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Beta-amyloid-acetylcholine structural interaction: evidence for neuroprotective effects of acetylcholine in neural cells

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Alzheimer's disease (AD) is regarded as a multifactorial disease characterized by a complex pathogenesis including a cholinergic deficit - due to degeneration of cholinergic projections from the basal forebrain - and the extracellular accumulation of amyloid beta (Aβ) peptide. Aβ containing 39 to 42 amino acids is the predominant component of the senile plaques that, together with neurofibrillary tangles, are regarded as the neuropathological hallmarks of AD (Sorrentino et al. 2014). Aβ may assume different conformations changing from random coil or α-helical monomers to β-sheet structures forming toxic oligomers and/or β-sheet mature fibrils. In this framework, we studied the effect of acetylcholine (ACh) on the conformation of Aβ by circular dichroism analysis. Moreover we investigated the ability of ACh to protect neuronal cells from the toxic action of amyloid peptide and to modulate the neuroinflammatory response occurring via the phospholipase A2 (PLA2). Results show that the amount of Aβ(25-35) β-strand raised linearly in absence of ACh, whereas it remained almost constant in presence of ACh. In addition, in a micelle solution mimicking the membrane environment ACh was found effective in increasing and stabilizing the soluble and not toxic helical content of Aβ(25-35) suggesting that ACh is capable to preserve the soluble form of Aβ(25-35), reducing the incipit of Aβ aggregation. In order to assess the neuro-protective ability of ACh against toxic Aβ(25-35) accumulation, we used neural cell (NCC) cultures containing both astrocytes and glial cells prepared from brains embryos from timed pregnant Wistar rats and infused ACh for 48h. By immunostaining, we observed that ACh reduced Aβ(25-35)-induced cell death. Then, we tested the protective effect of ACh on inflammation induced by Aβ administration. NCC were challenged with Aβ(25-35) in the presence and absence of ACh and immunostained for astroglial and neuronal markers: results showed a reduction of the morphological features of astrogliosys in ACh treated cells. PLA2 expression analysis corroborated these data also underlying that ACh can negatively regulate inflammation pathways in glial cells.

References

Sorrentino, P et al. (2014) The dark sides of amyloid in Alzheimer's disease pathogenesis. Febs Letters 588, 641-652.

Keywords

Amyloid beta-peptide; acetylcholine; neurotoxicity; neuroinflammation; Alzheimer's disease.