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The Alzheimer Amyloid β-Peptide $A\beta_{25-35}$ blocks a form of chemically-induced LTP.

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Progressive memory loss and deposition of amyloid beta (Aβ) peptides throughout cortical regions are hallmarks of Alzheimer's disease. Several studies in mice and rats have shown that overexpression of amyloid precursor protein (APP) or pretreatment with Aβ peptide fragments results in the inhibition of hippocampal LTP as well as impairments in learning and memory of hippocampal-dependent tasks. Previous work has focused on the effects of these peptides on LTP induced via high frequency electrical stimulation, after which a relatively small number of synapses in the affected subregion are potentiated. In order to investigate the biochemical basis of Aβ's inhibition of LTP, however, it may be advantageous to induce LTP in the majority of excitatory synapses in a slice. For these studies we have investigated the effects of the $A\beta_{25-35}$ peptide fragment on LTP induced by β-adrenergic receptor stimulation followed immediately by application of Mg^{++}-free aCSF ("chemLTP"; Makhinson et al., 1999). This protocol reliably induces LTP that is NMDA-R- and PKA-dependent, and chemically-induced late-phase LTP is protein synthesis-dependent. We found that the $A\beta_{25-35}$ peptide had no significant effect on basal synaptic transmission in area CA1, but that treatment of slices with the peptide for 20 min before inducing chemLTP resulted in complete blockade of LTP. In contrast, normal chemLTP was observed after treatment with the control peptide$A\beta_{35-25}$. These results show that $A\beta_{25-35}$ disrupts a cAMP-dependent form of LTP, whereas others (Freir et al., 2003) have shown that $A\beta_{25-35}$ may inhibit electrically-induced LTP by disrupting calcium dynamics in the postsynaptic cells. This chemical protocol for inducing LTP will allow us to further investigate the ways in which $A\beta_{25-35}$ and other beta amyloid peptides affect intracellular signals, such as second messenger levels and protein phosphorylation, that are necessary for synaptic plasticity and intact cognitive function.

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