Molecular Dynamics study of amyloid aggregates formed by heptapeptide GNNQQNY, and effect of natural polyphenol on their stability.

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Many proteins, when placed in appropriate conditions, can misfold and aggregate into a fibril agglomerates, called amyloids. These fibrils were found to have characteristic X-Ray diffraction pattern and are often identified by staining with Congo red. Amyloid-like fibrils had been associated with many fatal diseases, including Alzheimers disease, type II diabetes mellitus, and the transmissible spongiform encephalopathies, and prion diseases. Due to the non-crystalline and insoluble nature of the amyloid fibril, it was difficult to obtain atomic-resolution structures with traditional experimental methods. However, some short peptides are capable to form both fibrils and microcrystals under the same conditions. Recently, several crystal structures of a hexa- and heptapeptides, identified as fibril-forming segments of the known pathological proteins were reported by Eisenberg et al. (Nature 447:453, 2007). Atomic-resolution structures of these crystals make a good model for amyloids and can be used to investigate the mechanism of amyloid formation and disaggregation by molecular modeling methods. Effect of small molecules on this disaggregation can be investigated in order to design drug candidates for treatment and prevention of the diseases named above.

One of the crystal structures determined by Eisenberg et al. was that of the heptapeptide fragment (GNNQQNY) from Sup-35 yeast prion protein. In this contribution we investigate the amyloid decamer of this heptapeptide and the role, played by myricetin (a naturally occurring polyphenole) in its disaggregation. First we tested several AMBER force fields (ff96, ff99, ff99SB, and ff03) and implicit solvation models (igb1, igb2, igb5, igb7) for their ability to keep the decamer of GNNQQNY aggregated. The RMSDs of decamer of GNNQQNY with force field 99SB and implicit solvent models of igb2 and igb5, were maintained at within less than 4 Å in the 2 ns simulation, indicating remarkable stability of the structures with these combinations of force fields and solvents. Based on these results we selected 99SB force field and igb5 implicit solvent model for detailed investigation of the role played by myricetin in the GNNQQNY oligomer destabilization.

To examine the structural stability of GNNQQNY oligomers in the presence of the ligand and in its absence, we analyzed RMSD, the inter-strand, inter-sheet distances, H-bonds and energetic aspects of the ligand effect. Comparison of the MD simulations of the decamer of GNNQQNY and myricetin/decamer GNNQQNY complex demonstrates that myricetin disturbs the stability of decamer of GNNQQNY. The simulations show myricetin interacts with the β-sheet due to polar interactions with side chains of the peptide weakening the inter-strand hydrogen bonds, wrapping the β-sheet and disaggregating the outer layer. The detailed analysis show that both backbone to backbone and side chain to side chain hydrogen bonds are lost, and that the β-sheets are moving away from each other. This leads to the loss of the backbone H-bonding and eventual separation of one the β-strands in from the outer layer. The presented MD simulations unveil the new mechanism by which the small molecules may destabilize the ordered amyloid oligomers.