

AMYLOID PRECURSOR PROTEIN REGULATES SREBP-MEDIATED NEURONAL LIPID HOMEOSTASIS IN MICE AND HUMANS

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Introduction: Synthesis of cholesterol is controlled by sterol regulatory element binding proteins (SREBP). Following its translocation from the endoplasmic reticulum to the Golgi apparatus, cleavage of SREBP releases the mature SREBP transcription factor, which regulates the expression of genes controlling cholesterol and fatty acid biosynthesis.

Aims: Despite extensive evidences that Amyloid Precursor Protein (APP) has critical implications in Alzheimer disease, the neuronal function of APP remains unclear.

Methods: Human APP (hAPP) was expressed in rat cultured of cortical neurons and astrocytes using recombinant adenoviruses. Neo-synthesized cholesterol was quantified after ¹⁴C radiolabelling. The transcription of LDL receptor, HMG-CoA reductase, SREBF1 and SREBF2 genes were monitored by real time PCR. The expression of SREBP in cellular and transgenic mouse models was analyzed by western blotting. Subcellular localisation of SREBP and hAPP was analyzed by immunocytochemistry and their interaction by co-immunoprecipitation assays.

Results: Expression of hAPP decreased HMG-CoA reductase mRNA levels and neuronal cholesterol synthesis in rat cortical neurons but not in astrocytes. The interaction between hAPP and SREBP in the Golgi complex prevented the release of mature SREBP, leading to the inhibition of the transcription of SREBP target genes. Consequently, SREBP was decreased in hAPP expressing neurons. SREBP was also decreased in brain of hAPP transgenic mice, and increased in brain of APP knockout animals. In human brain, a reverse correlation was observed between SREBP and APP expression.

Conclusion: These results argue for a role of APP in the control of neuronal lipid homeostasis both in vitro and in vivo.