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Authors
Dube, Celine M
Brewster, Amy L
Richichi, Cristina
et al.

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SEIZURE SUSCEPTIBILITY AND EPILEPTOGENESIS IN HCN1-DEFICIENT MICE: ELECTROPHYSIOLOGICAL AND MOLECULAR CHARACTERIZATION

Céline M. Dubé, Amy L. Brewster, Cristina Richichi, Elyzabeth Custodio, and Tallie Z. Baram (Anatomy & Neurobiology and Pediatrics, University of California at Irvine, Irvine, CA)

Rationale: The current conducted by HCN channels (I_h) contributes to neuronal and network properties of the hippocampal formation. HCN channels are expressed in diverse hippocampal interneuronal and principal cell populations. Their function depends on their subcellular distribution and the hyper-or depolarizing nature of synaptic input (Santoro and Baram, 2003). We previously showed that experimental prolonged febrile seizures (FS) in immature rats causes an enduring downregulation of HCN1 channel expression and leads to a hyperexcitable hippocampal network. Frank epilepsy develops in 35% of rats (Brewster et al., 2002, 2005; Dubé et al., 2006). The generation of HCN1-deficient mice (HCN1-/-) provides a powerful tool to examine the potential *causal* role of reduced HCN1 channels in this hippocampal network dysfunction. These studies examined whether immature HCN1-/- mice are more sensitive to seizure provocation and prone to develop spontaneous recurrent seizures as adults. Concurrently, we examined the developmental expression and seizure-evoked regulation of the remaining hippocampal HCN isoforms in these mice.

Methods: The threshold temperature required for the onset of a hyperthermic 'febrile' seizure was studied as a measure of hyperexcitability in HCN1-/- mice and wild-type controls. Experimental FS were induced on postnatal day 14 and animals monitored as adults for the emergence of spontaneous seizures using digital video hippocampal EEG recordings. Seizure events were determined according to both EEG (i.e., polyspikes or sharp-waves with amplitude $> 200\%$ of background lasting over 6 seconds) and behavioral criteria (i.e, freezing and 'limbic' automatisms). Hippocampal mRNA and protein expression of HCN channel isoforms 1–4 was quantified using *in situ* hybridization and Western blots. The cellular and subcellular distribution of HCN isoforms was analyzed via immunocytochemistry.

Results: Threshold temperatures for experimental FS onset in HCN1-/- mice were significantly higher than those of controls: $41.9 \pm 0.2\ ^\circ C$ ($n = 22$) vs $40.7 \pm 0.2^\circ C$ ($n = 24$) $p < 0.0001$. These data indicate that HCN1-/- mice are *less* sensitive to seizure generation. EEGs were normal in all control mice and preliminary data have not yet revealed spontaneous seizures in HCN1-/- mice. Analyses of mRNA and protein expression are ongoing, but preliminary data support an absence of compensatory changes in HCN2 and HCN4 (Nolan et al., 2004).

Conclusions: These experiments suggest that *global* absence of HCN1 channels from all cell types and cellular compartments yields a '*hypo*excitable' network. In addition, they suggest that HCN1 channels contribute to hippocampal network properties in a complex manner that is dependent on the cell type (e.g., interneurons vs principal cells), subcellular compartment and perhaps developmental expression programs. (Supported by NIH NS 47993 (ALB); NS 35439 (TZB).)