Deficits in synaptic signalling and cytoskeleton organisation in early stages of Alzheimer disease (AD)

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Impairment of synaptic plasticity, neuronal dysfunction and synapse loss triggered by Abeta (Aβ) have been shown to correlate with the cognitive deterioration in AD but the underlying mechanisms are far from being understood in detail. Therefore, animal mouse models are valuable tools to investigate disturbed signalling pathways but still do not completely resemble the human situation.

We used a transgenic mouse model (arcAβ mice) to investigate Aβ-mediated disruption of synaptic plasticity. These mice exhibit several properties indicative of an AD-like pathology for example early, pre-plaque LTP deficits as well as dendritic spine loss. Further, by validating candidate genes obtained from a mircoarray gene expression analysis, we revealed dysregulation of two proteins involved in synaptic signalling and actin cytoskeleton organisation. First, Neurabin 1 (Nrb 1), a neuron-specific actin-binding protein, was reduced in young arcAβ mice. Nrb 1 has been shown to be involved in the regulation of protein phophatase 1 (PP1), one of the major protein phosphatases in the brain. Moreover, it has been shown that inhibtion of PP1 restores LTP deficits in arcAβ mice. Second, Profilin 1 (Pfn 1) expression was significantly diminished in transgenic arcAβ mice. Pfn 1 is an actin cytoskeleton-regulatory protein, involved in the elongation of F-actin. Its reduction could therefore account for spine destabilization and reduction. Altogether expression changes of these two proteins could be one explanation for misregulations of synaptic transmission, dendritic spine loss and cytoskeleton disturbances at early AD stages finally leading to synapse loss and neuronal death. Future investigations of brain tissue from demented patients will benefit in new insights of Aβ-mediated disturbances in synaptic plasticity in humans and could help to identify new molecular targets for the therapy of synaptic deficits in AD.