Effects of Portal and Peripheral Venous Insulin Infusion on Glucose Production and Utilization in Depancreatized, Conscious Dogs

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SUMMARY

The relation between portal vein insulin concentrations and suppression of hepatic glucose production, as well as peripheral venous insulin level and increase of peripheral glucose utilization, was compared in conscious, depancreatized, diabetic dogs after infusion of insulin at 0.25 and 0.5 mU/kg/min into either the portal system or the peripheral circulation. Glucose appearance and clearance was measured using [3-^{3}H]-glucose. Before infusion of insulin, portal vein insulin concentrations were undetectable. The intraportal infusion of insulin at 0.25 mU/kg/min increased portal vein insulin to 16 ± 1 μU/ml, significantly higher than the arterial concentration (9 ± 1 μU/ml). Infusion of the same amount of insulin into a peripheral vein raised peripheral insulin levels to 14 ± 1 μU/ml and portal vein concentrations to 12 ± 1 μU/ml. When 0.5 mU/kg/min of insulin was infused into the portal system, the portal vein insulin level was 28 ± 2 μU/ml and significantly greater than the arterial concentration (16 ± 1 μU/ml). After the same amount of insulin was infused into a peripheral vein, the arterial insulin level was higher than that of the portal vein (25 ± 1 μU/ml versus 20 ± 1 μU/ml, respectively). The ensuing hypoglycemia was greater after the 0.5 mU/kg/min infusion compared with the 0.25 mU/kg/min infusion. At each dose there was no significant difference between the peripheral venous or the portal route. Despite different portal vein insulin levels, suppression of glucose appearance (as measured by the area under the extended basal value) during insulin infusion was similar in all four groups (29 ± 6% at portal vein insulin concentration of 12 ± 1 μU/ml after 0.25 mU/kg/min insulin into the peripheral vein, 36 ± 4% at 16 ± 1 μU/ml after 0.25 mU/kg/min insulin into the portal system, 37 ± 6% at 20 ± 1 μU/ml after 0.5 mU/kg/min insulin into the peripheral vein, and 31 ± 7% at 28 ± 2 μU/ml after 0.5 mU/kg/min insulin into the portal system, respectively). Glucose clearance did not increase after infusion of insulin at 0.25 mU/kg/min into either the portal or the peripheral system despite an increase of peripheral venous insulin levels (9 ± 1 μU/ml and 14 ± 1 μU/ml, respectively). Glucose clearance (measured as the area above the curve) did increase significantly when 0.5 mU/kg/min was infused. The increase after peripheral infusion (197 ± 27 ml/kg) was significantly greater than after portal infusion (141 ± 22 ml/kg) of insulin. Under these two circumstances, the peripheral insulin concentrations were 25 ± 1 μU/ml and 16 ± 1 μU/ml, respectively. These results demonstrate that the liver in diabetic dogs is more sensitive than peripheral tissue to small changes in the plasma insulin concentration. While the peripheral administration of small amounts of insulin is equally effective as portal insulin infusion in suppressing hepatic production of glucose, glucose clearance is more directly related to peripheral insulin concentrations. DIABETES 1984; 33:984–90.

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Received for publication 9 December 1983 and in revised form 8 March 1984.

Numerous studies have compared the effect of intraportal and peripheral intravenous (i.v.) insulin infusion on blood glucose in normal dogs[1–9] and in diabetic animals.[8,10–18] Some of these studies demonstrated similar hypoglycemic response to the two routes in normal[2,5,7] and in diabetic dogs.[8,12,16] Others have indicated the superiority of the peripheral route in normal dogs[1,3,4,6,9] or greater effects of portal vein infusion in diabetic animals[10,11,13–15,17,18] The route of insulin delivery may be important in the development of an artificial pancreas, since the administration of insulin into a peripheral vein of diabetic subjects did not completely normalize glucose metabolism even when normoglycemia or hypoglycemia was achieved.[10,15,17,18] Such peripheral infusion of insulin has also been associated with elevated insulin concentrations in the peripheral circulation. While considerable data exist concerning the peripheral venous insulin concentrations after intraportal insulin infusion,[8,10,14,19,20] the portal vein insulin lev-

els after peripheral i.v. administration of insulin are not known.

The present study compared the effects of intraportal and peripheral i.v. infusion of insulin concentrations in peripheral and portal circulations and glucose appearance and clearance in conscious, depancreatized, diabetic dogs.

MATERIALS AND METHODS

Animals and surgery. Twelve healthy, adult, mongrel male and female dogs weighing 20–30 kg were anesthetized with i.v. sodium pentobarbitol (25 mg/kg body wt) after an overnight fast. After a midline incision, a portal vein blood sampling microbore siliconized plastic catheter was inserted via the superior pancreaticoduodenal vein.[21] The insulin infusion catheter was placed in the superior mesenteric vein and its tip lay approximately 10 cm caudad from the portal vein sampling catheter. Other microbore siliconized plastic catheters were inserted into the carotid artery for sampling and into the external jugular vein for the infusion of insulin and, when appropriate, [3-^{3}H]-glucose. Total pancreatectomy was performed by the method of Markowitz et al.[22] Postoperatively, the catheters were flushed with 2 ml heparinized saline (50 U/ml) daily to prevent thrombosis.

Experimental procedures. The diabetic dogs were treated with porcine NPH insulin (Eli Lilly and Company, Indianapolis, Indiana) subcutaneously (s.c.) each morning except the day before and the day of study. The insulin doses (10–25 U/day) were modified depending on the blood glucose determined at frequent intervals every day to maintain the blood glucose between 100 and 200 mg/dl. On the day before an experiment, porcine regular insulin (Eli Lilly and Company) was given in the morning so that on the morning of the experiment the animal's blood glucose ranged between 200 and 400 mg/dl, suggesting very little residual insulin. This was corroborated by the absence of detectable insulin in the portal or peripheral blood before the infusion of insulin. The urinary and serum ketone bodies were negative using Labstix (Ames, Elkhart, Indiana). The animals were fed each morning a meal consisting of a mixture of 425 g of soft meal and 200 g of dry chow. Ten capsules of digestive enzymes (Cotazym, Organon Pharmaceuticals, West Orange, New Jersey) were mixed with the food to compensate for the pancreatic exocrine deficiency.

At least 2 wk postsurgery, experiments were done after an overnight fast in conscious, unrestrained dogs. The order of each experiment was random with an interval of at least 8 days between them. Experiments were done only in animals whose hematocrits were over 30%, appeared in healthy condition, and had a good appetite and normal stools. Four groups of studies were performed. After a 30-min control period, porcine regular insulin at 0.25 or 0.5 mU/kg/min was infused into either the superior mesenteric vein or a peripheral vein from 0 to 180 min using a Harvard infusion pump (Harvard Apparatus Company, Dover, Massachusetts). For isotopic determination of glucose appearance and disappearance rates, a priming dose of 60 μCi [3-^{3}H]-glucose (New England Nuclear, Boston, Massachusetts, sp act 12.3 Ci/mmol made up in 0.9% NaCl, 50 μCi/50 ml) was administered rapidly at −150 min followed by a constant tracer infusion at a rate of 0.5 μCi/min using a Harvard infusion pump. A 2-h equilibration period was employed to insure that plasma specific activity of the [3-^{3}H]-glucose had reached a stable plateau before measurement of changes in glucose kinetics. The coefficient of variation of glucose specific activity during the final 30 min of the equilibration period (4 samples) was 2.5 ± 0.2% (mean ± SEM). Blood samples for glucose, insulin, and glucose specific activity were obtained at −30, −20, −10, 0, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, and 180 min from the portal vein and carotid artery simultaneously. They were collected into chilled tubes containing 500 U Trasylol (FBA Pharmaceutical, Inc., New York, New York) and 1.2 mg EDTA/ml of blood.

Analysis. Blood glucose concentration was determined by the glucose-oxidase method with a Beckman Glucose Analyzer. Plasma immunoreactive insulin was assayed employing separation with dextran-coated charcoal.[23] For the measurement of plasma [3-^{3}H]-glucose specific activity, plasma was deproteinized with equal volumes of 5% zinc sulphate and 0.3 N barium hydroxide. Because tritium in the third carbon is lost as H_2O in the glycolytic pathway, separation of glucose from its C-3 metabolites is not necessary. To eliminate any tritium in the form of ^3H_2O, the supernate was evaporated to dryness at 70°C. The dry residue was dissolved in 1 ml of distilled water. Half of it was used for glucose determinations and the other half for glucose radioactivity. Radioactivity was counted in a refrigerated liquid scintillation spectrometer after the addition of 10 ml Scinti Verse (Fisher Scientific Corp., Fairlawn, New Jersey). Correction for quenching was done using the method of external standard ratio. The glucose radioactivity of each plasma sample was divided by its glucose concentration to obtain glucose specific activity. Calculated infusion rates of the isotope were verified by measuring the volume of the radioactive glucose infusate before and after each experiment. Recovery of radioactive glucose (as determined by adding known amounts of radioactivity to plasma samples) averaged 88 ± 6%.

Calculations. Rates of endogenous glucose production and clearance were calculated in the steady state before insulin by the isotope-dilution equation: turnover rate = F/SA_E, where F is the infusion rate of tritiated glucose (nCi/kg/min) and SA_E is the specific activity of glucose at equilibration (nCi/mg). In the non-steady state after insulin infusion, rates of glucose appearance and disappearance (mg/kg/min) were calculated employing the equation of Steele[24] as modified by DeBodo et al.[25] This method has been shown to accurately reflect glucose kinetics over a wide range of non-steady-state plasma glucose levels.[26] The volume of 0.65 (pool fraction) was used to correct for the noninstantaneous mixing within the entire glucose pool.[24,27] Glucose clearance rate (ml/kg/min) was obtained as the ratio of the rate of glucose disappearance and plasma glucose concentration. Glucose clearance has been used as an index of tissue removal of glucose from plasma independent of plasma glucose concentration.[28] The use of [3-^{3}H]-glucose as a nonrecycling tracer has been discussed in detail.[29]

The data are presented as mean ± SEM. The basal value was the mean ± SEM of the four values obtained from −30 to 0 min. Paired Student's *t*-test and nonpaired Student's *t*-test were employed for statistical analysis of the difference within a group and between groups. P-values < 0.05 were considered to be significant.

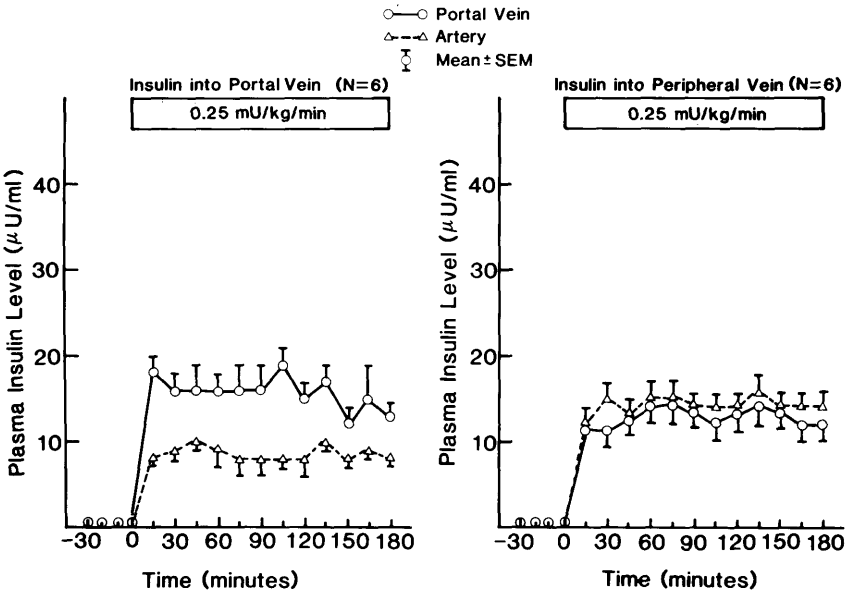

FIGURE 1. Plasma insulin concentrations of the portal vein and artery after 0.25 mU/kg/min insulin was infused into either the portal system (left) or a peripheral vein (right) in pancreatectomized, diabetic dogs.

RESULTS

Plasma insulin concentrations. During the control period, the portal and arterial plasma insulin levels in the diabetic dogs were < 2 μU/ml (Figure 1). After intraportal infusion of insulin (0.25 mU/kg/min), the portal vein insulin increased to 16 ± 1 μU/ml, which was significantly higher than the arterial concentration of 9 ± 1 μU/ml. When the same amount of insulin was infused into a peripheral vein, the portal vein insulin level increased to 12 ± 1 μU/ml while the arterial level averaged 14 ± 1 μU/ml. Intraportal infusion of 0.5 mU/kg/min insulin raised portal vein and arterial insulin concentrations to 28 ± 2 μU/ml and 16 ± 1 μU/ml, respectively (Figure 2). The same amount of insulin infused into a peripheral vein increased the arterial insulin level to 25 ± 1 μU/ml, while the portal vein insulin level was 20 ± 1 μU/ml.

Plasma glucose concentration. The arterial plasma glucose fell from the basal level of 310 ± 47 mg/dl to 171 ± 24 mg/dl during the intraportal infusion of 0.25 mU/kg/min insulin (55 ± 8% of the basal value) (Figure 3). A similar reduction of the plasma glucose was observed after the same amount of insulin was infused into a peripheral vein (51 ± 9% of the basal value). Intraportal and peripheral infusion of insulin at 0.5 mU/kg/min produced somewhat greater reductions in the plasma glucose. The peripheral i.v. infusion of 0.5 mU/kg/min insulin decreased the plasma glucose to 38 ± 6% of the basal value, significantly greater than that achieved by 0.25 mU/kg/min infused either peripherally or intraportally. Although the effect of 0.5 mU/kg/min insulin infused intraportally (46 ± 8%) was greater than that of 0.25 mU/kg/min, it was not significant.

Glucose appearance. The glucose appearance rate during the control period was 8.6 ± 1.1 mg/kg/min (Figure 4, average of all four groups). It significantly decreased to 5.6 ± 0.6 mg/kg/min at 30 min and reached a nadir of 4.0 ± 0.4 mg/kg/min at 135 min after intraportal infusion of 0.25 mU/kg/min insulin. During this time, the portal vein

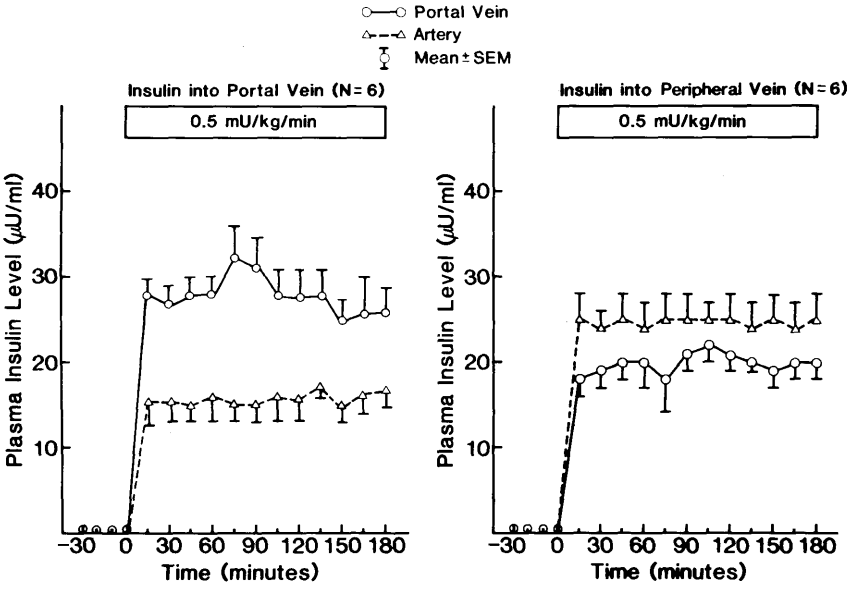

FIGURE 2. Plasma insulin levels of the portal vein and artery after 0.5 mU/kg/min insulin was infused into either the portal system (left) or a peripheral vein (right) in pancreatectomized, diabetic dogs.

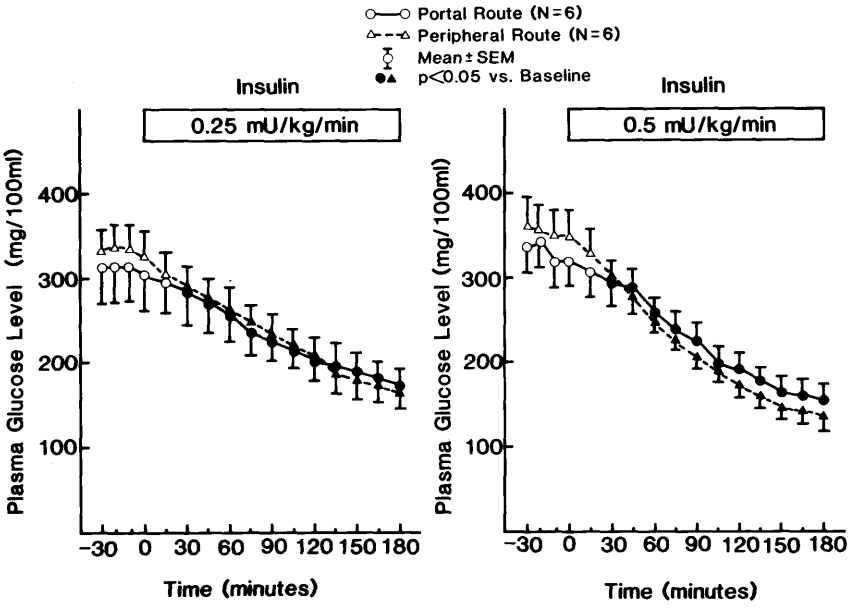

FIGURE 3. Comparison of the effect of 0.25 mU/kg/min (left) and 0.5 mU/kg/min (right) insulin infused into either the portal circulation or a peripheral vein on plasma arterial glucose concentrations in pancreatectomized, diabetic dogs.

insulin concentration averaged 16 ± 1 μU/ml. After the same dose of insulin was infused into a peripheral vein, suppression of glucose appearance was delayed but eventually was similar to that achieved after intraportal insulin infusion. The portal vein insulin concentration was 12 ± 1 μU/ml. The suppression of glucose appearance in each experimental group (as measured by the area under the baseline as extended from the control value of hepatic glucose production before administration of insulin) was somewhat smaller after peripheral i.v. infusion of insulin compared with intraportal infusion of insulin (421 ± 86 mg/kg/min versus 512 ± 52 mg/kg/min, respectively), but it was not significant. After 0.5 mU/kg/min insulin was infused into the portal vein (mean portal vein insulin concentration was 28 ± 2 μU/ml), glucose appearance decreased to 4.5 ± 1.2 mg/kg/min at 90 min and the area under the basal level was 462 ± 101 mg/kg/min, similar to that after 0.25 mU/kg/min insulin was infused into either the portal or a peripheral vein. Glucose appearance decreased to 5.7 ± 1.0 mg/kg/min at 60 min after 0.5 mU/kg/min insulin was infused into a peripheral vein. This infusion produced mean portal vein insulin levels of 20 ± 1 μU/ml. The area of glucose suppression (607 ± 102 mg/kg) was also similar to that obtained by the intraportal infusion of 0.5 mU/kg/min of insulin.

Glucose clearance. During the control period, the mean basal glucose clearance was 2.6 ± 0.2 ml/kg/min (average of the four groups). It did not change significantly after insulin infusion at 0.25 mU/kg/min into either the portal or a peripheral vein (Figure 5). The peripheral insulin concentrations were 9 ± 1 and 14 ± 1 μU/ml, respectively. After 0.5 mU/kg/min of insulin was infused into the portal system (peripheral insulin level of 16 ± 1 μU/ml), glucose clearance significantly increased to 4.3 ± 0.7 ml/kg/min at 105 min and 4.2 ± 0.6 ml/kg/min at 135 min. Peripheral i.v. infusion

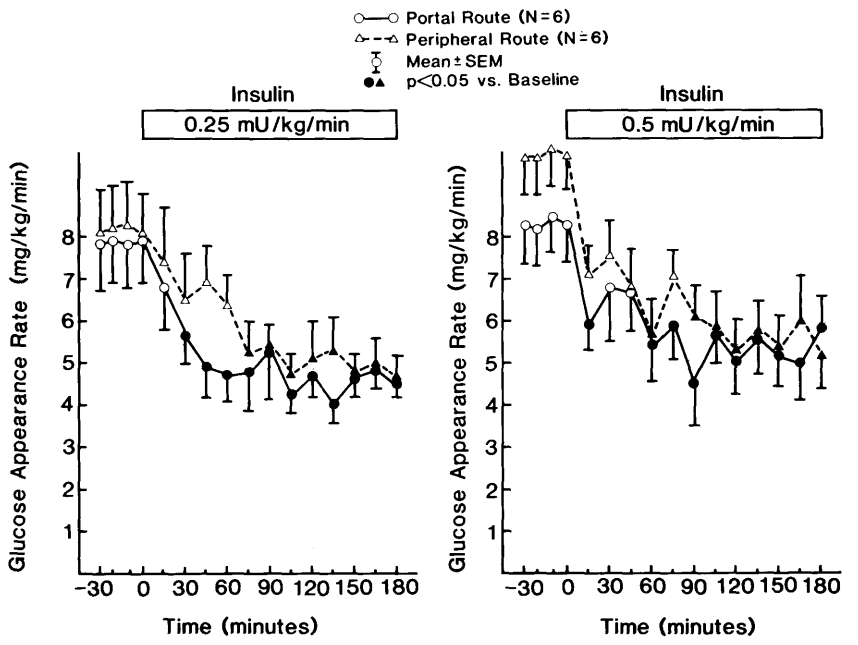

FIGURE 4. Comparison of the effect of 0.25 mU/kg/min (left) and 0.5 mU/kg/min (right) insulin administered into either the portal system or a peripheral vein on glucose appearance rate in pancreatectomized, diabetic dogs.

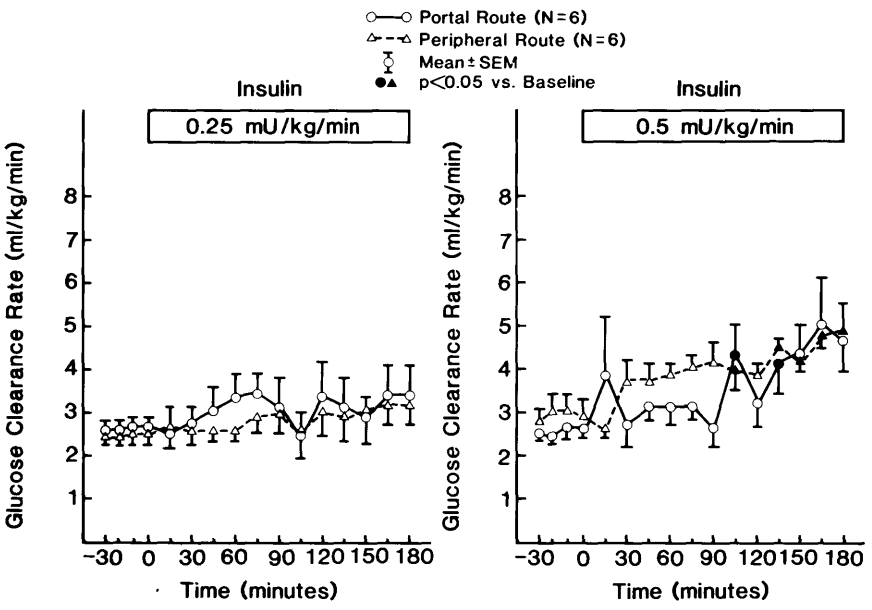

FIGURE 5. Changes in glucose clearance rate after intraportal or peripheral i.v. infusion of insulin at a rate of 0.25 mU/kg/min (left) and 0.5 mU/kg/min (right) in pancreatectomized, diabetic dogs.

of insulin at 0.5 mU/kg/min (peripheral insulin concentration was 25 ± 1 μU/ml) increased glucose clearance significantly to 3.8 ± 0.5 ml/kg/min at 105 min and it reached a peak of 4.8 ± 0.8 ml/kg/min at 180 min. The incremental area above the basal line during 180 min after peripheral intravenous infusion of insulin at 0.5 mU/kg/min was 197 ± 27 ml/kg, which was significantly greater than after intraportal infusion of the same dose of insulin (141 ± 22 ml/kg). However, both these areas were significantly greater compared with those after 0.25 mU/kg/min of insulin infused into either the portal or the peripheral circulation (56 ± 25 ml/kg after the peripheral route versus 64 ± 24 ml/kg after the intraportal route, respectively).

DISCUSSION

The completeness of the pancreactectomy was demonstrated by the basal portal vein plasma insulin concentrations. Although the dogs had received insulin treatment, they did not develop insulin antibodies during the studies. As would be expected, after intraportal infusion of insulin, the portal venous insulin concentration was higher than the peripheral venous insulin level. The portal vein–peripheral vein insulin ratio of between 1.5 and 2 is consistent with hepatic extraction of approximately 40–50% of the insulin presented to that organ after a single transhepatic passage in normal conscious[21,30] and depancreatized diabetic dogs.[31] Such fractional hepatic extraction of insulin was not influenced by the increased amounts presented to the liver after either intraportal or peripheral i.v. infusion of insulin in both normal[19,20] and diabetic dogs.[31] In contrast, after peripheral i.v. infusion of insulin, the portal venous insulin concentration was lower than the arterial insulin levels. This finding indicates a significant nonhepatic splanchnic extraction of insulin and confirms our previous observations in anesthetized and conscious normal dogs[19,31] and in conscious, depancreatized dogs.[31] The magnitude of this extraction is very similar to that we had observed in normal anesthetized dogs[19] and the 11–15% in conscious, diabetic dogs.[31] The presence of nonhepatic splanchnic extraction indicates that, after peripheral administration of insulin, portal vein insulin concentrations are less than peripheral vein levels.

In the present study, the reduction of blood glucose was greater after 0.5 mU/kg/min of insulin infused compared with after 0.25 mU/kg/min, but the difference was only significant for the peripheral i.v. route. At each dose level, there was no significant difference between the two routes of insulin administration. A similar hypoglycemic effect of the two different routes of insulin delivery was observed by others in diabetic dogs.[8,10,12] While Stevenson et al. demonstrated similar blood glucose reduction after 0.1 mU/kg/min insulin infused into either a peripheral vein or into the portal system in alloxan- and streptozotocin-diabetic dogs, they obtained greater blood glucose reduction after 0.85 mU/kg/min insulin infused into the peripheral compared with the portal route.[18] Despite similar changes in the blood glucose after such low doses of insulin infused into either the portal or peripheral circulation, the mechanism could be quite different and the insulin concentrations in the portal and peripheral vein could be important in mediating the different mechanisms. The blood glucose concentration represents the balance between hepatic glucose production and peripheral glucose utilization. Changes in hepatic glucose production are probably related to the portal vein insulin concentrations, while peripheral glucose utilization reflects peripheral arterial insulin levels.[2,18,32–34]

Hepatic glucose production was suppressed equally in the present studies after infusion of insulin at 0.25 and 0.5 mU/kg/min into either route despite unequal increases of the portal vein insulin levels (from 12 ± 1 μU/ml after 0.25 mU/kg/min insulin was infused into the peripheral vein to 28 ± 2 μU/ml after 0.5 mU/kg/min insulin was infused into the portal vein). The basal hepatic glucose production of 8.6 mg/kg/min significantly exceeds normal fasting hepatic glucose output of approximately 2 mg/kg/min[20,21,30] and reflects the lack of adequate portal vein insulin. The present results indicate that an increment of as little as 12 mU/ml insulin in the portal vein is sufficient to significantly reduce hepatic glucose output. No greater suppression was obtained with

portal vein insulin concentrations somewhat greater than twice this amount, even though hepatic glucose output still exceeded the normal value. This augmented hepatic glucose appearance is compatible with the blood glucose still being greater than normal, although it had fallen from the even higher control values. The failure to demonstrate a more direct relationship between the portal vein insulin concentration and reductions in hepatic glucose production may reflect the small number of animals used and the relatively narrow limits of the variation in the portal vein concentration. It may also be related to the nature of the experiment. Thus, the experiment represents the effect of an acute transition from chronic insulin deficiency and hyperglycemia to a very short period of insulin replacement and reduction of blood glucose. Obviously, the more prolonged treatment with insulin and restoration of normal blood glucose would be associated with reduction of hepatic glucose production to normal.

While suppression of hepatic glucose production was similar after both routes and doses of insulin, peripheral glucose utilization, as reflected by glucose clearance, was influenced by the route and dose of insulin infused. Glucose clearance reflects glucose uptake by both peripheral tissues and liver; however, under the conditions of our experiments, in which there is persistent hepatic glucose production, the glucose clearance represents primarily peripheral utilization. Glucose clearance was not significantly increased by infusion of 0.25 mU/kg/min insulin into either the peripheral or the portal circulations despite an increase in the peripheral insulin concentration to 14 and 9 μU/ml, respectively. These results are similar to those reported by Stevenson et al.[18] and suggest that an increase in peripheral insulin concentration greater than 14 μU/ml is necessary to demonstrate an unequivocal effect on glucose utilization. Glucose clearance was significantly augmented when 0.5 mU/kg/min insulin was infused into either the peripheral or portal systems. The effect was significantly greater after the peripheral infusion of insulin, consistent with the higher concentration of insulin in the peripheral artery (25 μU/ml compared with 16 μU/ml). Thus, a reasonable relationship existed between the peripheral insulin concentration and augmented glucose clearance. This is consistent with the observation of Stevenson et al. that 0.85 mU/kg/min insulin infused into the peripheral circulation significantly increased glucose utilization.[18]

The present study suggests that the liver in diabetic dogs is more sensitive than is peripheral tissue to small changes in the plasma insulin concentrations. This is consistent with the observations that the peripheral administration of 0.7 and 1 mU/kg/min insulin to diabetic subjects exerted a direct hepatic action without any peripheral effect.[32,34] It is not clear why these amounts of insulin, which exceeded our largest dose, did not increase peripheral glucose utilization. This confirms the previous results of Altzuler et al.[29] and Sacca et al.[35] that the insulin-deficient liver is more sensitive to small changes in portal vein insulin concentrations than in the control state. Since hepatic glucose production was suppressed to a similar degree by both amounts of insulin infused by both routes, the results might suggest that peripheral administration of insulin, with its higher peripheral plasma insulin levels, would be preferred to the intraportal route in the treatment of patients with diabetes. The greater effect on glucose clearance of 0.5 mU/kg/min infused into a peripheral vein compared with the intraportal route would be consistent with this. However, these were acute experiments with a rapid transition from an insulin-deficient state to a relatively short period of insulin administration and, therefore, may not be applicable to the long-term treatment of diabetes. The superiority of intraportal insulin delivery over the peripheral i.v. route in diabetic animals has been emphasized by others.[10,11,13-15,17,18] Brown et al.[11] demonstrated the complete reversal of diabetes when the venous drainage from fetal pancreatic transplants was diverted to the portal circulation, but not when the venous drainage was into the systemic circulation. Goriya et al.,[13,14] using an open-loop insulin infusion device in pancreatectomized dogs, observed that less insulin was necessary to maintain a normal fasting blood glucose when it was infused into the portal system compared with a peripheral vein. After a meal, more insulin had to be infused into a peripheral vein to normalize the blood glucose compared with intraportal infusion. Stevenson et al.[18] also reported that even when normoglycemia is achieved with peripheral insulin delivery, metabolic substrates and glucose recycling are still abnormal unless insulin is delivered into the portal system. Thus, while the liver in diabetes may be more sensitive to insulin than in the control state, peripheral tissues in the diabetic subjects appear to be less sensitive to insulin than in normal subjects.[36,37]

ACKNOWLEDGMENTS

The authors are indebted to the staff of Cardiovascular Sciences for their superb help in the execution of these experiments. We would also like to thank Barbara Sims and Jamie Hubbard for their outstanding assistance in the preparation of this manuscript.

This work was supported by USPHS grant AM-25253 and the Diabetes and Endocrinology Research Center (AM-27685) of the NIH.

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