

Targeting synaptic plasticity disrupting Alzheimer's disease amyloid β *in vivo*

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Prior to the onset of significant neurodegeneration in Alzheimer's disease, the structural and functional integrity of synapses in mnemonic circuitry is severely compromised. There is extensive evidence that certain assemblies of amyloid- β protein ($A\beta$) cause rapid disruption of synaptic plasticity and memory impairment in animals. Recently we found that water soluble extracts of post mortem brains of patients with Alzheimer's disease that contained SDS-stable $A\beta$ dimer aggregates both inhibited LTP and facilitated LTD in the anaesthetized rat hippocampus *in vivo*. Our data are consistent with the view that metabotropic glutamate 5 receptor-dependent mechanisms are paramount. The importance of cellular prion protein in mediating these effects was also determined using antibodies, including a humanized version. We also study synaptic plasticity disruption in a transgenic model of amyloidosis longitudinally in freely behaving rats prior to $A\beta$ plaque formation. Brief treatment with either drugs reducing $A\beta$ production or an anti- $A\beta$ antibody transiently and rapidly reverse the deficit in LTP. These studies emphasize the potential benefit of targeting synaptic plasticity-disrupting $A\beta$, and associated mechanisms, in the development of novel early therapeutic interventions.