BACE1 Gene Regulation: A Novel Drug Target in Alzheimer's Disease

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Alzheimer's disease (AD) is the most common form of dementia in the elderly in the United States. AD is characterized by the presence of amyloid-β (Aβ) peptide plaques. Aberrant deposition is believed to result from the misregulation of the production or the clearance of Aβ. The rate-limiting step in Aβ production is the processing of amyloid- β precursor protein (APP) by β-site APP-cleaving enzyme (BACE1). BACE1 could play a critical role in the development of AD and is a promising drug target. In this study, we aim to reduce BACE1 enzyme levels by reducing *BACE1* gene expression. We previously analyzed the promoter activity of BACE1 and the 5' untranslated region of BACE1 mRNA. The BACE1 promoter contains many transcription factor sites including SP1, MEF2, and STAT1, which have been shown to play a role in the regulation of *BACE1* gene expression. Mithramycin A (MithA) has been previously shown to selectively inhibit SP1-mediated transcriptional activation. We expect inhibition of SP1 to lead to downregulation of BACE1 and decreased Aβ, providing a novel target for AD. We have tested several BACE1 promoter-deletion constructs by DNA transfection in human neuronal cultures, treatment with MithA, and performed luciferase reporter assays. In a neuroblastoma (NB) cell line, we observed the significant increase in luciferase reporter activity of two BACE1 plasmid constructs after treatment with MithA. Treatment also correlated with an increase in BACE1 protein expression and a decrease in APP expression. This suggests that the mechanism by which MithA influences the BACE1 promoter could be complex and or due to other transcription factor sites as well. Further experiments will include using differentiated NB cells and human primary fetal neurons, along with the use of other Sp1 inhibitors including tolfenamic acid to elucidate the regulation of APP and BACE1 promoters leading to lower Aβ levels.

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