Beta Amyloid and cholinergic system: old actors for new different roles

M. Grilli[1], G. Olivero[1], J. Chen[1], E. Mura[2], S. Preda[2], S. Govoni[2] and M. Marchi[1,3]

Department of Pharmacy, School of Medicine, University of Genoa, Italy[1]; Department of Experimental and Applied Pharmacology, Centre of Excellence in Applied Biology, University of Pavia, Italy[2], Center of Excellence for Biomedical Research, University of Genoa, Italy[3]

Several studies in the literature report on a possible effect of β-amyloid peptides (Aβ) on the muscarinic receptor (mAChR) and nicotinic receptor (nAChR) function. However, much is yet to be clarified about the precise interactions between the Aβ and the various mAChRs and nAChR subtypes and about the Aβ mechanism of action at this level.
This presentation will describe some effects of Aβ1-40 on the nicotinic-evoked neurotransmitter release from rat superfused nerve endings from different brain areas. The *in vitro* data on release will be implemented with other findings obtained exploiting different molecular biology techniques.
The nicotinic-evoked [^{3}H] dopamine (DA) overflow from rat nucleus accumbens was partially counteracted by Aβ1-40 (100nM). This inhibitory effect involved both α4*nAChRs and α6*nAChRs present on DA nerve terminals. The concomitant presence in the medium of perfusion of Aβ 1-16 6E10, a specific monoclonal antibody against amyloid fragment, with Aβ1-40 strongly reduced the inhibitory effect above described. However, when this antibody was inserted in the cytoplasm of synaptosomes it failed in blocking Aβ1-40. Interestingly, the inhibitory effect of Aβ1-40 on the nicotinic-evoked [^{3}H] DA overflow was partially counteracted by desformylflustrabromine hydrochloride, a specific α4*nAChR allosteric agonist. Aβ1-40 was also able to antagonize the stimulatory effects of the α4* and α7 nAChRs present on hippocampal glutamatergic and GABAergic nerve endings but was ineffective on the nAChRs (α3β4) present on the noradrenergic nerve terminals.
Taken together our results support the hypothesis that Aβ1-40 modulates selectively the function of some nAChRs possibly by acting at the level of the cell membrane.