EPIGENETIC REGULATION OF EGR-1 EXPRESSION BY THE AMYLOID PRECURSOR PROTEIN OF ALZHEIMER DISEASE

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Objectives: Although the function of the Amyloid Precursor Protein (APP) remains unclear, recent data suggest that APP is able to regulate gene transcription. Following comparison of their transcriptome, we identified Egr-1 mRNA as differently present in APP expressing (APP+/+) or APP knockout (APP-/-) neurons. Since Egr-1 is involved in synaptic plasticity and memory, we studied how APP was able to regulate Egr-1 gene transcription.

Methods: Primary cultures of APP+/+ and APP-/- neurons from the same genetic background were analyzed using qRT-PCR, Western blotting (WB) , or chromatin immunoprecipitation (Chip) assays. Behavioral tests were performed using APP+/+ and APP-/- mice and their brain analyzed using qRT-PCR, WB and Chip.

Results: In primary cultures of cortical neurons, APP significantly down regulated Egr-1 expression at both mRNA and protein levels. Egr-1 expression was regulated by histone acetylation, since trichostatin A up regulated Egr-1 mRNA levels, but more efficiently in APP-/- neurons. APP did not interact with Egr-1 gene promoter, but hyper acetylation of histone H4 at the Egr-1 promoter region was measured in APP-/- neurons. Overexpression of Egr-1 was also measured in APP-/- mice, which were not able to induce Egr-1 expression during exploration behavior in an open field.

Conclusions: Although APP does not interact with EGR-1 gene promoter, it inhibits EGR-1 gene transcription both in vitro and in vivo, by decreasing H4 acetylation in the promoter region. In APP-/- mice, constitutive overexpression of Egr-1 in the brain impairs induction of this early transcriptional regulator during exploration behavior.