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Amyloid and Transplanted Islets

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TO THE EDITOR: In their letter to the editor, Westermark and colleagues (Aug. 28 issue)¹ report on their identification of amyloid in 43% of intrahepatically transplanted islets on postmortem examination of a recipient with type 1 diabetes. Amyloid is composed of amylin (islet amyloid polypeptide [IAPP]) that is cosecreted from the beta cell with insulin but normally is inhibited from forming amyloid by appropriate proportions of insulin and other factors in the beta cell.^{2,3} Proportions of insulin and amylin within the beta cell are best estimated in vivo following secretion after acute stimulation.⁴ To determine whether insulin and amylin are secreted in appropriate proportions after human islet transplantation, we measured plasma concentrations of both hormones before and after arginine stimulation under fasting and hyperglycemic-clamp conditions in four insulin-independent islet recipients and matched controls; the characteristics and C-peptide data of the subjects were reported previously.⁵ Insulin responses to arginine were relatively more reduced during the hyperglycemic clamps than were amylin responses, resulting in markedly lower ratios between insulin and amylin (Fig. 1). These data indicate that during hyperglycemia, intrahepatically transplanted islets secrete disproportionately more amylin than normal, suggesting that hyperglycemia in the islet recipient may have contributed to the observed amyloid deposition.

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Figure 1. Plasma Insulin, Amylin, and Molar Ratios between Insulin and Amylin in Four Insulin-Independent Recipients of Islet Transplantation and Four Control Subjects without Diabetes

Insulin and total amylin concentrations were measured by radioimmunoassay and enzyme-linked immunosorbent assay, respectively, in samples collected before and 2 to 5 minutes after the injection of 5 g of arginine under fasting conditions and hyperglycemic-clamp conditions with plasma glucose concentrations of 230 mg per deciliter and 340 mg per deciliter. Islet-transplant recipients had received a median of two islet infusions a median of 3 months before the study. Among islet-transplant recipients and control subjects, mean ($\pm$ SE) values were similar for age (48 ± 4 years vs. 43 ± 3 years), body-mass index, defined as the weight in kilograms divided by square of the height in meters (20.4 ± 1.1 vs. 23.2 ± 1.4), and glycated hemoglobin ($5.9\pm 0.1\%$ vs. $5.5\pm 0.2\%$). The incremental insulin responses to arginine among islet-transplant recipients and control subjects were 107 ± 19 pmol per liter versus 193 ± 46 pmol per liter under fasting conditions (P not significant), 209 ± 26 pmol per liter versus 1028 ± 208 pmol per liter with a plasma glucose concentration of 230 mg per deciliter ($P<0.01$), and 296 ± 54 pmol per liter versus 1322 ± 379 pmol per liter with a plasma glucose concentration of 340 mg per deciliter ($P<0.05$). The corresponding amylin responses among islet-transplant recipients and control subjects under the three conditions were 2.8 ± 0.8 pmol per liter versus 7.3 ± 2.9 pmol per liter (P not significant), 8.7 ± 1.7 pmol per

liter versus 8.4 ± 1.5 pmol per liter (P not significant), and 8.5 ± 1.2 pmol per liter versus 21.3 ± 3.6 pmol per liter ($P < 0.05$). The corresponding secretory ratios of insulin to amylin were 14.4 ± 7.5 versus 13.4 ± 8.3 (P not significant), 1.9 ± 5.3 versus 27.2 ± 4.9 ($P < 0.05$), and 8.2 ± 2.8 versus 24.5 ± 5.4 ($P < 0.05$). Comparisons between groups were performed with the use of two-tailed unpaired Student's t-tests.