Glycemic Control Mechanisms After Canine Islet Autografting

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THE THESIS that diabetic complications are halted or prevented by continuous, precise glycemic control is central to the concept of islet transplantation. Therefore, it is essential to establish whether islet transplantation can produce adequate long-term metabolic control. The main focus in the islet transplantation field has been on technical and immunologic issues, and metabolic control generally received limited attention. The clinical work is still anecdotal, and experimental metabolic studies in preclinical models are generally confined to the intravenous glucose tolerance test (IVGTT)[1]; thus, detailed studies are needed that address the insulin-secreting capacity, insulin action, and particularly the performance of transplanted islets under normal physiologic conditions. The function of native islets is a result of anatomic, neural, hormonal, and other interrelations at several levels of the gastro-entero-pancreatic axis: (1) the architecture of the islet, (2) the intrapancreatic intrinsic neural web, coordinating pulsatile delivery by the islet population, and (3) interrelations between the islet population and other gastrointestinal organs. Islet isolation and transplantation leads to disturbance or destruction of at least the anatomic and neural interrelations. The hormonal branch of the entero-insular axis, however, may remain largely intact.

Our preliminary studies suggest that the insulinotropic effect of gut hormones (incretin) may account for most (80% to 90%) of the postprandial insulin response after islet transplantation.[1,2] Further, in vitro perfusion studies[1,2] demonstrated that isolated islets still do respond to physiologic stimulation with incretins such as glucagon-like peptide-1 7-36 amide (GLP-1); however, as yet, similar studies after transplantation of islets have not been published. We therefore studied the insulin-secreting capacity, insulin action, and performance of transplanted islets under physiologic conditions—focusing on preservation of the incretin effect—in established islet autografted dogs.

MATERIALS AND METHODS

Metabolic studies were performed in 8 beagle dogs at 6 to 9 months after intrasplenic islet autotransplantation, and 30 normal controls.

After total pancreatectomy, islets were isolated by manual, static, collagenase digestion and dextran density gradient purification. The purified islets were transplanted by retrograde venous infusion in the spleen. The islet dose per kg body weight averaged 3679 ± 849 islet equivalents (IEq; normalized islets with 150 μm diameter), which corresponds to ~25% of the average native islet mass (14,668 IEq/kg, as assessed by stereology in 14 control pancreases). Purity of the grafts was 70% ± 10%.

For conventional assessment we included the intravenous glucose tolerance test. The near-maximum[3] insulin secretory capacity was assessed by intravenous arginine injection during an intravenous 35 mmol/L glucose clamp. After physiologic stimulation by mixed-meals (500 mL, semisolid) the glucose, insulin, glucagon, and pancreatic polypeptide (PP) responses were determined. Insulin action was assessed by the two-step hyperinsulinemic (~160 and ~750 pM), euglycemic clamp method. The entero-insular axis after islet transplantation was examined by infusion of the insulinotropic gut hormone GLP-1 (1.75 pmol/kg · min) during an 8 to 9 mmol/L glucose clamp, mimicking postprandial glycemic conditions after transplantation.

RESULTS AND DISCUSSION

The data are summarized in Fig 1. Fasting glucose and hormone levels (except for a 66% reduction of PP) were normal. Both the acute insulin response during IVGTT and the secondary insulin response to intravenous glucose during the 35 mmol/L glucose clamp were reduced after transplantation to ~10% of normal values ($P < .0001$). The insulin secretory capacity—as measured by arginine stimulation during the hyperglycemic clamp—was reduced to ~25% of the normal value ($P < .0001$), which mirrored the reduction in islet mass. Postprandially, by contrast, normal insulin levels and an increase of the incremental insulin response to ~140% of the normal value ($P < .05$) were observed. The postprandial glucose level, however, had also increased to ~8.5 mmol/L. Comparison of the posttransplant insulin levels after meals vs the levels at intravenous arginine stimulation during the 35 mmol/L glucose clamp, demonstrated similar stimulation of the grafted β-cells, indicating chronic, repetitive, near-maximum stimulation of the grafted β-cells after meals. Low-dose GLP-1 infusion in the graft recipients potentiated (175%) the insulin response during 8.5 mmol/L glucose clamps ($P < .01$). Thus, since the incretin effect was preserved after islet transplantation, hyperglycemic potentiation of the entero-insular axis may explain the postprandial normo-insulinemia after islet transplantation. Apart from the reduced islet mass, other factors that may have contributed to the postprandial glucose intolerance were: (1) reduction of insulin action to

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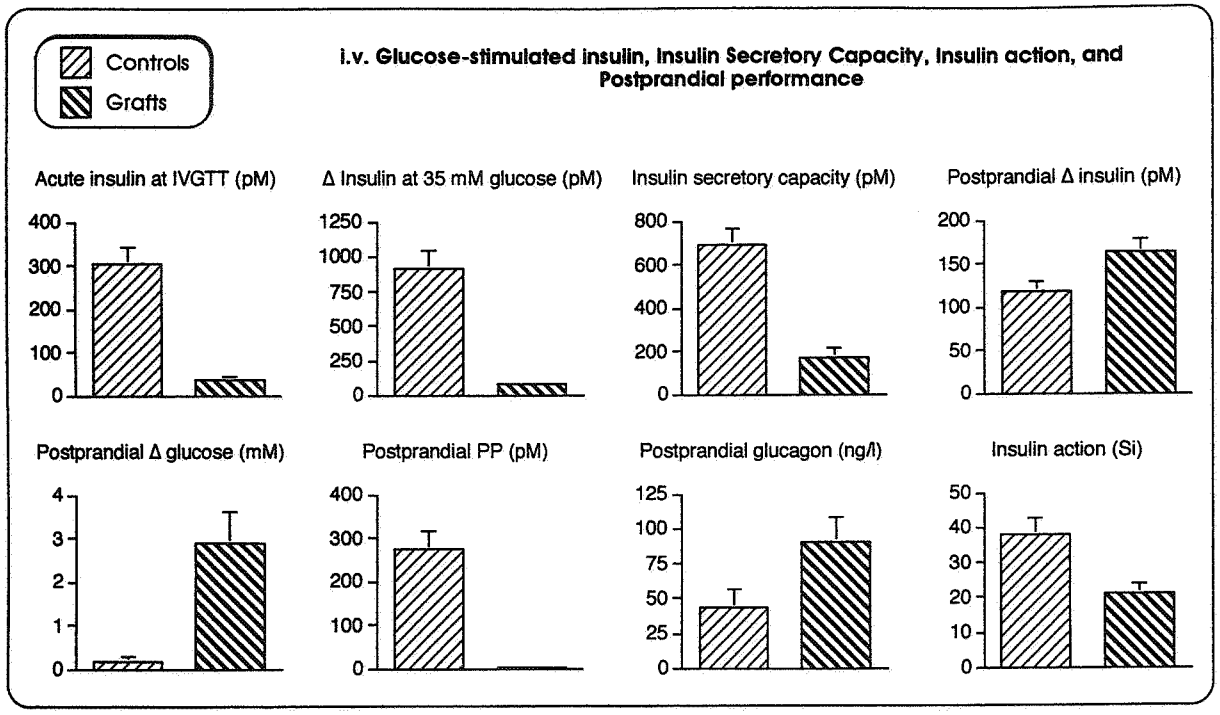

Fig 1. Metabolic control in 8 beagles at 6 to 9 months after intrasplenic islet autotransplantation (Grafts), compared with 30 normal controls. Stimulated glucose and hormone data are integrated responses weighed for the duration of the tests. Sensitivity index (Si) expressed in $10^2 \cdot L \cdot kg^{-1} \cdot min^{-1}$ per pM. Data are means ± SE.

55% of the normal value ($P < .05$), (2) postprandial hyperglucagonemia ($P < .05$), and (3) postprandial PP-deficiency ($P < .0001$). Correlation analysis of the post-transplant data in each animal indicated the insulin secretory capacity to be a common determinant of both insulin sensitivity and postprandial glucose excursions. With reduction of the secretory capacity, insulin action decreased ($r = 0.71$; $P < .05$), and glucose excursions increased ($r = -0.93$; $P < .001$).

In conclusion, after transplantation of a suboptimal islet mass, a postprandial hyperglycemia-enhanced insulinotropic effect of GLP-1 and other gut hormones, may (1) account for the marked difference in the insulin response to the intravenous and oral challenges; (2) limit the postprandial glucose excursion; (3) lead to (near-)maximum stimulation of insulin secretion, eventually perhaps leading to functional failure of the graft. Apart from a reduced insulin secretory capacity, insulin resistance and excessive hepatic glucose production—due perhaps to (1) a deranged insulin pulsatility, (2) hyperglucagonemia, and (3) PP deficiency—may have been conducive to the postprandial glucose intolerance. Reduction of the insulin secretory capacity appears to be the common determinant of both postprandial hyperglycemia and insulin resistance. Transplantation of a larger islet mass should, therefore, allow prolonged near-normal glycemic control.

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