

## **Synapse weakening pathway: A new conceptual understanding of Alzheimer's disease**

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Alzheimer's disease is the leading form of dementia, characterized in its late stages by significant neuronal death linked to plaques of amyloid- $\beta$  and tangles of tau protein (Ballard et al., 2011). Evidence from a variety of experimental models demonstrates that aberrantly enhanced downscaling of synaptic transmission is at the heart of Alzheimer's disease pathology; driving AMPA receptor endocytosis and synapse elimination. In this regard, a growing body of evidence now supports the hypothesis that Alzheimer's disease results from aberrant synaptic elimination that is similar to and/or associated with mechanisms of long-term depression in synaptic transmission (LTD). Inhibition of LTD signals prevents neurotoxic effects from Alzheimer's disease pathogenes. Here we have developed a working hypothesis that greater understanding of key molecular LTD signalling mechanisms could perhaps ultimately lead to the identification of novel therapeutic strategies for the prevention and/or reversal of Alzheimer's disease pathogenesis.