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All atoms molecular dynamics analysis of the basic amyloidogenic fragment of IAPP

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The major component of the pancreatic amyloid found in typ-2 diabetes is aggregates of islet amyloid polypeptide (IAPP). IAPP is a 37 residue peptide secreted from β-cells of the pancreas. Spectroscopic and biophysical similarities are observed between amyloid fibers formed by full-length IAPP and its short peptide fragment consisting of residue 22-27 (NFGAIL). In 2001 Azriel and Gazit studied the role of each residue in the octapeptide segment 'NFGAILSS' by alanine scanning and analyzed the mechanism of its aggregation using different experimental techniques. Here, in-order to understand the aggregation mechanism of NFGAILSS at atomic level we used all-atom molecular dynamics (MD) approach. We simulated the wild type and seven alanine-scanned mutants of this octapeptide for 100 ns (a total of 800 ns). Each MD simulations consisted of 27 peptides and approximately 30000 water molecules and was performed using AMBER8 on a special purpose MD-GRAPE3 computer. Large peptide clusters (size 18-26 mers) were observed for the wild type as well as all the alanine scanned mutants. The wild type had the highest β-structure content (~14%), as calculated by DSSP. This result is in line with experimental observations. We also observed that I5A and G3A mutants had the highest amount (~20%) of helical residues and the β-structure content was considerably reduced in both peptides. We also performed Markov state analysis which showed that in all the 8 simulations, the peptides completely lost their monomeric states by ~20 ns. They also indicated initial accumulation (before 10 ns) of helical monomeric state. Moreover, these analyses also supported the fact that isoleucine and glycine are the most important residues, indicating that the aggregate formation is largely mediated via hydrophobic interactions.

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