Investigation of the misfolding of β-amyloid induced by phenyl pyridinium derivatives and heavy metals : A Computational Study

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Abstract

The intention of this work is to understand the structural changes occurring in β-amyloids at the early stages of misfolding. The study uses molecular dynamics (MD) simulations to describe specific observations made in published, experimental and theoretical work. A series of MD simulations were carried out to study the structural changes in the β-amyloid 1-42 protein, which is implicated in the pathology of Alzheimer's disease. The β-amyloid 1-42 is known to go through structural changes (misfold) and aggregate. The proteins aggregate into a soluble proteinaceous aggregate called amyloid oligomers, which are toxic to the human brain. The molecule 1-Methyl-4-phenylpyridinium and its derivatives are known to induce structural changes in proteins and four phenylpyridinium derivatives were chosen to study their effect on the misfolding of β-amyloid 1-42 monomer with respect to their inhibition kinetics. According to the results the 4'-trifluromethyl-phenyl pyridinium derivative can induce structural changes that trigger misfolding of β-amyloid 1-42 protein.

Heavy metals play a vital role in amyloid toxicity. Thus a single heavy metal ion (Cu^{2+}) was first chosen and the effect of the Cu^{2+} ion on amyloid misfolding is also studied. The Cu^{2+} is bound to β-amyloid 1-42 protein at the methionine residue (position 35 of the β-amyloid 1-42 sequence) and structural changes in the complete protein is studied through MD simulations. This study has identified a new binding site for Cu^{2+} at MET-35. Furthermore the effect of Cu^{2+} on amyloid oligomers is also studied by simulating penta-peptide systems of β-amyloid 1-42. This part of the study indicated physiological conditions where Cu^{2+} can initiate β-sheet formations in β-amyloid oligomers.