Lipid Interaction and Membrane Perturbation of Human Amylin by Molecular Dynamics Simulations

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The aggregation of human islet amyloid polypeptide (hIAPP or amylin) is associated with the pathogenesis of type 2 diabetes mellitus. Increasing evidence suggests that the interaction of hIAPP with ß-cell membranes plays a crucial role in cytotoxicity. However, hIAPP-lipid interactions and subsequent membrane perturbation are not well understood at atomic level. In this study, as a first step to gain insight into the mechanism of hIAPP-induced cytotoxicity, we have investigated the detailed interactions of hIAPP monomer, dimer, and hexamer with anionic palmitoyloleolyophosphatidylglycerol (POPG) bilayer using all-atom molecular dynamics (MD) simulations. Multiple MD simulations have been performed by employing the initial configurations where the N-terminal region of hIAPP is pre-inserted in POPG bilayer. Our simulations show that electrostatic interaction between hIAPP and POPG bilayer plays a major role in peptide-lipid interaction. In particular, the N-terminal positively-charged residues Lys1 and Arg11 make a dominant contribution to the interaction. During peptide-lipid interaction process, peptide dimerization occurs mostly through the C-terminal 20–37 region containing the amyloidogenic 20–29-residue segment. Membrane-bound hIAPP oligomers display a pronounced ability of membrane perturbation than monomers. The higher bilayer perturbation propensity of hIAPP oligomer likely results from the cooperativity of the peptide-peptide interaction. This study provides insight into the hIAPP-membrane interaction and the molecular mechanism of membrane disruption by hIAPP oligomers.