ANALYSIS OF Aß-MEDIATED DISRUPTION OF SYNAPTIC PLASTICITY IN TRANSGENIC ARCAß MICE

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Introduction: Oligomeric Aß aggregates, derived from the endoproteolytic cleavage of β-amyloid precursor protein (APP), are suspected to be the main neurotoxic species leading to Alzheimer’s disease (AD). Moreover, Aß oligomers have been shown to impair memory and hippocampal long-term potentiation (LTP). ArcAß mice, previously described to show Aß oligomer-mediated learning deficits, were analysed by Affymetrix GeneChip revealing changes in the expression levels of candidate genes compared to wildtype mice.

Aims: To identify proteins that are involved in the Aß oligomer-mediated disruption of synaptic plasticity and to elucidate the signalling cascades leading to structural changes.

Methods: Mice were exposed to a novel environment (NE), which triggers synaptic plasticity. Dys-regulated genes in the brain were verified by real-time PCR and in situ hybridization. Furthermore, we performed Western blot analysis of stimulated neuronal cultures from ArcAß mice and their non-transgenic littermates (wt).

Results: Exposure to NE significantly increased the expression of the immediate-early gene Arg3.1/arc in distinct brain regions of wt mice in contrast to ArcAß mice. Transgenic mice also showed altered expression of cytoskeleton-associated proteins on mRNA as well as protein levels. Moreover, phosphorylation of the cAMP response element-binding protein (CREB) was altered in neuronal cultures of ArcAß mice after stimulation.

Conclusions: The results suggest that activity-regulated nuclear signalling and gene expression is impaired in ArcAß mice. Changes in cytoskeleton-associated proteins imply that synaptic deficits in transgenic mice might be caused by alterations in the cytoskeleton and protein targeting.