Human IAPP drives painful diabetic peripheral neuropathy

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Background

Peripheral neuropathy is a common complication in type 2 diabetes mellitus (T2DM). Insulin treatment reduces hyperglycaemia but not neuropathy in T2DM, indicating that hyperglycaemia is not sufficient to cause neuropathy in T2DM. Human islet amyloid polypeptide (hIAPP) is overproduced with insulin by the pancreatic islet β-cells as a consequence of insulin resistance. Human IAPP forms pathogenic aggregates and amyloid leading to beta-cell death and possible damage to other tissues. Here, we investigated whether hIAPP contributes to neuropathy in transgenic mouse models of T2DM.

Methods

Pain-like behaviours were assessed in hIAPP mice, obese hIAPP mice (hIAPP/ObOb) and wildtype (WT) mice. In addition, the ability of hIAPP to induce nerve damage was assessed in vivo by assessing intraepidermal nerve fiber (IENF) density.

Results

hIAPP Ob/Ob mice had hyperglycaemia and elevated blood IAPP levels as compared to WT mice (glucose: 29 vs 10 pM; $p<0.0001$; IAPP 729 vs 4.28 pM; $p<0.0001$). hIAPP Ob/Ob mice developed signs of neuropathy because they had reduced skin IENF density (16.3 vs 47.2 IENF/mm; $p<0.0001$), mechanical hypersensitivity (50% threshold of 0.0875 vs. 0.4398 g; $p<0.0001$) and thermal hyposensitivity (thermal withdrawal latency time of 10.02 vs 7.112 sec; $p<0.0001$). hIAPP transgenic mice had elevated hIAPP levels (35 vs. 4.2 pM; $p<0.05$) but normal glycaemia. Intriguingly, hIAPP mice developed mechanical hypersensitivity (threshold 0.155 vs. 0.438 g; $p<0.0001$) and had reduced IENF density compared to WT mice (25.5 vs. 47.2 IENF /mm; $p<0.0001$). Moreover, hIAPP injection, into the paw or intravenously in WT mice dose-dependently induced long lasting (1-2 weeks) mechanical hypersensitivity and reduced skin IENF numbers at 1 week after injection (24.1 vs. 35.6 IENF /mm; $p<0.01$), whilst non-amyloidogenic mouse IAPP did not.

Conclusions

Human IAPP, contrary to non-aggregating mIAPP, induces signs of peripheral neuropathy in mice. Therefore, human IAPP is a potential driver of peripheral neuropathy in T2DM patients.