Rats With Portal-Caval Vein Transposition Show Hyperinsulinemia and Insulin Resistance

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To compare the metabolic effects of portal and systemic delivery of insulin, we used portal-caval transposition (PCT) in rats to provide total systemic diversion of splanchnic venous blood. PCT rats exhibited normal weight gain, liver histology, liver-function tests, glycosylated hemoglobin, arterial blood pressure, and hepatic blood flow. Mean liver weight relative to body weight was 12% lower in PCT rats than in sham-operated control (CTR) rats 30 days following transposition. Indwelling venous catheters were established to facilitate metabolic studies in conscious, minimally restrained animals. Postabsorptive plasma glucose and C-peptide (CPEP) levels were similar in PCT and CTR rats; however, postabsorptive immunoreactive insulin (IRI) levels were elevated in PCT rats (67 ± 3.1 *v* 49 ± 3.5 pmol · L^{-1}, $P < .002$, n = 11 *v* 11), as were postabsorptive plasma glucagon levels (570 ± 67 *v* 240 ± 11 ng · L^{-1}, $P < .001$, n = 11 *v* 16) at similar body weights. The postabsorptive CPEP/IRI concentration ratio was lower in PCT than in CTR rats (4.0 ± 0.3 *v* 6.0 ± 0.6, $P < .02$), suggesting reduced hepatic extraction of insulin. Insulin sensitivity (IS), determined by minimal model analysis of frequently sampled intravenous glucose tolerance tests yielding the sensitivity index (SI), was reduced in PCT compared with CTR (61 ± 5.6 *v* 86 ± 9.0 (μmol · L^{-1})$^{-1}$ · min^{-1}, $P < .04$, n = 9 *v* 10). During euglycemic-hyperinsulinemic clamps, glucose infusion rates (GIRs) from 60 to 120 minutes were lower in PCT than in CTR rats (6.0 ± 0.3 *v* 8.0 ± 0.4 g · kg^{-1} · min^{-1}, $P < .002$, n = 9 *v* 7) with matching plasma IRI levels, confirming the reduced IS in PCT rats. Areas under the concentration curves ([AUCs] 0 to 150 minutes) for glucose tolerance tests (gavage) indicated that plasma glucose excursion was similar in PCT and CTR rats whereas AUC IRI was significantly higher in PCT than in CTR rats (23 ± 1.3 *v* 18 ± 0.6 nmol · L^{-1} · min, $P < .009$, n = 11 *v* 11). However, AUC CPEP for oral glucose tolerance tests was lower in PCT than in CTR rats (55 ± 3.4 *v* 68 ± 4.8 nmol · L^{-1} · min, $P < .05$), indicating decreased insulin secretion. Thus, the mean ratio AUC CPEP/AUC IRI was significantly lower in PCT rats (2.5 ± 0.2 *v* 3.8 ± 0.3, $P < .002$), again suggesting reduced hepatic extraction of insulin. Thus, euglycemia after PCT was accompanied by elevated postabsorptive and glucose-stimulated levels of IRI in systemic blood, postabsorptive hyperglucagonemia, and decreased insulin secretion in response to glucose challenge (gavage), with diminished hepatic extraction of insulin and decreased IS. The PCT model illustrates the insulin-resistant adaptive state that results from systemic delivery of insulin, and indicates the importance of hepatic portal delivery of insulin and possibly of other gastroenteropancreatic hormones in the maintenance of IS and physiological metabolic control.

IN RECENT-ONSET and chronic insulin-dependent diabetes mellitus in humans, conventional insulin therapy is associated with hyperinsulinemia[1] and insulin resistance.[2] During the clinical remission phase of the disease, exogenous insulin need decreases and insulin sensitivity (IS) improves. Subsequently, progressive loss of β-cell function is accompanied by recurrence of insulin resistance.[2-4] The findings in human recipients of pancreas transplants with systemic venous drainage[5-7] are consistent with the hypothesis that systemic delivery of insulin contributes to generation of insulin resistance, and observations in human recipients of pancreas[8] and islet[9,10] transplants with hepatic portal venous drainage support this hypothesis.

Most studies of systemic delivery of endogenous insulin have made use of surgical preparations in dogs, with systemic diversion of pancreatic venous effluent achieved by anastomosis of the pancreaticoduodenal or hepatic portal vein to the inferior vena cava[11-15] or by complete transposition of the portal and inferior caval veins.[11] Results of studies in animals with systemic diversion of the pancreaticoduodenal vein have been inconsistent. After end-to-side portal-caval anastomosis, with or without ligation of the portal vein, hepatic blood flow and function may be compromised, confounding interpretation.[13,16,17] Systemic diversion of the pancreaticoduodenal or portal veins in dogs did not modify glucose tolerance with[12,13] or without[11] alterations in the associated insulin responses. In rats, it has been reported that postabsorptive levels of insulin in systemic blood are normal after total diversion of hepatic portal blood to the systemic venous system, but these animals show exaggerated responses of plasma insulin during absorption of glucose from the intestine.[18] Among the studies in animals, only one documented plasma concentrations of insulin-connecting peptide (C-peptide [CPEP]), which were not significantly affected in the postabsorptive state in dogs with pancreaticoduodenal-caval vein anastomosis.[14] Inconsistencies among the findings may be related to liver atrophy, altered hepatic blood flow, nutritional status, and/or the interval from surgical preparation to study.

We have assessed surgical transposition of the portal vein and the inferior vena cava in rats as a procedure providing total systemic delivery of pancreatic venous effluent. The animals recover rapidly from the surgery, regaining normal rates of growth and maintaining euglycemia. We have examined this model in terms of glucose tolerance, pancreatic endocrine function, and IS to characterize the metabolic adaptation to systemic diversion of pancreatic endocrine secretions.

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Submitted February 20, 1995; accepted April 16, 1995.

Supported by grants from the Canadian Diabetes Association (501) and the Medical Research Council (MA2119).

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0026-0495/96/4501-0018$03.00/0

MATERIALS AND METHODS

Portal Caval Vein Transposition

Male Sprague-Dawley rats weighing 260 to 280 g (Charles River, St. Constant, Quebec, Canada) were housed in individual metal cages at 21°C on a 12-hour light-dark cycle. Standard rat chow (Prolab 3000; Agway, Syracuse, NY) and water were available ad libitum. Before surgery, food was withheld for 8 hours. Atropine (MTC Pharmaceuticals, Cambridge, Ontario, Canada) 0.05 mg · kg^{-1} injected intramuscularly and xylazine (Haver, Etobicoke, Ontario, Canada) 5 mg · kg^{-1} injected intraperitoneally were used as preanesthetics. Rats were anesthetized with 30 mg · kg^{-1} sodium pentobarbital (Maple Leaf Foods, Cambridge, Ontario, Canada) injected intraperitoneally. Surgery was performed on a warm-water heating pad. Through a midline incision, the portal vein and inferior vena cava were exposed. The portal vein was clamped above the pancreatic veins, and the inferior vena cava was clamped at the same level. After transection of these veins, the inferior stump of the vena cava was anastomosed end-to-end with the portal vein entering the liver using 10-0 silk and an operating microscope. Then the caudal stump of the portal vein was anastomosed to the cephalad stump of the vena cava in a similar manner (Fig 1). Total clamping time was less than 25 minutes. In sham-operated control (CTR) animals, the portal vein and inferior vena cava were transected and reanastomosed to simulate the procedure and ischemic time for the experimental animals with portal-caval transposition (PCT). After the anastomoses had been established, the veins were checked for intactness before closure of the incision. Saline was administered by tail vein as required to maintain hydration; heat lamps and the heating pad were used to support body temperature until recovery was complete. Buprenorphine (Reckitt and Colman Pharmaceuticals, Hull, UK) 2 mg · kg^{-1} injected intramuscularly was administered every 2 hours as required for 24 hours. Standard rat chow and 10% sucrose were provided ad libitum for 24 hours after surgery.

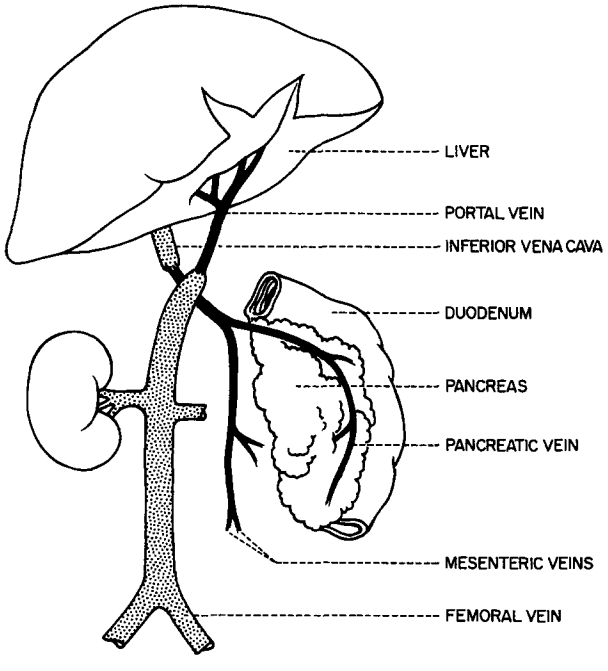

Fig 1. Portal-caval transposition.

Metabolic Tests

Following resumption of weight gain, indwelling silastic catheters (0.635-mm ID × 1.19-mm OD; Dow Corning, Midland, MI) were placed in the right jugular vein and the left femoral vein as previously described.[19] Studies were initiated between 9 and 10 AM in conscious animals with minimal restraint, 14 to 30 days after initial surgery and at least 3 days after placement of catheters. Before testing, food was withdrawn overnight. Rats were killed at 30 days after PCT or CTR surgery by intraperitoneal injection of 4 mol · L^{-1} urethane 3 mL · kg^{-1} (Sigma, St Louis, MO).

For glucose tolerance tests, 1.5 g glucose · kg^{-1} body weight was administered by gavage as a 25% dextrose solution in normal saline. Blood samples were withdrawn at −5, 10, 15, 20, 30, 45, 60, 90, 120, and 150 minutes with saline replacement. Two different protocols were used to determine IS. The first protocol was a modified frequently sampled intravenous glucose tolerance test,[19] in which an intravenous bolus of 32 μg · kg^{-1} somatostatin (Sigma) was administered 0.5 minutes before 0.3 g glucose · kg^{-1} at 0 minutes followed by 10 mg tolbutamide (Orinase Diagnostic; Upjohn, Kalamazoo, MI) in 0.2 mL saline at 5 minutes. Blood samples were withdrawn at −5, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 30, 45, 60, and 90 minutes. SI and the total glucose effectiveness index ([SG] glucose-dependent glucose disposal) were calculated by applying Bergman's minimal model[20] to the plasma glucose and insulin responses. The second protocol was the euglycemic-hyperinsulinemic clamp procedure described in rats by Kraegen et al.[21] Regular porcine insulin (U-100 R; Lilly, Indianapolis, IN) 10 nmol · kg^{-1} · min^{-1} was infused intravenously, and 10% dextrose solution was infused at a rate adjusted to maintain basal levels of whole-blood glucose determined at 5-minute intervals with a YSI Glucose Analyzer 2300 (YSI, Yellow Springs, OH). The mean glucose infusion rate from 60 to 120 minutes (GIR) was calculated for each test as the measure of IS. Blood samples were collected in tubes containing NaF (Sigma) and kept on ice before collection of plasma, which was stored at −20°C until analyzed.

Mean arterial blood pressure was determined in the right carotid artery of conscious rats[22] using a chronically placed polyethylene catheter (0.76-mm ID × 1.22-mm OD; Clay Adams, Parsipany, NJ) connected to a pressure transducer (model P-1000B; Narco Bio-Systems, Houston, TX) and a physiograph (model MK-II; Narco Bio-Systems). Hepatic blood flow was assessed by calculating the half-life of intravenous indocyanine green (Sigma).[23] In fed animals at time of death, blood samples were collected from portal and hepatic veins to determine the insulin gradient across the liver; arterial blood samples were obtained to determine plasma amino acid concentrations. All protocols were approved by the Animal Care Committee of the University of Western Ontario.

Assays

Plasma glucose concentrations were determined using a Beckman Glucose Analyzer II (Fullerton, CA) immediately following each experiment. Plasma immunoreactive insulin (IRI) level was measured by radioimmunoassay with dextran-coated charcoal separation using ^{125}I-insulin (Amersham Canada Limited, Oakville, Ontario, Canada), rat insulin from Novo (Copenhagen, Denmark), and insulin antibody from P. Wright (Cambridge, UK). Plasma immunoreactive glucagon was determined with ^{125}I-glucagon from Cedarlane (London, Ontario, Canada) and 30K antibody from R.H. Unger (The University of Texas Southwestern Medical School, Dallas, TX). Plasma immunoreactive CPEP was determined using a rat CPEP radioimmunoassay kit from Linco Research (St Louis, MO). Plasma amino acid concentrations were determined with a Beckman model 119CL single-column analyzer. Glycosylated hemoglobin was determined colorimetrically.[24] Total

Table 1. Postabsorptive Plasma Glucose, IRI, Immunoreactive CPEP, CPEP/IRI Concentration Ratio, Immunoreactive Glucagon, and Body Weight in PCT and CTR Rats 15 to 30 Days After Surgery (mean ± SE)

	Glucose (mmol · L^{-1})	IRI (pmol · L^{-1})	CPEP (nmol · L^{-1})	CPEP/IRI	Glucagon (ng · L^{-1})	Body Weight (g)
PCT	5.5 ± 0.1 (29)	67 ± 3 (11)	0.26 ± 0.01 (11)	4.0 ± 0.3 (11)	570 ± 67 (11)	280 ± 3 (29)
CTR	5.6 ± 0.2 (28)	49 ± 3 (11)	0.33 ± 0.04 (11)	6.0 ± 0.6 (11)	240 ± 11 (16)	290 ± 3 (28)
P	NS	.002	NS	.02	.0002	NS

NOTE. Sample sizes are shown in parentheses.

areas under the concentration curves (AUCs) were calculated geometrically. Statistical analysis comparing PCT and CTR rats was performed using Student's unpaired *t* test. *P* less than .05 was considered significant. All values are reported as the mean ± SE.

RESULTS

Presurgical weight was regained 3 to 4 days after surgery, and thereafter weight gain was similar in PCT and CTR rats. In the postabsorptive state, mean values for systemic plasma glucose and CPEP did not differ significantly between PCT and CTR rats, but mean values for plasma IRI and glucagon were significantly higher and mean values for the ratio of CPEP/IRI were significantly lower in PCT than in CTR rats (Table 1). At death, mean ratios of liver weight to body weight were 12% lower in PCT than in CTR rats (26 ± 0.4 *v* 30 ± 0.6 g · kg^{-1} body weight, respectively, $P < .05$, n = 18 *v* 15). Liver-function tests and histology were normal in both groups. Mean glycosylated hemoglobin did not differ in PCT and CTR rats (6.0 ± 0.3 *v* 6.4 ± 0.2%, n = 8 *v* 7). Mean arterial blood pressure in the carotid artery was not significantly different in PCT and CTR rats (93 ± 1.9 *v* 95 ± 2.0 mm Hg, n = 8 *v* 8). Indocyanine green half-life also was not significantly different in PCT and CTR rats (5.4 ± 0.2 *v* 5.1 ± 0.3 minutes, n = 11 *v* 11). In fed animals at time of death, we observed no significant concentration gradient between plasma IRI levels in portal and hepatic veins in PCT rats, whereas in CTR rats plasma IRI concentration in the portal vein was greater than in the hepatic vein (concentration gradient: PCT *v* CTR, −30 ± 33 *v* 240 ± 110 pmol · L^{-1}, $P < .02$, n = 9 *v* 5). Mean plasma arterial concentrations of amino acids in the fed state in PCT rats relative to CTR rats were lower for branched-chained amino acids (58 *v* 88 μmol · L^{-1} isoleucine, 90 *v* 144 leucine, and 107 *v* 171 valine), higher for aromatic amino acids (94 *v* 61 tyrosine, 86 *v* 44 phenylalanine) 383 *v* 212 glycine, and 495 *v* 289 alanine, $P < .02$, two-way ANOVA, and similar for the other amino acids, as well as for all amino acids in the postabsorptive state (n = 2 *v* 2 for each state).

Plasma glucose, IRI, and CPEP responses to glucose by gavage are shown in Fig 2. AUCs (0 to 150 minutes) show that the mean glucose excursions were similar in PCT and CTR rats (Table 2), whereas mean AUC plasma IRI was significantly elevated in PCT compared with CTR rats. For plasma CPEP responses, the mean AUC was lower in PCT than in CTR rats. As a result, the mean ratio of AUC CPEP/AUC IRI was significantly lower in PCT rats.

Mean values for plasma glucose responses in the frequently sampled intravenous glucose tolerance test were virtually identical in PCT and CTR rats (Fig 3), as were the AUCs. Mean values for AUC IRI (0 to 30 minutes) were significantly higher in PCT compared with CTR rats (25 ± 1.3 *v* 19 ± 1.7 nmol · L^{-1} · min, $P < .05$). Minimal model analysis applied to these data showed significantly lower values for SI in PCT than in CTR rats; no difference was noted in values for SG (Table 3). Results qualitatively consistent with the SI values were obtained with the euglycemic-hyperinsulinemic clamp technique. During the steady state from 60 to 120 minutes, plasma IRI was similar in PCT and CTR rats (160 ± 18 *v* 130 ± 11 pmol · L^{-1}), mean plasma glucose values were clamped at postabsorptive levels (5.4 ± 0.2 *v* 5.5 ± 0.2 mmol · L^{-1}), and GIR for PCT rats was lower than for CTR rats (Fig 4). The mean GIRs (Table 3) demonstrate that SI was significantly decreased in PCT compared with CTR rats.

DISCUSSION

After PCT, rats in the present study resembled dogs subjected to this procedure in earlier studies,[11,13,16] maintaining normal glycemia with normal growth, total hepatic blood flow, and liver function. The modest reduction in wet weight of the liver relative to body weight in PCT rats may

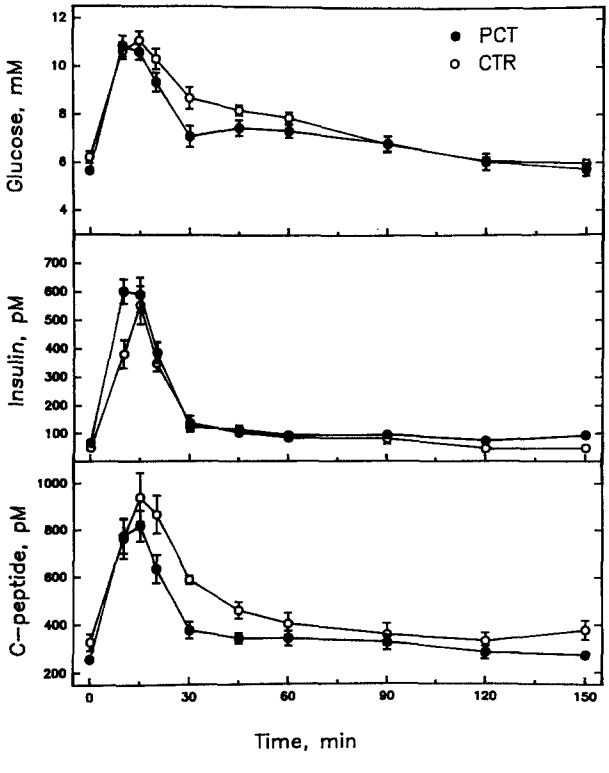

Fig 2. Plasma glucose, IRI, and immunoreactive CPEP responses to glucose 1.5 g · kg^{-1} by gavage in 11 PCT and 11 CTR rats (mean ± SE).

Table 2. AUC (0 to 150 minutes) for Plasma Glucose, IRI, and CPEP Responses to Gavage Glucose and AUC CPEP/AUC IRI in 11 PCT and 11 CTR Rats (mean ± SE)

	Glucose (mol · L^{-1} · min)	IRI (nmol · L^{-1} · min)	CPEP (nmol · L^{-1} · min)	CPEP/IRI
PCT	1.1 ± 0.04	23 ± 1.3	55 ± 3.4	2.5 ± 0.2
CTR	1.1 ± 0.03	18 ± 0.6	68 ± 4.8	3.8 ± 0.3
P	NS	.009	.05	.002

be due to decreased exposure to trophic effects of gastroenteropancreatic hormones and nutrients that normally reach the liver in portal blood at relatively high concentrations. Presumably because blood flow to the liver is maintained in PCT rats, the severe liver atrophy noted in end-to-side portal-caval anastomosis is not present in our model.

In this study, we tested the hypothesis that systemic diversion of pancreatic endocrine secretions results in insulin resistance. Because the surgical preparation might influence interpretation of measures of IS, we assessed this quantity both by minimal model analysis dependent on the effect of endogenous insulin and by the euglycemic clamp technique using exogenous insulin. Identification of SI by minimal model analysis depended on temporary inhibition of the insulin response to intravenous glucose by somatostatin, followed by stimulation of endogenous secretion of insulin by tolbutamide. The appropriateness of minimal model analysis in these animals could be questioned, both

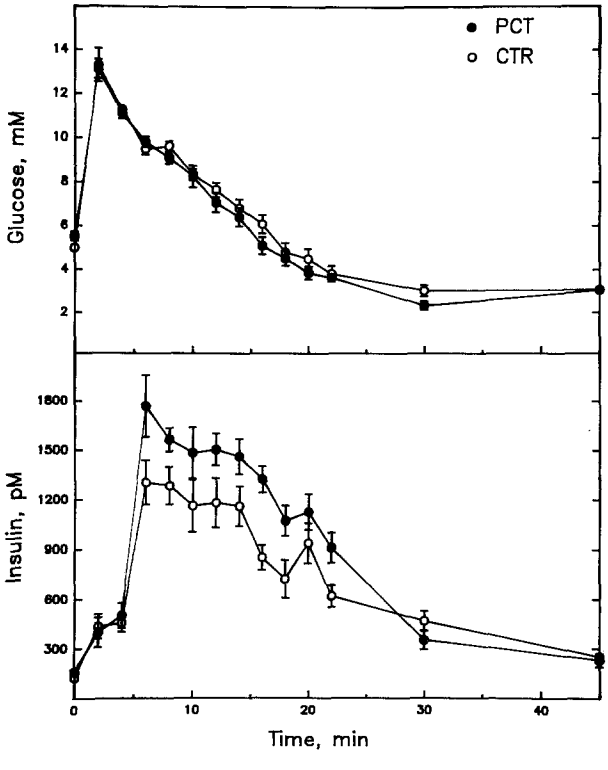

Fig 3. Plasma glucose and IRI responses to a modified frequently sampled intravenous glucose tolerance test with 32 μg · kg^{-1} intravenous somatostatin, 0.5 minutes before 0.3 g glucose · kg^{-1} as 10% glucose, followed by 10 mg tolbutamide at 5 minutes, in 9 PCT and 10 CTR rats (mean ± SE).

Table 3. SI and SG, and GIR, in PCT and CTR Rats (mean ± SE)

	SI ((μmol · L^{-1})$^{-1}$ · min^{-1})	SG (min^{-1})	GIR (mg · kg^{-1} · min^{-1})
PCT	61 ± 5.6 (9)	4.7 ± 0.41 (8)	6.0 ± 0.3 (9)
CTR	86 ± 9.0 (10)	4.4 ± 0.27 (10)	8.0 ± 0.4 (7)
P	.04	NS	.002

NOTE. Sample sizes are shown in parentheses.

because of the lack of hepatic-portal delivery of endogenous insulin in PCT rats and because apparently passive early-phase hyperinsulinemia resulting from PCT might invalidate the model. However, the presence of insulin resistance was confirmed by the euglycemic-hyperinsulinemic clamp studies. For this assessment, exogenous insulin and glucose were delivered via the femoral catheter in PCT rats and reached the liver at relatively high concentration in portal-diverted caval vein blood. The technique thus reproduced the physiological condition, with relatively high concentrations of insulin and glucose arriving at the liver via the portal route. This would presumably favor physiological action of the hormone in PCT rats, given that similar systemic blood levels of IRI were achieved in PCT and CTR rats; however, under these conditions the GIR necessary for maintenance of euglycemia was significantly reduced in PCT rats. Thus, both measures of IS demonstrated that systemic diversion of pancreatic endocrine secretions is associated with moderate insulin resistance.

The PCT model diverts first-pass nutrient flux, as well as pancreatic endocrine secretions, and this condition may in

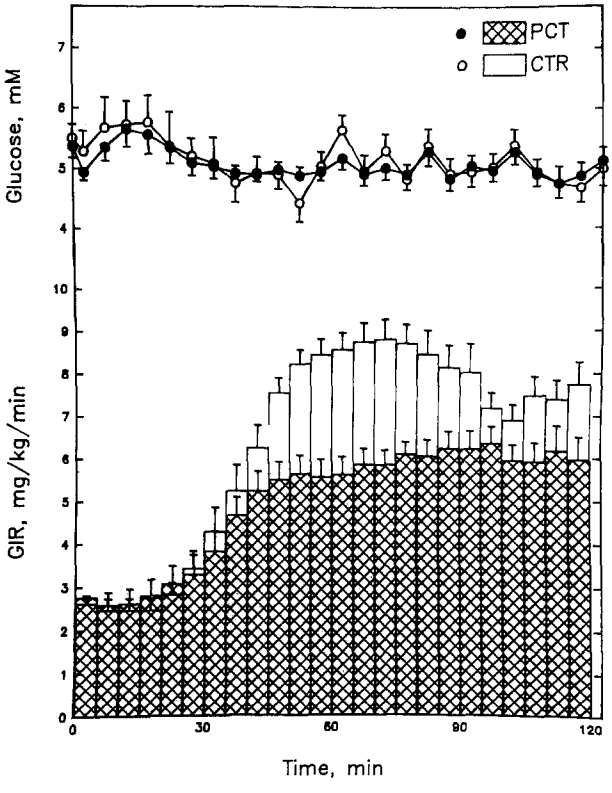

Fig 4. Plasma glucose and GIR during intravenous infusion of insulin 10 nmol · kg^{-1} · min^{-1} and varying rates of 10% glucose to maintain euglycemia in 9 PCT and 7 CTR rats (mean ± SE).

itself have an impact on IS and glucose tolerance. Indeed, net hepatic glucose uptake in dogs was higher with portal rather than peripheral glucose delivery.[25] The amino acid results may also reflect route-related effects in addition to alterations imposed by insulin and glucagon. However, in diabetic dogs treated with pancreatic autotransplants delivering insulin into the peripheral circulation, abnormalities in glucose, lactate, pyruvate, and alanine were noted although nutrient flux was via the normal portal route.[26] Furthermore, SG was not affected in PCT rats, a finding previously reported in type I diabetes in humans with peripherally vascularized pancreatic grafts.[6] Thus, the diversion of first-pass nutrient flux in PCT rats may partially account for apparent alterations in SI.

With respect to the cause of the modest hyperinsulinemia in PCT rats, the reduction of CPEP/IRI concentration ratios, both in the postabsorptive state and in response to administration of glucose by gavage, is consistent with diminished hepatic extraction of insulin after PCT. However, if these abnormalities are viewed simply as a result of systemic diversion of an abnormally high proportion of insulin released by the pancreas, with diminished hepatic extraction of the hormone, interpretation in physiological terms calls for explanation of the failure of insulin secretion to decrease to levels that would prevent systemic hyperinsulinemia. The observed equilibrium presumably results from regulatory mechanisms serving the requirements of peripheral and hepatic tissue for exposure to appropriate blood levels of insulin and glucagon in postabsorptive and postprandial states. Exposure of peripheral insulin-sensitive tissues to elevated concentrations of insulin could lead to increased glucose disappearance, and to compensatory hypersecretion of glucagon to enhance hepatic glucose production under postabsorptive conditions. Few previous studies of systemic diversion of pancreatic vein blood in surgical preparations in animals have documented plasma glucagon levels. In dogs with portal-caval anastomosis and ligation of the portal veins, the mean concentration of glucagon in systemic blood was elevated, but this abnormality was not statistically significant.[12] Systemic hyperglucagonemia was also absent in dogs with anastomosis of the pancreaticoduodenal vein to the portal venous system.[13] Nor is it clear whether glucose turnover is normal in animals with systemic diversion of portal or pancreatic vein blood. Only two animal studies of portal systemic diversion have documented tracer-determined glucose turnover, and results of these studies, both in dogs with pancreaticoduodenal-systemic vein anastomoses, were conflicting. In one, glucose turnover was normal,[13] and in the other it was increased.[15] Due to limitations of blood sampling in the small animals studied in the present experiments, we were not able to determine glucose turnover concurrently. Further studies of glucose turnover in appropriate animal preparations are necessary to resolve this question. If it is confirmed that total systemic diversion of pancreatic endocrine secretions is associated with increased glucose turnover, it will be necessary to find an explanation in terms of the endocrine and metabolic regulatory mechanisms involved.

These questions are of clinical and pathophysiological interest in the context of diabetes mellitus, due to the importance of determining the optimal site and route of delivery of insulin from tissue grafts or other sources of insulin. In consideration of conflicting results among animal studies of systemic diversion of pancreatic endocrine secretions, it is clear that the problem is not simply related to differences among species and/or surgical procedures. The nutritional condition of the animals and the interval between surgical preparation and metabolic studies, with possible development of collateral venous connections, are potentially important variables. It is therefore important in the present study that continued normal weight gain was demonstrated in PCT rats, and that the alterations of portal-systemic concentrations of plasma IRI and of arterial plasma amino acids through the 30-day interval to death were consistent with continuing systemic diversion of splanchnic blood.

In summary, systemic delivery of pancreatic endocrine secretions after PCT is accompanied by metabolic adjustments resulting in euglycemia, with postabsorptive hyperinsulinemia and hyperglucagonemia, and decreased IS; thus, normal concentrations of plasma glucose are maintained by virtue of these adaptations. These characteristics of PCT are associated with decreased hepatic extraction of insulin. Our results support the hypothesis that hepatic portal delivery of insulin and other gastroenteropancreatic hormones is important in maintenance of IS.

ACKNOWLEDGMENT

We gratefully acknowledge the assistance of Diane T. Finegood, University of Alberta, who calculated the minimal model parameters. We thank Drs Huifang Chen, Gang He, Zheng Zhang, and Linfu Zhu for surgical preparation of rats with PCT.

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