A New Pathway for Alzheimer’s Drugs: Modification of BACE1 to Decrease the Release of Beta Amyloid in the Brain

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Alzheimer’s disease is the 5th leading cause of mortality in the elderly population. The disease progresses through the formation of plaques in neuronal synapses, leading to neuronal death. BACE1, a naturally occurring enzyme in the brain, attacks the APP molecule, causing the release of beta amyloid. This leads to the formation of plaques and progression of dementia. In this paper, a new method towards a cure has been proposed and studied by using molecular simulation modeling and structural protein analysis. The objective is to decrease the affinity between BACE1 and the APP molecule through the use of Dithiothreitol (DTT), a reducing agent of disulfide bonds. Via analysis of individual protein molecular structures, it was seen that BACE1 contained 6 disulfide bonds, the target of modification in this study. It is envisioned that the reduced binding affinity of BACE1 with APP will prevent the release of beta amyloid and thus prevent the progression of Alzheimer’s disease. Results from the molecular modeling simulation indicate that the binding affinity of BACE1 with APP in the presence of DTT is reduced to -5.2 kcal/mol from its previous high value of -5.8 kcal/mol. Furthermore, the analysis of molecular modification of BACE1 due to the action of DTT revealed a 40% decrease in affinity, yielding a value of -3.7 kcal/mol. The new drug protocol is superior to the existing ones because existing protocols focus on inhibiting BACE1 which results in impaired motor function. By adding DTT, BACE1 is not inhibited, but adjusted, creating minimal side effects.

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