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Human islet amyloid polypeptide (IAPP) aggregates contribute to the pathogenesis of painful diabetic neuropathy

Aim: Islet amyloid formation is associated with β cell failure and cellular toxicity as well as organ and cell dysfunction in type 2 diabetes (T2DM). This experimental study tested the hypothesis that human islet amyloid polypeptide (hIAPP) aggregates were involved in the pathogenesis of peripheral neuropathy.
Methods: Experiments were conducted in four groups of mice: transgenic mouse model of T2DM (Ob/Ob), mice that produce hIAPP by their β-cells (hIAPP Ob/Ob), non-obese hIAPP-mice (hIAPP), in Ob/Ob mice and wild type (WT) mice. In mice aged 7-18 weeks, T2DM parameters (body weight, blood glucose, IAPP, insulin) and pain-associated behaviors were measured. For intra-epidermal nerve fibre density (IENFD) quantification, skin of hind paw was taken after mice underwent euthanasia. Cell cultures came from dissection of adult mouse dorsal root ganglia. This cell suspension was incubated with hIAPP, mIAPP, pramlintide or vehicle. Thereafter, neurite outgrowth and mitochondial superoxide production were analysed. For human studies, skin samples were taken from hands and feet of T2DM subjects (n=6) and non-T2DM controls (n=9).
Results: In vitro, hIAPP diminished neurite outgrowth and increased levels of mitochondrial oxidative stress. hIAPP-transgenic mice developed painful peripheral neuropathy. hIAPP Ob/Ob mice having elevated plasma hIAPP levels and hyperglycaemia had more severe signs of peripheral neuropathy. Inplantar and intravenous injection of hIAPP caused allodynia and decreased IENFD in wild-type mice. Neither non-aggregating murine IAPP, mutated IAPP (pramlintide) nor hIAPP with pharmacologically inhibited aggregation induced such effects. T2DM patients had decreased IENFD and more hIAPP oligomers in skin biopsies compared to non-T2DM controls.
Conclusions: The authors provided evidence that hIAPP aggregates have neurotoxic effects. The abundance of hIAPP oligomers in skin biopsies of T2DM patients with neuropathy indicate that hIAPP potentially contributes to the pathogenesis of diabetic neuropathy in human.

Comments. hIAPP forms toxic aggregates in β-cells and many organs of T2DM patients such as brain, heart and kidney. This study is the first demonstrating evidence that amyloidogenic hIAPP also contributes to the development of diabetic peripheral neuropathy. hIAPP transgenic mice develop sensory nerve fibre damage and allodynia and the damage is more severe in diabetic hIAPP mice. Furthermore, the role of hIAPP oligomer formation was proven and reaffirmed in skin samples of T2DM patients. Direct cytotoxic effects and mitochondrial damage were proposed as pathogenetic mechanisms. As hIAPP Ob/Ob mice show more characteristics of T2DM (obesity, hyperglycaemia, insulin resistance and amyloid expression) than usual animal models for human T2DM, hIAPP Ob/Ob mice were also suggested a better model to study diabetes and its complications. The findings may contribute to developing new strategies for treatment or prevention of diabetic neuropathy.

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Reference. Albariqi MM, Versteeg S, Brakkee EM, Coert JH, Elenbaas BO, Prado J, Hack CE, Höppener JW, Eijkelkamp N. Human IAPP is a contributor to painful diabetic peripheral neuropathy. J Clin Invest. 2023 Apr 17;133(8):e156993. doi: 10.1172/JCI156993. PMID: 36917177; PMCID: PMC10104883.
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