Title
The hyperpolarization-activated HCN channels in human and experimental hippocampal epilepsy: A novel, acquired channelopathy?

Journal
ANNALS OF NEUROLOGY, 54

ISSN
0364-5134

Authors
Bender, RA
Mathern, GW
Brewster, AL
et al.

Publication Date
2003

139. The Hyperpolarization-Activated HCN Channels in Human and Experimental Hippocampal Epilepsy: A Novel, Acquired Channelopathy?

Roland A. Bender, Gary W. Mathern, Amy L. Brewster, and Tallie Z. Baram; Irvine and Los Angeles, CA

Changes in ion channel expression, influencing neuronal excitability, are emerging as contributory mechanisms in human epilepsies. Previously, we found isoform-specific altered expression of hyperpolarization-activated cAMP-gated channels (HCNs), correlating with long-term hippocampal hyperexcitability, in immature rat model of prolonged febrile seizures (PFSs). PFSs commonly precede temporal lobe epilepsy (TLE), suggesting that transcriptional HCN dysregulation might contribute to the epileptogenic process. Therefore, we analyzed HCN expression in TLE hippocampus. HCN1&2 mRNA and protein expression were measured in three hippocampi groups: TLE+hippocampal sclerosis (HS; n = 17), TLE without HS (NHS; n = 10); and autopsies (n = 10). In autopsy and NHS, HCN1mRNA expression was robust in pyramidal cell layers and lower in granule cells (GCs). However, HCN1mRNA increased drastically in GCs from epileptic hippocampus once GC density was reduced by greater than 50%. Increased HCN1 immunoreactivity in GC dendritic fields accompanied these mRNA changes, whereas HCN2mRNA changes were modest. Thus, HCN expression is dynamically regulated in TLE. After experimental PFS

(early in epileptogenesis), preserved, augmented inhibition may reduce HCN1 levels. Conversely, in chronic TLE+HS, hilar cell loss and consequent reduced inhibition, coupled with increased dendritic excitation of surviving GCs, might enhance "compensatory" HCN1 expression. Supported by NIH, NINDS NS35439 (T.Z.B.) and NS28912 (A.L.B., T.Z.B.), NS02808 and NS38992 (G.W.M.), and by an Epilepsy Foundation of America, Milken Foundation postdoctoral research fellowship (R.A.B.).