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Effect of insulin on glucose metabolism in the dog after portacaval transposition[1]

THOMAS E. STARZL,[2] WILLIAM A. SCANLAN, FRED H. THORNTON, ROBERT M. WENDEL, BURTON STEARN, ROBERT E. LAZARUS, WILLIAM McALLISTER, AND WILLIAM C. SHOEMAKER
Department of Surgery, Northwestern University Medical School; Department of Surgical Research, Hektoen Institute, Cook County Hospital, Chicago, Illinois; and Departments of Surgery, University of Colorado and Denver Veterans Administration Hospital, Denver, Colorado

STARZL, THOMAS E., WILLIAM A. SCANLAN, FRED H. THORNTON, ROBERT M. WENDEL, BURTON STEARN, ROBERT E. LAZARUS, WILLIAM MCALLISTER, AND WILLIAM C. SHOEMAKER. *Effect of insulin on glucose metabolism in the dog after portacaval transposition.* Am. J. Physiol. 209(1): 221–226. 1965.—The effect of insulin on hepatic glucose metabolism was studied by a multiple-catheter technique in unanesthetized dogs with Eck fistula and with portacaval transposition. With the latter preparation, blood entering and leaving the liver was sampled from peripherally inserted catheters. In the unanesthetized Eck-fistula animals, insulin infusion produced a decrease in the hepatic glucose output. In the dogs with portacaval transposition, a constant infusion of insulin was given alternately by systemic and by intraportal routes. There was no significant difference between the effects of insulin administered by the two routes. During insulin infusion, glucose concentration differences across the liver were reduced, hepatic plasma flow was transiently elevated, and hepatic glucose output was decreased. After discontinuance of insulin, there was a transient rise of hepatic glucose output to above control values.

hepatic glucose metabolism hepatic blood flow
Eck fistula hepatic glucose response to insulin

THE INFLUENCE OF INSULIN on the hepatic release of glucose has been a recurring and often controversial subject. An array of conflicting evidence has been reported, based on direct and indirect measurements, procured from normal and altered experimental subjects, in anesthetized and waking states, with varying doses and routes of insulin administration, and with differing conditions of nutrition.

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[2] Markel Scholar. Present address: University of Colorado Medical School, Denver, Colo.

In general, those who have measured hepatic glucose output in normal dogs directly by use of multiple-catheter techniques have failed to demonstrate a significant decrease during insulin infusion (8, 17, 21–23, 28) or have observed such an effect only under very specific experimental conditions (12). In contrast, Madison and his associates (14–16) have consistently demonstrated a sharp fall in hepatic glucose output of anesthetized dogs with Eck fistulas. The significance of the latter results is subject to some reservation, since dogs with Eck fistula have impaired liver function (9, 11, 21), reduced hepatic blood flow (10, 13, 27), and a modified response to insulin (25). Further, the Eck-fistula animals were fed a diet richer in carbohydrates than the customary kennel ration, metabolic studies were performed only 2 weeks after surgery, and anesthesia was used. Nevertheless, these findings have been confirmed in cirrhotic humans who have been subjected to therapeutic portacaval operations (6).

In the present study, a portacaval-transposition preparation was used in an attempt to clarify some of the divergent views on this subject. The experiments of Madison and his associates with Eck fistula first were repeated in unanesthetized dogs. A multiple-catheter technique was developed for use in unanesthetized dogs with portacaval transposition (26). With this preparation, the portal venous blood flow was diverted to the inferior vena cava and the blood from the inferior vena cava was diverted into the liver. Responsiveness to insulin (25), liver function (24), and hepatic blood flow (10, 27) in dogs with portacaval transposition remained essentially normal. The transposition preparation has certain features of the normal animal and of the animal with Eck fistula which make it a useful preparation for evaluation of the action of insulin on hepatic carbohydrate metabolism.

METHODS

Preparations

A total of 26 experiments were carried out in 11 unanesthetized mongrel dogs weighing 14–20 kg. The mean body weight was 15.9 ± 0.4 (SE) kg.

An Eck-fistula operation was performed on three animals. For a 3-week period after recovery from this operation, the dogs were fed once daily a diet of approximately 70% carbohydrate and 5% protein. Then, five experiments were performed on these animals.

In eight dogs, the modified portacaval-transposition operation (4, 26) was carried out 2 months or more before the experiments. All tributaries entering the vena cava from the inguinal ligaments to the diaphragm, except the renal veins, were ligated so that infusions into the ileocaval system could pass only into the liver (Fig. 1). Postoperatively, these animals were maintained at constant weight on a standard kennel diet fed once daily for 2 or more months after operation. Twenty-one experiments were performed in eight of these dogs; insulin was infused via the systemic route in eleven and via the intraportal route in ten.

Protocol

After a 14- to 18-hr fast on the morning of each animal's initial experiment, 1% procaine anesthesia was administered subcutaneously and catheters were inserted through peripheral "cut-downs." A catheter was placed into the left common hepatic vein via the external jugular vein (Fig. 1). A second catheter was placed in the abdominal aorta via a side branch of the femoral artery. A catheter for constant Bromsulphalein (BSP) infusion was placed into a foreleg vein. In the dogs with transpositions another catheter was inserted into a side branch of the femoral vein, through the inferior vena cava, and into the proximal portal vein for sampling the venous inflow tract. The "portal venous" (PV) blood from this catheter represented venous blood from the hindquarters and kidneys en route to the liver. Catheters were placed in a foreleg vein for systemic insulin infusion and into the inferior vena cava for "intraportal" insulin infusion (Fig. 1).

The glucagon-free insulin infusions were given to the animals with Eck fistulas at the rate of 0.001 U/kg per min for 50 min. In portacaval transposition, insulin infusions, 0.0007 U/kg per min, were given either systemically (via a forelimb vein) or intraportally (via the femoral-iliac-caval system). Usually experiments were performed on each dog daily for 2–4 days with a different route of insulin infusion (forelimb vein or portal vein) each day in randomized order. Between experiments, catheters were left in situ protected by a specially constructed jacket. The animals were fed daily after each experiment. If the dogs failed to eat or for any reason did not appear to be in optimal condition, the catheters were removed and the animal was restudied after 1 or 2 weeks. Each animal was studied at least once with each

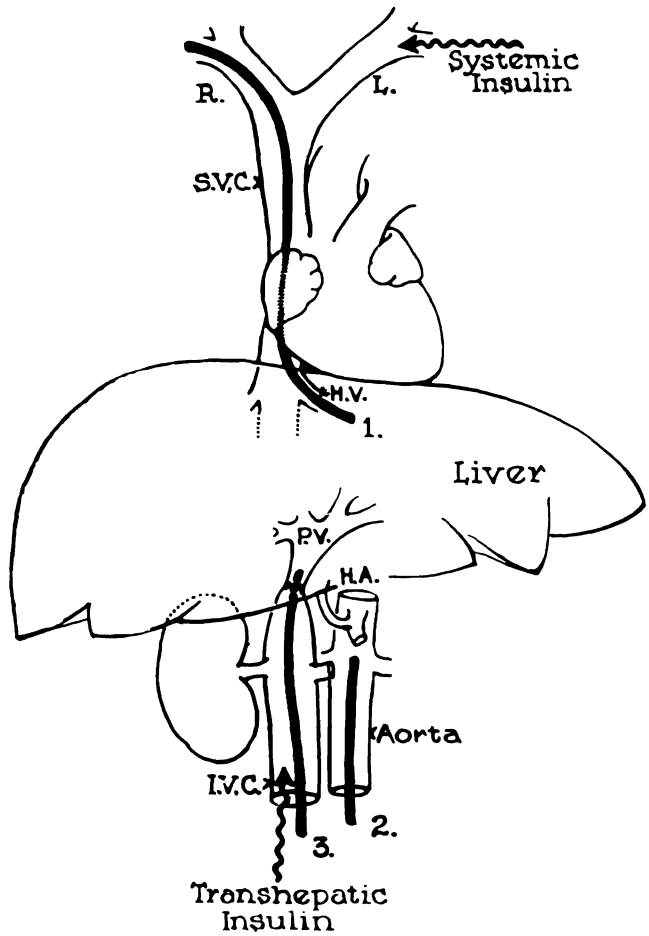

FIG. 1. Diagrammatic representation of experimental preparation with the vena cava anastomosed to the proximal portal vein. Blood leaving the liver is sampled from the left common hepatic vein with the catheter adjacent to no. 1. Arterial blood entering the liver is sampled from the aorta with the catheter adjacent to no. 2. Venous blood entering the liver is sampled from the distal vena cava (which has been anastomosed to the proximal portal vein) with catheter no. 3. Insulin is given either systemically (by an arm vein) or intraportally (via the inferior vena cava).

route of insulin administration. About 6 hr before the experiment, 175 ml fresh whole homologous blood was given as replacement for the blood loss of sampling.

Analyses

Samples were collected in chilled heparinized test tubes and centrifuged immediately. Hepatic plasma flow was measured by a modified Bromsulphalein method (20). Plasma glucose was analyzed colorimetrically on a Technicon AutoAnalyzer. Reproducibility of ±2% was obtained with glucose standards in each experiment. At least three control measurements, over a period of 1 hr, were obtained before insulin was started.

The data of each group of experiments were analyzed statistically for means and SE. Paired comparisons were made between the control data and the data from each

TABLE 1. *Response of dogs with Eck fistula to insulin*

Control Period	Min After Onset of Insulin Infusion				Min After Cessation of Insulin Infusion		
	8	20	32	44	22	54	98
Arterial glucose concentration, mg/100 ml							
93.8 ± 2.6	86.4±2.6*	79.4±5.1*	70.0±5.03†	66.4±6.2†	76.0±8.4*	81.2±7.5	78.6±6.6
Hepatic plasma flow, ml/min							
486 ± 117	617±190	357±105	378±118	513±168	434±132	425±125	609±207
Hepatic glucose output, mg/min							
80.0 ± 17.9	98.8±19.0	41.6±12.7†	57.8±23.7*	109.8±44.0	110.0±31.9	77.6±20.1	122.4±63.2

Data are means ± SE of observed and derived values in control period, during infusion, and after cessation of infusion in 5 experiments on 3 dogs. Statistical evaluations were calculated on the basis of paired distributions where the control measurement of each experiment was compared with the corresponding measurement taken at each time period. * $P < 0.05$. † $P > 0.01$.

sampling time during and after insulin infusion. An analysis of variance (13) also was employed to determine whether the response to physiologic doses of insulin administered into the systemic circulation was significantly different from the responses to insulin administered into the portal venous inflow. The F ratios for the interactions (13) were determined.

RESULTS

Eck-Fistula Preparation

The data of the series of Eck-fistula animals are summarized in Table 1. Hypoglycemia was progressive during insulin infusion; an average decrease in arterial glucose of 23 mg/100 ml was reached 44 min after onset of infusion. The gradual return to control values was not quite complete 100 min after the termination of the insulin infusion. The mean control hepatic venous-arterial (HV-A) plasma glucose concentration differences averaged 18.2 ± 2.8 (SE) mg/100 ml. This decreased 7 mg/100 ml during the insulin infusion. During the recovery phase after insulin infusion, these concentration differences increased above preinfusion control levels.

Twenty minutes after onset of the infusion the mean control glucose output decreased 38 mg/min. Toward the end of the insulin infusion and during recovery from hypoglycemia, the mean hepatic glucose outputs exceeded control values but were not significantly different from them (Table 1). In essence, studies on the unanesthetized Eck-fistula dog confirmed the work of Madison et al. (14–16) by demonstrating decreased hepatic glucose output during insulin infusion.

Portacaval-Transposition Preparation

Effect of insulin by systemic venous and intraportal administration. The data obtained from over 200 blood samples obtained from each of three catheters before, during, and after insulin infusion are shown in Table 2. Paired comparisons were made of the effects of insulin given by systemic and intraportal routes. There was no demonstrable difference between the two routes of infusion in terms of glucose concentrations, glucose concentration difference across the liver, hepatic glucose output, and plasma flow. The F ratios for time and route of administration and the interactions between time and route of administration were obtained. Only time yielded a significant F (less than 1%). Thus, the two routes were similar and about equally effective. The data of both groups were combined for analysis as follows.

Arterial plasma glucose concentration. A fall of 27 mg/100 ml in plasma glucose was reached at the end of the insulin infusion. The reduction in plasma glucose during and after insulin was highly significant (Table 2).

Plasma glucose concentration differences. The hepatic-portal venous (HV-PV) and hepatic venous-arterial (HV-A) plasma glucose concentration differences were decreased throughout the insulin infusion. The HV-PV concentration difference decreased 5 mg/100 ml and the HV-A concentration difference decreased 4 mg/100 ml 32 min after onset of the infusion. Twenty-four minutes after the infusion was stopped, the concentration differences were increased over control levels. Then they returned to control values.

Hepatic plasma flow. The mean hepatic plasma flow increased 28% 8 min after insulin infusion had started. The mean hepatic plasma flow obtained from pooling all points throughout insulin administration was increased 11% over control values. There was a prompt return to control values after the infusion was stopped.

Hepatic glucose output. Because of the double inflow to the liver, the hepatic glucose output was calculated assuming both extremes in the proportionality of portal venous to hepatic arterial blood flow; i.e., outputs were calculated as if the inflow were either all venous or all arterial. On the assumption that all the hepatic inflow was from the vena cava, the calculated mean control hepatic glucose output was 58 ± 4.9 mg/min or 3.6 mg/kg per min. At the second, third, and fourth sample periods, a sharp, statistically significant decrease in hepatic glucose output occurred (Table 2). After discontinuance of insulin, hepatic glucose output increased well above control values and then returned toward control values.

On the unlikely assumption that all blood flow to the liver was arterial, the calculated mean control hepatic

TABLE 2. *Response to insulin of dogs with portacaval transposition*

	Control Period	Min After Onset of Insulin Infusion				Min After Cessation of Insulin Infusion		
		8	20	32	[illegible]	2[illegible]	54	[illegible]
Arterial glucose concentration, mg/100 ml								
Systemic	95.4±3.3	90.3±3.3†	81.5±2.7†	73.3±2.6†	66.2±2.4†	69.0±7.4†	82.1±5.0†	87.0±5.4
Portal	94.5±3.4	91.1±3.4*	84.1±3.3†	75.9±3.1†	69.4±3.2†	79.2±3.8†	85.8±3.8*	89.5±2.7
Combined	94.9±2.3	90.7±2.3†	82.8±2.1†	74.5±2.0†	67.7±1.9†	76.2±2.8†	83.9±3.1†	88.2±3.1†
HV-A glucose concentration difference, mg/100 ml								
Systemic	11.4±1.7	10.8±3.2	7.5±1.3†	7.8±2.0*	9.4±2.0	15.5±2.2*	14.0±2.0*	11.3±2.2
Portal	10.3±1.3	8.3±1.0*	6.2±1.0†	6.1±1.5†	5.2±1.7†	14.1±3.4	9.9±2.5	9.1±1.9
Combined	10.9±1.2	9.6±1.7	6.9±0.8†	7.0±1.2†	7.4±1.4†	14.6±1.9*	12.0±1.6	10.2±1.4
HV-PV glucose concentration difference, mg/100 ml								
Systemic	13.6±1.8	12.9±3.1	9.3±1.2†	9.2±2.1†	10.7±1.7*	15.5±2.4	16.0±2.2	13.7±3.1
Portal	13.5±1.1	11.7±1.2	9.9±0.5†	7.3±1.6†	7.5±1.3*	18.3±2.7*	13.2±2.1	12.5±1.6
Combined	13.6±1.0	12.3±1.7	9.6±0.7†	8.3±1.3†	9.2±1.1†	16.9±1.8*	14.7±1.5	13.1±1.7
Hepatic plasma flow, ml/min								
Systemic	496±56	653±123*	587±66	587±127	501±80	501±116	460±62	506±48
Portal	430±77	524±114	460±90	445±65	408±57	445±56	447±67	437±61
Combined	464±46	592±83*	490±54	519±73	457±50	475±65	454±44	473±38
Hepatic glucose output: (HV-A) flow, mg/min								
Systemic	49.6±3.9	61.1±14.4	33.3±6.4*	33.6±5.8†	38.7±6.9*	68.0±11.5	60.6±8.4	39.5±11.8
Portal	42.1±9.0	39.2±8.8	27.8±7.1*	25.9±6.3*	19.8±5.7*	56.8±12.7	35.6±9.4	35.8±7.9
Combined	46.1±7.6	50.7±8.8	30.7±4.7†	29.9±4.3†	29.7±4.9†	62.7±8.4*	48.7±6.7	48.2±7.6
Hepatic glucose output: (HV-PV) flow, mg/min								
Systemic	60.9±5.6	77.4±17.8	44.2±6.6*	41.0±6.3†	46.7±6.7*	69.6±12.4	73.0±10.2*	75.2±11.7
Portal	54.3±8.4	42.5±6.2	42.6±6.7	31.1±7.4†	29.6±4.9†	70.5±12.6	50.3±7.7	51.8±9.5
Combined	57.8±4.9	60.8±10.3	43.4±4.6†	36.3±4.8†	38.6±4.5†	72.4±8.0*	62.2±6.8	64.0±7.9

Data are mean values ± SE of the means in 11 experiments with systemic insulin administration, in 10 experiments with intraportal insulin administration, and 21 in the combined series. Measurements include arterial glucose, glucose concentration gradients, hepatic plasma flow, and calculated hepatic glucose outputs in control period, during infusion, and after cessation of infusion. Statistical evaluations were calculated on the basis of paired distributions where the average of 3 or more control measurements of each experiment was compared with the corresponding measurement taken at each of 7 time periods; thus a total of over 200 measurements in each category are summarized. * $P < 0.05$. † $P < 0.01$.

glucose output was 46 ± 7.6 mg/min or 2.9 mg/kg per min. During insulin infusion, the hepatic glucose output decreased significantly. After cessation of insulin, a statistically significant rebound of hepatic glucose output occurred followed by a return to control values. It may be seen that calculations of hepatic glucose output, assuming the hepatic blood supply was either entirely arterial or entirely venous, resulted in substantially the same conclusions. It follows that irrespective of the relative contributions of portal venous and arterial blood flow, the rate of hepatic glucose output was decreased after insulin in the dog with portacaval transposition.

DISCUSSION

The portacaval-transposition animal has certain advantages over other preparations. Liver function (4, 18, 24) and hepatic blood flow (20, 27) are relatively normal; special diets are not necessary. Catheterization may be done readily through peripheral cut-down procedures under local anesthesia so that studies may be done in unanesthetized animals shortly after introduction of the catheters. Relatively constant blood glucose values were found in the arterial, portal venous, and hepatic venous sampling sites. Finally, this preparation afforded a relatively simple means to compare the effects of intraportal and systemic routes of insulin administration.

With small doses of insulin in this preparation, a consistent and significant decrease was observed in the hepatic glucose output. The suppression of glucose output lasted during most of the period of insulin infusion. When insulin was stopped, a temporary increase of hepatic glucose output over control levels occurred. This postinsulin over-reaction also has been observed by others (7, 12, 14, 22).

Previous investigations (8, 21–23, 28) on dogs with unaltered hepatic vasculature that were studied in the unanesthetized state with multiple-catheter techniques have revealed no decrease in the hepatic glucose output after insulin administration. In dogs maintained on a high protein diet, Leonards and associates (12) showed that insulin infusion caused no decrease in hepatic glucose output even when hypoglycemia was prevented by concomitant glucose infusion. Further, in dogs fed a

high carbohydrate diet, suppression of hepatic glucose output was not demonstrable with insulin alone. However, decreased glucose output was detected when sufficient glucose to avoid hypoglycemia was given concomitantly with insulin in the carbohydrate-fed animals (12), and in the animal fed a mixed diet (8).

Why an hepatic glucose effect of insulin is so readily demonstrable in dogs with Eck fistula or portacaval transposition, as compared with animals whose hepatic circulatory system is unaltered, is a question that has not been answered. One possibility is that diversion of the nonhepatic splanchnic blood flow in the Eck-fistula and portacaval-transposition preparations results in subtle changes in the homeostatic glucose mechanisms operative between the liver and peripheral tissues. Further, glycogenolytic products of the pancreas or other nonhepatic splanchnic organs may be diverted from the liver in these preparations. If such products ordinarily participate in counterregulatory mechanisms, prevention of their passage through the liver might unmask an insulin action which is not otherwise demonstrable.

Another possible explanation for the difference in the hepatic response to insulin in dogs with normal hepatic vascular anatomy, as compared with that in dogs with Eck fistula or portacaval transposition, may lie in the difference in availability of glucose to the liver. The carbohydrate and amino acids absorbed from the gastrointestinal tract go first to the peripheral tissues in the animal with Eck fistula and portacaval transposition in contrast with the normal. Decreased hepatic glycogen stores have been demonstrated in the portacaval-transposition animal (19). It may be postulated that availability of carbohydrate and carbohydrate precursors to the liver may be limited in the Eck-fistula and portacaval-transplantation preparation. This limitation may affect the balance in carbohydrate movements between the liver and the peripheral tissues in both absorptive and postabsorptive conditions.

Further, the hepatic metabolic changes induced by insulin administration in the face of diminished carbohydrate reserves may also limit the capacity of the liver to supply glucose to the periphery.

Although insulin may be shown to have an action on hepatic glucose output under conditions of altered hepatic vasculature, it does not necessarily follow that this action is operative under normal conditions.

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