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Structure and Thermodynamic Stability of Islet Amyloid Polypeptide Monomers and Small Aggregates CHI-CHENG CHIU, University of Chicago, SADANAND SINGH, University of Wisconsin-Madison, JUAN DE PABLO, University of Chicago — Human islet amyloid polypeptide (hIAPP, also known as human amylin) is associated with the development of type II diabetes. It is known to form amyloid fibrils that are found in pancreatic islets. Pramlintide, a synthetic analog of hIAPP with three proline substitutions, is not amyloidogenic and has been applied in amylin replacement treatments. In this work, we use molecular simulations with advanced sampling techniques to examine the effect of these proline substitutions on hIAPP monomer conformations. We find that all three proline substitutions are required to attenuate the formation of β-sheets encountered in amylin. Furthermore, we investigate the formation of hIAPP dimers and trimers, and investigate how that process is affected by the presence of various additives. Our simulations show that hIAPP can form a β-sheet at the N-terminus and the C-terminus independently, in agreement with experimental observations. Our results provide valuable insights into the mechanism of hIAPP early aggregation and the design of fibril formation inhibitors.

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