Insulin Sensitivity and Glucose Effectiveness in Long-Term Islet-Autotransplanted Dogs

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Parameters determining glucose tolerance were quantified with Bergman's minimal-model method applied to frequently sampled intravenous glucose tolerance tests in five normal and five islet-autotransplanted mongrel dogs 8–10 mo posttransplantation. Despite normal fasting glucose and insulin levels, glucose tolerance was reduced in the islet-transplanted dogs (1.5 ± 0.4 vs. 4.2 ± 0.4%/min in normal controls, $P < .002$). The reduction in glucose tolerance was due to a reduced insulin response to glucose injection (4 ± 1 vs. 32 ± 5 μU/ml, $P < .001$) and reduced glucose effectiveness (1.7 ± 0.5 vs. 5.3 ± 0.6 × 10^2 min^{-1}, $P < .005$) but not to a reduction in insulin sensitivity (8.4 ± 0.6 vs. 7.8 ± 0.7 × 10^4 $min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$, $P > .5$). Our results suggest that reduced insulin secretory response as a result of islet transplantation may result in a defect in glucose's ability to promote its own disposal but not necessarily in a defect in insulin sensitivity. *Diabetes* 38 (Suppl. 1):189–91, 1989

The particular importance of transplantation as a therapeutic modality for insulin-dependent diabetes mellitus (IDDM) is not just its ability to eliminate a patient's requirement for insulin but its potential for normalizing glucose tolerance. Tolerance to a glucose load is dependent on the insulin secretory response as well as the sensitivity of tissues to the action of the circulating insulin (insulin sensitivity) and the ability of the glucose to promote its own disposal (glucose effectiveness) (1).

Warnock et al. (2,3) previously demonstrated that dogs bearing autografts of islets of Langerhans refluxed into the spleen maintained normal fasting glucose and insulin levels during the year after transplantation. Although the fasting levels were normal and the animals did not require insulin, tolerance to oral and intravenous glucose loads was reduced. This reduced glucose tolerance was clearly due, at least in part, to a subnormal insulin secretory response of the islet autografts (3). We determined the contribution of insulin sensitivity and glucose effectiveness to the reduced glucose tolerance in dogs 8–10 mo after islet autotransplantation.

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MATERIALS AND METHODS

We quantified glucose tolerance (K_G), insulin response (IR), insulin sensitivity (S_I), and glucose effectiveness (S_G) in five normal mongrel dogs and five dogs bearing autografts of islets of Langerhans. Islets were isolated and then refluxed into the spleen according to previously described methods (2). Dogs bearing islet autografts were studied 8–10 mo postoperation. These studies were in accordance with humane practice as described by the Canadian Council on Animal Care and were approved by the Health Sciences Animal Welfare Committee of the University of Alberta.

The parameters determining glucose tolerance were quantified by the minimal-model, frequently sampled intravenous glucose tolerance test method of Bergman and colleagues (4). The experimental protocol consisted of an injection of glucose (300 mg/kg body wt) and an injection of insulin (0.03 U/kg) at 20 min. This approach is a modification of the standard protocol (5), because the transplanted dogs had an insufficient insulin response to either glucose or tolbutamide to allow determination of insulin sensitivity (6). Samples for determination of plasma glucose and insulin were drawn according to the standard schedule (4) and handled as previously described (7). S_I and S_G were calculated with the MINMOD program, which applies the minimal model of glucose kinetics to the dynamics of glucose and insulin after the glucose load (8). K_G was calculated as the slope of the regression of the logarithm of glucose versus time 2–19 min after the glucose injection. IR was the weighted mean increase in insulin above basal level between 0 and 20 min. Data are expressed as means ± SE.

TABLE 1
Parameters of glucose tolerance

Dog no.	Fasting plasma glucose (mg/dl)	Fasting plasma insulin (μU/ml)	K_G (%/min)	IR (μU/ml)	S_I ($\times 10^4$ min^{-1} · μU^{-1} · ml^{-1})	S_G ($\times 10^2$ min^{-1})
Normal controls						
H145	92	3	2.97	20	5.1	3.0
H151	96	5	3.38	22	8.8	4.6
H222	98	6	4.87	30	10.0	6.2
H338	99	3	4.91	34	7.7	6.0
H331	94	9	5.05	50	7.5	6.8
Mean ± SE	96 ± 1	5 ± 1	4.24 ± 0.44	32 ± 5	7.8 ± 0.7	5.3 ± 0.6
Islet transplanted						
G356	71	1	1.55	3	8.8	2.8
G316	95	3	0.36	3	8.6	0.4
G328	88	6	1.25	2	9.8	0.3
G502	97	5	1.57	5	5.7	2.3
G288	68	3	2.63	4	8.9	2.8
Mean ± SE	84 ± 5	4 ± 1	1.47 ± 0.36	4 ± 1	8.4 ± 0.6	1.7 ± 0.5
*P**	>.05	>.20	<.002	<.001	>.50	<.005

*Statistics are reported for comparison of the islet-transplanted group with controls by 2-sided Student's *t* test for unpaired data.

RESULTS

As in the previous studies by Warnock et al. (2,3), fasting plasma glucose and insulin were normal in the islet-transplanted group (Table 1). K_G determined between 8 and 10 mo posttransplantation was reduced by 65% in the islet-transplanted dogs. This reduced glucose tolerance was due, at least in part, to a reduction in IR from 32 ± 5 to 4 ± 1 μU/ml (Table 1).

Although K_G was reduced in the presence of endogenous insulin, glucose disposal responded well to the injection of exogenous insulin at 20 min (Fig. 1). From these data we were able to quantify separately the contribution of insulin sensitivity and glucose effectiveness to overall glucose tolerance (Table 1). S_I was not different between the two groups ($P > .05$). S_G, however, was significantly reduced in the islet-transplanted group ($P < .001$).

The dynamics of glucose and insulin during these studies also suggests that the initial glucose-distribution volume is somewhat enlarged in the islet-transplanted group because the plasma glucose response to the glucose injection was reduced by 23% at 2 min ($P < .01$). The similarity of the fall in the plasma insulin concentration after the insulin injection suggests that insulin clearance was not different between the two groups.

DISCUSSION

The promise of islet and pancreas transplantation as a therapeutic approach to IDDM is its potential for near-normal metabolic regulation. The techniques developed by Warnock and colleagues (2,3) result in normalization of the fasting plasma glucose and insulin levels in pancreatectomized islet-autotransplanted dogs. Despite normalization of periph-

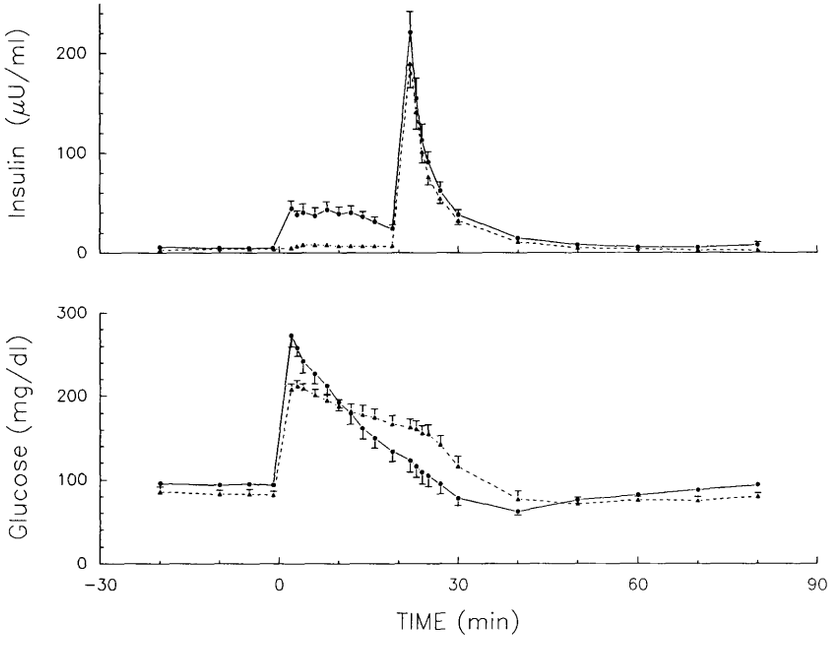

FIG. 1. Dynamics of plasma glucose and insulin during frequently sampled intravenous glucose tolerance test. Data are means ± SE. *Solid lines*, normal control dogs (n = 5); *dashed lines*, islet-autotransplanted dogs (n = 5).

eral fasting plasma glucose and insulin levels, these animals had a reduced glucose tolerance. This reduced glucose tolerance was due, at least in part, to the inability of the transplanted islets to respond normally to secretagogues such as glucose or tolbutamide.

Reduced insulin secretory capacity has been associated with insulin resistance, another factor that determines overall glucose tolerance. Studies of recently diagnosed IDDM patients suggest that insulin resistance occurs concomitantly with reduced insulin secretory capacity and may increase as residual insulin secretion diminishes (9). Insulin resistance has also been demonstrated in association with a modestly reduced insulin secretory capacity in nondiabetic HLA-identical siblings of IDDM patients (10). The results of these studies are in contrast to this association, because the large reduction in secretory capacity in these islet-transplanted dogs did not induce insulin resistance. This result leaves open the possibility that the insulin resistance associated with the early phases in the progression toward overt IDDM is due not to the reduced insulin secretory capacity but to some independent pathogenic factor. Likewise, there may be a threshold secretory capacity above which normal insulin sensitivity is maintained and below which insulin resistance is induced. The direct relationship between the magnitude of the insulin secretory response and insulin sensitivity in our islet-transplanted dog model remains to be determined.

We did find, however, a defect in S_G. The minimal-model method quantifies S_G as the ability of glucose to enhance its own disposal at the basal level of insulin. Our results suggest that this defect in S_G is not due simply to a lowering of the basal insulin level, because peripheral venous fasting insulin levels were normal. A relationship between reduced chronic insulin secretion and decreased glucose effectiveness implies that the reduced insulin levels alter the ability of glucose to suppress its own production by the liver and/or reduce the ability of glucose to enhance glucose uptake into glucose-utilizing tissues. The mechanism of the observed reduction in glucose effectiveness while insulin sensitivity remains at normal levels remains to be determined.

In summary, our results suggest that the reduced glucose tolerance observed in islet-autotransplanted dogs is due to both a reduction in insulin secretory response to intravenous glucose and a reduction in glucose's ability to promote its own disposal.

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