

Oophorectomy Promotes Islet Amyloid Formation in Human Islet Amyloid Polypeptide Transgenic Mice

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Islet amyloid polypeptide (IAPP) (amylin) is the unique peptide component of the amyloid deposits found at autopsy in >90% of subjects with type 2 diabetes (1). These amyloid deposits are thought to replace islet mass and to thereby contribute to the β -cell dysfunction of the disease. The mechanism(s) underlying islet amyloid deposition is unclear, but an amyloidogenic sequence in IAPP is required. Islet amyloid can develop in humans, nonhuman primates, and cats, but it never develops in rodents because their IAPP lacks the critical amino acid sequence and is thus non-amyloidogenic.

Several groups have generated transgenic mice expressing human IAPP (hIAPP) (2). We successfully induced amyloid formation in our hIAPP transgenic mice by feeding a diet containing an increased quantity of fat (9% wt/wt) (3). Interestingly, we noted a gender-dependent difference, as islet amyloid deposits were found in 81% of male transgenic mice but in only 11% of female transgenic mice. This observation suggested that either testicular products promote or ovarian products protect against islet amyloid deposition. Recently, another group has observed a similar gender-dependent difference in islet amyloid deposition in double-transgenic hIAPP *ob/ob* mice, with 83% of male mice compared with 20% of female mice developing islet amyloid deposits (4).

To test the hypothesis that ovarian products protect against the development of islet amyloid in hIAPP transgenic mice, we performed a bilateral oophorectomy ($n = 11$) or a sham procedure ($n = 6$) in female hIAPP transgenic mice at 6–8 weeks of age. The animals were followed for 1 year on a 9% fat (wt/wt) diet. Body weight was measured every 2 weeks throughout the study. At 57 weeks, an intraperitoneal glucose tolerance test was performed after an overnight fast to determine whether glucose tolerance or β -cell function were altered and contributed to amyloido-

genesis. When the animals were killed, 4-h fasting plasma glucose, immunoreactive insulin (IRI), and hIAPP levels were measured. The pancreas was harvested and used to quantify IRI and hIAPP content and to determine the prevalence and severity of islet amyloid by thioflavin S staining. The severity of amyloid deposition was determined using an arbitrary scale of 0–3, where 0 denoted no amyloid and 3 denoted extensive amyloid deposits. A minimum of six islets in each section were examined, and the mean score was calculated.

No amyloid was detected in the six sham-operated mice. In sharp contrast, 7 of 11 (64%) oophorectomized mice developed islet amyloid ($P < 0.05$), with the mean (\pm SE) severity of amyloid in this group being 0.40 ± 0.18 arbitrary units (range 0–2.00). Incremental body weight (oophorectomized 39 ± 3 vs. sham-operated 32 ± 3 g, $P = 0.2$), 4-h fasting plasma glucose (oophorectomized 8.0 ± 0.7 vs. sham-operated 8.5 ± 1.3 mmol/l), IRI (oophorectomized $1,085 \pm 396$ vs. sham-operated $1,098 \pm 395$ pmol/l), and hIAPP levels (oophorectomized 33 ± 7 vs. sham-operated 43 ± 6 pmol/l) were comparable between the two groups. Glucose tolerance, expressed as incremental area under the curve (AUC) of glucose (oophorectomized 812 ± 113 vs. sham-operated 700 ± 169 mmol/l per 120 min), did not differ between the groups, but there was a tendency to a decrease in β -cell function expressed as the AUC IRI/AUC glucose in the oophorectomized animals (oophorectomized 108 ± 56 vs. sham-operated 307 ± 185 pmol/mmol, $P = 0.2$). Furthermore, oophorectomy was not associated with alterations in either pancreatic IRI content (oophorectomized 417 ± 96 vs. sham-operated 324 ± 82 pmol/mg protein) or hIAPP content (oophorectomized 15 ± 4 vs. sham-operated 11 ± 3 pmol/mg protein).

These data demonstrate that oophorectomy in female transgenic hIAPP mice fed a high-fat diet is associated with an enhancement of islet amyloid formation. The increased incidence of amyloid deposition was not associated with changes in incremental body weight, circulating glucose levels, IRI levels, hIAPP levels, or glucose tolerance, but there was a tendency toward reduced β -cell function. Amyloid deposition did not appear to be mediated by increased pancreatic hIAPP content.

In conclusion, islet amyloidogenesis in our hIAPP transgenic mouse model of the islet amyloid of type 2 diabetes appears to be independent of glucose tolerance, with ovarian products having a protective role. This observation raises the possibility of a potential benefit of estrogen in the protection of islets against the development of amyloid early in the course of type 2 diabetes.

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AUC, area under the curve; hIAPP, human IAPP; IAPP, islet amyloid polypeptide; IRI, immunoreactive insulin.

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