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Jasper's Basic Mechanisms of the Epilepsies

Hyperpolarization-Activated Cyclic Nucleotide-Gated (HCN) Ion Channelopathy in Epilepsy

Nicholas P Poolos, MD, PhD

Department of Neurology and Regional Epilepsy Center, University of Washington, Seattle, WA 98104

Abstract

Hyperpolarization-activated, cyclic nucleotide-gated (HCN) voltage-gated ion channels are widely expressed in cortex, hippocampus, and thalamus, brain regions that underlie the generation of both focal and generalized-onset seizures. Greater understanding of the contribution of HCN channel function to neuronal physiology has been paralleled by increasing evidence for their role in epilepsy. Genetic deletion of the HCN2 channel subtype leads to an absence epilepsy phenotype, while deletion of the HCN1 subtype produces hypersensitivity to provoked seizures and accelerates epileptogenesis. Pharmacological blockade of HCN channels likewise produces neuronal hyperexcitability, while one or more antiepileptic drugs appear to upregulate HCN channel function. In animal models of acquired epilepsy, loss of HCN channel expression and function occurs during the earliest phases of epileptogenesis, and promotes the occurrence of seizures. Thus, numerous lines of evidence point to a role for HCN channels in epilepsy, especially in acquired syndromes. In this chapter, I describe how the biophysical properties of HCN channels position them to play a significant role in epileptogenesis; how emerging evidence suggests the existence of HCN channelopathy in human epilepsy; and how the mechanisms underlying HCN channelopathy could be targeted in antiepileptic therapies.

Hyperpolarization-activated, cyclic nucleotide-gated (HCN) ion channels represent a unique class of voltage-gated ion channels. Initially characterized in the heart as "pacemaker" channels,[1] they are now understood to be an essential modulator of neuronal excitability in cortex, hippocampus, and thalamus.. Their diverse contributions to neuronal excitability stem from a constellation of unusual features: they are both voltage- and ligand-gated; they open with hyperpolarization of membrane potential rather than with depolarization; and in the principal neurons of cortex and hippocampus, they are localized almost exclusively to the apical dendrites where they exert a strong influence on the flow of excitatory synaptic inputs to the cell soma. Because of the influence of HCN channels on neuronal physiology, they also play an important role in epilepsy. Genetic deletion of the HCN2 channel subtype causes absence epilepsy in mice,[2] while deletion of the HCN1 subtype exerts a proconvulsive effect and accelerates epileptogenesis.[3] Loss of HCN1 channel expression and function also occurs during epileptogenesis in animal models of acquired epilepsy, contributing to neuronal hyperexcitability and promoting further seizures.[4] Conversely, upregulation of HCN channel function by antiepileptic drugs may be constitute part of their anticonvulsant mechanism of action.[5] Thus, there is substantial new evidence that has emerged just in the past 10 years that link HCN channel dysfunction with epilepsy.

In this chapter, I describe how the unique biophysical properties of HCN channels lead to an influential role in seizure generation; whether recent evidence truly supports the existence of HCN channelopathy in human epilepsy; and how the mechanisms underlying acquired HCN dysfunction could be targeted by antiepileptic therapies.

Correspondence to: Nicholas P. Poolos, 325 9th Ave, Box 359745, Seattle, WA 98104, Telephone: +1 206-897-5423, npoolos@uw.edu.

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HCN CHANNEL BIOPHYSICAL PROPERTIES

HCN channels are voltage-gated ion channels that structurally resemble K^+ channels, with a six-transmembrane domain topology, including a pore region that conducts ion flow. However, HCN channels possess biophysical properties that make them virtually unique in comparison to other voltage-gated channels.[6] First, despite structural similarity to K^+ channels, HCN channels are relatively less selective for K^+ ions, allowing inward passage of Na^+ ions. Because at typical neuronal resting potential the driving force for Na^+ is so much greater than for K^+, HCN channels primarily conduct Na^+ current under physiological conditions, thus depolarizing neuronal membrane potential. Second, the voltage-dependent activation of HCN channels is also anomalous compared to most other channels: HCN channels are fractionally open at resting potential, and their activation increases with hyperpolarization from rest rather than with depolarization as is common with other channels. Thus neuronal depolarization tends to turn off HCN channels while hyperpolarization tends to activate them. Third, HCN channels do not display inactivation, thus are constitutively active around resting potential. The current mediated by HCN channels, I_h, is estimated to comprise about half of the resting conductance of many neuron types. This allows HCN channels to exert a strong influence on the "passive" properties of the neuron, such as resting potential and input resistance. (The term "passive" of course is a misnomer, since these properties are modulated by HCN and other voltage-gated channels that by definition are "active" conductances.) Fourth, HCN channels open remarkably slowly, with activation time constants that range from tens to hundreds of milliseconds, i.e., several orders of magnitude slower than those of most ion channels. Finally, HCN channels are partly gated by intracellular levels of cyclic nucleotides such as cyclic adenosine 3′,5′-monophosphate (cAMP). This allows channel activity to be modulated by both voltage and intracellular second messengers.

The net result of these biophysical features is a current that inherently stabilizes the neuron at its resting potential, minimizing the influence of synaptic inputs. When the neuron becomes depolarized by a synaptic input, the tonic depolarizing Na^+ current mediated by HCN channels is turned off, since the channels deactivate with depolarization. This hyperpolarizes membrane potential back towards rest. Conversely, a hyperpolarizing input (such as an inhibitory postsynaptic potential, IPSP) will turn on I_h, depolarizing the neuron back towards rest. Thus I_h displays an inherent negative-feedback property that imparts a stabilizing effect on neuronal excitability. While it might seem that this stabilizing action might equally apply to excitation and inhibition, it turns out that I_h will disproportionately modulate these two types of synaptic inputs depending on how the conductance is distributed throughout the cell. One of the most intriguing themes to emerge in the last 15 years of research in ion channel function is the non-uniformity of ion channel distribution within the neuron, particularly in pyramidal neurons. HCN channels represent a prime example of this non-uniform or segregated distribution at a subcellular level, causing them to disproportionately diminish the impact of excitatory postsynaptic potentials (EPSPs). This is discussed further below.

HCN channels are encoded by four separate genes, *HCN1-4*.[7] Ion channels encoded by each of the isoforms have differing biophysical properties (such as speed of gating and sensitivity to cAMP), and are also differentially distributed throughout the brain. HCN1 and HCN2 are the main brain isoforms, with HCN1 predominant in the neocortex and hippocampus, and HCN2 predominant in the thalamus. HCN3 has diffuse but low-level distribution in the brain, while HCN4 is a subtype present mostly in thalamic relay neurons.[6] In this review, we will mainly consider HCN1 as the cortical/hippocampal subtype; it has relatively fast activation times (tens of milliseconds), but virtual insensitivity to cAMP. HCN2 is the main subcortical (e.g., thalamic) isoform, with intermediate (several hundreds of milliseconds) activation time constants, and a depolarizing shift in its voltage-dependence on exposure to cAMP. As

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described below, these biophysical differences among HCN subtypes account for their functional roles in the brain regions in which they are found.

HCN CHANNEL EFFECTS ON NEURONAL EXCITABILITY

As discussed above, HCN channels tend to stabilize neuronal membrane potential against either excitatory or inhibitory inputs. Interestingly, their slow activation time course, particularly for the HCN2 and HCN4 subtypes, can be exploited to produce membrane potential oscillations. This occurs when an inward current that activates at hyperpolarized potentials, such as the T-type Ca^{2+} current, is paired with I_h. Indeed, the first characterization of HCN channels was in the sinoatrial node of the heart, where HCN2 and HCN4 channels help set the frequency of firing that produces sinus rhythm. In fact, it is the modulation of I_h by changes in intracellular cAMP concentration that contributes to the autonomic control of heart rate by β-adrenergic and cholinergic receptor activation.[1] A similar oscillatory function occurs in thalamocortical projection neurons that underlie synchronization of cortical rhythms seen in sleep and in primarily generalized seizures such as absences.[8] An interesting feature of this interaction is that HCN channels need to function in a narrow range of activity in order to mediate oscillations. Either downregulation or upregulation of steady-state I_h has the potential to abolish oscillations.[9] Similarly, blockade of the T-type Ca^{2+} channels will abolish the thalamocortical burst firing underlying absence seizures, a well-described mechanism of action of the antiepileptic drug (AED) ethosuximide (ETX).[10] Because of these contributions to oscillatory activity, HCN channels have often been labeled “pacemaker” currents. However, in principal neurons of cortex and hippocampus, their role is quite different.

In neocortical and hippocampal pyramidal neurons, the actions of HCN channels have been intensely investigated over the past decade. As was first described in 1998, HCN channels in pyramidal neurons show a strikingly non-uniform pattern of distribution: rather than being homogeneously distributed across the cell membrane, they are instead arrayed in a gradient pattern along the somatodendritic axis, being present at low levels in the cell body, but at increasingly high density (7–10-fold compared to the soma) in the apical dendrites.[11] The high dendritic density of HCN channels places them in proximity to excitatory inputs, the vast majority of which arrive in the dendrites. Because HCN channels are open at rest, they diminish the input resistance of the dendrites to incoming synaptic currents, decreasing the voltage change produced by an EPSP; conversely, when HCN channels are inactivated, input resistance is higher, and EPSPs are increased in magnitude. In essence, I_h makes for “leaky” dendrites that do not faithfully transmit excitatory inputs. While I_h also causes resting potential depolarization that opposes its inhibitory effect on action potential firing, it appears than in pyramidal neurons the high dendritic density of I_h and its attenuating action on synaptic inputs (particularly repetitive inputs) predominates. This is illustrated in Figure 1, where it can be seen that the inhibitory actions of I_h on input resistance and EPSP summation outweigh its excitatory actions on resting potential.

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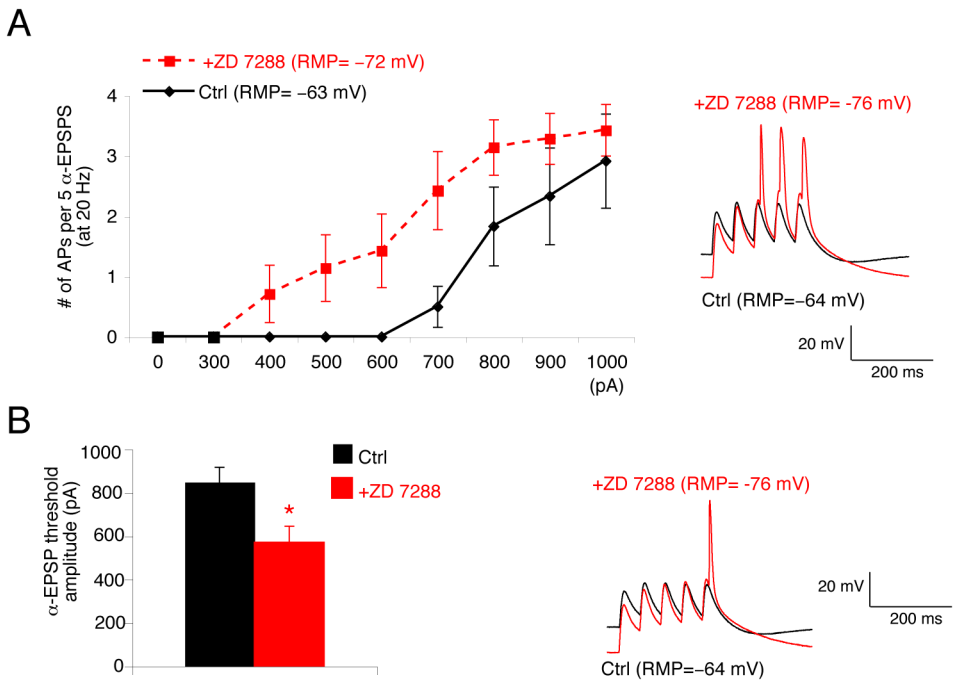

Fig. 1. Blockade of HCN channels increases excitability in pyramidal neurons

A. Action potential (AP) firing elicited by current injection of α waveforms during dendritic current clamp recordings (~200 μm from the soma) under control conditions and after blockade of HCN channels with ZD 7288. Despite the hyperpolarization of RMP that occurs after HCN channel blockade, increased temporal summation produces increased AP firing through a wide range of α-EPSP amplitudes. **B**. Measurement of the "threshold" α-EPSP amplitude needed to produce a single AP shows that threshold is decreased following HCN channel blockade, again showing increased excitability.

In the early years following the first characterization of I_h in CNS neurons, much was made of its dual influence on neuronal excitability, with suggestions by more than one reviewer of the field that I_h could be described as neither an excitatory nor an inhibitory conductance.[12,13] Now, with many investigations of its action published, it is clear that I_h has a net inhibitory action in the principal neurons of cortex and hippocampus: it reduces temporal summation (TS) and action potential (AP) firing from dendritic EPSPs; it inhibits forward propagation of dendritic APs and increases the threshold for dendritic calcium spikes; and dendritic HCN channels reduce acquisition of learning and memory in several *in vivo* paradigms. These findings are summarized in Table 1.

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Table 1

Actions of HCN channels in pyramidal neurons

Neuron	Action of HCN channels on excitability
CA1	Reduces and normalizes TS; reduces AP firing from dendritic inputs;[5,11,48,63] inhibits dendritic Ca^{2+} spikes[64]
	Reduces LTP and spatial learning[65]; reduces intrinsic excitability after LTP via CAMKII;[66] loss of I_h increases intrinsic excitability after LTD via mGluR[67]
	Increases rebound AP firing after hyperthermia-induced seizures[31,39]
	Loss of I_h post-SE increases TS and AP firing[4]
NC	Reduces and normalizes TS;[68,69] inhibits dendritic Ca spikes;[70] inhibits dendritic Ca spikes and burst firing in WAG/Rij epileptic rats[26,27]
EC	Inhibits AP firing; loss of HCN post-kainate increases excitability;[33] inhibits AP firing after D1 receptor activation[71]
	Knockout of HCN1 increases excitability and sensitivity to convulsants[3]
PFC	Reduces spatial learning in primates and rats; I_h blockers in vivo increase neuronal firing;[72] inhibits excitability and dendritic Ca spikes; α2-NARs inhibit I_h and increase excitability[73,74]

Abbreviations: CA1, hippocampus cornu ammonis area 1; CAMKII, Ca^{2+}/calmodulin-dependent protein kinase II; D1, dopamine receptor type 1; EC, entorhinal cortex; LTD, long-term depression; LTP, long-term potentiation; mGluR, metabotropic glutamate receptor; NAR, noradrenergic receptor; NC, neocortex; PFC, prefrontal cortex; TS, temporal summation.

In non-pyramidal inhibitory interneurons of cortex and hippocampus, it appears that I_h has a predominantly somatic localization and therefore its influence on excitability is mediated more through its depolarization of resting potential, opposite to its action in principal neurons.[14] Thus, inhibition of HCN channels in interneurons reduces AP output while activation of HCN channels increases firing. However, this opposite sign of HCN influence in inhibitory neurons is concordant with its excitatory effect in principal neurons: both actions of HCN channels serve to diminish the overall excitability of cortex and hippocampus.

CONTRIBUTION OF HCN CHANNELS TO EPILEPSY

Evidence for human HCN channelopathy

Evidence for HCN channelopathy in human epilepsy is thus far limited. Since virtually all clear-cut evidence for any ion channelopathy in epilepsy derives from the inherited or genetic epilepsies, we must first consider these conditions. There are no descriptions yet of genetic epilepsy with mendelian inheritance of an HCN channel mutation as have been reported for certain Na^+, K^+, and other voltage-gated ion channels.[15] This of course does not mean that such mutations do not exist, and it is possible that large-scale screening projects such as the Epilepsy Phenome-Genome Project will uncover them. Since only a small fraction of all epilepsies display mendelian patterns of inheritance, if HCN channels are to be implicated in genetic epilepsy, they are more likely to be implicated as a polygenic or susceptibility trait. Several medium-scale screening projects of sporadic epilepsy have reported polymorphisms in HCN genes occurring at higher frequency in case versus control patients. One study of 84 patients with idiopathic generalized epilepsy identified a single *HCN1* polymorphism (A881T) that was not identified in 510 controls. There was a far higher degree of sequence variation in the *HCN2* gene; however there were only two non-synonymous mutations.[16] One of these, R527Q, was analyzed using heterologous expression; I_h generated from the mutant channels was found to have similar biophysical properties to that from wild-type channels. A 3-proline deletion in HCN2 identified in one patient in the first study was also independently observed in another study of patients with idiopathic generalized epilepsy (IGE) or febrile seizures (FS).[17] This variant was found in 3 out of 65 (2.3%) unrelated epilepsy patients, all of whom

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had FS, but in 0/72 patients with IGE and 3/772 controls. Analysis of expressed mutant channels suggested an increase in I_h. Again, since this particular mutation has not thus far been found to co-segregate with disease, it cannot at this point be regarded as causative of epilepsy but only as a possible susceptibility trait.

It is worth noting that several studies have identified *HCN4* mutations in association with inherited cardiac arrhythmia.[18,19] Thus at present, the strongest association of HCN channelopathy and disease is for this subtype which is minimally expressed in the adult brain.

Investigation of HCN channel expression in human brain tissue from patients with epilepsy has similarly been limited. A comparison of HCN channel mRNA expression from temporal lobe resections overall found no significant change in comparison to autopsy controls; however, a subgroup of patients with the greatest degree of hippocampal sclerosis appeared to have an increase in *HCN1* expression limited to the dentate gyrus (DG).[20] This finding was surprising, since DG neurons normally demonstrate very little I_h, and was interpreted as a potential "compensatory" upregulation of expression in the most severely affected patients. Other investigators found that I_h magnitude measured in neocortical neurons from brain tissue acutely removed during epilepsy surgery inversely depended on the frequency of presurgical seizures, suggesting that more severe epilepsy was associated with a loss of neocortical HCN channel function.[21] In this study, however, no control comparisons were made, a common limitation of studies involving live human tissue.

In summary, the human evidence for genetic HCN channelopathy in epilepsy is thus far anecdotal. However, a significant body of evidence obtained from animal modeling suggests that HCN channelopathy could be causative of genetic epilepsy, and develops in the setting of acquired epilepsy as well.

HCN channels in animal models of genetic epilepsy

The above human studies provide suggestive, but still anecdotal, evidence for human genetic HCN channelopathy. Studies in animal models of genetic deletion of HCN channels advance a far more compelling case that this ion channel may be relevant to epilepsy. Constitutive knockout of the *hcn2* gene produced a phenotype consistent with the high density of the HCN2 subunit in the thalamus: a tendency of thalamocortical neurons studied in brain slices to fire bursts of action potentials, and spontaneous absence seizures, marked by generalized 5 Hz spike-wave discharges, detected in the mutant animals.[2] These mice also displayed a cardiac sinus arrhythmia, consistent with loss of HCN2 from sinoatrial node cells.

Two studies have examined *hcn1* deletion for evidence of epilepsy.[3,22] Neither of these studies detected spontaneous seizures in knockout animals. However, both studies demonstrated that hcn1 deletion increased the severity of seizures whether provoked by kindling or chemoconvulsants, with a high rate of death from status epilepticus (SE). In the kainic acid (KA) model of epilepsy, even after the dose of KA was halved to reduce death from SE, the latency period from SE to the occurrence of the first spontaneous seizure was shortened from 386 hours to 60 hours.[3] This study went one step further to examine pyramidal neuron excitability in *hcn1* knockout mice. Consistent with prior work showing an inhibitory effect of HCN channels on excitability in cortex and hippocampus (Table 1), pyramidal neurons lacking the principal HCN subunit mediating I_h demonstrated both increased intrinsic excitability as well as prolonged excitatory responses to synaptic stimulation. Both studies confirmed the role of HCN channels as exerting an inhibitory and even anticonvulsant role on cortical and hippocampal excitability. That *hcn1* deletion produces cortical and hippocampal hyperexcitability while not producing epilepsy is interesting and at this point not subject to easy explanation. One possible explanation is that constitutive deletion of HCN1 channels leads to compensatory upregulation of tonic $GABA_A$ receptor-mediated current that may partially

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suppress hyperexcitability.[23] Use of conditional knockout animals of HCN channels might help support or disprove this idea. A similar situation is reported for the K^+ channel subunit Kv4.2, a predominantly dendritic subunit that exerts a significant influence on neuronal excitability. In fact, deletion of the gene encoding for Kv4.2 does not result in epilepsy.[24]

HCN channel dysfunction has also been identified in inbred rodent models of genetic epilepsy. One such model of absence epilepsy, the Wistar Albino Glaxo/Rij (WAG/Rij) rat, shows loss of HCN channel function. WAG/Rij rats display spontaneous spike-wave discharges associated with behavioral absence-like episodes, with seizures appearing to begin from a cortical focus, then generalizing via rapid intracortical spread.[25] The cortical origin of seizures has been found to correlate with loss of I_h in neocortical neurons, accompanied by a loss of HCN1 protein expression;[26] this loss of HCN1-mediated currents was confined to the dendrites of neocortical neurons, progressed during development, and paralleled the onset of behavioral seizures.[27] Neither of these studies addressed the question of whether the changes in HCN channel expression and function were cause or effect of seizures in this animal model (that most likely has numerous gene mutations contributing to epilepsy); however, a subsequent study suppressed developmental seizures in the WAG/Rij rat with ETX administration for the first five months of life, then measured changes in HCN1 expression as well as that of two Na^+ channel proteins known to be dysregulated in this model, Nav1.1 and Nav1.6.[26] Surprisingly, epilepsy-associated changes in all three ion channels were reversed when seizures were chronically suppressed, and although spontaneous seizures recurred when ETX treatment was stopped, the time course of their development was markedly prolonged.[28] These intriguing results suggest that HCN1 channels in the WAG/Rij model of epilepsy, while not causative of epilepsy, may potentially contribute to the course of epileptogenesis by amplifying the effect of spontaneous seizures. This phenomenon in other contexts has been referred to "seizures beget seizures" and may be relevant in acquired models of epilepsy as well, as discussed below.[29]

HCN channel downregulation in animal models of acquired epilepsy

It is interesting that the first studies to link HCN channels and epilepsy were landmark publications that launched much of future investigation in the field, yet turned out not to predict subsequent developments. This work used a newly characterized model of febrile seizures, in which immature rats were exposed to high temperature, provoking SE.[30] This stimulus produced an unexpected, long-lasting increase in GABAergic inhibition in CA1 pyramidal neurons accompanied by an increase in I_h measured at the soma. It was suggested that hyperexcitability might result following IPSPs as the increased I_h triggered rebound AP firing.[31] However, follow-on work using the same model but investigating regulation of the *hcn1* gene transcription and protein production found persistent downregulation of expression; *hcn2* was transiently upregulated then returned to baseline.[32]

Subsequent work in other animal models of acquired epilepsy has consistently found downregulation of HCN channel expression and function, changes that were opposite to the upregulation of I_h initially seen in hyperthermia model. The first study to look at I_h changes in a model of SE induced by KA used whole-cell patch clamp recordings in the dendrites of entorhinal cortical neurons.[33] This was an important advance in methodology since, as described above, the vast majority of HCN channels are localized to the dendrites of pyramidal neurons, raising the possibility that in epilepsy they are differentially regulated compared to somatic channels. (Most subsequent studies have used dendritic patch clamp recording to study changes in I_h in epilepsy.) These authors found that dendritic excitability increased in an HCN channel-dependent fashion within 24 hours of KA-induced SE and remained so at 1 week post-SE, demonstrating an early change in HCN channel function that promoted hyperexcitability.

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Subsequent work tracked changes in I_h during the development of epilepsy and confirmed the association of decreased I_h during epileptogenesis. When dendritic recordings were made from CA1 pyramidal neurons in animals exposed to pilocarpine-induced SE, I_h was significantly reduced at two different time points, an acute period one week post-SE when the animals, as verified by EEG recordings, started to manifest spontaneous seizures, and at 1 month after SE, when the animals were chronically epileptic.[4] In both cases, there were two changes in I_h properties that reduced its overall magnitude: a reduction of dendritic I_h density that was reflected in a loss of HCN protein expression, and a hyperpolarizing shift in I_h activation that reduced the amount of current active at rest. The downregulation of I_h gating progressively worsened as seizure frequency increased from the 1 week to the 1 month time points, while the loss of I_h density was constant. Both of these changes were associated with increased excitability of CA1 pyramidal neurons.

A second study essentially replicated these findings, and further observed that loss of I_h altered the intrinsic resonance of pyramidal neurons for synaptic excitation at theta frequencies,[34] possibly underlying deficits in hippocampal-dependent memory tasks that accompany temporal lobe epilepsy.[35] Similar chronic loss of I_h was observed following KA-induced SE, although the authors also observed a transient (1–2 days post-SE) increase in I_h at the soma.[36] Loss of I_h and HCN channel expression has been observed in other animal models of epilepsy, including perinatal hypoxia[37] and cortical dysplasia.[38] This suggests that the loss of I_h seen in chemoconvulsant models is not model-specific, and may be a general feature of animal models of epilepsy.

It is not entirely clear why the discordant result of increased I_h was observed in the initial hyperthermia model. It is probably not explained by recordings done exclusively at the soma in those first studies, as a subsequent report using dendritic recordings in hyperthermia-exposed animals found a similar upregulation of I_h.[39] Possibly the discrepancy results from the mild epilepsy phenotype that results from hyperthermia-provoked SE, yielding only brief electrographic seizures in a minority of animals and at later time points than those studied in the original description.[40] By contrast, the chemoconvulsant models produce a much more robust epilepsy phenotype with a rapid developmental onset.

Mechanisms of HCN channel downregulation in acquired epilepsy

The findings in the pilocarpine model revealed that HCN channelopathy in acquired epilepsy consists of two separate mechanisms of ion channel dysfunction: a loss of I_h current density manifested by reduced HCN1 protein expression, and a downregulation of voltage-dependent gating of the remaining channels. It is important to ask whether either or both of these phenomena are cause or effect of epilepsy. This question was at least partially answered by controlling seizures with phenobarbital administration for the first week post-SE, and then measuring I_h properties.[4] Preventing spontaneous seizures reversed the hyperpolarizing shift in I_h gating, demonstrating that this was a seizure-dependent phenomenon. The loss of I_h density and HCN1 protein expression, however, was independent of ongoing seizures. Preliminary evidence suggests that the loss of HCN channels begins as rapidly as 1 hr post-SE, well before the onset of spontaneous seizures, thus may be a contributor to the development of the epileptic condition.[41] While gating changes in the remaining channels are caused by seizures rather than the other way around, it is conceivable that by promoting neuronal hyperexcitability, this HCN channelopathy mechanism could contribute to the gradual run-up in seizure frequency that occurs during epileptogenesis. Some support for this latter idea comes from the observation that HCN1 knockout mice have a much more rapid development of epilepsy after chemoconvulsant-induced SE than wild-type mice.[3]

What are the molecular underpinnings of the separate processes producing HCN channelopathy in epilepsy? For the loss of HCN channel expression, it is clear that transcriptional

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downregulation is at least one mechanism. Several investigators have validated the loss of HCN1 mRNA expression at time points beginning 3 days after SE, and persisting into chronic epilepsy.[32,34,42] In an *in vitro* model of epilepsy using KA administration in organotypic slice cultures, this loss of HCN1 transcription was dependent on AMPA and Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII) activation,[43] although *in vivo* involvement of these entities is unknown. Whether transcriptional downregulation is the earliest process leading to loss of HCN channel expression is unclear. HCN channels, like other ion channels, are subject to dynamic regulation of their membrane localization and stability. The best-described mechanism involves an accessory protein, tetratricopeptide-repeat containing Rab8b interacting protein (TRIP8b). This protein, expressed as a multitude of alternatively spliced isoforms, interacts with HCN1 channels and stabilizes their somatodendritic expression.[44–46] It appears that the interaction between Trip8B and HCN1 channels is reduced in epilepsy, but this process does not appear to begin prior to the onset of transcriptional downregulation.[36]

More is known about the processes underlying the downregulation of HCN channel gating in epilepsy. It is well known that although cAMP upregulates the gating of HCN2 and HCN4 channels, the HCN1 isoform is largely insensitive.[47] However the gating of HCN1 channels is modulated by phosphorylation, notably by p38 mitogen-activated kinase (p38 MAPK), with kinase activation producing a depolarizing (upregulating) shift in gating, and kinase inhibition producing the opposite effect.[48] Dephosphorylation by the serine-threonine phosphatase calcineurin produces concordant effects on HCN1 gating, with increased phosphorylation upregulating gating, and decreased phosphorylation downregulating it.[49] Since HCN channel gating is downregulated in chronic epilepsy, it would be reasonable to ask whether these phosphorylation pathways are dysregulated as well; in fact, p38 MAPK is relatively deactivated in epileptic tissue, while CaN activity in enhanced.[49] These changes in phosphorylation activity were driven by unknown upstream signaling processes and not by changes in the protein expression of the individual entities. This suggests that the epileptic state is associated with dynamic changes in signaling processes that might be amenable to pharmacological targeting, as has been suggested for another phosphorylation pathway, the mammalian target of rapamycin.[50] Phospholipid pathways may also modulate HCN channels, but whether they are altered in epilepsy is unknown.[51,52]

Antiepileptic drug actions on HCN channels

The downregulation of HCN channels in epilepsy suggests that if this process could be pharmacologically reversed, an antiepileptic benefit might be realized. Interestingly, there are several reports of existing AEDs that interact with HCN channels. The first published report showed that acetazolamide (ACZ), a carbonic anhydrase inhibitor with some efficacy in absence epilepsy, upregulated I_h in thalamocortical neurons.[53] This effect was attributed to an alkalinization of intracellular pH, leading to a 5 mV depolarization of voltage-dependent gating. The AED lamotrigine (LTG) also upregulates I_h through an ~10 mV depolarizing shift of gating in hippocampal pyramidal neurons.[5] In the case of LTG, although its effect was demonstrated in hippocampal neurons, upregulation of I_h in neocortical or thalamic neurons might potentially explain its efficacy against generalized seizures. LTG application blocks spontaneous rhythmic firing in combined thalamocortical brain slices.[54] The action of LTG on thalamic neurons is dependent on HCN channels, as was shown in recordings from reticular thalamic neurons, spontaneously bursting-firing cells whose rhythmic output is dependent in part on HCN2 channels. When LTG was superfused on thalamic tissue slices, the frequency of rhythmic firing was markedly reduced; however, this action of LTG was abolished in cells from HCN2 knockout animals.[55] A similar test of the specificity of LTG action in hippocampus or neocortex using HCN1 knockout animals has not yet been reported. And although LTG also acts to reduce Na^+ currents in a manner similar to the AEDs phenytoin (PHT) and

carbamazepine (CBZ),[56] this mechanism of action is unlikely to explain its efficacy in generalized epilepsy, as PHT and CBZ are poorly effective in these syndromes.[57]

Another angle on the action of LTG is seen its effects in interneurons residing the stratum oriens that project to pyramidal neuron dendrites.[58,59] In these spontaneously active interneurons, HCN channels are presumably localized perisomatically such that upregulation of I_h depolarizes resting membrane potential and increases firing rate; this had the concordant effect of decreasing pyramidal neuron excitability by virtue of an increased frequency of spontaneous inhibitory post-synaptic currents. This result was notable because the actions of AEDs are often only considered from the perspective of inhibition of principal neurons, whereas the same action on interneurons might be expected to be counterproductive on overall brain excitability. This study demonstrated a potentially complementary action of LTG on interneurons compared to their pyramidal counterparts that arose from differing contributions of HCN channels to excitability in the two neuron types.

Aside from LTG and ACZ, the conventional AED gabapentin has also been shown to upregulate I_h.[60] It would seem straightforward to ask whether HCN channel inhibition by a drug such as ZD 7288 might have a pro-convulsant effect. Some studies using *in vitro* models of seizures to address this question have reported a paradoxical anticonvulsant action of HCN channel inhibition;[61] other studies have reported that ZD 7288 inhibits glutamatergic transmission, therefore it cannot be considered a selective antagonist for HCN channels when synaptic transmission is studied.[62] Because *hcn1* deletion lowers the threshold for provoked seizures and SE, and *hcn2* deletion results in generalized epilepsy, it seems reasonable to conclude that HCN channels exert an anticonvulsant effect on the brain as a whole. This would suggest that discovery of novel specific HCN channel agonists might be a productive avenue for future AED development.

CONCLUSIONS

The HCN channel has emerged as a compelling new candidate channelopathy in epilepsy. It plays a powerful inhibitory role in cortical and hippocampal excitability, both at single neuron and network levels, and influences the development of thalamocortical rhythms as a result of its high expression in thalamic nuclei. In animal models of acquired epilepsy, HCN channel expression is downregulated, contributing to pathological hyperexcitability. Conversely, several AEDs upregulate the function of HCN channels, offering the potential of a novel target for further AED development.

Evidence of human HCN channelopathy is thus far anecdotal. However, given the substantial support from animal models for a pathologic role of this channel in acquired epilepsy in particular, understanding the mechanisms by which HCN channels are dysregulated may provide insights applicable to the larger number of epileptic ion channelopathies that are continually being characterized.

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