BETA-AMYLOID IMPAIRS AMPAR TRAFFICKING BY AFFECTING GLUR1 SERINE 845 PHOSPHORYLATION

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Introduction: Beta-amyloid (Ab), a peptide generated from the amyloid precursor protein (APP) by neurons, is widely believed to underlie the pathophysiology of Alzheimer's disease (AD). Emerging evidence suggests that soluble Ab oligomers adversely affect synaptic function, which leads to cognitive failure associated with AD. The Ab-induced synaptic dysfunction has been attributed to the synaptic removal of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors (AMPAR); however it is unclear how Ab induces the loss of AMPAR at the synapses.

Aims: In this study we have examined the effect of Ab oligomers on phosphorylation levels of Glur1 serine 845 (ser-845) that play an important role in the trafficking of AMPARs to extrasynaptic sites for its subsequent delivery to synapses during LTP.

Methods: We used primary cultures of cortical neurons treated with freshly prepared soluble oligomers of Ab.

Results: We found that Ab oligomers reduce basal levels of ser-845 phosphorylation and surface expression of AMPARs. Moreover, Ab oligomers block the enhancing extrasynaptic delivery of AMPARs mediated by chemical potentiation (forskolin/rolipram).

Conclusion: These data indicates that Ab oligomers could act as a depressor playing a role in the mechanisms involved in the recycling and degradation of AMPARs from the synapses.