and that milder excitatory stimuli such as glutamate exposure for 10 min or stimulation that produces synaptic plasticity can at least transiently down-regulate I_A expression (Kim et al., 2007). With both SE and glutamate exposure, Kv4.2 channels undergo internalization from the surface membrane, thus acutely reducing functional I_A. How the acute loss of Kv4.2 expression in the first hour post-SE transitions into a chronic state of down-regulated Kv4.2 protein and mRNA expression 6 months later is thus far unknown.

HCN Channels

Our understanding of the role of HCN ion channels in epilepsy has evolved greatly over the last 15 years. An important factor driving interest in these unique ion channels was the discovery that, like A-type K^+ channels, HCN channel density is strikingly enriched in the dendrites of pyramidal neurons, to an even greater degree than that of A-type K^+ channels (Magee, 1998). Their unusual biophysical properties, which cause them mostly to influence neuronal excitability in the subthreshold voltage range, yield differing effects on excitability depending on neuron type and subcellular localization. In the principal neurons of cortex and hippocampus, HCN channels exert a net inhibitory effect on excitability by dampening the effects of temporally summated excitatory synaptic input (Magee, 1999; Poolos, 2012).

A variety of acquired epilepsy models have shown that HCN channel expression and function is diminished both early in the course of epileptogenesis and in chronic epilepsy. In post-SE models using both pilocarpine and kainate, HCN1 channels (the predominant subtype in cortex and hippocampus) undergo a >50% loss of activity in chronic epilepsy; this produces neuronal hyperexcitability in hippocampal and entorhinal cortical neurons (Shah et al., 2004; Jung et al., 2007; Marcelin et al., 2009). Of interest, when one looks at the biophysics of HCN1 channels post-SE in the pilocarpine model, the loss of HCN1 activity reflects two separate processes: a decrease in current density resulting from the loss of ion channel expression, and a down-regulation of voltage-dependent gating in the remaining ion channels (Jung et al., 2007). This latter process does not occur until the advent of spontaneous seizures following the post-SE latent period, whereas the loss of HCN1 channel expression occurs immediately post-SE, and preceding spontaneous seizure onset. Therefore, HCN1 channelopathy in acquired epilepsy really consists of two channelopathies: one that potentially contributes to the onset of spontaneous seizures and one that does not. This is an important distinction that has not always been examined in detail for acquired channelopathies, and requires study of ion channel expression and function at various time points during epileptogenesis. The influence of HCN1 expression on epileptogenesis has been confirmed by experiments in which the onset of spontaneous seizures postkainate was found to be accelerated sixfold in HCN1 knockout mice (Huang et al., 2009).

The characteristics of HCN1 channelopathy show animal model–dependent differences. Among the post-SE models, although both pilocarpine and kainate models

demonstrate loss of HCN1 expression in chronic epilepsy, the kainate models show more variable loss of I_h (the current generated by HCN channels) and HCN1 protein expression in the early phases of epileptogenesis, with one study demonstrating a transient increase in somatic I_h 24–48 h post-SE, a time point when dendritic I_h loss was not seen (Shin et al., 2008). In contrast, the pilocarpine model shows dendritic loss of I_h within the first hour post-SE, with no change in somatic I_h at any time point (Jung et al., 2007, 2011). A third model, in which seizures are provoked by hyperthermia, produces *increased* somatic and dendritic I_h at chronic time points (Chen et al., 2001; Dyhrfjeld-Johnsen et al., 2008). It appears that these variable presentations of HCN channelopathy depend on the severity of the epilepsy phenotype induced in each model. The pilocarpine model produces epileptic animals that achieve a steady-state rate of convulsive seizures within about 3 weeks post-SE, whereas animals postkainate do not achieve steady-state chronic epilepsy until about 6 months (Williams et al., 2009). The hyperthermia models produce only nonconvulsive seizures in a minority of treated animals examined beyond the 3 month posthyperthermia time point (Dube et al., 2006), thus the increases in I_h seen in that model may not necessarily be related to the epileptic state.

The mechanisms underlying HCN1 channelopathy have been studied in the most detail of any of the channelopathies discussed herein. The insights derived from these investigations may prove important for understanding how other ion channels are altered during epileptogenesis. HCN1 channelopathy in the postpilocarpine model appears to depend on several interwoven processes. Within the first hour post-SE, a fraction of HCN1 channels undergo internalization from the dendritic plasma membrane (Jung et al., 2011). This effectively reduces the number of functional dendritic ion channels, even though the total HCN1 channel protein content remains unchanged. Similar alterations in ion channel trafficking to the surface membrane post-SE have been described for A-type K^+ channels and $GABA_A$-receptor subunits, and thus may be a common theme in acquired channelopathy (Goodkin et al., 2008; Lugo et al., 2008; Terunuma et al., 2008). These latter examples are phosphorylation dependent, although such a mechanism has not yet been established for altered trafficking of HCN1 channels. Possible effectors of defective HCN1 channel trafficking include two accessory scaffolding proteins, Trip8b (Lewis et al., 2011; Piskorowski et al., 2011), and filamin A (Gravante et al., 2004). Trip8b expression is important for the establishment of the HCN1 channel gradient in CA1 pyramidal neuron dendrites, whereas filamin A appears to increase surface membrane expression of HCN1 channels, at least in heterologous expression systems.

After the acute loss of dendritic HCN1 surface expression post-SE, within 24 h HCN1 protein expression is reduced, presumably representing degradation of internalized ion channel subunits. Several days later, measures of HCN1 mRNA decline, demonstrating reduction of *HCN1* gene transcription. *HCN1* gene transcription and protein expression remain reduced in chronic epilepsy. The transcriptional loss appears to depend on the up-regulation of a master transcriptional regulator, neuron-restrictive silencer factor (NRSF) (McClelland et al., 2011). These results suggest that the development of HCN1 channelopathy results from several different mechanisms, each with a distinct temporal evolution. Whether these mechanisms proceed in a serial fashion, each dependent on signaling in the preceding mechanism, or exist as parallel signaling processes, is as yet unknown.

The evidence for HCN channelopathy in human epilepsy is thus far inconclusive. Analysis of temporal lobe tissue resected from patients with intractable epilepsy did not show an overall change in hippocampal HCN channel expression compared to autopsy control, but a subgroup of patients with mesial temporal sclerosis demonstrated up-regulation of I_h and HCN1 expression in dentate granule cells, which was interpreted as a potentially ''compensatory'' change (Bender et al., 2003; Surges et al., 2012). Another study found that I_h magnitude in neocortical pyramidal neurons from tissue resected during epilepsy surgery varied inversely with the frequency of seizures prior to surgery, suggesting an association between epilepsy severity and loss of I_h (Wierschke et al., 2010). Several studies have identified polymorphisms in *HCN1* and *HCN2* gene sequences in patients with epilepsy, although since these gene mutations have not clearly been shown to segregate with disease in affected kindreds, their contribution to epilepsy is thus far uncertain (Tang et al., 2008; Dibbens et al., 2010; DiFrancesco et al., 2011).

T-Type Ca^{2+} Channels

All known types of voltage-gated Ca^{2+} currents are distributed throughout the dendrites of CA1 pyramidal neurons, but the low-voltage activated, transient T-type channels, along with high voltage-activated R-type channels, are enriched compared to their somatic densities (Magee & Johnston, 1995). T-type Ca^{2+} channels have a long association with epilepsy, particularly due to their ability to promote neuronal burst firing by producing a depolarizing current that activates at voltages subthreshold to AP firing. The actions of T-type channels have been felt particularly relevant to thalamocortical neuronal excitability, and to generalized seizures such as absence that may depend on thalamocortical synchronized bursting. Indeed, T-type blockers such as ethosuximide and other more novel compounds have clinical efficacy against absence seizures (Tringham et al., 2012), and a transgenic mouse overexpressing the *CACNA1G* gene encoding the Cav3.1 T-type channel demonstrates absence epilepsy

(Ernst et al., 2009). Several polymorphisms in the human *CACNA1H* gene underlying Cav3.2 channels have been described in patients with epilepsy, although none segregating with absence epilepsy or in related kindreds with epilepsy (Heron et al., 2004).

T-type Ca^{2+} channels may also be relevant to acquired epilepsy. CA1 pyramidal neurons have been shown to develop bursting behavior, at least transiently, during epileptogenesis induced by pilocarpine, associated with an increase in $I_{Ca,T}$, the current mediated by T-type Ca^{2+} channels (Su et al., 2002; Yaari et al., 2007). Using focal application of pharmacologic blockers, the $I_{Ca,T}$ increase was localized to the dendrites. When the phenomenon of $I_{Ca,T}$ up-regulation during epileptogenesis was examined in more detail, only the Cav3.2 isoform of Ca^{2+} channels mediating T-type currents was found to be acutely up-regulated postpilocarpine, before the onset of spontaneous seizures (Becker et al., 2008). Cav3.2 channels appeared to be up-regulated initially by a transcriptional mechanism, with large subsequent increases in Cav3.2 protein content. Genetic deletion of Cav3.2 channels did not affect the incidence of epilepsy postpilocarpine—and so, strictly speaking, did not affect epileptogenesis—but did result in animals with significantly reduced seizure frequency, suggesting a potent antiepileptic action of T-type Ca^{2+} antagonism. Despite this compelling evidence linking T-type channels to seizure generation, no studies to date have determined whether the density or voltage-dependent properties of dendritic T-type channels are altered in epilepsy.

Other Ion Channels

Na^+ channels have become an intense focus of channelopathy research owing to their involvement in two genetic epilepsy syndromes, generalized epilepsy with febrile seizures-plus (GEFS+) and severe myoclonic epilepsy of infancy (SMEI). They would seem prime suspects in the investigation of the causes of acquired epilepsy. However, even in their associated genetic syndromes, the nature of Na^+ channel dysfunction remains unclear: initial evidence from heterologous expression systems suggested that mutations in Nav1.1 causing GEFS+ produced a toxic gain of function (a persistent Na^+ current), yet neurons from transgenic mice containing Nav1.1 mutations appear to show a loss of I_{Na} only in interneurons, whereas principal neuron I_{Na} is unchanged (Martin et al., 2010). Likewise, hippocampal pyramidal neurons from mice with a truncated Nav1.1, mimicking mutations seen in SMEI, show no significant alteration in I_{Na}, whereas hippocampal interneurons have a substantial loss of I_{Na} and decreased repetitive firing in response to stimulation (Yu et al., 2006). Therefore, when considering channelopathy in neurons, we must now consider which subset of neurons are affected, and contemplate the possibility that channelopathy in principal neurons may have quite different effects on brain excitability than channelopathy in inhibitory interneurons.

In models of acquired epilepsy, there is little specific evidence of altered Na^+ channel biophysical properties, with AP threshold appearing unchanged in chronic epilepsy (Sanabria et al., 2001). Although evidence exists that persistent Na^+ current is at least transiently increased in CA1 hippocampal neurons after pilocarpine, the exact subcellular localization of these altered currents, and their molecular identity, is thus far unknown (Chen et al., 2011). Part of the challenge with studying the contribution of I_{Na} to epileptogenesis may lie with the site of AP generation in the axon initial segment, a cellular compartment that is even more difficult to study electrophysiologically than the apical dendrites.

Similarly localized to the AIS are channels in the Kv7 family that are products of the *KCNQ* family of genes. These channels mediate the muscarinic acetylcholine receptor–sensitive K^+ currents known as I_M, exert a strong negative influence on sustained AP firing, and are localized in proximity to the high density of I_{Na} found in the AIS (Cooper, 2011). Kv7 channels have attracted increased interest not only for their role in BFNC, but as targets of a novel antiepileptic drug, retigabine/ezogabine. Conditional suppression of Kv7 channels in transgenic mice yields spontaneous seizures, confirming the importance of this ion channel in experimental genetic epilepsy (Peters et al., 2005). Yet there is little published evidence that their properties are altered in acquired epilepsy models, a somewhat surprising state of affairs. Again, their localization to the AIS may pose a significant challenge to their electrophysiologic study.

Conclusions

Ion channelopathy is a proven cause of human genetic epilepsy, and an abundance of animal model data suggests that it is likewise a mediator of epilepsy acquired from central nervous system (CNS) insults, including status epilepticus, hypoxia, and cortical malformation. The studies described here show that the dendrites and axon initial segment of pyramidal neurons represent fertile ground for the study of channelopathy due to the sheer number and variety of channels localized there, and their variation across the multiple dimensions of the neuronal somatodendritic axis, differing brain regions, and the temporal course of the development of epilepsy. The study of acquired channelopathies related to epilepsy offers great hope for a better understanding of the disease, particularly by understanding the mechanisms underlying them. Characterizing the transcriptional, translational, and posttranslational alterations of ion channel expression during epileptogenesis will allow understanding of the earliest cellular processes that led to neuronal hyperexcitability after a CNS injury. And although it is unlikely that acquired epilepsy will be found to depend on a derangement of a single ion channel

species—unlike the case for the Mendelian genetic epilepsies—it is possible that a unifying explanation will emerge to explain why the expression of multiple ion channels is altered, often in a way that affects excitability in a nonhomeostatic fashion. Ion channels, both ligand-gated and voltage-gated, also represent important molecular targets for pharmaceuticals (approximately 10–15% of all U.S. Food and Drug Administration (FDA)–approved drugs act on ion channels, Overington et al., 2006), and changes in their biophysical properties in the epileptic state provide both opportunities and challenges for the development of novel antiepileptic drugs.

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