The Yin and Yang of the H-Channel and Its Role in Epilepsy

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Voltage-gated ion channels clearly are involved in the pathogenesis of epilepsy, with evidence implicating derangement of Na^+, K^+, and Ca^{2+} voltage-gated channels, in both inherited and acquired forms of epilepsy (1). A newcomer to this list of ion channels involved in epilepsy is the hyperpolarization-activated cation channel or h-channel (otherwise known as I_h or the pacemaker channel). This voltage-gated channel now is known to play a significant role in regulating neuronal excitability and recently has been shown to be modulated by seizures. Unlike other channels implicated in epilepsy whose function in normal neurons can clearly be labeled "excitatory" (Na^+ and Ca^{2+}) or "inhibitory" (K^+), the unique physiologic behavior of the h-channel allows it to both augment and decrease the excitability of neurons. Thus the role of I_h in epilepsy, at present, is controversial and is a growing area of intense investigation (2,3).

H-Channels Are Both Inhibitory and Excitatory

The h-channel or I_h is widely distributed in the cortex, hippocampus, and thalamus, as well as in peripheral nerve and in the heart, where it was first described as a regulator of cardiac pacemaking (4). I_h possesses unusual biophysical properties that allow it to play a chameleon-like role in neuronal excitability. Its structure represents an evolutionary marriage between the voltage-gated K^+ channel (which it most strongly resembles) and the cyclic nucleotide–gated, non–voltage-gated K^+ channel. Thus I_h possesses a high permeability to K^+ ions, is voltage gated, but also is modulated by intracellular cyclic adenosine monophosphate (cAMP) levels, allowing activity-dependent regulation. More important, the channel has substantial permeability to Na^+, such that on opening at typical neuronal resting potential, it generates an inward current, causing the cell to depolarize; yet the channel is activated not by depolarization (as with virtually all voltage-gated channels) but by *hyperpolarization*. Because hyperpolarization produces activation, which in turn leads to depolarization (resulting in channel deactivation), the h-channel possesses an inherent negative-feedback property.

This negative-feedback principle is evident in the contribution of I_h to neuronal excitability, as illustrated in Fig. 1. In a neuron recorded at rest with I_h inactive, a small depolarizing or hyperpolarizing input rapidly produces a steady-state change in voltage. With I_h active, however, a hyperpolarizing input causes slow I_h activation, producing a depolarizing current that returns the membrane potential toward rest. Conversely, a depolarizing input causes deactivation of the I_h that was active at rest; the loss of a tonic depolarizing current causes a hyperpolarization, again returning membrane potential toward rest. Thus I_h tends to stabilize membrane potential toward the resting potential against either depolarizing or hyperpolarizing inputs. More precisely, I_h diminishes input resistance, the voltage change produced by a given synaptic current.

In physiological terms, I_h can be either excitatory or inhibitory with respect to its influence on action potential firing. As described earlier, I_h diminishes the effect of excitatory inputs and the likelihood they will produce action potential firing. Conversely, I_h helps set the level of resting potential, depolarizing it from the K^+ reversal potential and toward action potential firing threshold, a potentially excitatory influence. Furthermore, in cells with a tonically active inward current, addition of the negative-feedback behavior of I_h contributes to oscillatory behavior, such as is seen in sinoatrial node cells and thalamic relay neurons (5). Thus like the ancient Chinese principle of yin–yang, the h-channel embodies two opposing influences on neuronal excitability, preventing simple characterization as either inhibitory or excitatory.

Although all h-channels possess the fundamental properties described earlier, I_h represents a family of currents with differing kinetics and tissue distributions. I_h is encoded by the *HCN* family of genes, of which four subtypes have been identified (6). The predominance of various h-channel subtypes varies by location, with HCN1 and HCN2 most prevalent in cortex and hippocampus, and HCN2 and HCN4 predominating in the thalamus (7). *HCN3* is only modestly expressed in brain. Because the biophysical properties of HCN subtypes vary significantly (with HCN1 having faster kinetics but less cAMP modulation compared with HCN2 and HCN4), the contribution of I_h to neuronal behavior also varies by both location and neuron type in each region, with individual neurons expressing varying amounts of different HCN isoforms.

Epilepsy Currents, Vol. 4, No. 1 (January/February) 2004 pp. 3–6
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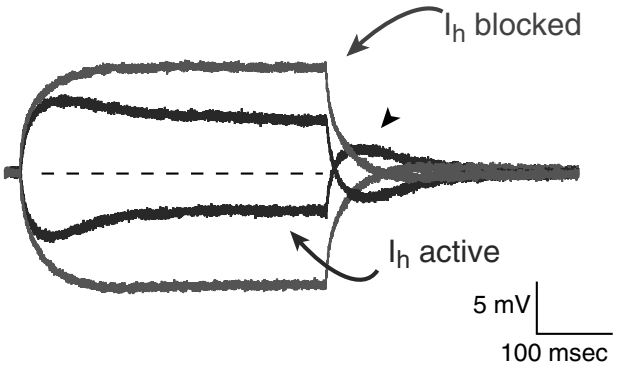

FIGURE 1 Actions of hyperpolarization-activated cation channel (I_h) on neuronal excitability. Current-clamp recording from CA1 hippocampal pyramidal neuron dendrite with superimposed responses to depolarizing and hyperpolarizing current injections (*lighter traces*) when I_h is blocked (with ZD-7288) show that the voltage response quickly reaches a steady-state plateau. When I_h is active (*darker traces*), a hyperpolarizing input elicits a slow, depolarizing "sag" in membrane potential, reflecting I_h activation. Note the rebound afterdepolarization (*arrowhead*) at the end of the hyperpolarizing input. Similarly, a depolarizing input yields a hyperpolarizing sag in membrane potential, representing I_h deactivation. Thus I_h tends to stabilize membrane potential toward resting potential (*dotted line*) against both hyperpolarizing and depolarizing inputs.

H-Channels Affect Neuronal Function

Because I_h has the potential to affect excitability in a number of ways, modulation of I_h can significantly affect neuronal behavior. Some of the first evidence in this regard involved a study of I_h in thalamocortical neurons (8). The work demonstrated that the frequency of slow oscillations underlying "spindle waves," mediated in part by I_h, was slowed when I_h was upregulated by a Ca^{2+}-dependent increase in intracellular cAMP concentration. The resulting persistent activation of I_h caused a sustained depolarization, thus breaking the oscillatory cycle. Other evidence showing that modulation of I_h can set the firing rates of rhythmically active neurons appears in studies involving pain transduction in dorsal root ganglion neurons. In a rat model of neuropathic pain, I_h was upregulated in response to neuronal injury, with the resulting depolarization of rhythmically active sensory neurons increasing pathologic action potential firing—possibly underlying pain sensation (9).

H-channels also exert powerful effects on the pyramidal neurons of the hippocampus and neocortex that are independent of their effects on rhythmicity. Understanding of their action in these neurons began with the startling observation that h-channels were distributed in pyramidal neurons in density gradients, with the apical dendrites possessing up to 10-fold the channel density seen at the cell body (10). This I_h gradient reduces the temporal summation of synaptic inputs in the dendrites compared with the soma, minimizing the influence of dendritic cable properties on synaptic inputs localized in the distal apical dendrites and "normalizing" their effect on action potential firing at the soma (11).

The gradient of h-channels in pyramidal dendrites may explain, in part, the action of a commonly used antiepileptic drug (AED), lamotrigine (LTG). A recent study demonstrated that LTG caused an upregulation of I_h by altering its voltage-dependent activation (12). In the dendrites, where I_h is at high density, synaptic inputs were attenuated in their ability to drive action potential firing at the soma. Conversely, at the soma, where I_h density is lowest, synaptic inputs and action potential firing were only minimally affected. Thus by virtue of a nonuniform cellular distribution, modulation of I_h by LTG can have differential effects on neuronal excitability, selectively inhibiting excitatory synaptic inputs, which are localized predominantly to the apical dendrites. LTG also may act on h-channels located on thalamic neurons, which may explain the drug's action on primarily generalized seizures. Other evidence suggests that the AED gabapentin (GBP) also may act in part via upregulation of I_h (13).

Are H-Channels Involved in Epilepsy?

Evidence is accumulating that suggests a role in for I_h in epileptogenesis. The first studies to connect h-channels and seizures demonstrated that in an animal model of provoked seizures (the hyperthermia model of febrile seizures), both I_h and γ-aminobutyric acid (GABA)-mediated inhibition were enhanced as measured at the soma of hippocampal pyramidal neurons (14,15). Although the increase in inhibition might be a compensatory response to seizure activity, its conjunction with increased I_h appeared to produce hyperexcitability by facilitating rebound action potential firing after the hyperpolarization induced by a GABAergic inhibitory postsynaptic potential (I_h supplying the transient rebound potential, as shown in Fig. 1). The increase in I_h was mediated by a small depolarizing shift in its half-maximal activation *voltage* but with a slowing in its activation and deactivation *kinetics*—a result that cannot be explained solely by greater cAMP modulation.

A closer inspection of the molecular determinants of I_h seen in animals after febrile seizures revealed the reason for this paradoxical shift in I_h properties: HCN1, the predominant isoform in pyramidal neurons, was persistently downregulated after seizures, whereas HCN2, an isoform with slower kinetics, was upregulated (although not as persistently as HCN1) (16). This switch to a predominance of the HCN2 isoform explained the slowed kinetics of I_h seen after hyperthermia-induced seizures. Notably, these changes were most pronounced in area CA1 and less so in CA3.

A similar result was obtained in animal studies in which the entorhinal cortex was lesioned. These animals exhibited

spontaneous "limbic" seizures and demonstrated an early diffuse downregulation of HCN expression throughout the hippocampal formation, which later recovered after reinnervation by afferents from the contralateral cortex (17). This reduction in I_h could be interpreted as compensatory with regard to decreased levels of afferent input from the entorhinal cortex; however, it is similarly possible that decreased HCN expression contributed to the acute seizures.

Whereas the animal model studies have demonstrated a convincing link between epileptiform activity and modulation of h-channels, they do not address whether such changes occur in the setting of human epilepsy. However, in a recent study conducted with human tissue resected from patients with temporal lobe epilepsy, dentate granule cells, which normally express low levels of I_h, showed an upregulation of HCN1 messenger RNA (mRNA) with little change in HCN2 (18). The change in HCN expression was evident only in cases of end-stage hippocampal sclerosis, long after the onset of epilepsy, suggesting that it represented a "compensatory" change in granule cell excitability in an attempt to reduce excitatory inputs into the hippocampal formation. Interestingly, in these patients, ~80% of CA1 neurons had degenerated, but HCN1 mRNA did not appear to be reduced in surviving neurons; rather, significant HCN1 mRNA expression was seen in CA1 interneurons.

H-channels affect the behavior of interneurons as well as principal neurons and have been shown to be present in at least several classes of hippocampal interneurons (19–21). So far, limited investigation has occurred of I_h in interneurons, but several studies suggest that the presence of I_h supports spontaneous and rhythmic firing of hippocampal interneurons either by depolarizing resting potential or by mediating pacemaker activity, thus increasing the tonic inhibition of pyramidal neurons (20,21). These finding suggest that increases in I_h in interneurons tend to oppose hyperexcitability.

Pharmacologic evidence for the role of h-channels in epilepsy remains contradictory. As mentioned, upregulation of I_h by AEDs would suggest that I_h exerts a fundamentally anticonvulsant effect (12,13), yet blockade of h-channels with the organic blocker ZD-7288 raised afterdischarge threshold in an in vivo model of stimulus-evoked seizures, and blockade of I_h in vitro was not observed to produce epileptiform discharges (22,23). Of course, the specificity of pharmacologic agents acting on I_h is far from absolute: AEDs likely act on multiple ion channel targets, and doubt has been cast on the specificity of ZD-7288, suggesting it may block excitatory synaptic transmission in an I_h-independent fashion as well (24).

Perhaps the strongest evidence linking h-channels with epilepsy relates to the role of I_h in the thalamocortical discharges underlying primarily generalized epilepsy. *HCN2* is strongly expressed in thalamus and is clearly involved in spontaneous firing of thalamocortical neurons, whether in spindle oscillations or in the 3-Hz spike-and-wave pattern characteristic of absence epilepsy. Previous in vitro studies suggested that I_h played a critical role in determining the frequency of these oscillations and that either up- or downregulation of I_h could abolish rhythmic firing (25,26). However, a recent study using genetically modified mice, in which *HCN2* was deleted, demonstrated that these animals had spontaneous absence seizures as well as a cardiac sinus arrhythmia, suggesting that the absence of *HCN2* at least is strongly proconvulsive. Similar knockouts of the *HCN1* gene have yet to be fully characterized (27).

H-Channels and Epilepsy: Causation or Compensation?

The findings from an outpouring of research on h-channels incontrovertibly show that these ion channels contribute to the excitability of neurons and are modulated by neuronal activity. The question is, "What does this mean for epilepsy?" Given the multitude of actions that this current may exert—varying across brain regions, HCN channel subtypes, even within the same neuron—it is impossible to make generalizations about I_h activity as exclusively either excitatory or inhibitory. With regard to epileptogenesis, the question is further complicated by whether an observed change in I_h represents causation (producing the state of hyperexcitability) or compensation (amelioration of the hyperexcitable state). So far, the evidence is not conclusive in either direction.

Further experiments may clarify the role for I_h in epileptogenesis. Such research would ideally include studies in animal models that probe changes in I_h during the development of the epileptic state; analysis of *HCN* mutant animals, with conditional and brain region–specific knockouts of *HCN* subtypes; the identification of human *HCN* mutants and their correlation with disease; and the development of new pharmaceutic agents with channel-subtype specificity. Even with these data, controversy is likely to persist, but given the ubiquity of h-channels in the central nervous system (CNS) and their multiple actions on neuronal excitability, a better understanding of I_h is clearly imperative in the aim of curing epilepsy and other neurologic diseases.

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