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**EXPRESSION, SUBUNIT ASSEMBLY AND TRAFFICKING OF HIPPOCAMPAL HYPERPOLARIZATION-ACTIVATED CYCLIC NUCLEOTIDE GATED (HCN) CHANNELS ARE SPECIFICALLY AND COORDINATELY REGULATED**

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**Rationale:** The HCN-mediated current (I<sub>h</sub>) contributes to the regulation of intrinsic neuronal properties and network excitability. In developing and adult hippocampus, several isoforms of these channels (HCN1,2 and 4) are expressed, and this expression is regulated by seizure activity and during development. In addition, co-assembly of the different isoforms and creation of heteromeric channels with likely distinct biophysical properties, is regulated by seizure activity. Here we established the mRNA and protein expression levels, sub-cellular distribution patterns and heteromerization state of the HCN channel isoforms in hippocampal CA1 neurons, and examined whether the expression and trafficking of a given HCN isoform is influenced by the expression of other isoforms.

**Methods:** Area CA1 and whole hippocampi were dissected, and subjected to sub-cellular fractionation, western blots, and co-immunoprecipitation. Intact slices were probed using immunocytochemistry and in situ hybridization. Tissue from mice lacking the HCN1 isoforms was used to examine the effect of the absence of HCN1 on HCN2 expression and trafficking.

**Results:** In area CA1, HCN1 constituted 35% of all HCN channels on postnatal day 2 (P2), 39% on P6, 53% on P14 and 66% in adult. The vast majority of HCN1 channels were in complex with HCN2 during the first postnatal week ( $82.3 \pm 17.6\%$  on P2–4), and this degree of heteromerization decreased rapidly with age ( $27.6 \pm 0.6\%$  on P11,  $15.8 \pm 5.1\%$  on P18,  $11.8 \pm 2.8\%$  in adult). These data are consistent with the evolving properties of I<sub>h</sub> recorded from CA1 pyramidal cells. In the absence of HCN1 expression, HCN2 levels increased in area CA1, and enhanced dendritic expression of HCN2 was found.

**Conclusions:** The age-dependent expression and co-assembly of HCN channels predict age-specific properties of I<sub>h</sub> in CA1 pyramidal cells. In addition, altered levels of one isoform (e.g., HCN1) in genetically engineered mice or induced by seizures, influence the expression levels and sub-cellular distribution of other HCN isoforms.