Insulin-mediated and glucose-mediated glucose uptake following hemipancreatectomy in healthy human donors

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Summary Healthy humans undergoing hemipancreatectomy for the purpose of donation to a family member with IDDM have previously been demonstrated to maintain serum glucose values equal to matched control subjects during short-term glucose infusion despite significant decrements in glucose- and arginine-induced insulin secretion. In order to determine whether humans compensate for hemipancreatectomy by increasing insulin- or glucose-mediated glucose uptake, we measured glucose turnover and insulin sensitivity by three protocols. Insulin-mediated glucose uptake was measured during sequential infusions of insulin at rates of 0.25, 1.0, and 10.0 mU · kg⁻¹ · min⁻¹ in 12 donor subjects and 12 matched control subjects maintained at euglycaemia. Both groups displayed similar increases in rates of glucose disappearance and similar decreases in rates

of hepatic glucose production. Glucose-mediated uptake was calculated as the difference between the rates of glucose disappearance measured during a hyperglycaemic clamp and a euglycaemic clamp performed at identical rates of insulin infusion and was also found to be similar in both donor subjects and control subjects. Both groups also had indistinguishable measures of insulin sensitivity and glucose effectiveness as determined by the minimal model technique. Therefore, donor subjects appear to compensate for diminished insulin secretion following hemipancreatectomy by an unidentified mechanism since neither insulin- nor glucose-mediated glucose uptake are increased. [Diabetologia (1994) 37: 1036–1043]

Key words Insulin action, pancreatectomy, glucose uptake, pancreas transplantation, minimal model.

The metabolic effects of partial pancreatectomy have drawn much attention in recent years because of the insights this model provides in understanding the role of beta-cell mass in glucose homeostasis. While most investigation has been performed using animal models [1–6], observations made in hemipancreatectomized humans, especially in those who are healthy

at the time of surgery and undergo the procedure for the purpose of organ donation to a family member with diabetes, are particularly applicable to the understanding of human physiology and disease. Hemipancreatectomy in humans for the purpose of organ donation causes abnormal glucose tolerance in 25 % of subjects examined 1 year after surgery [7]. Daily glucose profiles were normal in 17 donor subjects studied by Kendall et al. [7] 1 year after donation and donor subjects have been reported to maintain normal fasting glucose concentrations for many years after hemipancreatectomy [7, 8]. However, significant defects in pancreatic beta- and alpha-cell function have been observed even in healthy hemipancreatectomized human donor subjects with normal glucose tolerance. We have previously reported that these subjects experience an approximately 50 % reduction in glucose- and arginine-induced insu-

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Abbreviations: R_d, Rate of glucose disappearance; HGP, hepatic glucose production rate; IDDM, insulin-dependent diabetes mellitus; S_I, insulin sensitivity index; S_G, glucose effectiveness.

lin secretion, glucose potentiation of arginine-induced insulin secretion, and arginine-induced glucagon-secretion following hemipancreatectomy [8]. Surprisingly, despite these striking abnormalities in islet secretion, hemipancreatectomized human donor subjects maintain glucose values identical to control subjects during short-term glucose infusion [8]. These observations led us to propose that donor subjects might maintain normal glucose homeostasis following hemipancreatectomy through a compensatory increase in their rates of glucose disposal.

In the fasting state, glucose disposal occurs largely through glucose-mediated mechanisms [9]. Postprandially, or following insulin infusions, insulin-mediated glucose uptake becomes the dominant process through which glucose enters cells. Alterations in either glucose-mediated or insulin-mediated glucose uptake could allow healthy donor subjects to maintain normal glucose homeostasis despite diminished insulin secretory capacity following a reduction in their beta-cell mass. Consequently, we measured both glucose-mediated and insulin-mediated glucose uptake in hemipancreatectomized healthy human donor subjects characterized by non-diabetic glucose tolerance tests and diminished insulin secretion. In our study we used a 2-day hyperinsulinaemic clamp protocol with euglycaemia maintained on day 1 and hyperglycaemia with a concurrent somatostatin infusion maintained on day 2. Insulin-mediated glucose uptake was measured during the first day of the protocol and compared with the glucose disposal rates measured on the second day which allowed for a calculation of glucose-mediated glucose uptake. These measures of glucose turnover were then compared to measures of insulin sensitivity (S_I) and glucose effectiveness (S_G) determined by the minimal model technique.

Subjects and methods

Patient selection. Hemipancreatectomized subjects were recruited from patients at the University of Minnesota who had served as pancreas donor subjects for family members with IDDM. As of 1 January 1993, 77 individuals have undergone this procedure, the details of which are included in a previous publication [7]. Healthy control subjects were selected to match the donor subjects with respect to age, sex, and body mass index. These studies were approved by the Committee on the Use of Human Subjects in Research at the University of Minnesota and all the participants provided written consent.

Glucose tolerance and insulin secretion studies. Glucose tolerance was assessed through measurement of serum glucose concentrations obtained following ingestion of 1.75 g glucose $\cdot$ kg body weight⁻¹, as previously described [7]. Insulin secretion was measured as serial serum insulin values obtained at -5, 0, 2, 3, 4, and 5 min after the administration of 20 g of glucose as an intravenous bolus [8].

Hyperinsulinaemic clamp studies. All testing was performed at the General Clinical Research Center at the University of

Minnesota following a 10–12 h overnight fast. Three intravenous catheters were placed in each subject more than 120 min before the first sample was drawn. One catheter was placed in an antecubital vein for the infusion of glucose (as 50 % dextrose) and insulin. A contralateral hand vein was cannulated retrogradely and served as the source for blood samples. In order to arterialize the venous blood, the hand bearing the catheter for blood sampling was placed in a warming chamber set at 55–60 °C 30 min before the first sample was obtained and held there for the duration of the study. A forearm vein proximal to the hand vein was cannulated for the continuous infusion of trace amounts of [3-³H]-glucose (NEN-Dupont, North Billerica, Mass., USA) and potassium phosphate. Subjects were instructed to remain supine for the duration of the study. The hyperinsulinaemic euglycaemic clamp (day 1) was performed at least 1 day and not more than 5 days before the hyperinsulinaemic hyperglycaemic clamp study (day 2).

On the first day of study, subjects were given a bolus of [3-³H]-glucose (6 μ Ci) at -120 min followed by continuous infusion at a rate of 6 μ Ci/h for the duration of the test. The insulin infusion (Humulin, Eli Lilly, Indianapolis, Ind., USA) was begun at time 0 and three sequential infusion rates of insulin were administered: 0.25 mU $\cdot$ kg⁻¹ $\cdot$ min⁻¹ for 180 min, then 1.0 mU $\cdot$ kg⁻¹ $\cdot$ min⁻¹ for 120 min, and then 10.0 mU $\cdot$ kg⁻¹ $\cdot$ min⁻¹ for the final 120 min. Euglycaemia was maintained at 5.3 mmol/l by a variable infusion of 50 % dextrose that was adjusted according to plasma glucose determinations made at 5-min intervals. The dextrose used to maintain euglycaemia was radiolabelled with [3-³H]-glucose to bring it to the same specific activity as the subject's plasma at the end of the 120-min isotopic equilibration period. The specific activity (SA) of the subject's plasma was estimated by the equation:

$$SA = \frac{F}{(\text{Basal rate endogenous glucose production}) (\text{kg body weight})}$$

where: SA = dpm/mg glucose

F = flow rate of isotopic tracer

Basal rate of endogenous glucose production
~ 2 mg $\cdot$ kg⁻¹ $\cdot$ min⁻¹

Infusions of insulin and [3-³H]-glucose were delivered by Harvard pumps (Model 22 Multi, Harvard Apparatus, South Natick, Mass., USA). Blood samples were obtained every 20 min for later determination of insulin and specific activity.

On the second day of study, a clamp procedure was performed as on day 1 except that somatostatin was administered throughout the experimental period. The goal infusion rate of somatostatin was 0.16 μ g $\cdot$ kg⁻¹ $\cdot$ min⁻¹ and subjects were brought up to this rate within 60 min depending on their tolerance to the drug. The somatostatin infusion was well tolerated by both the donor and the control subjects. On day 2 two sequential insulin infusion rates were administered: 0.25 mU $\cdot$ kg⁻¹ $\cdot$ min⁻¹ for 180 min followed by 1.0 mU $\cdot$ kg⁻¹ $\cdot$ min⁻¹ for 120 min. Hyperglycaemia was maintained at 11.1 mmol/l throughout the study day. Urine was collected during the experimental period for later determination of glucose excretion during hyperglycaemia.

Minimal model evaluation. Some subjects were also evaluated using the minimal model technique [10]. For these examinations, subjects were studied in the morning after an overnight fast. Intravenous catheters were placed in each arm and the arm containing the sampling catheter was placed in a warming chamber set at 55–60 °C 30 min before the first sample was drawn. Four baseline samples for glucose and insulin were obtained before glucose was administered intravenously at a dose of 300 mg $\cdot$ kg⁻¹ (given as 50 % dextrose) over 1 min at

Table 1. Subject characteristics

	Sex (Male/Female)	Age (years)	Body mass index (kg/m ²)	Fasting glucose (mmol/l)	Months since pancreas donation
Hyperinsulinaemic clamp protocol					
Control subjects	0/12	38 ± 4	24.0 ± 1.0	5.1 ± 0.01	–
Donor subjects	0/12	40 ± 3	24.9 ± 1.1	5.5 ± 0.15	75 ± 13
Minimal model protocol					
Control subjects	2/3	45 ± 5	26.4 ± 1.3	5.4 ± 0.2	–
Donor subjects	2/3	45 ± 4	26.4 ± 1.4	5.5 ± 0.3	117 ± 14

Table 2. Glucose tolerance and islet hormones in hemipancreatectomized donor subjects

Subject	Oral glucose tolerance test Glucose (mmol/l)					Fasting insulin (pmol/l)	Fasting glucagon (ng/l)	Acute insulin response to intra venous glucose (pmol/l)
	Min –5	30	60	90	120			
1	5.7	9.5	6.4	6.6	6.8	30	53	114
2	6.4	10.2	10.3	10.0	10.8	72	83	54
3	5.4	10.5	7.8	7.7	7.4	84	75	378
4	5.8	9.7	9.0	8.4	8.4	42	125	90
5	5.0		4.3	8.0	8.2	36	90	312
6	5.7	6.9	9.7	9.4	9.2	90		
7	5.7	9.8	11.1	11.9	8.3	36	53	42
8	4.7	10.4	9.1	8.8	7.0	43		
9	5.4	10.9	11.8	10.3	9.2	54	109	234
10	5.4	7.7	9.2	8.7	6.7	30	132	180
11	6.2	7.6	12.1	13.1	9.8	36		114
12	5.7	11.1	13.3	11.3	10.8	54		102
Mean	5.6	9.5	9.5	9.5	8.6	51	90	162
SEM	0.1	0.4	0.7	0.5	0.4	6	11	36

time 0. Samples for glucose and insulin were then obtained at min 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 19. At min 20 tolbutamide was administered intravenously over 30 s. Subjects with a body mass index less than 30 kg/m² were given 300 mg of tolbutamide whereas subjects with a body mass index greater than 30 kg/m² were given 500 mg tolbutamide. Additional samples for glucose and insulin were then drawn at min 22, 24, 25, 27, 30, 40, 60, 70, 90, 100, 120, 140, 160, and 180.

Assays. Plasma glucose values were measured immediately using a Beckman Glucose Analyser (Fullerton, Calif., USA). Other measurements were made using frozen serum that had been separated from whole blood within 30 min after the sample was obtained. Serum insulin was determined by radioimmunoassay using a double antibody method [11]. Samples for glucagon were collected into pre-chilled tubes containing 2.5 mg EDTA and 500 U Trasylol (Miles, Inc., FBA Pharmaceuticals, West Haven, Conn., USA) per milliliter and centrifuged immediately. Glucagon was measured by radioimmunoassay [12] with antibody 04A obtained from Dr. R. H. Unger (University of Texas, Dallas, Tx., USA). Serum specific activity was determined after deproteinization [13, 14].

Data analysis

Data are presented as the mean and SEM. The acute insulin response to glucose was calculated as the mean of the peak three values minus the basal insulin concentration. Glucose turnover rates were calculated using the equations of Steele [15], as modified by DeBodo [16]. Glucose-mediated glucose uptake

was determined as the difference in the rate of glucose disappearance measured between the euglycaemic (day 1) and hyperglycaemic (day 2) clamp studies during the final 40 min of the period during which insulin was infused at 1.0 mU · kg⁻¹ · min⁻¹. Correction for urinary glucose excretion on day 2 was unnecessary since no glucose was detected in the urine of subjects during this protocol. Insulin sensitivity and glucose effectiveness were calculated using the MINMOD program (copyright R.N. Bergman, 1986) from the data obtained using the minimal model protocol. Differences between groups were determined using non-parametric analysis or ANOVA where appropriate. A *p* value of < 0.05 was considered statistically significant.

Results

Subject characteristics. Twelve human donor subjects were studied using the hyperinsulinaemic clamp protocol 75 ± 13 months following hemipancreatectomy (Table 1). All had non-diabetic responses (eight normal, four impaired, according to National Diabetes Data Group criteria) to the ingestion of 1.75 g glucose · kg ideal body weight⁻¹ and diminished acute insulin responses to glucose (Table 2). On average, the donor subjects were within 5 kg of their pre-operative weight and all were eating a normal diet. Twelve healthy control subjects were selected to match the

Fig. 1. Glucose and insulin values during hyperinsulinaemic euglycaemic clamp. Twelve donor subjects (■) and 12 control subjects (□) were clamped at approximately 5.3 mmol/l glucose (left panel) for 420 min. Insulin was infused at a rate of $0.25 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ from min 0–180, a rate of $1.0 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ from min 180–300, and a rate of $10.0 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ from min 300–420. No differences were observed in the glucose and insulin values in donor and control subjects during the entire clamp study

donor subjects with respect to sex, age, and body mass index (Table 1). The fasting glucose values in the donor group were normal, but significantly higher than in the control subjects (5.5 ± 0.15 vs 5.1 ± 0.01 mmol/l, donor subjects vs control subjects, $p = 0.005$). Five donor subjects were studied using the minimal model protocol. They were studied 117 ± 14 months following donation and were matched to five healthy control subjects (Table 1). Fasting glucose values in this group of five donor subjects were also normal and were not different from control subjects (5.5 ± 0.3 vs 5.4 ± 0.2 mmol/l).

Hyperinsulinaemic euglycaemic clamp. Both donor subjects and control subjects were clamped at a euglycaemic level during the sequential infusions of insulin on day 1 (Fig. 1). The serum specific activities achieved during this investigation are shown in Table 3. In response to hyperinsulinaemia, each group demonstrated an increase in the rate of glucose disappearance (R_d , Fig. 2) to a maximum value of $14.92 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in the donor subjects and $15.17 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in the control subjects during the final 40 min during which insulin was infused at a rate of $10.0 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. No differences were found in the R_d values measured in donor subjects and control subjects.

Table 3. Specific activity

Protocol day	Time (min)	Donor subjects		Control subjects	
		Mean $\pm$ SEM		Mean $\pm$ SEM	
1	-10	1315	99	1041	200
	-5	1283	103	1020	195
	0	1292	86	1016	189
	20	1368	75	1057	194
	40	1486	72	1127	205
	60	1579	74	1198	216
	80	1641	65	1263	229
	100	1727	50	1306	240
	120	1789	64	1322	242
	140	1798	72	1320	239
	160	1793	76	1329	241
	180	1824	69	1381	252
	200	1865	60	1415	260
	220	1788	77	1344	246
	240	1688	89	1288	238
	260	1596	80	1209	224
	280	1521	66	1121	207
	300	1518	65	1114	205
	320	1479	73	1072	199
	340	1445	70	1046	193
	360	1404	69	1025	187
	380	1378	69	1005	185
	400	1413	79	1022	185
	420	1391	78	959	195
2	-10	1164	51	769	208
	-5	1208	61	792	214
	0	1253	90	818	215
	20	1325	87	843	219
	40	1385	57	875	236
	60	1407	65	882	237
	80	1409	69	907	244
	100	1496	54	974	266
	120	1502	60	970	264
	140	1498	65	977	265
	160	1545	55	1014	279
	180	1584	69	1039	282
	200	1581	65	1029	279
	220	1569	58	998	273
	240	1549	72	976	262
	260	1510	72	948	253
	280	1469	65	915	246
	300	1443	67	895	240

Fig. 2. Glucose turnover rates during hyperinsulinaemic euglycaemic clamp. Twelve donor subjects (■) and 12 control subjects (□) were clamped at approximately 5.3 mmol/l glucose for 420 min. Insulin was infused at rate of 0.25 mU · kg⁻¹ · min⁻¹ from min 0–180, a rate of 1.0 mU · kg⁻¹ · min⁻¹ from min 180–300, and a rate of 10.0 mU · kg⁻¹ · min⁻¹ from min 300–420. During these stepped sequential infusions of insulin both donor subjects and control subjects displayed similar increases in their rates of glucose disappearance (left panel) and decreases in their rates of the hepatic glucose production (right panel)

Rates of HGP were noted to decrease in each group following start of the insulin infusion (Fig. 2). Donor subjects and control subjects demonstrated complete suppression of HGP by insulin administered at a rate of 1.0 mU · kg⁻¹ · min⁻¹. No differences were found between the subject groups in the HGP measured during the period of study.

Hyperinsulinaemic hyperglycaemic clamp. A subset of eight donor subjects and eight control subjects completed both the euglycaemic and hyperglycaemic hyperinsulinaemic clamp studies. The serum specific activities achieved during this investigation are shown in Table 3. On the second study day both donor subjects and control subjects were clamped at approximately 11.1 mmol/l during the sequential infusions of insulin on day 2 (Fig. 3). The insulin levels measured were the same in each group and not different from the insulin values achieved during the euglycaemic clamp study (Fig. 3). Both donor subjects and control subjects demonstrated increasing R_d values as the insulin levels were elevated during day 2 (Fig. 3). No differences were found in the rates of R_d between the subject groups during the hyperglycaemic clamp study.

Glucose-mediated glucose uptake. Glucose-mediated glucose uptake (ΔR_d), which is equal to the difference between the R_d values measured during the euglycaemic and hyperglycaemic clamps performed at the same insulin infusion rate, was found to be the same in both donor and control groups. The ΔR_d value at the infusion rate of 1.0 mU · kg⁻¹ · min⁻¹ was 3.82 ± 1.01 mg · kg⁻¹ · min⁻¹ in donor subjects and 6.09 ± 1.24 mg · kg⁻¹ · min⁻¹ in control subjects ($p = \text{NS}$).

Minimal model. The index of insulin sensitivity (S_I) measured in five donor subjects was $11.1 \pm 6.0 \cdot 10^{-5}$ min⁻¹ · pmol/l⁻¹. This was not different from the S_I measured in five matched control subjects ($10.5 \pm 3.8 \cdot 10^{-5}$ min⁻¹ · pmol/l⁻¹, $p = \text{NS}$). Similarly, no increase in glucose effectiveness (S_G) was found in the donor subjects compared to control subjects ($2.1 \pm 0.6 \cdot 10^{-2}$ min⁻¹ vs $5.1 \pm 0.3 \cdot 10^{-2}$ min⁻¹; donor subjects vs control subjects, $p = \text{NS}$).

Discussion

Hemipancnectomy in healthy human donor subjects causes a decrease in glucose- and arginine-induced insulin secretion and diminished glucose potentiation of arginine-induced insulin secretion [8]. Despite these abnormalities, most donor subjects maintain normoglycaemia during daily living [7] and have serum glucose responses to prolonged infusions of glucose that are identical to those of control subjects [8]. This study was designed to determine whether normoglycaemia is maintained in donor subjects through an increase in rates of insulin- or glucose-mediated glucose uptake. We hypothesized that such an increase could be a mechanism through which healthy hemipancnectomized humans com-

Fig. 3. Glucose, insulin and glucose disappearance rates during hyperglycaemic hyperinsulinaemic clamps in hemipancreatectomized human donor subjects and control subjects. Eight donor subjects (■) and 8 control subjects (□) underwent hyperglycaemic clamps at insulin infusion rates of $0.25 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 180 min followed by $1.0 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 120 min on two separate days. Somatostatin ($0.16 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was infused from 0 to 300 min. Serum concentrations of glucose (top panel), insulin (middle panel), and rates of glucose disappearance were not different between hemipancreatectomized donor subjects and control subjects

compensate for diminished insulin secretion following reduction of beta-cell mass. From our investigation we have found that healthy hemipancreatectomized human donor subjects appear to maintain normal rates

of glucose turnover during a hyperinsulinaemic euglycaemic clamp, a process that is largely determined by insulin-mediated glucose uptake, and have normal rates of glucose-mediated glucose uptake. Donor subjects and control subjects were also found to have similar values for insulin sensitivity and glucose effectiveness using the minimal model protocol. These findings demonstrate that these methods do not detect the compensatory increases in insulin- or glucose-mediated hepatic or peripheral glucose disposal that we hypothesized to exist in human donor subjects. Therefore, the question remains: how do healthy hemipancreatectomized human donor subjects maintain normoglycaemia after a reduction of the pancreatic mass by half?

One potential mechanism underlying our findings can be understood by recognizing that human donor subjects lose not only half of their beta-cell mass following hemipancreatectomy, but half of their alpha-cell mass as well. Unlike dogs or rodents where alpha cells are concentrated in the tail of the pancreas and beta cells are concentrated in the head [17] humans have an equal distribution of both cell types throughout their pancreas [18]. Therefore, surgical excision of portions of the pancreas does not alter the relative amounts in glucagon and insulin secretory cells remaining in the organ remnant. If both hormones are secreted in the same appropriate physiologic balance after hemipancreatectomy as before, normal glucose tolerance and normal rates of glucose turnover may be maintained. We have previously demonstrated that arginine-induced glucagon secretion is markedly impaired in human donor subjects to a degree similar to that with which arginine-induced insulin secretion is altered [8]. It is thus possible that the maintenance of balanced glucagon and insulin secretion following organ donation allows for the normal rates of glucose turnover observed in healthy hemipancreatectomized subjects. Support for our thesis can be found in the report by Magnusson and colleagues [19] examining the effect of an 85 % pancreatectomy on insulin sensitivity in individuals suffering from carcinoma of the pancreatic head. These investigators found similar responses to bolus infusions of insulin before and after surgery and concluded that insulin action is not altered after a reduction in beta-cell mass, perhaps because of an equal decrease in glucagon and insulin secretion. However, other investigators have suggested that it is not the relationship between glucagon and insulin values that is important in the regulation of glucose turnover, but the absolute level of insulin that determines the rates of HGP and glucose utilization [20]. The applicability of these studies to our own are uncertain since they were performed in dogs under short-term experimental conditions, rather than in humans with prolonged relative hypoinsulinaemia and hypoglucagonaemia. Perhaps in the situation we studied the ratio of insu-

lin to glucagon assumes a more important role in the regulation of glucose metabolism than in the canine model studied previously. Indeed, investigations in totally pancreatectomized humans suggest that absolute glucagon levels may be more important in the overall regulation of glucose turnover than was once thought [21].

Another possible explanation for our findings is that the techniques used, while representing the standards with which to measure insulin action, are insufficiently precise to measure small but physiologically relevant differences in glucose turnover rates between our two subject groups. As recently suggested by Kahn and colleagues [22], a hyperbolic relationship may exist between measures of beta-cell function and insulin sensitivity in a healthy population such that changes in insulin secretion may have relatively small effects on insulin sensitivity if the S_I exceeds the median for a normal population [22]. Based on this model, healthy normoglycaemic individuals of average body mass, such as the donor subjects prior to hemipancreatectomy, would be expected to have a sufficiently high S_I to experience little change in response to even significant changes in beta-cell function. Therefore, a more precise method may be necessary to determine if donor subjects experience a difference in glucose turnover after hemipancreatectomy. Alternatively, examination of insulin secretion and glucose disposal under more physiologic circumstances than the hyperinsulinaemic clamp or the minimal model protocol, such as ingestion of a radioisotopically-labelled meal [23], may be required to more sensitively address whether donor subjects compensate for diminished beta-cell function by increasing insulin- or glucose-mediated glucose uptake following hemipancreatectomy.

In conclusion, hemipancreatectomy in healthy human donor subjects does not appear to alter insulin-mediated or glucose-mediated glucose uptake as determined by hyperinsulinaemic clamp and minimal model methodologies. Thus, our data indicate that donor subjects can maintain normal glucose tolerance without making compensatory changes in HGP or peripheral glucose uptake despite a markedly diminished insulin secretory response to glucose and arginine. The mechanisms through which hemipancreatectomized humans maintain euglycaemia remain uncertain, but may involve maintenance of normal glucagon to insulin ratios or small but physiologically relevant changes in glucose metabolism which are undetectable by the methods employed in our investigation.

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