Cyclic AMP modulates the metabolism of the amyloid-ß precursor protein

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Increasing evidence shows that, besides playing a pathogenic role in Alzheimer's disease, amyloid-ß (Aß) peptides are normally produced at low concentrations in the brain where they can modulate various physiological functions, including synaptic plasticity and memory. Indeed, picomolar concentrations of exogenous Aß enhance whereas anti-Aß antibodies reduce hippocampal long term potentiation (LTP), the neurochemical substrate of learning and memory processes; in addition, the modulation of LTP by exogenous and endogenous Aß is paralleled by evident effects on memory functions (Puzzo et al., 2008, 2011). On the other hand, it is well known that cyclic adenosine monophosphate (cAMP) is one of the second messenger involved in the molecular pathways influencing LTP and memory and that blockade of its phosphodiesterase 4(PDE4)-mediated degradation shows beneficial effects on cognition, both under physiological and pathological conditions (Reenerkens et al., 2009). Therefore, in the present study we have investigated possible neurochemical relationships between cAMP and Aß peptides in cultured neuronal N2a cells overexpressing the amyloid-ß precursor protein (APP). We here report that the selective PDE4 inhibitor rolipram enhanced the expression of APP in a concentration-dependent manner (0.1-10 μM) up to 200%; these effects were paralleled by the increase of Aß peptides (40 and 42, maximal effect 65-70%) and also of soluble APP alfa (sAPPalfa, maximal effect 140%). The results obtained with rolipram were reproduced by stimulating adenylyl cyclase activity with forskolin (1, 10 μM) or by exposing cells to the membrane-permeable analogue 8-Br-cAMP (1 μM-1 mM). In addition, APP, Aß peptides and sAPPalfa were all increased by the selective PKA activator N6-Monobutyryl-cAMP (1-100 μM). Surprisingly, however, the effect of rolipram was insensitive to the PKA inhibitor H89 (1 μM).

In conclusion, our data demonstrate that the selective PDE4 inhibitor, rolipram, stimulates APP expression and its amyloidogenic and non-amyloidogenic processing in neuronal cultures, resulting in the increase of Aß peptides and sAPPalfa, respectively. These effects of rolipram are mediated by the elevation of endogenous cAMP and the subsequent activation of PKA, although the experiments with H89 have given contradictory results probably due to the low concentration of the inhibitor used to maintain its PKA selectivity. In the light of the accumulating evidence of a positive role of sAPPalfa and Aß peptides on cognitive processes, we attempt to speculate that, in normal brain, elevation of intracellular cAMP positively influences LTP and memory through a physiological production of Aß peptides and/or sAPPa. On the other hand, an excessive elevation of cAMP could cause an abnormal production of these peptides, leading to the well known detrimental effects on cognitive functions.

Puzzo et al. (2008). J. Neurosci. 28, 14537-45
Puzzo et al. (2011). Ann. Neurol. 69, 819-30
Reneerkens et al. (2009). Psychopharmacol. 202, 419-43