

## H-CHANNELS AND SEIZURES: LESS IS MORE

## Seizure-induced Plasticity of h Channels in Entorhinal Cortical Layer III Pyramidal Neurons

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The entorhinal cortex (EC) provides the predominant excitatory drive to the hippocampal CA1 and subicular neurons in chronic epilepsy. Discerning the mechanisms underlying signal integration within EC neurons is essential for understanding network excitability alterations involving the hippocampus during epilepsy. Twenty-four hours after a single seizure episode when no behavioral or electrographic seizures occurred, we found enhanced spontaneous activity still present in the rat EC *in vivo* and *in vitro*. The increased excitability was accompanied by a profound

reduction in  $I_h$  in EC layer III neurons and a significant decline in hyperpolarization-activated cation (HCN)1 and HCN2 subunits that encode for h channels. Consequently, dendritic excitability was enhanced, resulting in increased neuronal firing despite hyperpolarized membrane potentials. The loss of  $I_h$  and the increased neuronal excitability persisted for 1 week after seizures. Our results suggest that dendritic  $I_h$  plays an important role in determining the excitability of EC layer III neurons and their associated neural networks.

## COMMENTARY

The h-channel recently has risen from obscurity to notoriety as an actor in the neuronal hyperexcitability associated with seizures. Unfortunately, a lack of clarity exists as to whether the ion channel's actions mediate neuronal inhibition or excitation and whether they promote or retard epileptogenesis. Recent work by Shah and colleagues firmly supports the view that h-channels dampen excitability and that prolonged seizures cause a downregulation of h-channel activity, thus potentially furthering network hyperexcitability during epileptogenesis. This significant publication may well swing the balance of how the h-channel is viewed in epilepsy.

h-Channels—the hyperpolarization-activated cation channel, or  $I_h$  for short—occupy a unique position in the neuron's roster of ion channels. Structurally resembling a potassium channel, they mostly conduct  $Na^+$  current. When activated by hyperpolarization, they cause the neuron to depolarize, and in hippocampal and neocortical pyramidal neurons, they are largely absent from the cell soma but are present at high density in the apical dendrites. In these neurons, increased  $I_h$  appears to make the dendrites “leaky” to excitatory input, thus diminishing overall excitability. However, because  $I_h$  makes a significant contribution to the resting potential of the cell, increased  $I_h$  also depolarizes the cell, potentially bringing the somatic site of action-potential initiation closer to threshold. Therefore,  $I_h$

may have opposing actions on excitability, even under normal conditions.

That  $I_h$  is modified by seizure activity was first demonstrated in a landmark pair of studies (1,2). These studies used the febrile seizure model of status epilepticus (3) to show that h-currents were persistently increased at the soma of hippocampal neurons. Additional studies found that divergent results were seen depending on which subtype of  $I_h$  was examined: the predominant hippocampal HCN1 (hyperpolarization-activated and cyclic nucleotide-gated channel) subtype was downregulated after febrile seizures, whereas the minority HCN2 subtype was upregulated (4). Further complicating this interpretation was the finding that the anticonvulsant lamotrigine upregulated  $I_h$  in pyramidal dendrites, supporting the idea that dendritic  $I_h$  inhibited neuronal excitability (5). Thus, the varying settings under which h-channels have been studied—at the soma or in the dendrites, under normal conditions or after seizures—make it difficult to achieve a consensus on how the channel is likely to affect excitability when its expression is altered by seizure activity.

The present work by Shah et al. continues the focus on  $I_h$  actions in dendrites, but uses the model of kainate-induced seizures. A novel aspect of this article is the study of entorhinal cortical layer III pyramidal neurons, an underappreciated component of the limbic circuit, which nonetheless is significantly involved in temporal lobe epilepsy in humans (6). Their central

finding is that  $I_h$  was acutely downregulated for at least a week after kainate-induced status epilepticus, causing hyperexcitability in entorhinal pyramidal neurons. This hyperexcitability was mirrored *in vivo* by interictal epileptiform spiking on entorhinal depth EEG. The authors also measured HCN protein levels and found corresponding downregulation of both HCN1 and HCN2 subtypes at 24 hours, although these had recovered to normal levels at 1 week.

The results unambiguously convey which side of the h-channel debate the investigators come down on. The authors exhaustively demonstrate that neuronal hyperexcitability specifically resulted from loss of dendritic h-currents. Notably, layer III neurons were hyperexcitable *despite* significant membrane hyperpolarization, demonstrating that for pyramidal neurons, the heightened dendritic integration of postsynaptic potentials occurring with loss of h-currents (i.e., less leakiness) trumps the change in resting potential in determining overall neuronal firing properties. Because this hyperexcitability occurred during the presumed latent period after kainate-induced status and before observation of spontaneous seizures, it is hypothesized that downregulation of  $I_h$  may be one of the mechanisms contributing to neuronal and network hyperexcitability that later results in a chronic epileptic state.

Several prominent questions are raised by the Shah et al. article. The first is that, unlike for CA1 pyramidal neurons, the ion channel complement of entorhinal cortical layer III pyramidal neurons under normal conditions is poorly characterized. It would appear from the data that the  $I_h$  density in entorhinal neurons is a small fraction of that in CA1 cells, raising the question of whether their function in entorhinal dendrites is comparable to that of their better-characterized counterparts. Another question is why h-channel function remained depressed at 1 week when protein levels had returned to normal; as the authors hypothesized, unknown, posttranslational mechanisms may be at work modulating  $I_h$  biophysical properties in the post-status epilepticus animals. Finally, it was not determined whether the experimental conditions used would have caused the animals eventually to go on to spontaneous recurrent

seizures—the hallmark of epilepsy. Thus, it is unknown whether the observed changes in  $I_h$  are truly part of the epileptogenic process.

This study improves our understanding of how  $I_h$  is altered by seizures and adds emphasis to the view that these channels provide a dampening influence on hyperexcitability that may be lost in epileptogenesis. Undoubtedly, further work will follow, examining the possibility of alteration of  $I_h$  in chronic epilepsy. If such evidence emerges, h-channels may join the A-type  $K^+$  channel, another voltage-gated channel localized to pyramidal dendrites, in defining a syndrome of “dendritic channelopathy” in experimental epilepsy (7).

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## References

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