DECREASE OF CREB CONTENT IN THE HIPPOCAMPAL NEURONS OF ALZHEIMER’S BRAIN

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Introduction: The transcription factor CREB plays a central role in learning, memory formation and neuronal survival, the functions that are impaired in Alzheimer’s disease (AD). We have previously reported that oxidants associated with AD decrease CREB-regulated gene expression. We have also demonstrated that under chronic conditions of decreased CREB activation, CREB content itself decreases, being an autoregulated gene.

Aims: The objective of the present study was to determine if CREB content is decreased in the hippocampal neurons of AD brain.

Methods: Western blot analysis was performed with the hippocampal tissue samples from AD post mortem brain. Hippocampal neurons from the brain sections of transgenic mice (Tg2576) for AD were isolated by Laser Capture Microdissection (LCM) for the quantitative RT-PCR analysis of CREB mRNA using Taqman probes. CREB promoter analysis was carried out in cultured rat hippocampal neurons exposed to Abeta aggregates.

Results: The protein levels of CREB and its targets, BDNF and BIRC3 (caspase inhibitor) decreased in AD post mortem hippocampi. These decreases correlated inversely with beta amyloid accumulation. CREB mRNA decreased in LCM-captured hippocampal neurons of Tg2576 mouse brain. The activity of CREB promoter linked to a luciferase reporter gene decreased in cultured rat hippocampal neurons exposed to Abeta fibrils and soluble oligomers prepared from Abeta peptide (1-42).

Conclusions: Findings from this study with three experimental models of AD suggest that chronic downregulation of CREB function results in decrease of CREB content in hippocampal neurons of AD brain which may exacerbate the progression of this neurodegenerative disease.