Comparison of Peripheral and Portal Routes of Insulin Infusion by a Computer-controlled Insulin Infusion System (Artificial Endocrine Pancreas)

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SUMMARY

This study was undertaken to determine the different consequences of portal and peripheral routes of insulin administration by the artificial endocrine pancreas. Intraportal glucose was infused (10 mg./min./kg. for 60 minutes) in anesthetized normal and pancreatectomized dogs while blood glucose concentrations were monitored continuously. During computer-controlled insulin administration normal glucose tolerance was restored by both portal and peripheral routes of insulin delivery. There were also no significant differences in (1) glycemic patterns, (2) insulin infusion patterns, (3) peripheral IRI levels, and (4) total insulin requirements between the two routes. It is apparent that the peripheral route, which is more readily accessible than the portal route, may be an appropriate infusion site for an implantable or portable prosthesis for controlling blood glucose concentration. DIABETES *25*:691-700, August, 1976.

Insulin administered by an artificial endocrine pancreas restores glucose homeostasis in anesthetized pancreatectomized dogs[1] given intravenous glucose challenges and in labile human diabetics[2] given regular meals. During the studies cited, insulin was infused under computer control into a peripheral vein although it is apparent that an intraportal rather than a peripheral route of administration would more closely approximate the physiologic situation in which pancreatic insulin is secreted into the portal system. Whether this route is necessary to restore all insulin-modulated metabolic processes to normal remains to be determined.[3]

Several aspects[4-7] of the effect of insulin on liver carbohydrate metabolism are unsettled. The significance of the anatomic arrangement wherein the liver is the first organ downstream from the site of insulin secretion, and thus subjected to relatively high insulin concentrations, remains unclear, as does the relationship between the hepatic action of insulin and its degradation by the liver. The advantages of the natural route can be questioned, particularly since various studies[8-14] indicate that the liver removes 30 per cent – 70 per cent of portal vein insulin in a single transhepatic passage. Insulin clearance also appears to increase when portal insulin concentration[8,9] rises or glucose concentration[10,14] increases. As to the physiologic significance of these observations, however, it has not been possible to reconcile them with data obtained from portacaval shunt experiments[15-17] that show neither peripheral plasma insulin levels nor glucose tolerance to be altered after such a procedure.

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In a recent study[18] it was also noted that hypoglycemic response to constant insulin infusion was not appreciably different with either the peripheral or portal route.

This study was undertaken to determine the different consequences of portal and peripheral routes of insulin administration by the artificial endocrine pancreas before, during, and following an intraportal glucose infusion. In selecting an appropriate insulin infusion site for an implantable prosthesis this information is of particular importance.

Our data indicate that the route of insulin infusion makes no significant difference to the glycemic excursion, the total amounts of insulin required, the patterns of insulin infusion, and the peripheral insulin levels attained in pancreatectomized dogs challenged with a uniform intraportal glucose-loading test.

MATERIALS AND METHODS

Animals and Surgical Procedures

Six nonobese male beagles, one to two years old and weighing from 9.5 to 13.5 kg., were fasted for 12 hours prior to each experiment. General anesthesia was induced by intravenously administered pentobarbitol (Nembutal sodium injection, Abbott Laboratories, N. Chicago, Ill.), 25 mg. per kilogram body weight. Anesthesia was maintained throughout the experiment by a slow infusion (27 mg./hour) of pentobarbitol through a 20-gauge catheter (Argyle Medicut, Aloe Medical, St. Louis, Mo.) placed in a saphenous vein. Dual-lumen catheters (DLCs) (Abjad Industries, Toronto) were placed in both superficial contralateral jugular veins and permitted continuous, clot-free blood withdrawal by mixing whole blood with a heparin solution (10 U./ml.) 1 mm. inside the tip of the catheter. One DLC was used exclusively for continuously monitoring blood glucose,[19] while the other was used intermittently to withdraw blood samples for insulin determinations. The heparin was pumped to the DLC tip at 0.05 ml./min. and the blood-heparin mixture withdrawn at 0.10 ml./min. To compensate for blood lost during surgery and sampling for biochemical analysis, at least twice the volume (500 ml.) of normal saline was infused.

A heating pad was used, and rectal temperature, arterial blood gases and pH, hemoglobin, hematocrit, and clotting time were periodically monitored to assure that they remained normal.

The abdomen was opened through a mid-line incision, and a loop of small bowel and subsequently the spleen was delivered into the wound. A PE 50 polyethylene catheter (Intramedic, Clay Adams, Parsippany, N.J.) was inserted into a mesenteric vein, kept patent by a saline infusion (0.6 ml./min.) and subsequently employed for the infusion of the glucose load. In the experiments on normal dogs prior to pancreatectomy another DLC, 15 inches in length, fashioned from a 3½-ft. umbilical artery catheter (Argyle, Aloe Medical, St. Louis, Mo.) was inserted through a splenic vein and advanced just beyond the anastomosis of the pancreaticoduodenal vein. Location of the catheter tip was verified by direct palpation before and after each experiment. Data are reported only for those cases where verification was affirmative. After the first glucose challenge, total pancreatectomy was performed as previously described.[1]

Analytic Methods

An AutoAnalyzer (Technicon Instrument Corp., Ardsley, N.Y.) employing a modified[20] glucose-oxidase (GOD-Perid, Boehringer Mannheim Corp., New York) methodology was employed to measure whole-blood glucose continuously. Plasma-immunoreactive insulin (IRI) was determined with an assay kit employing porcine insulin standard (Phadebas Insulin Test, Pharmacia AB, Uppsala, Sweden). Insulin used during computer control was crystalline zinc porcine insulin, 100 U./ml. (Connaught Laboratories Ltd., Toronto), diluted in normal saline to a concentration of 24 mU./ml. The precision of this dilution was verified by immunoassay. Pooled data populations were statistically compared by the Student's t test.[21]

EXPERIMENTAL DESIGN

The experiments were conducted in three stages: initially on healthy animals, then on the same but pancreatectomized animals, and finally repeated at a later date on these diabetic subjects.

Stage I. In five healthy dogs fasted overnight the blood glucose concentration was monitored continuously. After establishment of a normoglycemic baseline (60-85 mg. per cent) that did not change more than ±5 mg. per cent over 40 minutes, a standardized intraportal glucose loading test of 10 mg./kg./min. was infused as a 17 per cent glucose solution for 60 minutes through the mesenteric catheter. Blood samples for IRI determinations were obtained intermittently from the portal and jugular DLCs, starting 40 minutes before, during, and until 120 minutes after completion of the challenge. Sam-

ples were centrifuged and the plasma frozen at −20° C. for later assay.

Stage II. Immediately following the completion of stage I, the portal DLC was removed, the animal was pancreatectomized, and computer-controlled insulin infusion was begun. Insulin was administered through a peripheral route (saphenous vein) or, alternatively, an intraportal route (mesenteric vein). A normoglycemic baseline was again established and the same intraportal glucose challenge infused. As before, blood samples taken from a jugular DLC were used to determine peripheral insulin concentrations. Two hours after completion of the challenge and the recovery of normal glucose levels the insulin infusion was switched to the alternative route (from portal to peripheral or vice versa) and another standard intraportal challenge infused after the required normoglycemic baseline had been obtained. Two hours after the end of the challenge the second stage was completed by the removal of all catheters, the incision was closed, and the dog permitted to recover from surgery. Thereafter the animals were maintained daily and as indicated on six to eight pancreatic enzyme capsules (Cotazyme, Organon Ltd., Montreal) and 8 to 12 U. subcutaneous porcine NPH insulin (Connaught Laboratories, Toronto).

Stage III. The third stage of the experiment was conducted three to four weeks after the completion of the previous stage and consisted of repeating the two challenges of the previous stage but reversing the order of the route of insulin delivery. In three of the six subjects this stage was repeated several times, the order of the route of insulin infusion being reversed each time.

Control Algorithms and Parameters

In order to improve the response of the control system and simplify the comparison between portal and peripheral insulin infusion, the original control algorithm[22] was modified. The improved algorithm[23] is more effective in suppressing insulin infusion rates when glucose concentration is falling rapidly. This has resulted in eliminating the need for extra glucose infusion to prevent the reactive hypoglycemia prevalent in previously reported experiments[1] on pancreatectomized dogs.

Glucose data are fed into the computer approximately twice every second and the average determined at one-minute intervals. The appropriate rate of insulin infusion is calculated and updated every 60 seconds by the computer from the following equations:

$$1 = \tfrac{1}{2}M_I\left[1 + \tanh S_I(G_p - B_I)\right]$$

where

I is the insulin infusion rate in mU./min.,
M_I is the maximum insulin infusion rate,
S_I is the sigmoid steepness factor,
B_I is the glucose concentration at the half-maximum insulin infusion rate,
G_p is a calculated quantity called "projected glucose."

This "projected glucose" is the sum of the actual glucose level and a difference factor based on the rate of change of glucose concentration. That is,

$$G_p = G + DF, \qquad (2)$$

where

G is the measured glucose concentration and
DF is the difference factor defined as:

$$DF = K_1 \langle \dot{G} \rangle^3 + K_2 \langle \dot{G} \rangle, \qquad (3)$$

where

$\langle \dot{G} \rangle$ is the linearly weighted average rate of change of glucose concentration based on the previous four minutes of monitoring, and K_1 and K_2 are constants.

The values of the various parameters and constants were based on the results of our previous computer simulation experiments and remained unchanged over the entire course of this study. These values are listed below:

M_I = 0.5 mU./min/kg., S_I = 0.02/mg. per cent, B_I = 145 mg. per cent, K_1 = 1.0, and K_2 = 10.

RESULTS

Normals (Healthy, Nonpancreatectomized Subjects)

Data from experiments on five normal dogs is presented in figure 1 and table 1. The portal glucose infusion test (figure 1a) causes blood glucose concentration (figure 1b) to rise to about 140 mg. per cent from a stable baseline (70 mg. per cent). When the 60-minute glucose infusion is terminated blood glucose declines, recovering to baseline levels in 30 minutes and remaining stable until monitoring was terminated. The portal IRI concentrations (figure 1c)

TABLE 1

Response of normal dogs to intraportal glucose infusion

						Glucose (mg. per cent)									
Time (min.)	−40	−30	−20	−10	0	10	20	30	40	50	60	70	80	90	100
Mean blood glucose concentration	72.8	72.3	72.6	72.5	73.1	102.3	118.2	126.4	132.6	136.4	137.3	111.3	90.7	79.5	72.9
n = 5															
S.E.M.	1.8	2.0	2.1	2.2	2.2	1.8	1.8	1.8	1.9	2.3	2.7	3.5	4.0	4.7	4.9
						Peripheral IRI (μU./ml.)									
Time (min.)	−40	−10	−2	0	2	4	6	8	10	15	30	45	60	75	90
Mean peripheral plasma IRI	18.4	15.5	20.4	14.4	19.3	30.8	31.8	31.4	28.6	29	34.4	38.2	39	25	21.2
n = 5															
S.E.M.	4.0	3.0	3.0	2.9	4.5	3.7	5.2	2.7	3.0	4.6	5.7	4.7	2.0	3.7	6.7
						Portal IRI (μU./ml.)									
Time (min.)	−40	−10	−2	0	2	4	6	8	10	15	30	45	60	75	90
Mean portal plasma IRI	30.7	20.0	21.3	33.3	54.7	91.3	119.0	114.0	76.0	95.0	118.7	105.7	101.0	55.0	17.0
n = 3															
S.E.M.	8.1	6.6	6.8	13	13.7	33.1	42.7	41.5	16.3	33.8	25.6	36.2	38.7	20.4	4.0

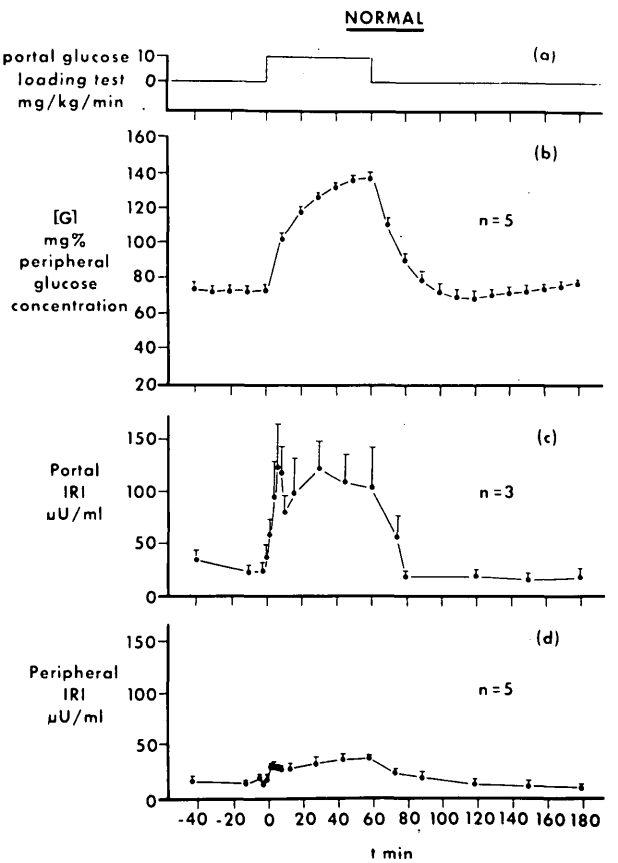

FIG. 1. The response of a normal, healthy dog to a 60-minute intraportal glucose challenge. (a) glucose load, (b) peripheral blood glucose concentration, (c) portal vein IRI, and (d) peripheral plasma IRI (all data shown mean ± S.E.M.).

show a "biphasic" pattern in response to this type of glucose challenge while peripheral IRI levels (figure 1d) exhibit a "monophasic" pattern increasing from a 10-15 μU./ml. baseline to 40-50 μU./ml. during the glucose challenge.

Data on the glycemic response of normal dogs to this type of glucose load are presented for five of the six animals used in this study, the first dog having been pancreatectomized before this set of experiments was begun. Peripheral IRI values are reported for five dogs, while portal plasma IRI values are reported for only three of these, since in the others the desired position of the portal-blood-sampling DLC could not be verified at the end of the experiment.

Control with Peripheral Insulin Infusion

The data from acutely pancreatectomized (stage II) and chronically pancreatectomized (stage III) dogs have been pooled and are shown in table 2.

Figure 2 shows graphically the blood glucose concentrations, peripheral IRI levels, insulin infusion rates, and total insulin requirements during computer-controlled insulin infusion into a peripheral vein. Before the glucose load the blood glucose concentration was 72 mg. per cent, peaking at 135 mg. per cent at the end of the 60-minute challenge and finally returning to baseline levels and remaining at 60 - 70 mg. per cent for two hours, when monitoring was terminated. Peripheral IRI levels rose from 15 μU./ml. to 80 μU./ml. during glucose loading, and a "biphasic" insulin infusion pattern is evident in figure

TABLE 1 (*cont'd.*)

110	120	130	140	150	160	170	180
70.2	69.8	71.6	73	73.8	75.6	76.8	79.2
4.7	4.2	3.0	2.8	2.6	2.4	2.3	1.2
120	150	180					
14.6	13.2	11.2					
3.9	5.5	2.5					
120	150	180					
20.3	15.7	19.0					
4.9	5.7	5.6					

4d. A total of 1.60 ± 0.14 U. of insulin was infused over the 220-minute course of the experiment. While the computer revises the insulin infusion rate every 60

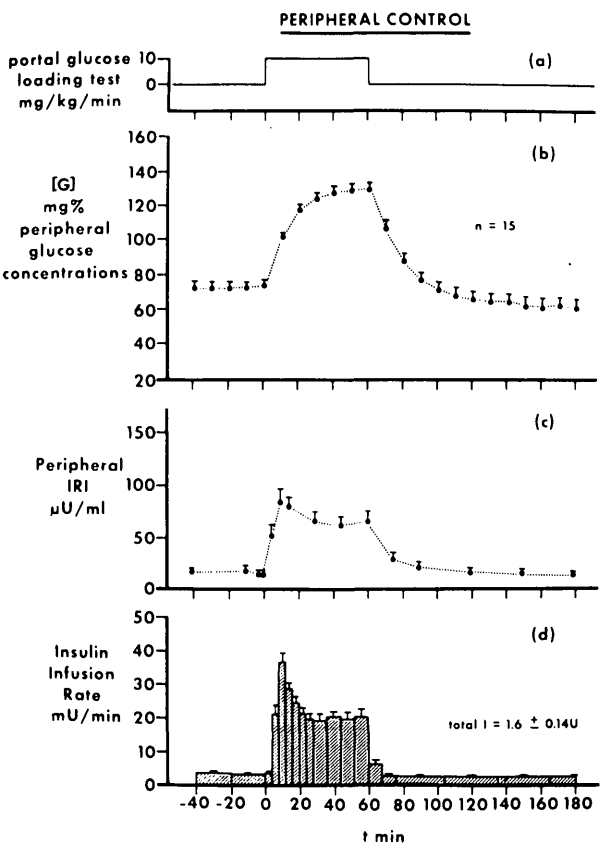

FIG. 2. The response to an intraportal glucose challenge of a pancreatectomized dog during computer-controlled insulin infusion into a peripheral vein. (a) glucose load, (b) peripheral blood glucose concentration, (c) peripheral plasma IRI, and (d) peripheral insulin infusion rate.

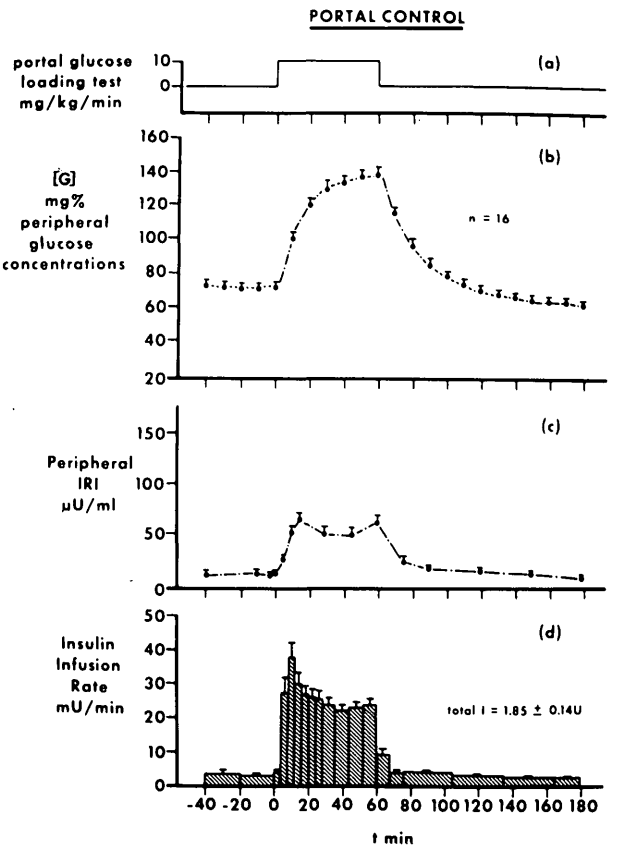

FIG. 3. The response to an intraportal glucose challenge of a pancreatectomized dog during computer-controlled insulin infusion into the portal circulation. (a) glucose load, (b) peripheral blood glucose concentration, (c) peripheral plasma IRI, and (d) portal insulin infusion rate.

seconds, it has been convenient for analytic purposes to pool some of these data points by averaging these rates over four, eight, or 20 minutes, depending on the variability of infusion rates during periods of rapidly changing blood glucose. The greatest minute-to-minute changes occurred in the first 15 minutes after the start of the glucose challenge, and the pooled data retain the salient features of this insulin infusion pattern. Pooling of stage II and stage III data can be justified since the results were comparable. Table 3 summarizes data obtained from experiments on acutely pancreatectomized dogs only. It is also evident that the total insulin requirements were not significantly different ($p<0.05$) between the two types of animal preparations.

Control with Portal Insulin Infusion

The results of experiments in which blood glucose concentration was controlled by portal infusion of insulin are shown graphically in figure 3 and listed in table 4. Blood glucose levels rose from 72 mg. per cent to 137 mg. per cent during glucose loading but

TABLE 2

Response of pancreatectomized dogs with peripheral insulin infusion

						Glucose (mg. per cent)									
Time (min.)	−40	−30	−20	−10	0	10	20	30	40	50	60	70	80	90	100
Mean blood glucose concentration n = 16	72.0	72.0	72.0	72.7	74.5	101.3	117.8	124.6	127.6	128.8	129.4	106.5	88.0	77.5	72.3
S.E.M.	3.2	2.8	2.5	2.2	2.4	2.4	2.4	3.3	4.0	4.0	4.0	4.5	4.1	3.8	3.8
						Peripheral IRI (μU./ml.)									
Time (min.)	−40	−10	−2	0	5	10	15	30	45	60	75	90	120	150	180
Mean peripheral plasma IRI n = 12	14.1	17.0	13.5	13.9	49.2	82.7	77.8	63.6	58.8	63.1	27	21.2	15.8	14.7	13.5
S.E.M.	4.8	4.0	2.8	3.0	11.0	11.8	8.6	10.6	8.6	9.9	5.8	4.3	3.7	3.3	2.6

					Peripheral insulin infusion rate (mU./min.)									
Time (min.)	−40--20	−20-0	0-4	4-8	8-12	12-16	16-20	20-24	24-28	28-36	36-44	44-52	52-60	60-68
Mean insulin infusion rate (internal average) n = 16	2.5	2.6	3.0	20.3	36.8	27.7	23.5	20.2	18.6	18.2	19.2	18.7	19.4	5.4
S.E.M.	0.22	0.26	0.33	3.3	2.5	1.7	2.2	1.9	1.7	2.1	1.8	2.0	2.3	1.1

returned to baseline values 30 minutes after termination of the challenge. Peripheral IRI levels reached 65 μU./ml. from basal levels of 10 - 15 μU./ml. A total of 1.85 ± 0.14 U. of insulin was infused.

Comparison of Portal and Peripheral Computer Control and Normal

The blood glucose concentration patterns of the normal healthy dog can be compared to those obtained by portal and peripheral infusion of insulin under computer control in figure 4b. There is no significant difference in these patterns until 90 minutes after termination of the glucose challenge, when glucose levels attained during portal and peripheral insulin administration are lower, although still in the normoglycemic (60-85 mg. per cent) range, than those observed in the normal dog. No difference in glycemic pattern is seen at any time between portal and peripheral insulin infusion. During the glucose challenge, peripheral IRI levels (figure 4c) in the insulin-infused dogs were higher than in the healthy animals, but before and after the challenge these insulin levels were not significantly different ($p>0.05$). No significant differences ($p>0.05$) in peripheral IRI values are seen between the two different routes of insulin administration. In figure 4d the patterns of insulin infusion through the peripheral and portal route are compared, showing no significant difference ($p<0.05$). This observation is consistent with the fact that the total insulin infused (area under bar graphs) by these two routes is not significantly different ($p<0.05$).

DISCUSSION

The work presented here follows the demonstration that glucose homeostasis can be restored by the

TABLE 3

Response of acutely pancreatectomized dogs infused with insulin

						Glucose (mg. per cent)								
Time (min.)	−40	−30	−20	−10	0	10	20	30	40	50	60	70	80	90
Mean blood glucose concentration n = 6	70.8	70.0	68.8	69.5	70.18	105.3	122.5	132	136.2	138.3	138.5	111.2	88.4	74
S.E.M.	4.7	4.4	4.2	4.1	4.2	4.1	4.5	5.3	5.0	5.6	6.4	7.9	7.2	7.3

Total insulin

Mean total insulin infusion over 220 min. = 1.88 units S.E.M. = 0.13 units
n = 6

TABLE 2 (*cont'd.*)

110	120	130	140	150	160	170	180
68.8	66.5	65.4	65.2	63.4	62.3	63.4	61.8
4.0	3.9	4.0	4.1	4.3	4.1	4.2	3.6

68-76	76-104	104-136	136-164	164-180	Total insulin infusion (units)
2.0	2.0	2.0	1.8	1.9	1.60
0.40	0.34	0.30	0.32	0.25	0.14

computer-controlled delivery of insulin (by an artificial endocrine pancreas), particularly since a marked economy of insulin can be obtained with the addition to the control algorithm of the difference factor, which depends on the rate of change of blood glucose concentration. The need for a derivative component had already been suggested by others[24,25] as a result of studies on a mathematical model of glucose homeostasis. Since insulin had been delivered only by a peripheral intravenous route in the reported studies,[1] it was important to establish whether an intraportal route might not result in an even more marked economy of insulin or perhaps an improvement of blood glucose regulation following a standardized glucose challenge.

The experimental subject chosen for this study was the healthy beagle dog in which diabetes can be easily and reliably produced by pancreatectomy. Experience had shown that intravenous glucose challenges were a highly reproducible method of stimulating the glucoregulatory system of a given subject, especially at closely spaced intervals. In these studies intraportal rather than peripheral intravenous glucose challenges were infused. Also, this route more closely approximates physiologic conditions, where glucose from the gastrointestinal tract is first delivered to the liver prior to reaching the peripheral tissues. While it is recognized that this type of glucose challenge is not entirely physiologic and that an oral glucose load would be more appropriate, it is also apparent, since gastrointestinal absorption may vary, that oral or, in the

TABLE 3 (*cont'd.*)

100	110	120	130	140	150	160	170	180
64.5	58.7	55.7	53.9	53.9	54.6	55.2	58	59.9
6.7	6.4	5.9	5.7	5.6	5.6	5.3	5.1	4.3

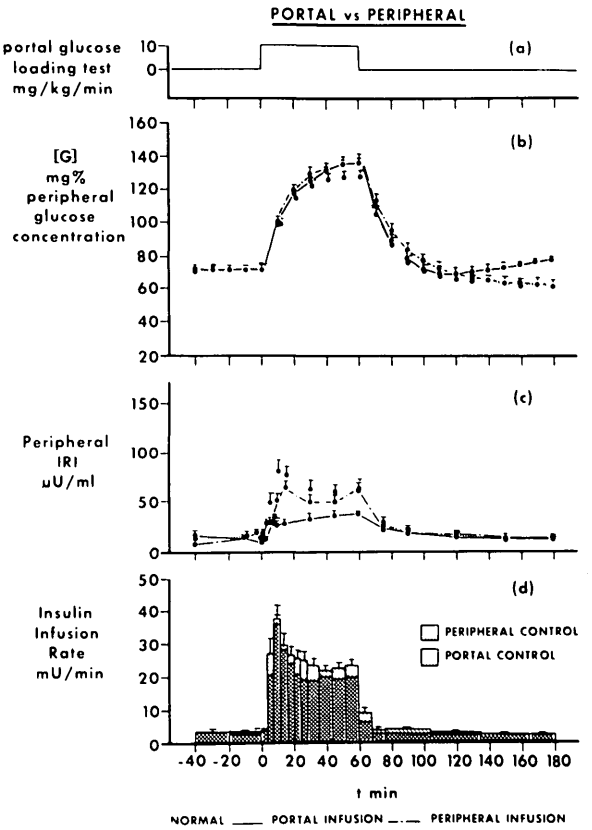

FIG. 4. Three-way comparison between the response of (1) the healthy dog (N = 5), (2) the pancreatectomized dog under computer-controlled insulin infusion into a peripheral vein (N = 15), and (3) the pancreatectomized dog under computer-controlled insulin infusion into a portal vein (N = 16).

case of an anesthetized dog, intragastric glucose loads would be less reproducible than intraportal glucose infusions. The possible role of gut secretagogues as modulators of insulin secretion makes the insulin response to oral and intraportal glucose difficult to compare, although the comparison of the effects of portal and peripheral insulin infusion remains valid if one assumes that these gastric hormones do not affect insulin action and glucose metabolism directly. Therefore, glucose was infused uniformly at 10 mg./kg./min. for 60 minutes into the portal system of the anesthetized dog. In this way the healthy dog was studied initially (stage I), then rendered surgically diabetic and restudied immediately (stage II). Following a recovery period of at least three weeks the same subject was restudied several times (stage III), at each occasion the order of the portal and peripheral insulin route of delivery being reversed to eliminate effects that might be due to the termination of the overnight fast and the order in the experiment of the two routes of insulin delivery.

In a preliminary series of experiments[23] not re-

TABLE 4

Response of pancreatectomized dogs with portal insulin infusion

						Glucose (mg. per cent)									
Time (min.)	−40	−30	−20	−10	0	10	20	30	40	50	60	70	80	90	100
Mean blood glucose concentration	73.1	72.8	71.9	72.3	73.6	101.1	120.7	130.7	133.6	137	138.4	114.8	96.7	85.6	78.8
n = 16															
S.E.M.	2.1	2.0	1.9	1.9	2.2	3.1	3.5	4.0	4.0	4.3	4.4	4.0	4.1	3.8	3.6
						Peripheral IRI (μU./ml.)									
Time (min.)	−40	−10	−2	0	5	10	15	30	45	60	75	90	120	150	180
Mean peripheral plasma IRI	8.7	12.3	10.2	12.6	25.3	52.8	64.9	51.6	49.7	63.5	25.0	18.2	15.8	11.6	9.4
n = 12															
S.E.M.	3.0	2.1	1.7	3.0	5.5	7.6	7.1	7.0	7.3	7.6	5.2	3.5	3.2	2.3	2.9

					Portal insulin infusion rate (mU./min.)									
Time (min.)	−40−−20	−20-0	0-4	4-8	8-12	12-16	16-20	20-24	24-28	28-36	36-44	44-52	52-60	60-68
Mean insulin infusion rate (internal average)	2.7	2.6	3.3	26.5	37.2	29.6	26.3	25.5	25.0	23.3	21.8	22.6	23.1	8.8
n = 16														
S.E.M.	0.24	0.21	0.41	5.0	4.3	3.3	2.6	2.2	2.5	2.2	2.1	2.0	2.0	1.8

ported here, the precise values of the parameters of the control algorithm were defined, so that the glycemic excursion obtained following an intraportal glucose loading test in the diabetic was similar to that recorded in the healthy subject, and furthermore, that an appropriate amount of insulin was infused during the challenge to ensure that no glucose was needed to prevent a reactive hypoglycemia. Otherwise, meaningful comparisons of the insulin requirements would not have been possible. This does not imply, however, that the insulin infusion dynamics of the artificial pancreas are assumed to be physiologic or identical to normal insulin secretion under similar situations. The 4½-minute glucose analyzer delay alone precludes such an assumption. Furthermore, to ensure the reproducibility of the results, it was necessary to establish a 40-minute baseline prior to each challenge and to follow the response for 120 minutes after the completion of the standardized 60-minute intraportal glucose loading test.

In the statistical comparison of the response of the healthy dogs and the pancreatectomized dogs infused with portal or peripheral insulin no significant differences were found at the 5 per cent level except in the peripheral plasma IRI during the intraportal glucose challenge. The higher IRI concentrations measured in insulin-infused dogs may be due to a difference in the specificity of the antibody (used to estimate immunoreactive insulin) for endogenous and exogenous (crystalline zinc) insulin. The lack of a statistically significant difference in glycemic response between normal and insulin-infused dogs does not necessarily mean they are the same. Nevertheless, considering the number of experiments (five normals and 16 in each insulin-infused group), the probability of a type II error (incorrectly assuming the groups are similar) is small and was further confirmed by calculations of the power function of the *t*-tests. This approach was also used in the comparison between portal and peripheral insulin infusion.

The results show no significant differences between intraportal and peripheral I.V. insulin infusion in terms of the glycemic response, the peripheral IRI levels, the insulin infusion patterns, and total insulin requirements during the steady state or the changing glucose concentrations that result from a glucose loading test. Thus, normal glucose tolerance can be achieved by peripheral insulin without high portal vein levels or large hepatic arteriovenous concentration differences. However, while it is recognized that regular crystalline insulin and native insulin have different binding and degradation characteristics[26] it is unlikely that this is a significant factor in the comparison of the two routes.

While there is statistically no significant difference in glucose tolerance and insulin infusion rates during portal and peripheral control it is nevertheless apparent from figure 4 that somewhat more insulin is re-

TABLE 4 (*cont'd.*)

110	120	130	140	150	160	170	180
74.1	70.7	68.5	66.9	65	64.5	64.5	62.3
3.4	3.3	3.4	3.4	3.5	3.4	3.6	3.3

68-76	76-104	104-136	136-164	164-180	Total insulin infusion (units)
3.4	3.5	2.7	2.0	2.1	1.85
0.57	0.60	0.54	0.26	0.23	0.14

quired for the portal route and results in marginally reduced glucose tolerance. These two observations taken together indicate that peripheral insulin is superior for controlling hyperglycemia in terms of insulin economy.

A rate of insulin infusion required to produce a unit level of peripheral IRI (i.e., I/IRI = rate of insulin infusion (mU./min.)/peripheral IRI (μU./ml.)) can be calculated for portal and peripheral insulin infusions.

This calculation is most valid when both blood glucose levels and insulin infusion rates are stable, such as during the 40-minute baseline and the last few minutes of the glucose challenge. It is apparent from figure 4d that there is no difference in insulin infusion rates or resulting peripheral IRI levels in the 40 minutes preceding the glucose infusion and consequently no discernible difference between the two routes. However, at t = 60 minutes, for portal infusion I/IRI is 3.27 ml./min. and for peripheral infusion it is 2.75 ml./min. Comparing the two routes, we find that about 20 per cent more insulin is required to achieve a given peripheral insulin level when the insulin is delivered intraportally. Hepatic clearance of insulin enhanced by the elevated portal insulin concentrations and by the rise in glucose levels may account for the observed difference.

If intraportal insulin does not appear to be essential for restoring normal glucose tolerance, why then does the pancreas secrete into the portal vein? Perhaps the other pancreatic endocrine hormone, glucagon, which influences carbohydrate homeostasis mainly by virtue of its hepatic effects, is more appropriately secreted into the portal circulation. Consequently, of the two pancreatic hormones, intraportal glucagon concentrations rather than intraportal insulin levels may have the greater metabolic significance. If this is the case, then the significantly lower glucose concentrations seen in figure 4 that develop under computer control 60 minutes after the termination of the glucose challenge may imply the lack of a counterregulatory response. This lack may be attributable to an acute deficiency of glucagon in our animal preparations. Certainly such hypoglucagonemia occurs immediately following pancreatectomy[27] and in the short term thereafter during which time these experiments were conducted, since it has been shown[28,29] that pancreatectomized dogs do not regain normal basal glucagon levels until four weeks after surgery. Alternatively, this lack of a counterregulatory response may suggest that either the secretory dynamics[27,28] or the physiologic activity of gut glucagon are not identical to those of pancreatic glucagon.

In these experiments the regulation of central venous glucose concentration by the peripheral or the portal delivery of insulin may not of itself restore normal glucose or metabolic homeostasis. Certainly growth hormone, gastrointestinal hormones, and amino acids all have profound effects on insulin secretion. More comprehensive experiments involving the measurement of glucagon, growth hormone, and intermediary metabolites as well as glucose turnover studies will be necessary in order to assess whether the metabolic homeostasis of the healthy animal can be completely restored.

This study has shown that for an intraportal glucose load the peripheral intravenous route of insulin delivery is equivalent to the intraportal route in terms of the degree of glucose regulation obtained, the amounts and patterns of insulin required, and the levels of peripheral insulin concentration achieved. Therefore it appears that the peripheral route, which is more readily accessible than the portal route, is appropriate for studies on the artificial endocrine pancreas.

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