Portal Insulin Delivery Is Superior to Peripheral Delivery in Handling of Portally Delivered Glucose

Masashi Kubota, Yoshimitsu Yamasaki, Masashi Sekiya, Minoru Kubota, Toyohiko Morishima, Michihiko Kishimoto, Ryuzo Kawamori, Motoaki Shichiri, and Takenobu Kamada

It is still controversial as to whether physiological portal insulin delivery has metabolic advantages over peripheral insulin delivery. To clarify this issue, glycemic regulation during intravenous (IVGTT) and oral (OGTT) glucose tolerance tests and hyperglycemic clamp studies with either peripheral or portal glucose infusion was investigated in left-segmentally pancreatectomized dogs with portal ([PPx] n = 7) or systemic ([Tx] n = 7) venous drainage of the remaining pancreas. In Tx dogs, systemic diversion of pancreatic venous effluent was accomplished by gastroduodenal-caval shunt. Data obtained were compared with those in normal control dogs ([NC] n = 7). The loss of pancreatic β-cell mass in PPx dogs decreased insulin responses to peripheral and portal glucose loads. In contrast, Tx dogs showed insulin responses comparable to those of NC dogs to glucose loads via both routes. Against peripheral glucose loads (IVGTT and hyperglycemic clamp with peripheral glucose infusion), PPx and Tx dogs showed deteriorated glucose handling. Against portal glucose loads (OGTT and hyperglycemic clamp with portal glucose infusion), deteriorated glucose handling was observed in Tx dogs, but not in PPx dogs. Deterioration in glycemic regulation against portal glucose loads in left-segmentally pancreatectomized dogs with peripheral insulin delivery but not in pancreatectomized dogs with portal delivery indicates that intraportal hyperglycemia and hyperinsulinemia are essential for promoting hepatic glucose handling.

IN NORMAL SUBJECTS, endogenous insulin is delivered to the portal vein to assimilate portally delivered carbohydrate such as meal intake. In contrast, in the current insulin therapy for diabetics, insulin is administered subcutaneously. Thus, this delivery through peripheral circulation may cause peripheral hyperinsulinemia, as well as relative portal hypoinsulinemia, which may alter glucose handling nonphysiologically. Some previous reports[1-3] supported the advantages of portal insulin delivery for normalizing carbohydrate metabolites[1,2] and hepatic glucose handling.[3] The other reports showed no significant differences either on glycemic and insulinemic responses[4,5] or on glucose kinetics.[6-12] In some of these reports, an elegant surgical model in which endogenous insulin is delivered directly to the systemic circulation through pancreaticocaval anastomosis was used to determine differences in carbohydrate metabolism and plasma insulin response depending on the difference in endogenous insulin delivery route. However, the remaining left limb of the pancreas[5] or the remaining 20% of the pancreas[10] might secrete insufficient insulin to normalize the glycemic response,[5,10] or the totally remaining pancreas with peripheral insulin delivery[11,12] might secrete a sufficient amount of insulin to cause hyperinsulinemia against intravenous glucose injection[11] and meal ingestion.[12] Furthermore, glucose handling against portally infused glucose by portally or peripherally delivered insulin remains to be evaluated for comparison to glucose handling against peripherally infused glucose. Therefore, in this study, left-segmental pancreatectomy leaving more than half of the pancreas, pancreaticocaval anastomosis, and hyperglycemic clamp by peripheral or portal glucose infusion were used to investigate the superiority of endogenous insulin delivery portally rather than peripheral insulin delivery for handling of portally delivered glucose.

From the First Department of Medicine, Osaka University Medical School, Osaka; the Department of Medicine, Metabolism and Endocrinology, Juntendo University School of Medicine, Tokyo; and the Department of Metabolism and Endocrinology, Kumamoto University Medical School, Kumamoto, Japan.

Submitted October 20, 1994; accepted June 7, 1995.

Address reprint requests to Yoshimitsu Yamasaki, MD, PhD, First Department of Medicine, Osaka University Medical School, Yamadaoka 2-2, Suita-city, Osaka 565, Japan.

0026-0495/96/4502-0003$03.00/0

MATERIALS AND METHODS

Animals and Surgery

Twenty-one mongrel dogs were divided into the following three groups: normal control dogs ([NC] 16 ± 2 kg body weight [BW]), left-segmentally pancreatectomized dogs ([PPx] 15 ± 3 kg BW), and left-segmentally pancreatectomized dogs with gastroduodenal-caval shunt ([Tx] 17 ± 2 kg BW). They were fed a 1,200-cal regular mixed meal every morning. All groups underwent laparotomy under general anesthesia with pentobarbiturate, and an indwelling catheter was inserted through the mesenteric vein and placed into the portal vein. The catheter was filled with heparinized saline and embedded under the abdominal skin until experiments. In PPx and Tx dogs, the left lobe of the pancreas, supplied with branches of splenic vessels, was excised just above the portal vein, and the remaining stump of the pancreas was ligated. The inferior pancreaticoduodenal vein and other vessels that enter the mesenteric vein were ligated to leave the gastroduodenal vein as the only major drainage route of the remaining pancreas. In NC and PPx dogs, the gastroduodenal vein was retained intact to maintain portal venous drainage. Sham procedures for shunting between the gastroduodenal vein and the portal vein were not attempted because of surgical difficulties in maintaining portal blood flow during suture. In Tx dogs, systemic venous drainage was accomplished by end-to-side anastomosis of the gastroduodenal vein to the inferior vena cava.

Experiments

From at least 4 weeks after operation, the following glucose tolerance tests were performed separately at least 3 days apart in random order: intravenous bolus glucose tolerance test ([IVGTT] 0.5 g glucose/kg BW), oral glucose tolerance test ([OGTT] 2 g glucose/kg BW), and hyperglycemic clamp studies with either peripheral or portal glucose infusion. IVGTT and OGTT were

performed in the conscious state. The animals had been accustomed to remaining quiet before the experiments. Hyperglycemic clamp studies were conducted using a closed-loop glucose-insulin clamp system as described previously.[13] The algorithm used in this study was based on the modified method of DeFronzo et al.[14] The animals were anesthetized to ensure continuous venous blood sampling for minute-by-minute plasma glucose monitoring. Before initiation of the clamp study, a urinary catheter was inserted to calculate urinary glucose losses during the hyperglycemic clamp. Glucose was infused either peripherally or intraportally through the indwelling portal catheter. All samples were taken through a catheter inserted into the femoral vein. Plasma and urinary glucose concentrations were measured by the glucose oxidase method with a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA) after adequate dilution, if needed. Blood samples for determination of plasma insulin levels were collected on ice, centrifuged at 4°C, and stored within 15 minutes at −20°C until assay. Plasma insulin levels were determined by a double-antibody method (IRI kit; Amersham, England). Intraassay and interassay variations were 3.6% and 6.5%, respectively. After all experiments were completed, a laparotomy was performed again in each dog. The gastroduodenocaval shunt in Tx was confirmed patent in all dogs. The dogs were then killed, and the remaining pancreas was excised and weighed.

Calculations and Statistical Analysis

Mean insulin levels in each study were calculated as the product of the area under the curve (AUC) of plasma insulin divided by its study interval. Mean plasma glucose levels in OGTT were determined the same way. The K value during IVGTT was calculated according to the method of Amatuzio et al.[15] Urinary glucose loss during the glycemic clamp was measured to calculate average urinary glucose excretion rate. Both the glucose infusion rate (GIR) during the last 30 minutes of the hyperglycemic clamp and the urinary glucose excretion rate were taken into account to calculate GIR according to DeFronzo et al.[14] Results are expressed as the mean ± SE. Statistical analyses were performed using Student's unpaired t test. Differences were considered significant at P less than .05.

RESULTS

Fasting plasma glucose levels of all three groups were similar. Fasting plasma insulin levels of all groups were also comparable. In IVGTT studies (Fig 1), peak plasma insulin levels of PPx dogs were 32 ± 2 mU/L at 5 minutes, significantly less than the 57 ± 8 mU/L of NC at 5 minutes. In Tx dogs, the peaks were prolonged but significantly increased to 53 ± 6 mU/L at 10 minutes, as compared with PPx dogs (Fig 1). Plasma insulin levels in Tx dogs were still significantly higher than in PPx dogs after the intravenous glucose load. However, there were no significant differences in plasma glucose concentrations between PPx and Tx dogs. The AUC of plasma insulin was significantly lower in PPx dogs than in NC dogs (356 ± 27 v 517 ± 41 mU · min/L, $P < .05$). K values during IVGTT were significantly decreased by approximately 30% in PPx dogs as compared with NC dogs (3.6% ± 0.3% v 5.1% ± 0.3%, $P < .05$). The K value in Tx dogs (4.0% ± 0.3%) was still significantly ($P < .05$) lower than in NC dogs, although peripheral insulin levels were increased comparably to those in NC dogs.

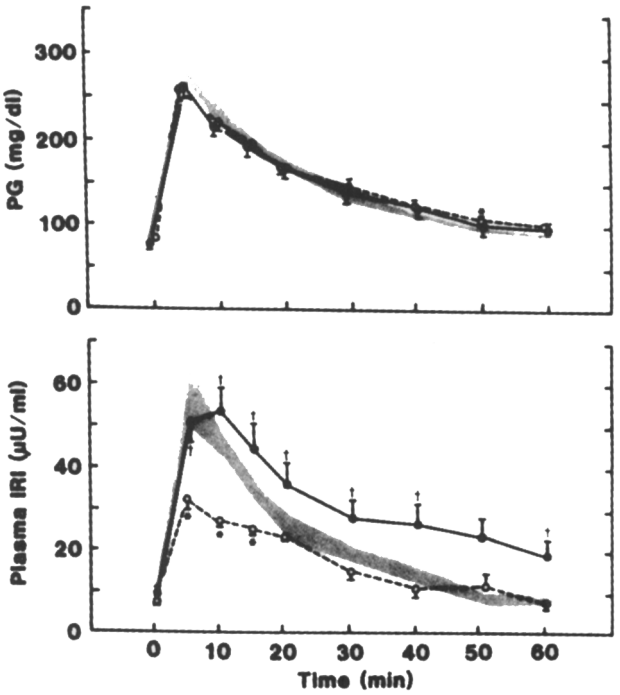

Fig 1. Plasma glucose (PG) and insulin levels during IVGTT (0.5 g glucose/kg BW) in NC dogs (▨), PPx dogs (○), and Tx dogs (●). Data are the mean ± SEM (n = 7 per group). * and † represent statistical significance v NC and PPx, respectively.

After OGTT (Fig 2), peak plasma insulin levels in PPx dogs were 36 ± 1 mU/L at 45 minutes, significantly less than in NC dogs at 45 minutes (55 ± 4 mU/L). In Tx dogs, the peak value was significantly higher (46 ± 5 mU/L) at 45 minutes than in PPx dogs, but was not significantly different from that in NC dogs. Plasma glucose concentrations in PPx dogs were significantly higher than in NC dogs at 90, 120, and 150 minutes, and returned to fasting levels at 180 minutes. In Tx dogs, plasma glucose was significantly higher than in PPx dogs at 120 and 150 minutes. AUCs of plasma insulin were not significantly different among the three groups (3,767 ± 503, 3,261 ± 201, and 3,774 ± 544 mU · min/L in NC, PPx, and Tx dogs, respectively). The mean plasma glucose concentration during 180 minutes was significantly higher in PPx dogs (115 ± 2 mg/dL) than in NC (100 ± 2 mg/dL). The value was significantly higher in Tx dogs (130 ± 3 mg/dL) than in the others.

During hyperglycemic clamp studies with peripheral glucose loads (Fig 3), plasma glucose concentrations reached the objective values at approximately 30 minutes and were maintained at comparable levels in all groups. Coefficients of variation of plasma glucose concentrations from 30 to 120 minutes were less than 1% in all groups. Plasma insulin levels in PPx dogs were significantly lower than in NC dogs during 120 minutes, except at 10, 20, and 30 minutes. In Tx dogs, plasma insulin levels were significantly higher than in PPx dogs during 120 minutes and were comparably as high as in NC dogs. GIRs were decreased in PPx dogs as compared with NC dogs. The AUC of plasma insulin levels

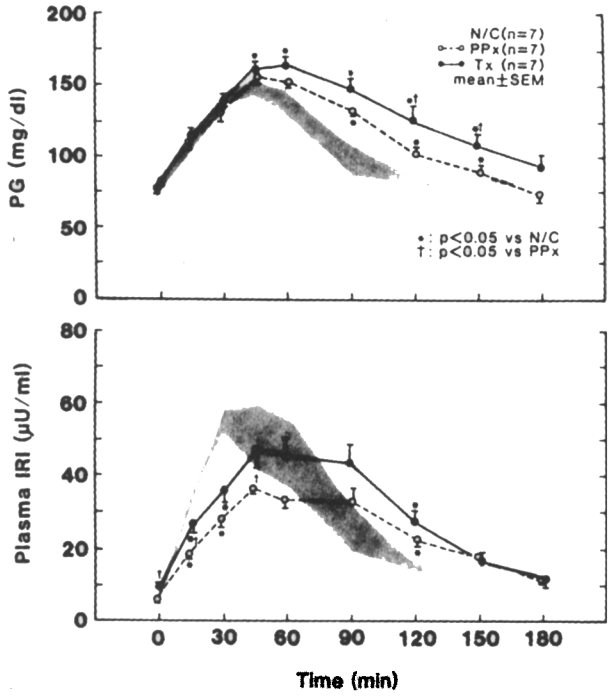

Fig 2. Plasma glucose (PG) and insulin levels during OGTT (2 g glucose/kg BW) in NC dogs, PPx dogs, and Tx dogs. * and † represent statistical significance *v* NC and PPx, respectively.

was significantly lower in PPx dogs than in NC and Tx dogs (2,960 ± 140, 3,640 ± 125, and 3,983 ± 155 mU · min/L, respectively). The mean glucose disposal rate during the last 30 minutes of the glucose clamp study (GIR) in PPx dogs (11.0 ± 1.4 mg/kg · min) was significantly less than in NC dogs (15.7 ± 0.5 mg/kg · min), but in Tx dogs, GIR (12.1 ± 0.7 mg/kg · min) showed a level comparable to that in PPx dogs despite normalization of peripheral plasma insulin levels.

During hyperglycemic clamp studies with portal glucose loads (Fig 4), plasma glucose concentrations were also effectively clamped after 40 minutes in all groups. Coefficients of variation of plasma glucose concentrations from 40 to 120 minutes were less than 2% in all groups. Plasma insulin levels in each group were similar to those in hyperglycemic clamp studies with peripheral glucose infusion as described earlier. In contrast, the GIR of PPx dogs was not significantly different from that of NC dogs from 40 to 120 minutes, whereas in Tx dogs, the GIR was significantly decreased as compared with NC dogs and was significantly lower than in PPx dogs from 95 to 120 minutes. AUCs of plasma insulin (3,553 ± 255, 2,698 ± 119, and 3,359 ± 102 mU · min/L in NC, PPx, and Tx dogs, respectively) were similar to the results obtained in hyperglycemic clamp studies with peripheral glucose infusion. GIRs were not significantly different between NC and PPx dogs (24.0 ± 1.3 and 21.4 ± 1.2 mg/kg · min), whereas the GIR in Tx dogs (17.6 ± 0.9 mg/kg · min) was significantly lower than the others.

DISCUSSION

Left-segmental pancreatectomy with portal insulin delivery (PPx) decreased fasting insulin levels and decreased plasma insulin responses during each glucose load, which levels remained at 75% of those in NC dogs. The weight of the right lobe of the pancreas was approximately 65% that of the whole pancreas, so the decrease in insulin responses in this group resulted from the decrease in the mass of pancreatic β cells. In contrast, left-segmentally pancreatectomized dogs with systemic venous drainage (Tx dogs) showed normalization of insulinemic responses against IVGTT, OGTT, and both hyperglycemic clamps. These normalizations of insulinemic responses in Tx dogs are different from previous observations in which insulin responses against IVGTT, OGTT, and hyperglycemic clamp were decreased in such dogs.[5,10] In these reports, the right limb and the body of the pancreas were removed[5] or 80% proximal pancreatectomy was performed.[10] Thus, in these

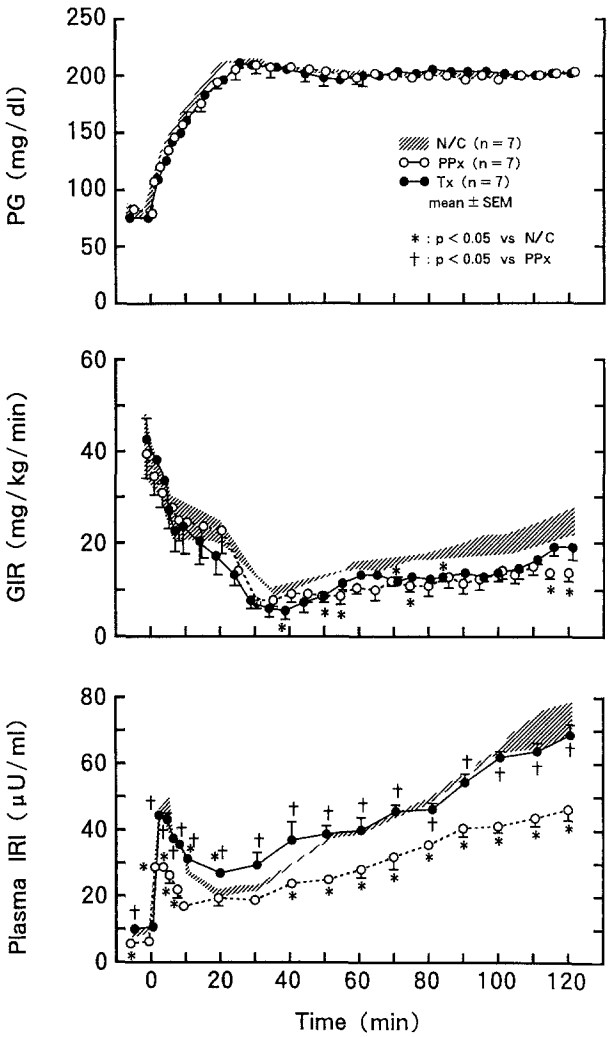

Fig 3. Plasma glucose (PG), GIR, and plasma insulin levels during hyperglycemic clamp studies in NC dogs, PPx dogs, and Tx dogs. Glucose was infused via the peripheral vein. * and † represent statistical significance *v* NC and PPx, respectively.

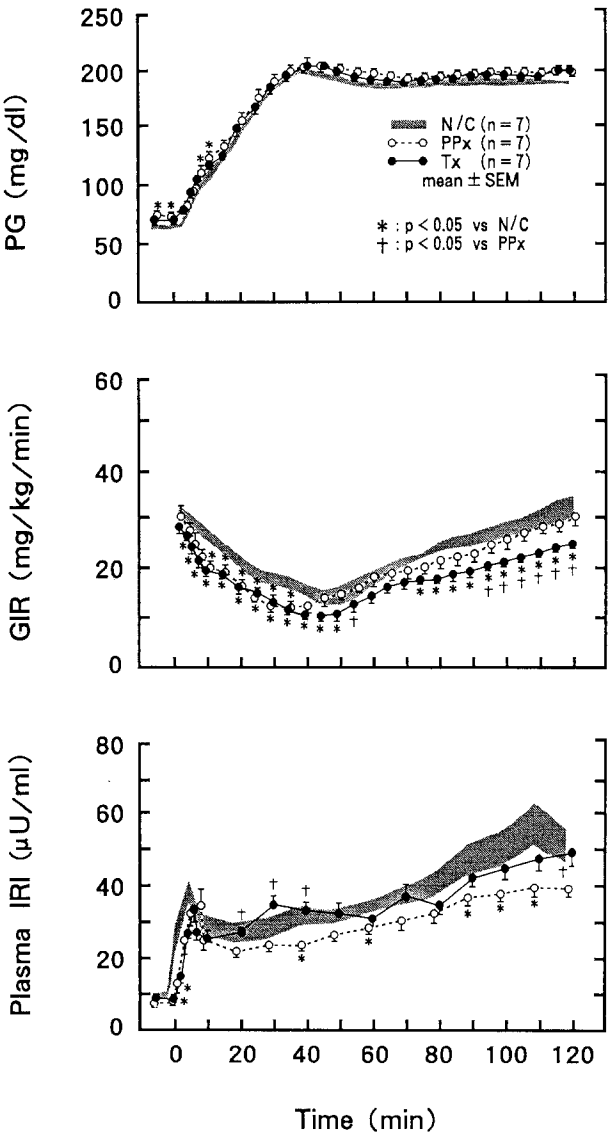

Fig 4. Plasma glucose (PG), GIR, and plasma insulin levels during hyperglycemic clamp studies in NC dogs, PPx dogs, and Tx dogs. Glucose was infused intraportally. * and † represent statistical significance v NC and PPx, respectively.

studies, considerable β-cell mass resection was supposed to reduce the insulinemic response significantly.[16] On the contrary, postprandial hyperinsulinemia against meal ingestion[11] and hyperinsulinemia against peripheral glucose injection[12] were reported in nonpancreatectomized dogs with peripheral insulin delivery. Thus, in these reports, the total remaining β-cell mass was supposed to induce hyperinsulinemia when endogenous insulin was delivered directly into the systemic circulation.

Gotoh et al[17] previously reported that there was no significant difference in cumulated plasma C-peptide levels during IVGTT in right-segmentally depancreatectomized dogs with systemic diversion of pancreatic venous effluent compared with control dogs. Kryshak et al[11] recently reported similar results after a mixed meal in their canine model. Although plasma C-peptide levels were not determined in this study, insulin secretion in both left-segmentally pancreatectomized groups (PPx and Tx dogs) was assumed to be comparable, at least in hyperglycemic clamp studies in which β cells in the remaining pancreas were stimulated by identical levels of arterial plasma glucose. According to this assumption, the increase in peripheral insulin levels in Tx dogs was speculated to be due to decreased insulin clearance because of bypassing initial hepatic extraction.[18] However, this plausible normalization in peripheral insulin responses in Tx dogs was not associated with the improvement of glucose tolerance during hyperglycemic clamp with peripheral glucose infusion.

Against peripheral glucose loads such as IVGTT and hyperglycemic clamp with peripheral glucose infusion, PPx dogs showed K values and glucose delivery rates comparable to those of Tx dogs. Using a similar animal model, no significant difference in glucose metabolism between the two routes of insulin delivery against a peripheral glucose load was reported by Braumgartner et al[5] and Krusch et al.[10]

Against portal glucose loads such as OGTT and hyperglycemic clamp with portal glucose infusion, PPx dogs (with physiological portal insulin delivery) showed slight hyperglycemia and slightly decreased glucose disposal (not significantly different), respectively. However, when endogenous insulin was delivered peripherally (Tx dogs), hyperglycemia and decreased glucose disposal were shown against the oral glucose load and the hyperglycemic clamp with portal glucose load, respectively. There results are different from previous reports in which partially pancreatectomized dogs (only the left limb was left) with portal venous drainage showed an impaired glycemic response against OGTT[5] and reduction of β-cell mass (20% of normal) with portal drainage resulted in a severely deranged glucose utilization rate.[10] Also, the present result is different from the previous report in which the glycemic response and glucose appearance and disappearance did not differ between nonpancreatectomized dogs with portal insulin delivery and those with peripheral delivery.[11] The present study indicates that a transplanted pancreas may handle portally delivered glucose more physiologically if sufficient endogenous insulin is secreted (75% of normal) and, further, is delivered portally rather than peripherally. Also, it is speculated that from the totally remaining pancreas endogenous insulin is secreted sufficiently to normalize glycemic responses against peripheral glucose infusion[12] and carbohydrate metabolism against meal intake[11] even if insulin is delivered peripherally through a pancreaticocaval shunt.

Neither glucose-tracer methods nor hepatic venous catheterization techniques were applied to investigate the precise mechanism of these results. However, hepatic glucose handling in the portal drainage group was speculated to be increased. And this augmented hepatic glucose handling might contribute to comparable or even better glycemic regulation despite lower peripheral insulin levels. As previously reported,[7] peripheral glucose uptake depends on plasma insulin levels in the physiological range.

Therefore, in PPx dogs, peripheral glucose uptake during hyperglycemic clamp was estimated to be less than in Tx dogs, independent of the route of glucose infusion. Furthermore, when glucose was loaded intraportally, hyperglycemia and intraportal hyperinsulinemia in PPx dogs promoted hepatic glucose handling, and this resulted in better glycemic regulation in PPx dogs than Tx dogs. In other words, deterioration in glycemic regulation against portal glucose loads in the Tx group was probably due to the relatively decreased hepatic glucose disposal. Further studies using glucose-tracer methods or hepatic venous catheterization techniques are needed to investigate the precise mechanisms involved.

In this study, we demonstrated the superiority of portal insulin delivery on portally loaded glucose handling over peripheral delivery. To achieve optimal glycemic regulation for complete amelioration of the defective metabolism in diabetics, portal insulin delivery is essential.

REFERENCES

1. Stevenson RW, Parson JA, Alberti KGMM: Comparison of the metabolic responses to portal and peripheral infusions of insulin in diabetic dogs. Metabolism 30:745-762, 1981
2. Albisser AM, Nomura M, Greenberg GR, et al: Metabolic control in diabetic dogs treated with pancreatic autotransplants and insulin pumps. Diabetes 35:97-100, 1986
3. Stevenson RW, Parson JA, Alberti KGMM: Effect of intraportal and peripheral insulin on glucose turnover and recycling in diabetic dogs. Am J Physiol 244:E190-E195, 1983
4. Botz CK, Leibel BS, Zingg W, et al: Comparison of peripheral and portal route of insulin infusion by a computer controlled insulin infusion system (artificial endocrine pancreas). Diabetes 25:691-700, 1976
5. Braumgartner D, Illing R, Sutherland DER: Effect of venous drainage to the vena cava and denervation on endocrine function of pancreatic segments in dogs. Transplant Proc 16:769-772, 1984
6. Kuzszynska YT, Home PD, Alberti KGMM: Comparison of portal and peripheral insulin delivery on carbohydrate metabolism in streptozotocindiabetic rats. Diabetologia 28:167-171, 1985
7. Morishima T, Kubota Mi, Saito Y, et al: Physiological significance of intraportal delivery of insulin on glucose regulation, in Brunetti P, Waldhausl WK (eds): Advanced Models for the Therapy of Insulin-Dependent Diabetes. New York, NY, Raven, 1987, pp 35-39
8. Fischer L, Rizza RA, Hall LD, et al: Comparison of peripheral and portal venous insulin administration on postprandial metabolic responses in alloxan-diabetic dogs. Effects of identical preprogrammed complex insulin infusion waveforms. Diabetes 31:579-584, 1982
9. Ishida T, Chap Z, Chou J, et al: Effects of portal and peripheral venous insulin infusion on glucose production and utilization in depancreatectomized, conscious dogs. Diabetes 33: 984-990, 1984
10. Krusch DA, Brown KB, Calhoun PC, et al: Peripheral insulin release after pancreatic resection: The effect of decreased B-cell mass with systemic or portal drainage. Endocrinology 123:426-432, 1988
11. Kryshak EJ, Butler PC, Marsh C, et al: Pattern of postprandial carbohydrate metabolism and effects of portal and peripheral insulin delivery. Diabetes 39:142-148, 1990
12. Homan M, Nicholson CP, Katz H, et al: Effects of chronic systemic insulin delivery on insulin action in dogs. Diabetologia 34:704-708, 1991
13. Shichiri M, Kawamori R, Yamasaki Y, et al: Clinical applications of a bedside-type artificial endocrine pancreas—Development and application of the control algorithm. Artif Organs Today 1:13-22, 1991
14. DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: A method for quantifying insulin secretion and resistance. Am J Physiol 237:E214-E223, 1979
15. Amatuzio DS, Stutzman FL, Vanderbilt MJ, et al: Interpretation of the rapid intravenous glucose tolerance test in normal individuals and in mild diabetes mellitus. J Clin Invest 32:428-435, 1953
16. Gotoh M, Monden M, Okamura J, et al: Insulin and glucagon secretion after pancreatectomies. Correlation of secretion and hormonal contents of remaining pancreas. Diabetes 38:861-867, 1989
17. Gotoh M, Okamura J, Monden M, et al: Comparison of A and B cell secretory responses in partially pancreatectomized pancreas and segmental autotransplanted pancreas. Horm Metab Res 12:128-130, 1982 (suppl)
18. Ishida T, Chap Z, Chou J, et al: Differential effects of oral, peripheral intravenous, and intraportal glucose on hepatic glucose uptake and insulin and glucagon extraction in conscious dogs. J Clin Invest 72:590-601, 1983