Effects of β-amyloid fragments on nicotinic modulation of dopamine release from rat nucleus accumbens nerve endings

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It's well known that the peptide beta-amyloid (Aβ) modulates cholinergic neurotransmission with different biological effects in a continuum between physiology and pathology. We have recently demonstrated that Aβ 1-40 inhibits nicotinic-evoked [^{3}H]-dopamine (DA) overflow from rat nucleus accumbens (NAc) synaptosomes by acting as a non-competitive antagonist on an extracellular site of α4β2* nicotinic receptors (nAChRs) (*Olivero et al., 2014)*. In order to clarify the interaction between Aβ and nAChRs, we extended our research to the identification of the active sequence of the peptide.
We exposed rat NAc dopaminergic nerve endings in superfusion to specific Aβ fragments (Aβ 16-20, 11-15 and 31-35), alone or in presence of nicotinic agonists, and compared their activity to the effects of full-length peptides (Aβ 1-40/Aβ 1-42).
Our preliminary results show that the fragment 16-20 (KLVFF) is able to mimic Aβ 1-40 in the negative modulation of nicotinic-evoked DA release, while the scrambled peptide (VLFKF) is ineffective. Similar to the full-length peptide, KLVFF exerts its inhibitory action at extracellular site since it becomes inactive when present only in the synaptosomal cytosol. According to the idea that this short sequence is the active domain of Aβ in controlling nicotinic receptors activity, the inhibitory effect of KLVFF is counteracted by two α4β2 positive allosteric modulators, desformylflustrabromine and galantamine, which interfere also with Aβ 1-40 action.
Our results support the hypothesis that the Aβ fragment 16-20 is the sequence that binds the extracellular site of nAChR. These data can be helpful to develop pharmacological tools to control specific synaptic activity of Aβ.

Olivero et al. (2014). Front Aging Neurosci. 6:166