The role of islet amyloid polypeptide (IAPP/Amylin) - membrane interactions in type 2 diabetes mellitus

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Type 2 diabetes mellitus is characterized by impaired insulin action ('insulin resistance') and impaired insulin production by the ß-cells in the islets of Langerhans of the pancreas ('ß-cell failure'). Histopathologically, type 2 diabetes is characterized by fibrillar protein depositions in the pancreatic islets ('islet amyloid'). The building block of these amyloid fibrils is the 37 amino acids human islet amyloid polypeptide (hIAPP, also named Amylin), which is co-produced and co-secreted with insulin by the islet ß-cells. Islet amyloidosis is thought to cause β-cell failure. This notion is strongly supported by *in vitro* cytotoxic effects of hIAPP, as well as by the results of *in vivo* hIAPP transgenic mouse studies. The toxicity of hIAPP is possibly related to the disruption of the cellular membrane due to integration of hIAPP aggregates in the membrane. In addition, it was recently suggested that cell membranes could be a major target of amyloid pathogenesis in general (Kayed, R., *et al*, *Science* 300, 486 (2003)). We study the aggregation and fibril formation of hIAPP in the presence of lipid membranes. Both model membranes, i.e. giant unilamellar vesicles, and cellular membranes, are used to study the role of membranes during the formation of hIAPP aggregates and fibrils. IAPP fibril formation, membrane leakage, and the morphology of the membrane are visualized by confocal fluorescence microscopy. The effect of membrane composition on the aggregation of hIAPP and the effect of hIAPP aggregation on membrane integrity and function are discussed. The obtained results further the understanding of the role of membrane interactions during IAPP aggregation and amyloid formation and may contribute to the development of novel therapeutic agents for type 2 diabetes mellitus.

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