Effect of Venous Drainage Site on Insulin Action After Pancreas Transplantation in the Rat—Is There Insulin Resistance and a Risk for Atherosclerosis?

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The aim of the present study was to determine the influence of the venous drainage site on insulin homeostasis and the possible risk for atherosclerosis development after pancreas transplantation. We studied inbred rats that received pancreas transplants with either systemic (STX) or portal (PTX) venous drainage after prior induction of diabetes with streptozotocin and sham-operated controls. The observation period was 6 months. Fasting plasma glucose and insulin levels were similar in all 3 groups, but fasting plasma glucagon levels were elevated in STX (mean ± SEM, 282 ± 35 ng/L) in comparison to PTX rats (119 ± 9 ng/L, $P < .05$), although the difference versus the control group (191 ± 31 ng/L) was insignificant. Glucose utilization and hepatic glucose production (HGP), assessed by a dose-response euglycemic-hyperinsulinemic clamp in combination with tritiated glucose infusion, were similar in all 3 groups. The groups were also similar with respect to the molar ratio of plasma C-peptide and insulin during basal steady state and the metabolic clearance rate (MCR) of insulin during the clamp studies, suggesting an unchanged hepatic insulin extraction (HIE) after transplantation with either technique. Factors known to be related to atherosclerosis, ie, blood pressure, intracellular magnesium, and fasting levels of plasma cholesterol, triglycerides, and high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, were similar in all 3 groups. Light microscopy of the aorta showed a slightly thicker intima in STX rats (24.3 ± 0.5 μm, $P < .05$) versus PTX rats (21.4 ± 0.7 μm) and control (21.4 ± 0.6 μm); however, atherosclerosis-like lesions were absent in all 3 groups. In conclusion, in a rat model with streptozotocin-diabetes and pancreas transplantation but no need for immunosuppression, both systemic and portal venous drainage avoid peripheral and hepatic insulin resistance; also, there is no increased risk for atherosclerosis.

HYPERINSULINEMIA in the presence of insulin resistance leads to an increase in risk factors for cardiovascular disease.[1-4] Since diabetic patients have an increased risk for macrovascular disease, pancreas transplantation should aim to avoid the development of combined hyperinsulinemia and insulin resistance. However, pancreas transplantation denervates the pancreas, which may lead to increased insulin secretion since the suppression of insulin secretion by insulin itself is neurally mediated.[5,6] Moreover, immunosuppression, which is vital for the survival of the graft in clinical transplantation, also adversely affects insulin sensitivity.[7-9] Reduced hepatic clearance of insulin resulting from systemic venous drainage of the pancreas is thought to be largely responsible for hyperinsulinemia in pancreas-transplanted type 1 diabetic patients, and might be prevented by pancreas transplantation with portal venous drainage. Published studies of pancreas transplantation, which is normally performed heterotopically with systemic venous drainage, vary with regard to changes in insulinemia and insulin sensitivity. Thus, the development of hyperinsulinemia and insulin resistance has been reported,[10-14] as well as minimal changes in insulin sensitivity in combination with basal hyperinsulinemia[15-18] or normoinsulinemia.[19] To interpret these divergent observations more closely is difficult due to the fact that the circumstances under which they were made varied, ie, involved different degrees of damage to the transplant during storage and transplantation leading to variations in the viability of the β-cell mass, an uncertain state of reinnervation of the denervated transplant, and immunosuppression.

Against this background, a study was designed using an inbred rat model. The major aim was to show whether portal venous drainage is superior to systemic venous drainage after heterotopic pancreas transplantation in comparison to normal controls in terms of the development of risk factors known to predispose to atherosclerosis independently of immunosuppression. We measured basal plasma insulin and glucagon levels, insulin sensitivity by an insulin dose-response clamp, the metabolic clearance rate (MCR) of insulin by the constant infusion technique, and blood pressure, intracellular magnesium, and blood lipids. The aorta was examined for intimal thickening and atherosclerosis-like lesions. Our results indicate that neither transplantation technique is associated with an increased risk for atherosclerosis.

MATERIALS AND METHODS

All studies were designed in conformity with the National Research Council Guide[20] and the current German Law on the Protection of Animals, and all were approved by the Governmental Animal Care and Use Committees.

Experimental Groups

Highly inbred (synonymous syngeneic) 12-week-old male Wistar-Lewis rats (N = 46) weighing between 280 and 320 g (Charles River Breeding Laboratories, Sulzfeld, Germany) were used. Organ transplants among these rats are uniformly accepted without rejection. The animals were housed in an environmentally controlled room with a 12-hour light/dark cycle and had free access to standard rat chow (Altromin, Lage, Germany) and water. After a 1- to 2-week acclimatization period, the rats were randomly assigned to one of 3 groups: sham-operation, ie, laparotomy only (controls, n = 17), pancreas transplantation with portal venous drainage (PTX, n = 14), or pancreas transplantation with systemic venous drainage (STX, n = 15). All operations were performed under ether anesthesia.

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Induction of Diabetes

Ten days before transplantation, PTX and STX rats were rendered diabetic by a single intraperitoneal injection of streptozotocin (60 mg/kg body weight; Fluka, Neu-Ulm, Germany). Only rats with a blood glucose level greater than 11.1 mmol/L, urinary glucose above 2.2 mmol/24 h, and significantly increased water and food intake and urine output on the fifth day after induction of diabetes were included in the experiment.

Whole Pancreas Transplantation

The pancreas was transplanted using a modification of the technique described by Klempnauer and Settje.[21] In short, the pancreaticoduodenal graft was harvested from an age-matched donor rat with a segment of the aorta from the celiac axis and the superior mesenteric artery supplying the graft, and also a segment of the portal vein for venous drainage. Portal venous drainage was obtained by end-to-side anastomosis between the donor portal vein and recipient superior mesenteric vein, and systemic venous drainage by end-to-side anastomosis between the donor portal vein and recipient infrarenal caval vein. The aortic segment of the graft was anastomosed end-to-side to the recipient infrarenal aorta. An ellipsoidal patch of the graft duodenum adjacent to the junction of the bile duct with the duodenum was isolated and anastomosed end-to-side to the middle portion of the recipient duodenum.

Metabolic Studies

Once per month except during the clamp studies, the rats were transferred to individual metabolic cages for 24 hours. Body weight (BW), food and water intake, fecal weight, and urinary volume were recorded. Aliquots of urine were stored at −30°C.

Euglycemic Clamp Study

Insulin-mediated whole-body glucose uptake was measured in awake, unstressed chronically catheterized rats using the euglycemic clamp in combination with tritiated glucose infusion in a modification of the technique described by Smith et al.[22] Four months after pancreas transplantation or sham-operation, the rats were anesthetized with ether, and indwelling catheters were inserted in the left carotid artery and both jugular veins. The venous catheters were advanced to the level of the right atrium, and the arterial catheter to the level of the aortic arch. The rats were allowed at least 7 days to recover from the effects of surgery. All studies were performed in the morning after 12 hours of food deprivation. External catheters (Thomafluid-Silikon-Hochtemperatur-Chemieschlauch High Flexible, 0.5 mm ID × 0.9 mm OD; Reichelt Chemietechnik, Heidelberg, Germany) were connected to the indwelling catheters and suspended overhead by means of a pulley system. The left venous line was used for infusion of a 25% glucose solution (Braun, Melsungen, Germany) at a variable rate, and the right venous line was used for a combined infusion of tritiated glucose (Amersham Buchler, Braunschweig, Germany; specific activity 488 GBq/mmol, high-performance liquid chromatography–purified ~99.2%) and saline or porcine insulin (Insulin S; Hoechst, Frankfurt am Main, Germany) at a constant rate (1,000 μL/h). Glucose was infused using a Precidor pump (infusion pump model 5003; Infors, Basel, Switzerland). Tritiated glucose and saline or insulin were infused from a reservoir (Eppendorf cup) with the aid of a peristaltic roller pump (Micro-Perpex Pumpe LKB 2132; LKB, Bromma, Sweden). The arterial blood-sampling tubing permitted frequent sampling. To prevent blood volume depletion, an equivalent volume of washed erythrocytes resuspended in saline was administered after each sampling. The total volume of blood drawn during the experiment was less than 6 mL. The hematocrit was measured at the beginning and end of each study and averaged 0.38 ± 0.01 and 0.39 ± 0.01, respectively. Sixty minutes before starting the insulin clamp, a primed (111 kBq)-continuous (3.7 kBq/min) infusion of tritiated glucose was started and continued throughout the study. Plasma samples for the determination of tritiated glucose specific activity were obtained at −30 minutes of this equilibration period and then every 5 minutes until time 0, when the insulin infusion began. The insulin infusion rate varied over a 20-fold range (14, 22, 29, 86, and 129 $pmol \cdot kg^{-1} \cdot min^{-1}$) to obtain increments in plasma insulin of approximately 359, 718, 1,435, 3,588, and 7,175 pmol/L. Repeat studies were performed at 5-day intervals as established by Smith et al.[22] No radioactivity was detectable in plasma samples from restudied rats before the start of the repeat clamp study. It must be noted that only those animals were studied again which had a normal hematocrit and regained more than their prestudy BW. Seventeen animals were studied once, 23 twice, and 6 three times. After starting the tritiated glucose infusion, a steady state of glucose specific activity was achieved at 30 minutes and again at 90 minutes from the start of the insulin infusion, confirming previous reports.[22,23] During the insulin clamp, plasma samples for glucose measurement were obtained at 10-minute intervals for the first 80 minutes and then at 5-minute intervals up to 100 minutes, at which time the clamp ended. At time points -25, -20, and -15 minutes and 3 times at 5-minute intervals during the last 15 minutes of the clamp, blood samples were collected for measurement of tritiated glucose, plasma glucose, plasma insulin, and plasma C-peptide.

Blood Pressure

Measurements were performed noninvasively using the tail-cuff method in the conscious resting state, once per week during the midmorning after the clamp study.[24]

Collection of Blood and Tissue

At the end of the study, ie, 6 months after pancreas transplantation or sham-operation, food was withheld for 12 hours overnight, after which the animals underwent a laparotomy under ether anesthesia and exsanguination from the aorta. Blood samples were collected into prechilled tubes containing either no additive or 2.5 mg EDTA and 500 U Trasylol per 1 mL blood to obtain serum and plasma. The pancreata and aortas were quickly removed, immediately frozen in liquid nitrogen, and stored at −30°C together with serum and plasma.

Analytical Procedures

Plasma and urine glucose levels were measured by the glucose oxidase method (Glucose Analyzer 2; Beckman Instruments, Munich, Germany). Basal and plasma immunoreactive insulin from blood samples obtained after porcine insulin infusion in the clamp studies were measured by radioimmunoassay[25] using rat and porcine insulin as a standard, respectively. This method of sample processing was justified because during all steps of the porcine insulin infusion, plasma levels of C-peptide were near the lower limit of detectability, demonstrating suppression of endogenous insulin secretion in all groups. Plasma glucagon, C-peptide, and pancreatic polypeptide (PP) levels were also measured by radioimmunoassay.[26-28] Plasma tritiated glucose radioactivity was measured in duplicate on the supernatants of barium hydroxide-zinc sulfate precipitates (Somogyi procedure) of plasma samples after evaporation to dryness to eliminate ^3H_2O. Two separate aliquots of the tracer infusate underwent the Somogyi procedure and were counted together with the plasma samples for 10 minutes in a liquid scintillation spectrophotometer. In specimens from the ventral and dorsal pancreas (host and graft pancreas of 5 PTX and 9 STX rats, respectively, and pancreas of 9 controls) extracted by boiling in 0.5 mol/L acetic acid as described by Byrant and Bloom,[29] insulin content was measured by radioimmunoassay using rat insulin as a standard,[25] and extracted total protein using the Coomassie Plus Protein assay reagent (Pierce, Rockford, IL). Routine methods were used for serum and urine creatinine (Autoanalyzer; Technicon, Frankfurt, Germany), total choles-

terol (commercial kit CHOD-iodide method; Merck Diagnostik, Darmstadt, Germany), and triglycerides (commercial kit; Böhringer Mannheim Diagnostika, Mannheim, Germany). For measurement of high-density lipoprotein (HDL) cholesterol, a precipitation reagent was used (Böhringer Mannheim Diagnostika). Intracellular magnesium in red blood cells was measured by atomic absorption spectrometry using the method described by Abraham and Lubran.[30]

After thawing, parts of the ascending aorta were fixed in 10% neutral Formalin, embedded in paraffin wax, and sectioned. Deparaffinized and hydrated sections were subsequently stained with hematoxylin and eosin. The thickness of the aortic intima was evaluated by light microscopy using an ocular micrometer. To obtain objective data, intima thickness was assessed at 4 randomly selected sites in 4 sections of the aorta. Thus, intima thickness was measured at 48 sites from controls, 20 from PTX rats, and 28 from STX rats.

Calculations and Statistics

Data for total-body glucose uptake and suppression of hepatic glucose production (HGP) represent the mean of values during the last 15 minutes (85- to 100-minute period) of the insulin clamp studies, because during this period the specific activity of glucose was at a steady-state plateau. During this steady state when the rate of glucose appearance (Ra) is equal to the rate of glucose disappearance (Rd), the total-body glucose uptake (= Ra = Rd in micromoles per minute) was calculated by dividing the tritiated glucose infusion rate (cpm per minute) by the steady-state value of glucose specific activity (cpm per millimole). Under these conditions, total-body glucose uptake is equal to the sum of the rates of exogenous infusion of glucose and HGP. From this equation, the rate of HGP can be calculated. The validity of the measurement of HGP by tritiated glucose infusion and the reproducibility of the euglycemic clamp studies in the rat have been shown previously.[22,31]

The MCR of insulin measured by the constant infusion technique was calculated by dividing the infusion rate of insulin by the mean steady-state insulin concentration.[32] This calculation is based on the assumption that endogenous insulin production is suppressed during insulin infusion, as evidenced by a decrease of C-peptide to values near the detection limit. Basal hepatic insulin extraction (HIE) was calculated from the molar ratio of C-peptide and insulin during the basal steady state. Insulin content of the pancreas is expressed as the ratio of insulin and protein (picomoles per milligram); the data represent the mean for the values from the dorsal and ventral pancreas, because they were similar.

Low-density lipoprotein (LDL) cholesterol was calculated as follows: LDL cholesterol (millimolars) = serum total cholesterol − (serum triglyceride/2.2) − serum HDL cholesterol. Creatinine clearance was calculated using the standard formula.

The red blood cell magnesium concentration (R, in millimolars) was calculated using the formula[30] $R = P + 100(W - P)/H$, where P (millimolars) and W (millimolars) are the magnesium concentration of plasma and hemolyzed whole blood, respectively, and H is the hematocrit expressed as a percentage.

All values are presented as the mean ± SEM. Statistically significant differences ($P < .05$) between groups were determined using 1-way ANOVA in conjunction with the Student-Newman-Keuls test.

RESULTS

General Characteristics of the Animals

The BW of the transplanted groups and controls is shown in Fig 1, and was similar in all 3 groups before transplantation or sham-operation and after surgery. This is reflected by the similar water and food consumption, feces weight, and urine volume in all groups (Fig 1). Creatinine clearance was similar in all 3

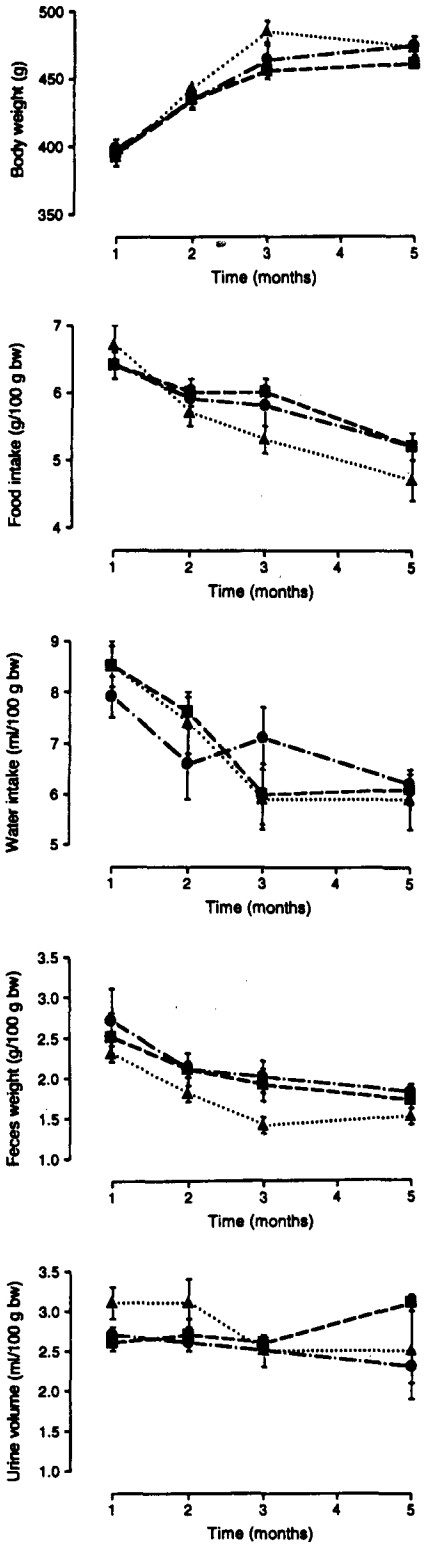

Fig 1. Change in BW, food and water intake, feces wet weight, and urine volume in control (■), PTX (▲), and STX (●) rats. Data are the mean ± SEM.

Table 1. Fasting Glucose Homeostasis

Group	No. of Rats	Glucose (mmol/L)	Insulin (pmol/L)	Glucagon (ng/L)	Insulin to Glucagon Ratio (mmol/mmol)	PP (pmol/L)
Control	8	5.55 ± 0.11	151 ± 43	191 ± 31	3.5 ± 1.1	6.36 ± 1.15
PTX	4	5.44 ± 0.17	129 ± 29	119 ± 9	3.0 ± 1.1	14.22 ± 2.37
STX	9	5.55 ± 0.11	265 ± 50	282 ± 35*	4.2 ± 1.1	15.89 ± 4.45

NOTE. Data are the mean ± SEM.
*$P < .05$ *v* PTX.

groups (controls, 0.21 ± 0.02 mL · min^{-1} · 100 g BW^{-1}; PTX, 0.27 ± 0.06; STX, 0.22 ± 0.03). Twenty-four-hour urine glucose excretion measured in these urine samples was less than 11.1 μmol/100 g BW, and excludes a recurrence of diabetes in the transplanted animals.

The insulin content of the host pancreata in transplanted rats was less than 6% of the mean content of the pancreata in control rats (controls, 170 ± 30 pmol/mg, n = 9; PTX, 4 ± 1 pmol/mg, n = 5; STX, 10 ± 2 pmol/mg, n = 9; $P < .05$ *v* controls, respectively), demonstrating that the streptozotocin-damaged β cells of the host pancreata did not functionally recover after transplantation. The insulin content of the graft pancreata in PTX and STX rats, although widely scattered, was statistically indistinguishable from that in the control rats (PTX, 123 ± 25 pmol/mg, n = 5; STX, 309 ± 76 pmol/mg, n = 9). The high tissue insulin content of STX rats likely reflects insulin stimulated via concomitantly high glucagonemia (described later). Fasting plasma glucose, insulin, and PP concentrations were similar in all groups, and fasting plasma glucagon was significantly higher in STX versus PTX rats, but the fasting molar insulin to glucagon ratio remained statistically unchanged (Table 1). This latter finding can be explained by the also slightly higher insulin concentration in STX animals, indicating further that in STX rats, the higher glucagon and higher insulin levels are likely due to the loss of first-pass extraction by the liver.

Euglycemic Insulin Clamp

Basal and steady-state plasma glucose, its specific activity, and insulin concentrations were similar in the 3 groups (Table 2). The coefficients of variation for steady-state plasma glucose and insulin were 6% ± 0.5% and 23% ± 1%, respectively.

Basal HIE, expressed as the molar ratio of basal steady-state C-peptide and insulin, was similar in STX (1.7 ± 0.6), PTX (1.5 ± 0.2), and control rats (1.7 ± 0.4). The MCR of insulin was also similar in all groups (Fig 2).

The glucose infusion rate during the insulin clamp is shown in Fig 3. In all studies, the mean glucose infusion rate reached a plateau 70 to 100 minutes after the start of the insulin infusion. All 3 groups had similar glucose infusion rates during steady

Table 2. BW, Glucose, Insulin, C-Peptide, HGP, and Specific Activity of Glucose During Euglycemic Clamp Studies

	Insulin Infusion Rate (pmol · kg^{-1} · min^{-1})					
Group	0	14	22	29	86	129
Control						
No.	32	6	7	7	6	6
BW (g)		429 ± 15	442 ± 15	414 ± 9	428 ± 13	427 ± 9
SSPG (mmol/L)	5.23 ± 0.06	5.83 ± 0.06	5.50 ± 0.39	5.77 ± 0.28	5.61 ± 0.33	5.94 ± 0.06
SSPI (pmol/L)	187 ± 14	409 ± 43	782 ± 86	1,148 ± 115	2,224 ± 208	5,597 ± 674
SSPCP (pmol/L)	358 ± 48	57 ± 4	38 ± 5	46 ± 6	44 ± 3	35 ± 7
HGP (pmol · kg^{-1} · min^{-1})	35.0 ± 1.1	18.3 ± 8.3	11.1 ± 8.9	12.2 ± 5.5	27.2 ± 11.7	0 ± 11.7
SA (cpm/mmol)	69.33 ± 2.45	29.42 ± 1.93	31.98 ± 3.03	25.90 ± 2.26	23.49 ± 3.44	23.76 ± 1.14
PTX						
No.	28	6	5	5	6	6
BW (g)		410 ± 9	440 ± 6	422 ± 13	440 ± 8	437 ± 8
SSPG (mmol/L)	5.16 ± 0.11	6.21 ± 0.06	5.94 ± 0.11	5.94 ± 0.06	5.83 ± 0.17	5.77 ± 0.11
SSPI (pmol/L)	230 ± 22	452 ± 36	1,119 ± 57	1,306 ± 129	3,286 ± 387	6,070 ± 825
SSPCP (pmol/L)	335 ± 34	99 ± 2	41 ± 5	42 ± 7	43 ± 7	33 ± 5
HGP (pmol · kg^{-1} · min^{-1})	35.5 ± 1.7	16.6 ± 5.5	16.1 ± 10.5	7.8 ± 5.5	20.5 ± 7.2	5.5 ± 10.5
SA (cpm/mmol)	68.33 ± 3.10	38.22 ± 3.63	24.36 ± 4.60	26.36 ± 1.43	23.51 ± 2.25	23.60 ± 2.50
STX						
No.	33	6	7	7	7	6
BW (g)		406 ± 10	442 ± 15	418 ± 10	441 ± 12	418 ± 16
SSPG (mmol/L)	5.0 ± 0.11	5.55 ± 0.28	5.88 ± 0.11	6.11 ± 0.11	5.83 ± 0.11	5.44 ± 0.33
SSPI (pmol/L)	194 ± 14	337 ± 43	710 ± 50	918 ± 86	2,425 ± 280	5,905 ± 882
SSPCP (pmol/L)	293 ± 86	55 ± 8	50 ± 6	53 ± 6	45 ± 6	35 ± 6
HGP (pmol · kg^{-1} · min^{-1})	34.4 ± 1.1	16.1 ± 6.7	12.8 ± 6.7	8.9 ± 8.3	12.2 ± 7.2	8.9 ± 12.2
SA (cpm/mmol)	70.44 ± 2.48	34.63 ± 2.30	31.89 ± 1.95	27.20 ± 2.01	23.02 ± 0.12	23.08 ± 1.95

NOTE. Data are the mean ± SEM.
Abbreviations: SSPG, steady-state plasma glucose; SSPI, steady-state plasma insulin; SSPCP, steady-state plasma C-peptide; SA, steady-state plasma glucose specific activity.

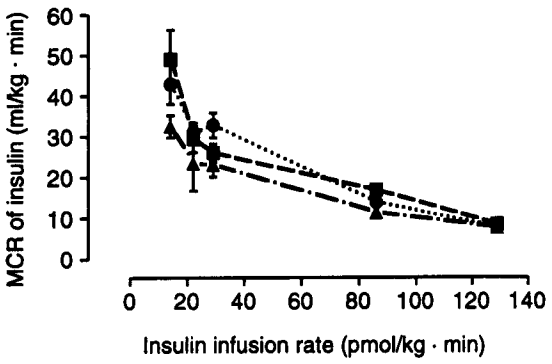

Fig 2. Effect of euglycemic insulin infusion on the MCR of insulin in control (■), PTX (▲), and STX (●) rats. Data are the mean ± SEM.

state (final 15 minutes of the clamp) at the respective clamp levels (Fig 4A).

Figure 4B shows the dose-response relationship between the plasma insulin concentration and whole-body glucose uptake. In all 3 groups, tissue glucose uptake was similar at all insulin concentrations examined. Basal levels were 35.0 ± 1.1 μmol · kg^{-1} · min^{-1} in controls, 35.5 ± 1.7 in PTX rats, and 34.4 ± 1.1 in STX rats at a basal insulin concentration of about 215 pmol/L. Tissue glucose uptake increased to 73.8 ± 7.8, 78.2 ± 8.9, 89.3 ± 6.7, 111.0 ± 11.7, and 98.2 ± 8.9 μmol · kg^{-1} · min^{-1} in controls, to 57.7 ± 6.1, 73.8 ± 10.5, 86.6 ± 5.0, 96.6 ± 11.7, and 93.2 ± 9.4 μmol · kg^{-1} · min^{-1} in PTX rats, and to 68.8 ± 5.5, 72.7 ± 6.1, 86.0 ± 5.5, 98.8 ± 7.8, and 98.2 ± 9.4 μmol · kg^{-1} · min^{-1} in STX rats at a steady-state plasma insulin concentration of about 359, 718, 1,076, 2,870, and 5,740 pmol/L, respectively.

Thus, the effect of hyperinsulinemia on tissue glucose uptake increased in a sigmoidal shape until it reached a maximum at about 2,870 pmol/L. Half-maximal stimulation was calculated from averaged group values and found to be similar in all 3 groups (509, 459, and 581 pmol/L in controls, PTX, and STX, respectively).

After 12 hours of food deprivation overnight, no significant difference in HGP was found between the 3 groups (Table 2). Suppression of HGP was therefore similar in all groups.

Indicators of Atherosclerosis Development

Fasting serum levels of cholesterol, triglycerides, and HDL and LDL cholesterol, as well as intracellular magnesium, and blood pressure were similar in all 3 groups (Table 3). The thickness of the aortic intima in STX rats (24.3 ± 0.5 μm) was slightly but significantly ($P < .05$) greater than that in controls (21.4 ± 0.6 μm) and PTX rats (21.4 ± 0.7 μm). However, structures representing atherosclerosis-like lesions as ascribed to hyperinsulinism in rats, ie, eosinophilic fiber bundles, deposition of amorphous ground substances, and irregularly arranged cells containing a long oval nucleus,[33] were not detected in the intima or the subendothelial aortic tissue in the 3 groups.

DISCUSSION

In the present investigation, an insulin dose-response euglycemic clamp study was unable to detect insulin resistance in pancreas-transplanted rats with either systemic or portal venous drainage in comparison to sham-operated controls. After pancreas transplantation with either technique, the dose-response curves for glucose uptake were similar to those in control rats in response to increasing levels of insulin. No difference could be detected in basal endogenous glucose production and suppression of HGP with increasing insulin levels. However, it must be noted that the insulin infusion rates may have been too high to obtain a close assessment of HGP. Statistically, the nadir for

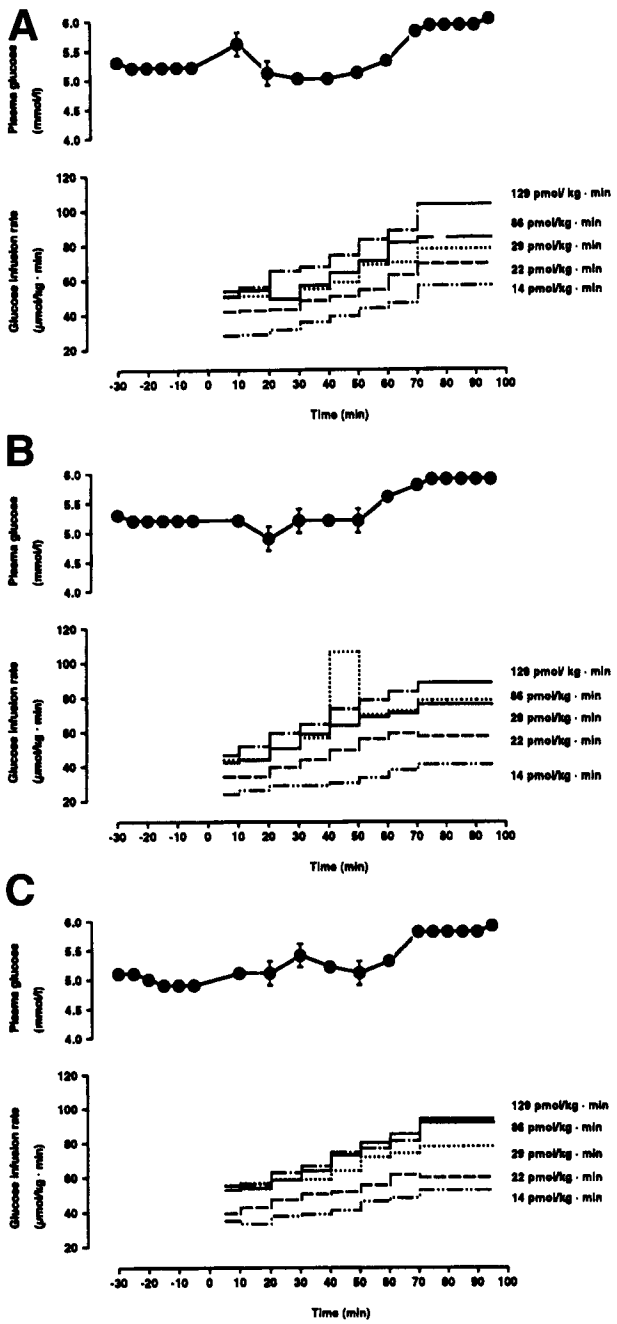

Fig 3. Plasma glucose and exogenous glucose infusion rate in 32 insulin clamp studies in 17 control rats (A), 28 studies in 14 PTX rats (B), and 33 studies in 15 STX rats (C). Data are the mean ± SEM. Insulin infusion rates are indicated.

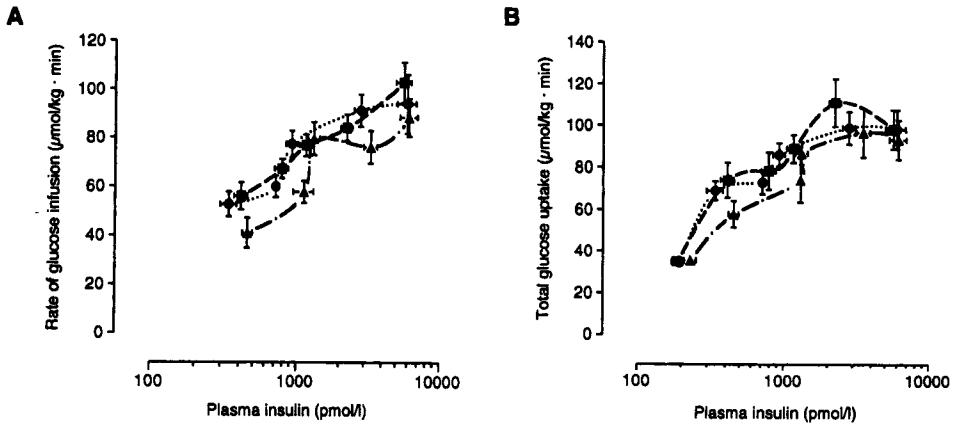

Fig 4. Dose-response relationship between plasma insulin concentration and glucose infusion rate during the steady state of the euglycemic clamp studies (A) and insulin-mediated glucose uptake (B) in control (■), PTX (▲), and STX (●) rats. Data are the mean ± SEM.

HGP is probably 14 $pmol \cdot kg^{-1} \cdot min^{-1}$. Therefore, more low-dose insulin infusions would have been useful. In addition, a statistical difference in HGP hardly could have been detected with the variation in HGP and the small number of observations made. Basal plasma insulin, lipids, intracellular magnesium, blood pressure, and aortic histology were similar in all groups, thus ruling out a higher risk for atherosclerosis after pancreas transplantation with either systemic or portal venous drainage.

The results of this insulin dose-response clamp study can be compared with the findings of Smith et al[22] and Rossetti and Giaccari.[34] Both studies evaluated insulin sensitivity in conscious unrestrained rats (BW 300 g) after an overnight fast. Insulin was infused at 5 doses, each of which produced a plateau of insulin concentrations ranging from physiological to pharmacological. In the study by Smith et al,[22] the half-maximally effective insulin concentration for glucose uptake was between 502 and 574 pmol/L, which is in accordance with our findings (509 pmol/L in controls). However, in both studies, the maximal rate of insulin-mediated glucose uptake was twice as high (~200 $\mu mol \cdot kg^{-1} \cdot min^{-1}$) as the 100 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ measured in our controls. These findings would imply that the rats in our study are insulin-resistant in comparison to those in the other studies. However, we interpret the difference as reflecting a slightly decreased responsiveness to insulin, which may be due to the higher BW and age of our animals.

To our knowledge, only one insulin dose-response euglycemic-hyperinsulinemic clamp after pancreas transplantation has been reported thus far.[10] In that study, pancreas-kidney transplant recipients with systemic delivery of insulin were compared with nondiabetic kidney transplant recipients undergoing similar immunosuppression and with nondiabetic control subjects. Insulin resistance was found in pancreas-kidney transplant recipients, attributed mainly to immunosuppression and, to a smaller degree, to chronic peripheral hyperinsulinemia. The causes for insulin resistance were found to be a reduced insulin sensitivity and a reduced responsiveness, which were primarily due to reduced insulin-stimulated nonoxidative glucose metabolism in peripheral tissues. At the hepatic level, insulin sensitivity was reduced only in the basal state, whereas in response to insulin, the sensitivity and responsiveness of HGP was normal in pancreas-kidney transplant recipients. In our study, neither peripheral nor hepatic insulin resistance was found after heterotopic pancreas transplantation with systemic venous drainage. The discrepancy between our study and that of Christiansen et al[10] can be explained by (1) the avoidance of immunosuppression in our study through the use of an inbred strain of rats, and (2) the absence of significant basal hyperinsulinemia after transplantation with systemic venous drainage.

In other studies of pancreas-kidney transplant recipients with systemic venous drainage, hyperinsulinemia and insulin resistance also have been shown.[11-14,17,35-37] The hyperinsulinemia in these patients was apparent in the basal state and during stimulation of endogenous insulin secretion and was ascribed mainly to reduced HIE by systemic drainage that bypassed the liver.[13,14] The endogenous pancreatic secretion of insulin was not investigated in our study, because Lück et al[38] have already shown that after glucose challenge, streptozotocin-diabetic rats with systemic venous drainage of the pancreas graft are hyperinsulinemic in comparison to both normal rats and recipients of pancreas grafts with portal venous drainage. The immunosuppression used in pancreas-kidney transplantation induces insulin resistance that is thought to be due to a decrease in both hepatic and extrahepatic insulin sensitivity.[17,35] However, Rooney and Robertson[37] implicated hepatic insulin resistance in pancreas transplant recipients with systemic venous drainage independently of immunosuppression, because basal HGP and the HGP response to glucagon infusion were significantly higher in pancreas recipients than in healthy control subjects but similar in healthy control subjects and kidney recipients receiving the same immunosuppressive agents. Fi-

Table 3. Indicators for Atherosclerosis Risk

Group	No. of Rats	Blood Pressure (mm Hg)	Red Blood Cell Magnesium (mmol/L)	Cholesterol (mmol/L)	Triglycerides (mmol/L)	HDL Cholesterol (mmol/L)	LDL Cholesterol (mmol/L)
Control	10	124 ± 6	1.5 ± 0.1	2.5 ± 0.1	0.75 ± 0.05	1.29 ± 0.13	0.91 ± 0.13
PTX	6	122 ± 10	1.6 ± 0.1	2.2 ± 0.1	0.56 ± 0.05	1.16 ± 0.13	0.83 ± 0.16
STX	8	130 ± 6	1.7 ± 0.1	2.3 ± 0.2	0.71 ± 0.07	1.09 ± 0.16	0.88 ± 0.10

NOTE. Data are the mean ± SEM.

nally, glucose metabolism is also dependent on β-cell function, which has been shown to be altered after pancreas transplantation.[35,36] Thus, the discrepancies between the results of different studies may be due to variations among protocols for immunosuppressive agents and surgical preparations resulting in a varying viable β-cell mass.

Previous studies on streptozotocin-diabetic rats with either systemic or portal venous drainage after pancreatic islet transplantation[19,40] or rats with portal-caval vein transposition[39] showed either hyperinsulinemia and insulin resistance in rats with systemic venous drainage and portal-caval vein transposition, respectively,[39,40] or normal insulinemia and no change in insulin sensitivity in rats with portal venous drainage[40] and systemic venous drainage.[19] However, the interpretation of the results after portal-caval transposition in rats is confounded by the systemic delivery of nutrients and gastrointestinal hormones. The variable findings after islet cell transplantation in rats may be due to the different degrees of correction of glucose tolerance.

Studies involving dogs are also inconclusive, because after transposition of the venous drainage of the pancreas to the systemic circulation, either insulin sensitivity remained merely unchanged despite peripheral hyperinsulinemia[41,42] or insulin resistance developed.[43] Discrepancies between the studies may be due to the fact that in the two former studies,[41,42] partial pancreatectomies of various degrees were performed, concealing the effect of the site of drainage alone.

However, in all published studies except Christiansen et al,[10] no insulin dose-response clamp study was performed. Thus, it was not possible to characterize the mechanism of insulin resistance, ie, reduced insulin sensitivity and/or reduced responsiveness to insulin, and the presence of insulin resistance may have been underestimated or even undetected.[44]

In the present study, systemic venous drainage was associated with only slightly higher basal plasma insulin levels versus those found in controls and PTX animals. This is in line with other studies involving streptozotocin-diabetic rats after pancreaticoduodenal transplantation[45] and pancreatic islet transplantation,[19,40] because in those studies a normal basal insulinemia was found with systemic venous drainage.

The slight elevation of basal plasma insulin in our study was large enough to counteract the higher plasma glucagon levels such that basal HGP remained normal. Basal hyperglucagonemia was also documented in other studies after pancreas transplantation with systemic venous drainage in diabetic patients[6,46-49] and streptozotocin-diabetic rats.[50,51] Since, in comparison to the controls, basal plasma glucagon levels were higher only with systemic venous drainage and remained unchanged with portal venous drainage, the higher basal plasma glucagon levels could be ascribed to decreased hepatic glucagon extraction as a result of direct systemic venous drainage bypassing the liver. This can be assumed, because normal hepatic glucagon extraction is about 20% to 25%.[52]

It should be noted that the mean plasma concentration of PP was high in our transplanted groups in comparison to the controls. This contrasts with the findings from the study by Brekke et al,[53] who found a significantly lower plasma PP concentration in streptozotocin-diabetic rats with systemic venous drainage of the pancreas graft. Since the graft pancreas was duct-ligated in that study,[53] whereas the exocrine drainage of the graft pancreas in our rats was restored to the duodenum, the difference in surgery may explain the discrepancy. It can be speculated that in our study the hyperplasia of PP cells and hypersecretion of PP, which are present in the streptozotocin-diabetic pancreas,[53] persisted in the host pancreas of our transplanted rats and accounted, at least in part, for the slightly higher fasting plasma PP concentrations. It can be assumed that plasma PP levels in our study were adequate after transplantation to normalize hepatic and peripheral insulin sensitivity, because it has been shown that PP is an important modulator of peripheral insulin action.[54]

Basal HIE was similar in all 3 groups in our study, contrasting with the findings of Osei et al,[11] who found a 70% and 60% decrease of HIE in pancreas-kidney transplant type 1 diabetic patients compared with kidney transplant patients and healthy control subjects, respectively. They attributed this finding to the direct systemic venous drainage of insulin that bypassed the first-pass extraction of insulin by the liver. However, changes in the half-life of C-peptide after kidney transplantation may have compromised the calculation of HIE from the basal molar ratio of C-peptide and insulin.[55,56] This might explain the discrepancy between our findings and those of Osei et al.[11]

To avoid the shortcomings of using the molar ratio of C-peptide and insulin to assess HIE, we measured the MCR of insulin by the constant infusion technique during the steady-state period of each clamp, and found no significant differences between the groups. However, it must be noted that the determination of the MCR was only made by central vein infusion of exogenous insulin and is thus incomplete, because it was not accompanied by studies of the MCR by exogenous insulin delivery via the portal system. Our insulin MCR data of 49 ± 7 mL · kg^{-1} · min^{-1} in controls during insulin infusion at 14 pmol · kg^{-1} · min^{-1} are in good agreement with the value reported by Guan et al[40] of 47 ± 7 mL · kg^{-1} · min^{-1} in normal conscious rats of comparable BW during porcine insulin infusion at 10 pmol · kg^{-1} · min^{-1}. However, in the latter study, the insulin MCR was significantly decreased after renal subcapsular islet transplantation with systemic venous drainage in comparison to the controls and transplant recipients with portal venous drainage. A possible reason for this discrepancy vis-a-vis our study may be the different techniques of transplantation, ie, islet cells versus whole-organ transplantation.

In our study, plasma lipid levels were similar in all groups. Type 1 diabetic patients who received a kidney and heterotopic pancreas transplant with systemic venous drainage reportedly were hyperinsulinemic but also had low postprandial lipemia and high HDL cholesterol.[57-60] The favorable lipid profile was attributed to an increased lipoprotein lipase activity in fatty tissue, which leads to an excellent triglyceride clearing capacity.[60] However, Falholt et al[61,62] showed that pancreatectomized dogs with systemic venous drainage of pancreatic autografts developed hyperinsulinemia together with markedly increased key enzymes of lipid synthesis and triglycerides in arterial smooth muscle, whereas portal insulin delivery in the same animal model resulted in normoinsulinemia and normal lipid synthesis in arterial smooth muscle. Insulin concentrations have

been shown to be positively correlated with a risk of coronary artery disease in the presence of insulin resistance.[3,63] Thus, it can be speculated that hyperinsulinemia and insulin resistance may also contribute to atherogenesis even when lipid levels are normal after pancreas transplantation.

In addition to the lack of change in lipids as an atherosclerosis risk factor and blood pressure, the magnesium concentration in erythrocytes was unchanged by pancreas transplantation with either type of venous drainage in the present study. It is worth noting that in the metabolic syndrome characterized by frequent atherosclerosis, low red blood cell magnesium and hyperinsulinemia coexist.[4]

The aortic intima thickness of 21.4 ± 0.6 μm in our controls is comparable to that reported by Sato et al[33] (19.2 ± 1.6 μm) in Wistar rats receiving daily subcutaneous saline injections. In the latter study, rats rendered hyperinsulinemic by daily insulin injection had double the aortic intima thickness of saline-injected controls after 1 year. The insulin-treated animals also developed atherosclerosis-like lesions, ie, eosinophilic fiber bundles, amorphous ground substances, and irregularly arranged cells in the subendothelial aortic tissues. In the PTX and STX rats of our study, aortic intima thickness was comparable and atherosclerosis-like lesions were absent. This is readily explainable by the fact that in the study by Sato et al,[33] plasma insulin levels were increased 15-fold 4 hours after injection of insulin, whereas in our study, transplanted animals had similar basal plasma insulin levels and no sign of insulin resistance, which should have occurred in the case of excessive insulin release after transplantation.

In conclusion, after pancreas transplantation in the streptozotocin-diabetic rat model with either systemic venous or portal venous drainage, neither hepatic nor peripheral insulin resistance was detected using the insulin dose-response clamp technique. Systemic venous drainage after pancreas transplantation carries no increased risk for atherosclerosis in comparison to portal venous drainage in this animal model, in agreement with the lack of change in basal insulin and lipids, red blood cell magnesium, and blood pressure and the absence of atherosclerosis-like lesions.

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