THE NEUROPEPTIDE PACAP SLOWS DOWN ALZHEIMER’S DISEASE-LIKE PATHOLOGY IN APP-TRANSGENIC MICE

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The accumulation of amyloid peptides (Aβ) in the brain is a central process leading to the development of Alzheimer’s disease (AD). The amyloid precursor protein (APP), the source of Aβ, can be proteolytically processed by two competing pathways: the amyloidogenic pathway, generating amyloid-β peptides and the non-amyloidogenic α-secretase-mediated pathway. Proteolytic cleavage of APP by α-secretase within the amyloid-β peptide sequence precludes formation of neurotoxic Aβ peptides and leads to the release of the soluble N-terminal APP ectodomain (sAPPα). Pituitary adenylate cyclase-activating polypeptide (PACAP) acts neuroprotective, neurotrophic and is a potent α-secretase activator. Down-regulation of PACAP in several transgenic mouse models of AD and in the human AD temporal cortex was demonstrated by comparative analysis of cortical gene expression. PACAP peptides and their specific receptor PAC1 are localized in CNS areas affected by AD. Our aim was to examine the role of the natural peptide PACAP as a valuable therapeutic approach in AD. We investigated the effect of PACAP in the brain of APP[V717I] transgenic mice. The long-term intranasal daily application of PACAP improved cognitive functions and enhanced non-amyloidogenic APP processing. In addition, we observed positive modulation of several genes and proteins that are neuroprotective. Finally, our results suggest that restoring or activating PACAP/PAC1 receptor function in the brain may provide therapeutic benefits, and nasal application of the natural neuropeptide PACAP may be valuable for AD treatment.