Inhibitory Effects of Dipeptide Analogue, DAPT, on γ-Secretase Causing Decrease in Amyloid-β Concentration in Neuroblastoma Cells

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Abstract

Alzheimer's disease is a very common type of dementia that destroys memory and other important mental functions[1,2]. It is a neurodegenerative disorder which affects over 5 million people in the United States alone[1,2,3]. In fact, it is the 6th leading cause of death in the United States, and on average, an American is diagnosed with Alzheimer's disease every 66 seconds[1,3]. This can be a familial or sporadic disease which is primarily caused by the destruction of neurons which starts from the hippocampus and spreads throughout the brain (cerebellum is spared)[4]. The apoptosis of the countless neurons seems to be caused by a multitude of factors including amyloid-beta plaques, Tau tangles, and neuronal loss[1,2]. For the sake of this investigation, there will be a primary focus on the amyloid-beta plaques because the accumulation or buildup of neurotoxic plaques on the neurons seems to be a key factor in Alzheimer's disease[1,2]. Enzymes called γ-secretase and β-secretase cleave a protein called an amyloid precursor protein (APP) to form these amyloid-beta peptides which can accumulate and form neurotoxic plaques[5,6]. Previous studies have found that DAPT, a dipeptide analogue, is effective in inhibiting γ-secretase thus decreasing amyloid-beta concentration in the brain[6]. This study confirms the efficacy of DAPT in inhibiting γ-secretase, but also investigates the alternative inhibitory effects of other drugs like Activase® rt-PA (alteplase), a tissue plasminogen activator typically used for treatment of stroke, and clonazepam (E64), a pill used to treat panic disorder and anxiety. Although the goal was to see the effects on Aβ40 (40 amino acid amyloid-beta chain) and Aβ42 (42 amino acid amyloid-beta chain) production, only the effects of Aβ40 production were examined due to possible contamination in the Aβ42 tests.