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Thema der Arbeit: „EXPRESSION UND FUNKTIONELLE RELEVANZ VON ZWEI-PORENEN K^+-KANÄLEN DER TASK-FAMILIE IN THALAMISCHEN SCHALT-NEURONEN“

Englische Zusammenfassung – Summary

The process of waking up is associated with the shift from rhythmic burst activity to tonic action potential generation in many neurons of the thalamocortical system. Transmitters of the ascending brainstem system are capable of mediating this change by the reduction of leak K^+ channels, resulting in a depolarization of the resting membrane potential. Unfortunately, the molecular nature of these channels has not been analyzed in the thalamus until now. Therefore the expression of TWIK-related acid-sensitive K^+ (TASK) channels, which contribute to the setting the membrane potential in different types of cells in the central nervous system, was probed in the dorsal lateral geniculate nucleus (dLGN) by combining whole cell patch-clamp recordings in brain slices and acutely-isolated cells, molecularbiological, immunocytochemical techniques and modelling procedures. Setting the membrane potential of thalamocortical relay neurons to a value of –20 mV induced a persistent outward current of 200 - 400 pA, which was significantly reduced by e.g. lowering the external pH from 7.2 to 6.4, application of ACh, muscarin, the local anaesthetic bupivacaine, the polyvalent cation spermine and Ba^{2+}. In addition, the steady state outward current was increased by bath application of the general anaesthetic halothane and removal of divalent cations from the extracellular solution, thereby completing the typical pharmacological and regulatory profile of TASK channels. Graphical substraction of ramp currents revealed blocker-sensitive currents with clear outward rectification and a reversal potential close to the expected K^+ equilibrium potential (-104 mV). RT-PCR analysis, antibody staining, and *in situ* hybridization demonstrated the expression of TASK1 and TASK3 in dLGN, thereby further confirming the electrophysiological findings. The functional role of these findings was probed during current clamp recordings: application of halothane hyperpolarized the membrane potential from about –60 to –70 mV, an effect that was accompanied by a change in the firing pattern (from tonic single spike to burst activity). Inhibition of TASK channels due to the mentioned blockers (e.g. bupivacaine, muscarine, pH lowering) resulted in a shift from burst firing to tonic action potential generation, associated with a significant depolarization of the membrane potential. Taken together these data indicate that several TASK channel subtypes are involved in setting the membrane potential of dLGN relay neurons and contribute to the production of anesthesia *in vivo*.

In a second part the interaction of TASK channels and HCN channel mediating the hyperpolarization-activated cyclic nucleotide gated current I_h was investigated. All known pacemaker channels (HCN1-4) are expressed in dLGN. The coexpression of the dominant isoforms, namely TASK3 and HCN2 to be existent in parvalbumin-positive relay neurons could be shown in cultured cells of the dorsal

thalamus. Components carried by HCN and TASK channels contribute to the standing outward current of TC neurons and the pH-sensitive component elicited by hyperpolarizing ramp protocols. Current clamp recordings in rats, $HCN^{-/-}$ mice, and computer modeling studies demonstrate that the counterbalancing effects of HCN2 and TASK3 / TASK1 channels play a pivotal role in setting the resting membrane potential of TC neurons thereby influencing the activity mode of thalamic neurons.