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NEURONAL ACTIVITY INFLUENCES THE SUB-CELLULAR DISTRIBUTION OF HYPERPOLARIZATION- ACTIVATED (HCN) CATION CHANNELS IN HIPPOCAMPAL NEURONS

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Rationale: Developmental febrile seizures in the animal model lead to persistent susceptibility of the hippocampal circuit to seizures, and to frank epilepsy. The role of the HCN channels in these changes is emerging. We have previously shown that normal neuronal activity regulates the expression of the HCN channels and that developmental seizures alter HCN1 and HCN2 expression differentially and enduringly. In addition to expression levels, sub-cellular distribution of the channels is a critical determinant of channel function. Here we studied 1) whether the sub-cellular distribution of HCN1, 2 or 4 is regulated by 'normal' neuronal activity, and 2) whether developmental seizures alter the sub-cellular distribution of these channel isoforms.

Methods: Somatic, dendritic and axonal expression of HCN isoforms was studied using immunohistochemistry. The effect of 'normal' neuronal activity on channel distribution was investigated in vitro (using TTX). Seizures were induced by low Mg2+ and kainate in vitro, and by kainate or hyperthermia in vivo.

Results: Sub-cellular distribution patterns of the HCN channels in developing hippocampus were isoform-specific, and evolved with age. Thus, in the dendritic field of CA1 pyramidal cells, HCN1 and HCN4 channels were present as early as P5. However, while HCN1 remained robust in dendrites throughout life, dendritic HCN4 expression decreased with maturation. Reduced dendritic HCN4 expression was 'compensated' by a concurrent increase of dendritic HCN2 expression. In the axonal compartment of entorhinal cortex neurons coursing through the perforant path, HCN1 (but not HCN2 or HCN4) was highly expressed. This expression peaked during the first two weeks of life- then waned. Both dendritic and axonal transport of HCN1 channels were influenced by normal neuronal activity: chronic TTX increased axonal HCN1 in perforant path and altered the dendritic distribution of the channel in CA1 pyramidal cells in vitro. Preliminary results suggest that seizures have opposite effects on HCN1, and studies of HCN2 and HCN4 isoforms are ongoing.

Conclusions: Transport of HCN channel isoforms to dendritic and axonal cellular compartments evolves during hippocampal maturation in an isoform-specific manner, suggesting that each isoform has age-specific roles in developing hippocampus. Neuronal activity, both 'normal' and epileptic, may influence the sub-cellular localization of HCN channels, resulting in altered functions of these channels in the developing hippocampus. (Supported by NIH 35439, Epilepsy Foundation of America.)