Initiation of β-ladder formation of the Osaka mutant of β-Amyloid: A computational study

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Alzheimer's disease (AD) is a progressive neurodegenerative disease. AD of the brains is characterized by the deposition of proteinaceous aggregates and these have two forms in Neurofibrillary tangles (NFT) and Amyloid plaque (senile plaque). It is believed that the major component of amyloid plaques is formed by misfolding that results in the aggregation of β-amyloid peptides with a length from 1- 39 to 1 – 42 amino acids. The mechanism of β-amyloid protein misfolding is not completely understood. The Osaka mutation, which was found in a Japanese AD patient, is a deletion of the Glu22 residue of β-amyloid protein and this was attributed to the enhancement of aggregation. Thus it is important to understand whether Osaka mutation brings about conformational changes to β-amyloid that result in protein aggregation.

β-amyloid and its Osaka mutant were subjected to 20 ns long MD simulation using GROMACS software package. Both proteins were in aqueous medium with 12470 SPC/E water molecules and under neutral electrostatic conditions. Temperature and pressure of the simulation systems were maintained at 300 K and 1 bar and the time step for the simulation was 2 fs.

Root mean square deviation (RMSD) of the wild type protein has indicated an equilibrium conformation while RMSD of the mutant exhibited large fluctuations with an increasing trend, indicating a conformational change. It was found that the conformational change amounted with mutant favours the formation of β-ladder which initiates the aggregation of the mutant in Alzheimer's disease. Further it appears that the alteration of salt bridge formation between Glu22 (and Asp23) and Lys28 may have an effect on the β-ladder formation and prompting the aggregation. Finally results reported in this study are in good agreement with the experimental findings.