Role of NMDA receptor (NMDAR) signalling and Caspase-3 activity for dendritic spine loss in AD

Trutzel, A. et al.

Division of Psychiatry Research, University of Zurich, Switzerland.

Loss of synapses is one of the best anatomical correlate of cognitive deficits in human AD and a better disease predictor than the amyloid plaque load. The involvement of the Aβ-peptide in AD is indisputable but how it exerts its toxic effect still needs to be elucidated in detail. Based on already published data it has been proposed that Aβ binds to a putative receptor like for example the NMDARs. Blocking NMDARs has also been shown to abrogate Aβ-induced dendritic spine loss.

By using organotypical slice cultures generated from an AD mouse model (arcAβ mice) we could distinguish the impact of different NMDAR subtypes on Aβ mediated dendritic spine loss. In addition, we could show that Aβ-induced dendritic spine loss requires Caspase-3 activity in transgenic arcAβ mice. Caspase-3 can be activated by Calcineurin, a key enzyme in long-term-depression which has been described to trigger Aβ-induced loss of dendritic spines. All these results contribute to understand the molecular mechanism leading to synapse loss in AD but are based on work with the arcAβ mouse model. Determining the expression pattern of different NMDAR types and examine caspase-3 activity in subcellular fractions of of human brain tissue from demented AD patients, non-demented controls will be beneficial to support our animal data.