Conformational Features of Amyloid Beta Peptides in Monomeric and Aggregated Forms and Their Interaction with Water from Simulation Studies

ABSTRACT

The primary objective of this thesis has been to probe the conformational features of the amyloid beta (Aβ) peptides, responsible for causing Alzheimer's disease, in their monomeric as well as aggregated forms and their interactions with the solvent (water). The investigations are carried out using state-of-the-art molecular dynamics (MD) simulations. The thesis consists of seven chapters. **Chapter 1** provides a brief overview of the current status of research in this area and the methodologies employed in this thesis. In **Chapter 2**, we have probed the conformational features of different full-length Aβ_{42} (or Aβ_F) peptide monomers and their nonuniform influence on the spatial arrangements and binding energies of the surrounding water molecules. The calculations revealed fluctuating conformations of the peptides with formation and breaking of different secondary structural elements. It is demonstrated that water around two crucial hydrophobic segments namely, *hp*1 and *hp*2, are relatively weakly bound as compared to the other segments of the peptide. This is an important finding, as such weakly bound water molecules are expected to be easily displaced during the hydrophobic collapse that leads to Aβ aggregation at higher peptide concentration. Attempts have been made to explore the driving force behind the early stages of the aggregation process of Aβ peptides in **Chapter 3**. It is shown that the formation of helix-helix linkages and nonpolar interactions between the peptides, and nonpolar solvation play important roles in bringing the unstructured regions of the peptides closer during self-assembly and the stabilization of the nucleated oligomer. In **Chapter 4**, we have examined the conformational properties and free energy profiles of truncated Aβ_{17-42} (or Aβ_T) protofilaments of different sizes (pentamer to tetradecamer). The results indicate that the addition of monomers along the axis of an existing protofilament with a critical size (decamer) proceeds via an intermediate step with relatively less stable twisted structure that allows the additional monomers to bind and form stable larger protofilaments with minor rearrangements among themselves. It is demonstrated in **Chapter 5** that the presence of both structurally ordered and disordered water molecules within the spatially heterogeneous confined environment of the protofilament cores can play equally important roles in controlling the growth and stability of the Aβ aggregates. Dynamic properties of water molecules confined within the distorted core regions of the protofilaments are analyzed in **Chapter 6**. The calculations revealed that the protein–water (PW) hydrogen bonds involving the core water molecules stabilize the aggregates, while breaking of the water–water (WW) hydrogen bonds within the cores initiates the required impetus in steering further growth of the aggregates. Finally, we have highlighted the important findings obtained from our studies and the overall conclusions reached therefrom in **Chapter 7**.

Keywords: Molecular Simulation, Amyloid β, Peptide Aggregation, Confined Water, Hydrogen Bonds