

KEEPING PACE WITH PACEMAKER CHANNELS

Developmental Febrile Seizures Modulate Hippocampal Gene Expression of Hyperpolarization-activated Channels in an Isoform and Cell-specific Manner

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Febrile seizures, in addition to being the most common seizure type of the developing human, may contribute to the generation of subsequent limbic epilepsy. Our previous work demonstrated that prolonged experimental febrile seizures in the immature rat model increased hippocampal excitability in the long term, enhancing susceptibility to future seizures. The mechanisms for these profound proepileptogenic changes did not require cell death and were associated with long-term slowed kinetics of the hyperpolarization activated depolarizing current (I_h). Here we show that these seizures modulate the expression of genes encoding this current, the hyperpolarization-activated, cyclic nucleotide-gated channels (HCNs): In CA1 neurons expressing multiple HCN isoforms, the seizures induced a coordinated reduction of HCN1 mRNA and enhancement of HCN2 expression, thus altering the neuronal HCN phenotype. The seizure-induced augmentation of HCN2 expression involved CA3 in addition to CA1, whereas for HCN4, mRNA expression was not changed by the seizures in either hippocampal region. This isoform- and region-specific transcriptional regulation of HCNs required neuronal activity rather than hyperthermia alone, correlated with seizure duration, and favored the formation of slow-kinetics HCN2-encoded channels. In summary, these data demonstrate a novel, activity-dependent transcriptional regulation of HCN molecules by developmental seizures. These changes result in long-lasting alteration of the HCN phenotype of specific hippocampal neuronal populations, with profound consequences on the excitability of the hippocampal network.

COMMENTARY

A large family of ion channels has recently joined those already implicated in epilepsy: the HCNs. These are hyperpolarization-activated, cyclic nucleotide-gated channels (or H-channels). Upon hyperpolarization, these channels carry cations inside the cell, leading to an inward (depolarizing) current. The unconventional activation (by hyperpolarization, rather than depolarization), and other characteristics, have led to such names as I_q (queer) or I_f (funny), as well as the more common term, I_h (for hyperpolarization; for review, see reference 1). Cloning of the family of genes that code for the subunits of these channels has clarified that these currents are one and the same (2). In addition, characterization of the HCN genes demonstrated that each codes for a different isoform (i.e., HCN1, HCN2), with different biophysical properties. Indeed, HCNs that are involved in cardiac pacing are mainly HCN2 and HCN4. Those involved in thalamic oscillations and sleep-wake cycles are composed primarily of HCN2, whereas the dominant isoform in hippocampal pyramidal cells is HCN1 (3).

The typical regulators of I_h , cyclic nucleotides, driven for example, by adrenergic stimulation, typically modulate the channels for only seconds to minutes. Now Baram et al. show that prolonged febrile seizures may produce long-lasting changes in HCNs. In the process, they provide a promising model of febrile seizures.

Earlier studies from this group showed that a relatively brief seizure induced by hyperthermia in immature rats could lead to a long-lasting increase of hippocampal excitability (4), despite increased inhibition (5,6). Providing a model of prolonged febrile seizures was an important advance, because it showed that hyperthermia-induced, experimental febrile seizures at an early age could lead to long-lasting changes in hippocampus. This added fuel to the fire, addressing the controversial association between febrile seizures and epilepsy later in life.

More recent studies have provided another important piece to the puzzle. Brewster et al. (7) analyzed HCN channel expression in hippocampus and found that HCN1 mRNA decreases after febrile seizures, specifically in area CA1, where the changes in excitability were characterized, whereas HCN2 expression increased. Thus febrile seizures led to an increase in slow, potentially higher conductance HCNs (HCN2) and re-

duction in fast-activating and deactivating, low-conductance HCN1 channels, which are normally the predominant form in the hippocampal CA1 pyramidal cells. The authors suggest that conversion of predominantly HCN1-expressing to predominantly HCN2 channels could allow more depolarization in response to inhibitory (hyperpolarizing) input, thus promoting hyperexcitability. It also is possible that the increased inhibition characterized in previous studies might act in concert with altered HCN expression to provide additional stimulation of I_h . Increased inhibition in other models of epilepsy that has been previously interpreted as counterintuitive can now be interpreted differently: perhaps increased inhibition leads to hyperexcitability by activation of I_h .

One of the most intriguing aspects of the study was that the changes in HCN1 and HCN2 lasted into adulthood. Thus a novel mechanism for *long-lasting* changes in excitability has now been identified: regulation of gene expression of HCNs.

Other recent studies provided additional information regarding the ways I_h may control hippocampal excitability. The new data suggest a mechanism that might underlie the changes in excitability that occur after HCN channel expression changes. By whole-cell recording from hippocampal dendrites, Poolos et al. (8) showed that I_h acts primarily in dendrites, and it appears to dampen dendritic depolarization. Given that HCN1 predominates in this region, a reduction in HCN1 after seizures could lead to a reduction in the normal inhibitory effect of I_h on dendrites, leading to increased dendritic excitation and altered seizure susceptibility. In other words, if HCN1 normally functions to decrease dendritic depolarization, seizure-induced reduction in HCN1 could produce an increase in dendritic excitability. Consistent with this hypothesis, Poolos et al. (8) showed that lamotrigine (LTG), a commonly used anticonvulsant (AED), increased dendritic H channel function. However, the actions of I_h may not be so simple as they seem, because the authors found that changes in dendritic depolarization were not always translated to a change in action-potential generation at the soma.

Other stimuli besides seizures may produce changes in HCN expression. Brauer et al. (9) reported that entorhinal cortex lesion in the adult rat led to decreased HCN1 mRNA, although a change in HCN2 was not detected, and the change in HCN1 persisted only for a few weeks. Thus it would appear that both seizures and injury can alter HCNs, and do so in a similar manner, by decreasing HCN1. If Baram et al. are correct, the change is likely to be long lasting if the stimulus (seizures or injury) occurs at a particular time during development, but even if not, it appears likely that effects might persist at least for several weeks, which is certainly not trivial. These stud-

ies, taken together, may explain one of the reasons that seizures or injuries, particularly early in life, can lead to epilepsy: by a prolonged influence on HCN channel expression. Indeed data from studies outside the field of epilepsy have described a perhaps analogous effect on a different set of ion channels, those associated with serotonin_{1A} receptors. It appears that manipulation of serotonin receptors early in life can lead to behavioral deficits lasting well into adulthood, whereas the same manipulations during adulthood do not have such long-lasting effects (10).

In light of the new data, based on hyperthermia-induced seizures, as well as the other studies described earlier, it seems that in the foreseeable future, the question of treating an early seizure may just be "heating" up.

by Helen E. Scharfman, Ph.D.

References

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