Anke Tappe
Dr. sc. hum.

Functional significance of synaptic proteins of the Homer1 family in the spinal cord and forebrain.

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Doktormutter: Frau PD Dr. R. Kuner

In this thesis project, we have characterized the role of Homer1 proteins in the spinal cord and brain. We observed that Homer1 proteins are strongly and differentially expressed in pain pathways following peripheral inflammation. We could show that peripheral hindpaw inflammation leads to the selective induction of the immediate early gene Homer1a in nociceptive laminae of the spinal dorsal horn. The NMDA receptor- Src kinase- ERK1/2 pathway was found to underlie activity-induced upregulation of Homer1a in the spinal cord. By selectively knocking down Homer1a upregulation in the spinal dorsal horn, we observed that endogenous Homer1a is important in limiting nociceptive hypersensitivity which develops after tissue inflammation. Conversely, simulation of Homer1a-induced upregulation by exogenous expression of the Homer1a in the spinal dorsal horn led to a significant reduction of hyperalgesia. Major aspects of basal pain sensitivity and motor behaviour were not significantly affected by Homer1a.
Our experiments provided insights into molecular mechanisms underlying changes in the assembly and signalling cascades of glutamate receptors at spinal nociceptive synapses following tissue injury. We found that the expression of Homer1a led to a reduction of intracellular calcium release downstream of activated glutamate receptors. Furthermore Homer1a expression led to a reduction in ERK1/2 phosphorylation in spinal neurons *in vitro and in vivo*. We could also show that Homer1a influences the formation of dendritic spines in spinal neurons *in vitro* as well as *in vivo*. Taken together, our results show that

Homer1a is induced in spinal neurons following persistent nociceptive activity and functions as a negative feed-back modulator of nociceptive hypersensitivity. Our results lay a basis for testing the potential of Homer1a as a therapeutic target in the treatment of inflammatory pain.

To evaluate the modulation of neurological functions by Homer1a in the forebrain, we generated transgenic mice expressing Homer1a in the forebrain in an inducible manner. However, we only obtained stable expression in the striatum. We observed that transgenic overexpression of Homer1a in striatal projection neurons leads to multiple defects in motor performance, coordination and drug-induced stereotypy, indicating a critical role for mGluR1/5-Homer1 signalling mechanism in modulation of striatal output. Moreover, using this genetic approach, we were able to address the distinct roles of the striatal sub-compartments, namely the striosomes and the matrix in modulation of complex motor tasks and drug-induced stereotypic behaviours.