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IAPP in type II diabetes: basic research on structure, molecular interactions, and disease mechanisms suggests potential intervention strategies.

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ABSTRACT:

Islet amyloid polypeptide (a.k.a. IAPP, amylin) is a 37 amino acid hormone that has long been associated with the progression of type II diabetes mellitus (TIIDM) disease. The endocrine peptide hormone aggregatively misfolds to form amyloid deposits in and around the pancreatic islet β-cells that synthesize both insulin and IAPP, leading to a decrease in β-cell mass in patients with the disease. Extracellular IAPP amyloids induce β-cell death through the formation of reactive oxygen species, mitochondrial dysfunction, chromatin condensation, and apoptotic mechanisms, although the precise roles of IAPP in TIIDM are yet to be established. Here we review aspects of the normal physiological function of IAPP in glucose regulation together with insulin, and its misfolding which contributes to TIIDM, and may also play roles in other pathologies such as Alzheimer's and heart disease. We summarize information on expression of the IAPP gene, the regulation of the hormone by post-translational modifications, the structural properties of the peptide in various states, the kinetics of misfolding to amyloid fibrils, and the interactions of the peptide with insulin, membranes, glycosaminoglycans, and nanoparticles. Finally, we describe how basic research is starting to have a positive impact on the development of approaches to circumvent IAPP amyloidogenesis. These include therapeutic strategies aimed at stabilizing non-amyloidogenic states, inhibition of amyloid growth or disruption of amyloid fibrils, antibodies directed towards amyloid structures, and inhibition of interactions with cofactors that facilitate aggregation or stabilize amyloids.

Keywords: amylin, insulin, diabetes mellitus, amyloids, structure-based drug design, membrane

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