NIH Award from the National Institute of Neurological Disorders and Stroke

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- Project: HCN Channel Trafficking In Epilepsy
- Start Date: July 27, 2009
- Total Award Amount: $14,752

How the results of this project will benefit society:
Temporal lobe epilepsy (TLE) is a common cause of refractory seizures. Increased seizure propensity in TLE is caused by abnormal neuronal excitability. With respect to public health, despite numerous new medical and surgical treatments, refractory seizures remain a significant cause of disability in patients with TLE. The ultimate goal of this work is to gain a better understanding of molecular factors controlling the onset of spontaneous and refractory seizures in TLE, with the hope of identifying novel targets for the prevention and treatment of this common cause of epilepsy.

The problem the project is trying to solve:
One candidate for manifesting excitability changes in TLE is the hyperpolarization-activated cyclic nucleotide-gated channel (h channel). H channels mediate the hyperpolarization-activated current, Ih, which is critical for membrane potential homeostasis and neuronal excitability. In hippocampal pyramidal neurons, h channel subunits HCN1 and HCN2 are dramatically enriched in distal compared to proximal dendrites, a phenomenon critical for neuronal excitability; upregulation of dendritic Ih reduces excitability, whereas reduction increases excitability. In a rat model of TLE, we found that excitability was reduced and Ih and distal enrichment of HCN1 was enhanced 24 hours after status epilepticus, a time point before onset of spontaneous seizures (latency). In contrast, after onset of spontaneous seizures, we found increased excitability coupled with reduced Ih and relocalization of HCN1 from distal dendrites to soma. Interestingly, interaction with an h channel binding protein was dramatically reduced after onset of spontaneous seizures. Furthermore, in slice cultures we found that HCN1 distal dendritic localization is controlled in an activity-dependent manner, requiring activation of N-methyl-D-aspartate receptors (NMDAR) and calmodulin-dependent protein kinase II (CaMKII) activity.

We reason that early enhancement of h channel distal enrichment in TLE is a homeostatic response to increased activity that reduces excitability, whereas h channel relocalization from distal dendrites to soma during hippocampal epileptogenesis represents an aberrant process that contributes to increased excitability and the development of spontaneous seizures. We hypothesize that:
(1) control of h channel localization regulates excitability in TLE; (2) activity of inputs from entorhinal cortex to CA1 dendrites controls h channel localization through NMDAR-mediated activation of protein kinases and HCN subunit phosphorylation; and (3) Abnormal phosphorylation of HCN subunits disrupts h channel trafficking and overrides normal homeostatic, activity-dependent control of h channel localization, leading to onset of spontaneous seizures in TLE.

How this project will work:
We will utilize physiological, cell biological and biochemical techniques to address the following specific aims: To determine whether (1) distal dendritic h channels are increased during latency and reduced after onset of spontaneous seizures in TLE; (2) Temporoammonic inputs from entorhinal cortex to CA1 dendrites controls h channel localization through NMDAR activation, CaMKII activity, and phosphorylation of HCN subunits control h channel localization; and (3) abnormal HCN subunit phosphorylation prevents interactions important for trafficking and targeting and mislocalizes h channels in chronic TLE.

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