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Leptin signaling at the confluence of neurodegenerative mechanisms in Alzheimer's disease

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The accumulation of Amyloid-β peptide derived from the proteolytic processing of Amyloid-β precursor protein (AβPP) by BACE1) is implicated in the pathogenesis of Alzheimer's disease (AD). BACE1 catalyzes the rate-limiting in the genesis of Aβ and BACE1 expression levels and activity are increased in the autopsied brains of AD patients. We showed that the oxysterol 27-hydroxycholesterol (27-OHC) increases BACE1 expression levels in hippocampal organotypic slices from adult rabbits. In this study we determined the molecular mechanisms, signal transduction cascades as well as the transcription factors involved in the 27-OHC-induced upregulation of BACE1 expression. We found that 27-OHC induces NF-κB activation and increases NF-κB-mediated transcription of BACE1. Specifically, EMSA, ChIP, and dual-luciferase studies show that 27-OHC induced a substantial increase in NF-κB binding to the BACE1 promoter and subsequent increase in BACE1 transcription and Aβ production. The NF-κB inhibitor, sc514, significantly attenuated the 27-OHC-induced increase in NF-κB-mediated BACE1 expression and Aβ genesis. Furthermore, we demonstrate that the 27-OHC-induced NF-κB activation and increased NF-κB-mediated BACE1 expression is contingent on the increased activation of the ER stress induced transcription factor C/EBP homologous protein (CHOP). siRNA mediated silencing of CHOP expression alleviated the 27-OHC-induced increase in NF-κB activation, NF-κB binding to the BACE1 promoter and subsequent increase in BACE1 transcription and Aβ production. Our study implicates a potential crosstalk between the CHOP and NF-κB signaling pathways in the regulation of 27-OHC-induced increase in BACE1 expression.

Biography

Othman Ghribi has completed his Ph.D in 1994 at the University René Descartes, Paris France, and postdoctoral studies from The University of Quebec and the University of Virginia. He has published more than 60 papers in reputed journals and serving as a Senior Editor of The Journal of Alzheimer's Disease and is a member on the editorial board of the Journal of Alzheimer's Disease and Parkinsonism as well as the Journal of Neurodegenerative Diseases.

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