Title

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Publication Date

2009

3.033

POSTNATAL EXPRESSION PATTERN OF HCN CHANNEL ISOFORMS IN THALAMIC NEURONS: RELATIONSHIP TO MATURATION OF THALAMOCORTICAL OSCILLATIONS

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Rationale: Hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channels are the molecular substrate of the hyperpolarization-activated inward current (Ih). This current plays a key role in the initiation and regulation of rhythmic-oscillatory activity in the thalamocortical network. To date the developmental profile of HCN channels in the thalamus is not well understood.

Methods: We combined electrophysiological, molecular biology, immunohistochemical, EEG recordings in vivo, and computer modeling techniques to examine HCN gene expression and Ih properties in rat thalamocortical relay (TC) neurons in dorsal part of the lateral geniculate nucleus (dLGN) and the functional consequence of this maturation.

Results: Recordings of TC neurons revealed a ~6-fold increase in Ih density between postnatal day (P) 3 to P 106, which was accompanied by significantly altered current kinetics, cAMP-sensitivity, and steady-state activation properties. Quantification of tissue levels revealed a significant developmental decrease in cyclic AMP (cAMP). Consequently the block of basal adenylyl cyclase activity was accompanied by a hyperpolarizing shift of the Ih activation curve in young but not adult rats. Quantitative analyses of HCN channel isoforms revealed a steady increase of mRNA and protein expression levels of HCN1, 2 and 4 with reduced relative abundance of HCN4. Computer modeling in a simplified thalamic network indicated that the occurrence of rhythmic delta activity, which was present in the EEG at P12, differentially depended on Ih conductance and modulation by cAMP at different developmental states.

Conclusions: These data indicate that developmental increases in Ih density results from increased expression of three HCN channel isoforms and that isoform composition and intracellular cAMP levels interact in determining Ih properties to enable progressive maturation of rhythmic slow-wave activity patterns.

Epilepsia, 50(Suppl. 11): 342, 2009
doi: 10.1111/j.1528-1167.2009.02377.x