Dissecting Membrane-Amyloid Peptide Interactions at the Atomic Level: Insights from Peptide Monomers and Oligomers

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Growing evidence suggests that membrane surfaces may serve as templates for adsorption and aggregation of amyloid peptides, a process associated with cell dysfunction and death in devastating amyloid-associated diseases such as Alzheimer's disease and diabetes. However, the underlying molecular mechanism is not well understood. We performed microsecond molecular dynamics (MD) simulations to (i) investigate the interactions of amyloid beta-peptide (Aβ) and amylin (hIAPP) with lipid membranes, (ii) investigate the importance of histidine 18 of hIAPP by mutation to arginine, lysine, glutamate, (iii) model the influence of lipid composition on these interactions, including the composition of a neuronal membrane, and (iv) describe the effects of free lipids in the aqueous phase on peptide structure. For MD data analysis, we construct transition networks as they provide insight into conformational transitions and aggregation pathways. For Aβ, we reported a transition from disorder to order after binding to a small cluster of POPC lipids in solution, which is similar to the folding of Aβ triggered by its self-assembly. [1, 2] Gangliosides, on the other hand, as found in neuronal membranes, decrease order in Aβ due to competition for the formation of H-bonds with Aβ. [1] In the case of hIAPP, we found that membrane binding induced the formation of an amphipathic helix, which we hypothesized to be an intermediate step to hIAPP amyloid aggregation. [3] These studies provide valuable insight into the interactions between Aβ/hIAPP and various lipid bilayers, which is useful for understanding membrane-mediated cytotoxicity.

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