CURRENT LITERATURE

H-CHANNELS IN COMPLEX FEBRILE SEIZURES

Persistently Modified H-Channels after Complex Febrile Seizures Convert the Seizure-Induced Enhancement of Inhibition to Hyperexcitability

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Febrile seizures are the most common type of developmental seizures, affecting up to 5% of children. Experimental complex febrile seizures involving the immature rat hippocampus led to a persistent lowering of seizure threshold despite an upregulation of inhibition. Here we provide a mechanistic resolution to this paradox by showing that, in the hippocampus of rats that had febrile seizures, the long-lasting enhancement of the widely expressed intrinsic membrane conductance Ih converts the potentiated synaptic inhibition to hyperexcitability in a frequency-dependent manner. The altered gain of this molecular inhibition-excitation converter reveals a new mechanism for controlling the balance of excitation-inhibition in the limbic system. In addition, here we show for the first time that h-channels are modified in a human neurological disease paradigm.

COMMENTARY

Developmental complex febrile seizures can predispose to later epilepsy; however, the mechanisms underlying this tendency toward hyperexcitability are probably the least well understood in the field. The authors previously developed a rat model of complex febrile seizures consisting of exposing animals to hyperthermia at postnatal day 10, which produces seizures. They also previously identified that this procedure led to a persistent increase in perisomatic inhibition of CA1 hippocampal pyramidal neurons. Paradoxically, this increased inhibition was associated with a persistent decrease in seizure threshold. The present report offers an explanation for these contradictory results.

H-type potassium channels are present in both cardiac and neuronal tissues, where they are involved in the generation of the pacemaker current in the heart and sleep rhythms in thalamocortical neuronal circuits. H-channels are activated by hyperpolarization (hence their name) and generate a depolarizing current. The authors demonstrate that a single episode of hyperthermia-induced seizure leads to a long-term enhancement of this current in CA1 pyramidal cells. The augmented H-current more effectively opposed intracellular injections of hyperpolarizing current, resulting in greater depolarizing "sag" in the voltage trace. Furthermore, the larger, more slowly deactivating H-current led to an enhanced rebound depolarization following termination of the pulse. Of particular note, a train of (but not single) fast inhibitory postsynaptic potentials triggered post-inhibitory rebound depolarization and firing in these neurons. Thus the enhanced H-current converts the potentiated inhibition to hyperexcitability in animals that experienced febrile seizures during development.

The results presented show a novel interaction of modified synaptic and intrinsic cellular properties that in turn modulate the excitation-inhibition balance. The results may have implications for understanding how complex febrile seizures occurring early in development may predispose to later epilepsy. Criticisms of the model are that postnatal day 10 in rats corresponds to a prenatal time point in humans, and that the rats sustaining early complex febrile seizures do not go on to develop late seizures.

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