Amyloid modulation of neurotransmission at synaptic level

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We previously showed that in the hippocampus (a brain area which is sensitive to Alzheimer's Disease pathology) beta-amyloid (Ab) 1-40 acts as a neuromodulator affecting the nicotinic-evoked neurotransmitter release in absence of neurotoxicity [Mura et al Plos one 2012; 7(1): e29661]. Particularly, we considered neurotransmitters that are usually involved in learning and memory: glutamate, aspartate and GABA. Both *in vivo* (microdialysis technique on freely moving rats) and *in vitro* (hippocampal rat synaptosomes in superfusion), high, likely not physiological concentrations of Ab (10μM *in vivo* and 100nM *in vitro*) greatly impaired the cholinergic control of the release of both excitatory and inhibitory neurotransmitters. This action was mediated by both alpha7- and alpha4beta2 nicotinic acetylcholine receptors (nAChRs). Conversely, physiological concentrations of Ab (pM-low nM) potentiated the cholinergic-elicited release of glutamate and aspartate, particularly acting on alpha7-nAChRs.
Using hippocampal isolated nerve endings from male Wistar rats, in the present work we explored the possible mechanism of the neuromodulatory action of Ab. We particularly evaluated the effects of different concentrations of the peptide (100pM up to 10microM) on the phosphorylation of kinases downstream the activation of nAChRs. We studied the extracellular signal-regulated kinase (ERK1/2) and the calcium/calmodulin-dependent kinase II (CAMKII). The activation of these proteins was analyzed by means of the western blotting technique.
The 90s-long administration of the alpha7 selective agonist PNU-282987 (PNU, 10microM) stimulated the phosphorylation of both ERK (particularly ERK2, the 42KDa isoform of ERK) and CAMKII. At the various concentrations tested Ab1-40 affected the PNU-induced activation of both ERK2 and CAMKII, although these effects were modest.
These results suggest that ERK1/2 and CAMKII may be indirectly involved in the interplay between nAChRs and Ab regulating neurotransmitter release. At the same time the data suggest the need for the search of other primary targets.

This work was supported by a grant from the Alzheimer's Association (NIRG-11-205183)