Computational Investigations of Intrinsically Disordered Peptides in Monomeric and Aggregated States in Aqueous Solutions

ABSTRACT

The primary objective of this thesis has been to study the microscopic properties of the intrinsically disordered peptide (IDP) α-synuclein, responsible for Parkinson's disease, in monomeric state. Efforts have been made to explore the conformational fluctuations and structural stabilities of the on-pathway protofilaments of different orders formed by α-synuclein. Besides, attempts have also been made to probe the role of metal ions in modulating the conformational features and thermodynamic stabilities of full-length amyloid β or Aβ_{42} peptide, believed to be responsible for Alzheimer's disease. The calculations are carried out using atomistic molecular dynamics (MD) simulation method. The thesis consists of six chapters. A concise overview of the present status of knowledge in this area and the methodologies employed in the thesis have been documented in **Chapter 1**. In **Chapter 2**, we have examined momentary formation and breaking of secondary structural elements and local conformational motions of seven imperfect repeat units (R1 to R7) of α-synuclein. The calculation revealed relatively greater rigidity of the hydrophobic R6 unit as compared to the other repeat units. In addition, due to its hydrophobic character, water molecules around R6 have been found to be less structured and weakly interacting with the peptide. These are key insights as the R6 unit with reduced conformational motions can act as the nucleation site, while less structured weakly interacting water around it can help triggering hydrophobic collapse of the peptide monomers and their association during the early stages of α-synuclein aggregation at higher concentrations. Attempts have been made to explore the dynamic environment at the interface of α-synuclein peptide in the monomeric state in **Chapter 3**. The calculations revealed that the diffusivity of water molecules near the surfaces of the peptide repeat units are significantly hindered due to their solid-like caging motions, the extent of restriction being more around the hydrophobic R6 unit. It is further demonstrated that due to more restricted dynamic environment around R6, water molecules on breaking weaker PW hydrogen bonds with R6 cannot diffuse away, thereby causing slower hydrogen bond structural relaxations around it. In **Chapter 4**, we have investigated the conformational properties and relative stabilities of on-pathway protofilaments of different orders (tetramer to tetradecamer) formed by the 'non-amyloid β component' (NAC) domain of α-synuclein. It is found that the disordered C-terminal loop (CTL) and the central *core* regions of the peptide units lead to more flexible and distorted structures of the lower order protofilaments (tetramer and hexamer) as compared to the higher order ones. Importantly, the nonpolar interaction between the peptides and the corresponding nonpolar solvation free energy have been found to play a dominant role in stabilizing the aggregated protofilaments. It is further discovered that reduced cooperativity during the binding of a peptide unit beyond a critical size of the protofilament (dodecamer) leads to less favorable binding free energy of a peptide. The effects of metal ions (Na^+ and Zn^{2+}) in modulating the conformational characteristics and thermodynamic stabilities of Aβ_{42} peptide in its monomeric state have been presented in **Chapter 5**. The calculations revealed that in presence of metal ions the peptide conformations become more compact with the formation of distant non-local contacts between the hydrophobic segments. Importantly, it is demonstrated that though the Zn^{2+} binding to the peptide is highly specific, Na^+ exhibits small but noticeable non-specific binding propensity with the peptide. Finally, the overall conclusions based on the results presented in the thesis have been summarized in **Chapter 6**.

Keywords: Molecular dynamics, α-Synuclein, Amyloid β, Interfacial water, Hydrogen bonds