Differential Effects of Oral, Peripheral Intravenous, and Intraportal Glucose on Hepatic Glucose Uptake and Insulin and Glucagon Extraction in Conscious Dogs

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ABSTRACT The effect of equal (1.1±0.1 g/kg body wt) amounts of glucose administered orally, or by peripheral intravenous or intraportal infusion on hepatic glucose uptake and fractional hepatic extraction of insulin and glucagon was studied in conscious dogs with chronically implanted Doppler flow probes on the portal vein and hepatic artery and catheters in the portal vein, hepatic vein, carotid artery, and superior mesenteric vein. Portal vein and hepatic vein plasma flow increased only after oral glucose administration. Arterial plasma glucose increased equally to 150–160 mg/100 ml after all three routes of glucose administration. Portal vein glucose was similar after oral (195±15 mg/100 ml) and intraportal glucose infusion (215±11 mg/100 ml) and significantly higher than after peripheral intravenous glucose. Hepatic glucose uptake after oral (68±4%) and intraportal glucose administration (65±7%) significantly exceeded that after peripheral intravenous glucose infusion (23±5%). The amount of insulin above basal presented to the liver during the 180 min after oral glucose was 7.6±1.3 U, 4.3±0.6 U after intraportal glucose, and 4.1±0.6 U after peripheral intravenous glucose. Hepatic extraction of insulin increased significantly after oral glucose (42±3 to 61±4%), but was unchanged after intraportal and peripheral intravenous glucose administration. When the portal vein glucose levels achieved during peripheral intravenous glucose infusion for 90 min were maintained by a subsequent 90-min intraportal glucose infusion, hepatic glucose uptake was significantly greater during the intraportal glucose infusion. Glucagon secretion was suppressed equally after oral glucose, intraportal glucose, and peripheral intravenous glucose administration; fractional hepatic extraction of that hormone, which was significantly less than that of insulin, was unchanged.

These results indicate that hepatic glucose uptake is significantly greater after oral and intraportal glucose administration than after peripheral intravenous glucose infusion. This difference is not simply related to the amount of glucose or insulin presented to the liver and the increased hepatic glucose uptake did not depend solely upon the augmented fractional hepatic extraction of insulin. Hepatic extraction of insulin and hepatic glucose uptake appear to be regulated independently.

INTRODUCTION

The liver is important in glucose homeostasis. Splanchnic removal of glucose was greater after oral glucose compared with peripheral intravenous administration of glucose (1–6), but the mechanism of this effect is not clearly understood. DeFronzo et al. (5, 6) implicated gut factors released after ingestion of glucose but Bergman et al. (7) reported similar hepatic uptake of glucose after intraportal glucose infusion and oral glucose administration. Abumrad et al. (8) also excluded a significant role for gut factors and concluded that both hyperglycemia and hyperinsulinemia were major factors in modulating hepatic glucose uptake (8). Cherrington et al. (9) suggested that insulin concentrations were of major importance in regulating the net hepatic glucose uptake after peripheral intravenous glucose infusion.

Hepatic removal of insulin and glucagon is also important in both the homeostasis of these hormones and
hepatic glucose metabolism. Hepatic extraction of these hormones is incompletely understood and seems to be independently regulated (10-15). Oral or intraduodenal administration of glucose increased the fractional hepatic insulin extraction (16, 17), whereas it remained unchanged after infusion of insulin (13, 18) or tolbutamide (13). The present studies in conscious dogs compared the oral, intraportal, and peripheral intravenous administration of equal amounts of glucose on hepatic glucose uptake and hepatic extraction of insulin and glucagon.

METHODS

Animals and surgery

Healthy, adult male and female mongrel dogs, weighing 20-36 kg were anesthetized with intravenous sodium pentobarbital (30 mg/kg body wt) after an overnight fast (18 h). After a midline incision, pulsed range-gated ultrasonic Doppler flow probes were placed around the portal vein and the hepatic artery and catheters positioned in the portal, mesenteric, and left common hepatic vein and the carotid artery, as described previously (14). The portal vein flow probe was located 0.5 cm caudal from the branch of the superior pancreaticoduodenal vein. The hepatic artery flow probe was placed ∼4 cm from the origin of the vessel. The portal vein blood sampling microbore siliconized plastic catheter (Scientific Products Div., American Hospital Supply Corp., McGaw, IL) was inserted via the superior pancreaticoduodenal vein, which was ligated. Its multiple sidehole sampling tip lay immediately below the portal vein bifurcation. The catheter for infusion of glucose into the portal vein was placed at the root of the superior mesenteric vein, and its tip lay ∼10 cm caudal from the portal vein sampling catheter. Left common hepatic vein catheterization was done through the superficial jugular vein using subdiaphragmatic control by hand. The tip of the multihole catheter was advanced ∼1 cm into the left common hepatic vein and anchored into the vein by a suture. Another microbore siliconized plastic catheter was inserted into the carotid artery for samples and the external jugular vein for the peripheral intravenous glucose infusion. After the abdomen was closed, the free end of each catheter and the wires of the Doppler flow probes were threaded through a long needle, which was routed subcutaneously to the back of the dog’s neck and pushed out through the skin around the midline ∼5 to 10 cm below the base of the skull. Each catheter was flushed with heparin sodium (50 U/ml) and the ends were then closed with short stainless wire plugs. Postoperatively, the catheters were flushed with 2 ml heparinized saline (50 U/ml) daily to prevent thrombosis. After at least 2 wk of recovery from surgery, experiments were done after an overnight fast in conscious, unrestrained dogs. The order of each experiment was random with an interval of at least 7 d between them. Experiments were done only on animals whose hematocrits were >30% and who appeared in healthy condition with a good appetite and normal stools.

Phasic and mean control arterial blood pressure were measured with a Statham P23dB pressure transducer (Statham Instruments, Inc., Oxnard, CA) connected to the arterial catheter. The blood pressure did not change significantly throughout each experiment, except for an initial transient increase with the ingestion of glucose. Blood samples for glucose, insulin, and glucagon were obtained simultaneously from the portal vein, hepatic vein, and carotid artery, with continuous measurements of the portal vein and hepatic artery blood flows. Saline was infused into the cephalic vein to compensate for blood loss.

Experimental procedures

Oral glucose administration. After a 30-min control period, 11 dogs consumed a 10% glucose solution (1.0±0.1 g/kg body wt) in 2 min. Blood samples were obtained at −30, −20, −10, 0, 10, 20, 30, 45, 60, 75, 90, 105, 120, and 180 min.

Intraportal glucose infusion. After a 30-min control period, 5% glucose was infused (1.0±0.1 g/kg body wt) into the superior mesenteric vein in 10 dogs at a rate (8 mg/kg per min from 0 to 10 min, 13 mg/kg per min from 10 to 60 min, 8 mg/kg per min from 60 to 75 min, 4 mg/kg per min from 75 to 90 min, and 3 mg/kg per min from 90 to 120 min) to match the glucose concentration in the portal vein achieved after oral glucose administration. Blood samples were obtained as in oral glucose administration.

Peripheral intravenous glucose infusion. After a 30-min control period, 5% glucose was infused into the jugular vein in 11 dogs at the same rate as during the intraportal glucose infusion. Blood samples were obtained as in oral glucose administration.

Peripheral intravenous glucose infusion followed by intraportal glucose infusion. After a 30-min control period, 5% glucose was infused into the jugular vein in seven dogs from 0 to 90 min at a rate of 12.4±0.7 mg/kg per min. The infusion was then changed to the superior mesenteric vein from 90 to 180 min at a rate of 10.0±0.2 mg/kg per min to maintain the glucose concentration in the portal vein that had been achieved during the peripheral intravenous glucose infusion period. Blood samples were obtained at −30, −20, −10, 0, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, and 180 min.

Analysis

Blood flow was measured with an ultrasonic range-gated pulsed Doppler flow meter designed by Hartley et al. (19, 20) in each of the vessels described in detail elsewhere (14). Volume flow (Q) was calculated according to the formula: \( Q = 1.24 \times D^2 \times \text{Doppler frequency shift (kHz)} \), where D is the diameter of the vessel. Since the portal vein and hepatic artery were exposed and completely cleaned and each flow probe was fitted to the vessel, the diameter of the vessel was almost the same size as the diameter of the flow probe used on each vessel. This approach was very stable and reproducible and the calculated volume flow (Q) correlated very well with the measured volume flow based on in vivo calibration (14). The validity of this method of measuring flows has been confirmed by others (21).

Plasma glucose was measured by a Beckman glucose autoanalyzer (Beckman Instruments, Inc., Fullerton, CA), using a glucose oxidase method. Plasma immunoreactive insulin was assayed using dextran-coated charcoal (22). Plasma immunoreactive glucagon was assayed with Unger’s 30K antibody (23).

Calculations

Blood samples were collected in chilled tubes containing 500 U TrasyloL (FBA Pharmaceutical Inc., New York) and
1.2 mg EDTA/ml of blood. The blood-flow measurements were corrected to plasma flow based on hematocrits obtained every 30 min since glucose, insulin, and glucagon were measured in plasma. The flux of glucose and hormones in each vessel was determined by multiplying plasma flow by plasma concentration. Hepatic vein plasma flow was the sum of the plasma flow in the portal vein and hepatic artery. The hepatic extraction of hormones and the net hepatic glucose balance were calculated as described in detail elsewhere (16, 18). The amount of glucose and hormones presented to the liver was the sum of the contribution from the portal vein and hepatic artery (concentration times flow). The amount leaving the liver was the product of hepatic vein concentration and hepatic vein plasma flow. The fractional hepatic extraction of hormones was calculated as follows:

\[
\text{(hormone presented to the liver)} - \text{(hormone leaving the liver)}
\]

\[
\times 100\, \%.
\]

Calculation of the mean value of the hepatic extraction of hormones was based on the percentage of hormone extracted in each individual dog and not the mean amounts of hormones reaching and leaving the liver that are presented in the figures.

The net hepatic glucose balance was determined by the following formula: \([(\text{glucose leaving the liver}) - (\text{glucose presented to the liver})]/\text{body wt (mg/kg per min)}\). A positive balance represents net hepatic glucose output, while a negative balance represents net hepatic glucose uptake. The total hepatic glucose uptake during the 180 min after glucose administration was calculated for each individual dog by determining the total area under the basal level of hepatic glucose output as determined during the 30-min control period rather than from the value of 0. Although this leads to a greater percentage of uptake of the administered glucose load, it does not change the interpretation of the results. The data are presented as mean±SEM. The basal value was the mean±SEM of the four values obtained from -30 to 0 min. The paired t test was used for statistical analysis of the fluctuation from the basal value within a group. Differences in mean values between groups were detected by the unpaired t test. \(P\) values < 0.05 were considered to be significant.

RESULTS

Plasma flows after oral, intraportal, and peripheral intravenous glucose. The plasma flow was 404±29 ml/min in the portal vein, 107±10 ml/min in the hepatic artery, and 512±32 ml/min in the hepatic vein. Portal vein and consequently hepatic vein plasma flow increased significantly only after oral glucose administration (Fig. 1).

Plasma glucose concentrations after oral, intraportal, and peripheral intravenous glucose. During the control period, the hepatic vein plasma glucose level of 85±1 mg/100 ml significantly exceeded both the artery and portal vein (79±1 mg/100 ml and 77±1 mg/100 ml, \(P < 0.005\), respectively) in all three different experiments (Fig. 2). Arterial glucose concentration increased equivalently to \(~150-160\) mg/100 ml at 60 min after oral, intraportal, and peripheral intravenous glucose administration. However, the portal vein glucose level increased to a peak of 195±15 mg/100 ml at 45 min after oral glucose, which was similar to that after intraportal glucose (215±11 mg/100 ml at 45 min) but significantly higher than after peripheral intravenous glucose infusion (141±9
mg/100 ml at 45 min). Hepatic vein glucose level also increased to a peak of 166±12 mg/100 ml at 45 min after oral glucose and was similar after intraportal glucose (177±10 mg/100 ml at 45 min). Both peaks were significantly lower than those in the portal vein. Hepatic vein glucose concentration increased to 140±9 mg/100 ml at 45 min after peripheral intravenous glucose and was similar to that in the portal vein and artery.

Hepatic glucose balance after oral, intraportal, and peripheral intravenous glucose. Before glucose administration, the liver produced 1.5±0.2 mg glucose/kg per min (Fig. 3). After oral glucose administration, the total amount of glucose reaching the liver increased to 783±67 mg/min at 10 min, while the total amount of glucose leaving that organ was 708±44 mg/min, indicating that the liver was now retaining glucose. Hepatic glucose balance rapidly changed from the basal level to an uptake of 4.3±1.6 mg/kg per min at 10 min and increased to 7.3±1.4 mg/kg per min at 30 min. The liver removed 16.1±2.2 g glucose over 180 min, which was 68±4% of the oral glucose load. The amount of glucose presented to the liver after intraportal glucose administration was similar to that after oral administration and was significantly greater than that after peripheral intravenous infusion of glucose. The difference between the amount of glucose presented to the liver and leaving that organ was similar after oral and intraportal administration and significantly greater than that after peripheral intravenous infusion of glucose (140 and 135 mg/min vs. 20 mg/min, respectively) (Fig. 3). 65±7% of the glucose infused into the portal system was taken up by the liver over 180 min, whereas only 23±5% was removed by that organ during peripheral intravenous glucose infusion over 180 min.

Plasma insulin levels after oral, intraportal, and peripheral intravenous glucose. Portal vein plasma insulin levels increased rapidly from 34±3 to 135±27 μU/ml at 10 min after oral glucose, peaked at 186±53 μU/ml at 20 min and then gradually returned to the basal level at 180 min (Fig. 4). Portal vein insulin levels after intraportal and peripheral intravenous glucose infusion peaked at 134±37 and 150±21 μU/ml, respectively. Although the values were less than after oral glucose, the differences were not significant. The hepatic vein insulin level increased from 15±2 to 66±13 μU/ml at 20 min after oral glucose and returned to the basal level at 180 min. The increment of hepatic vein and arterial insulin levels after intraportal and peripheral intravenous glucose was similar to that after oral glucose.

Insulin balance across the liver and hepatic extraction of insulin after oral, intraportal, and peripheral intravenous glucose. During the control period, 42±3% of the 15±2 mU/min insulin delivered to the liver was extracted in a single transhepatic passage (Fig. 5). The amount of insulin reaching the liver significantly increased to 103±28 mU/min at 20 min after oral glucose. This peak was significantly greater than the peak achieved after intraportal or peripheral
intravenous glucose infusion (54±12 and 60±8 mU/min, respectively). Over 3 h, 7.6±1.3 U insulin above basal level reached the liver after oral glucose. This was significantly greater than the 4.3±0.6 U after intraportal and the 4.1±0.6 U after peripheral intravenous glucose infusion. After oral glucose, the fractional hepatic extraction of insulin increased significantly to a peak of 61±4% at 105 min, whereas it was unchanged after intraportal and peripheral intravenous infusion of glucose.

**Plasma glucagon levels and hepatic extraction of glucagon after oral, intraportal, and peripheral intravenous glucose.** During the basal state, portal vein glucagon level was 229±28 pg/ml. After glucose administration by all three routes, it decreased equally reaching a nadir of ~110 pg/ml at 105 min and then returned to the basal level at 150 min (Fig. 6). During the control period, 15±5% of the 111±10 ng/min glucagon presented to the liver was extracted by a single transhepatic passage. The amount of glucagon reaching the liver decreased significantly to 47±7 ng/min at 105 min, but its fractional hepatic extraction did not change significantly after oral, intraportal, or peripheral intravenous administration of glucose (Fig. 5).

**Peripheral intravenous glucose infusion followed by intraportal glucose infusion.** Portal vein glucose concentration was maintained at a level of 160 to 175 mg/100 ml during the two different infusion routes, whereas arterial glucose level was 160 to 170 mg/100 ml during the peripheral intravenous glucose infusion but significantly decreased to 120 to 130 mg/100 ml after changing to the intraportal infusion (Fig. 7). The amount of glucose presented to the liver was similar during the two infusions, whereas the amount of glu-

**FIGURE 3** Total glucose balance across the liver (milligrams per minute) (left panel) and hepatic glucose balance (milligrams per kilogram per minute) (right panel) during three different routes of glucose administration. Oral glucose (upper panel), intraportal glucose (middle panel), and peripheral intravenous glucose (lower panel) administration. © and © as in Fig. 1.
insulin level was maintained at ~160 μU/ml during the peripheral intravenous glucose infusion, whereas it decreased slightly to 120 μU/ml during the subsequent intraportal glucose infusion (Fig. 8). The arterial concentration of insulin was very similar during both routes of glucose infusion. The basal fractional hepatic extraction of insulin (43±3%) was unchanged during both infusions. The portal vein plasma glucagon level was suppressed to ~100 pg/ml during both infusion periods and its fractional hepatic extraction (22±2%) did not change significantly (Fig. 8).

**DISCUSSION**

This study confirms previous results that hepatic glucose uptake is significantly greater after oral glucose administration than after peripheral intravenous glucose infusion (1–6). Our finding of 68% hepatic uptake after oral glucose is similar to the 54–85% reported by others (2–4). Radziuk et al. (24) and Ferrannini et al. (25) observed that the net splanchnic glucose uptake and the fractional splanchnic extraction of glucose was two- to threefold greater after oral than after peripheral glucose. However, Bergman et al. (7) and Abumrad et al. (8) calculated that significantly less glucose (23 and 24%, respectively) was removed by the liver after 1.2 and 1.6 g/kg body wt glucose, respectively, was administered orally to conscious dogs. Although the changes they found in hepatic glucose balance were similar to ours, the different hepatic glucose uptake in the three studies could reflect their method of calculation (7, 8). Hepatic glucose uptake was calculated from a basal of zero rather than the level of hepatic glucose output during the control period. If Bergman et al. (7) had calculated total hepatic glucose uptake as the change from the basal value (as we did), 70% of the oral glucose administered would be retained, similar to the 68% we found. Jaspan and Polonsky (17) reported a significantly smaller hepatic glucose uptake after 25 g of glucose administered orally in conscious dogs, compared with our results. Part of the difference might reflect underestimation of the portal vein blood flow, since they measured total hepatic blood flow and estimated the portal vein/hepatic artery blood flow to be 2.4. Such a constant ratio would not take into consideration the significant increase in portal vein but not hepatic artery plasma flow observed after ingestion of glucose (Fig. 1). Abumrad et al. (8) also measured total hepatic blood flow, but they attributed all of the increase after glucose ingestion to the change in the portal vein.

Changes in hepatic glucose balance after intraportal glucose infusion are controversial. In man, White and Dupre (26) observed greater hepatic glucose uptake after oral glucose compared with intraportal glucose

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**Figure 4** The plasma insulin concentrations in the portal vein, hepatic vein, and artery during three different routes of glucose administration. Oral glucose (upper panel), intraportal glucose (middle panel), and peripheral intravenous glucose (lower panel) administration. □, ○ and ◦ as in Fig. 1.

cose leaving that organ was significantly less during intraportal glucose infusion. Thus, the total net hepatic glucose uptake during the intraportal glucose infusion significantly exceeded that during the peripheral intravenous glucose infusion (Fig. 7). The portal vein
infusion, based on higher portal vein compared with peripheral vein glucose levels after oral glucose, but similar levels in both vessels after intraportal glucose. In conscious dogs, Lickley et al. (27) demonstrated better glucose tolerance after intraduodenal than after intravenous or intraportal glucose. These results could reflect augmented insulin secretion after oral glucose. DeFronzo et al. (5, 6) postulated that gut factors released in response to oral glucose were the major determinants of the greater effect of oral glucose on net splanchnic glucose uptake. In contrast, Bergman et al. (7) concluded that putative gut factors were unnecessary to explain increased hepatic glucose uptake after oral compared with peripheral glucose administration, since hepatic glucose uptake was similar after oral and intraportal glucose. This conclusion is supported by our present results, as well as those of Abumrad et al. (8).

The mechanism of increased hepatic glucose uptake after oral or intraportal compared with peripheral intravenous glucose is not clear. Scow and Cornfield (1) attributed it to the higher glucose level in the portal vein. Abumrad et al. (8) suggested that the peak blood glucose and insulin levels after oral glucose were major factors responsible for the increased hepatic glucose uptake. Such an important role for hyperglycemia is supported by in vitro studies (28–30). The isolated, perfused rat liver rapidly took up glucose from hyperglycemic perfusate (28). Net hepatic glucose uptake occurred in isolated cross-perfused puppy livers when the portal vein plasma glucose level exceeded 136 mg/dl (29). Above that concentration, the uptake increased linearly with portal vein glucose levels. Previous studies as well as ours indicate that there is an apparent relationship between increases in blood glucose and hepatic uptake of glucose, but the present
study suggests that the arterial glucose level is not the important determinant. Although arterial glucose concentrations were similar after all three routes of glucose administration, net hepatic glucose uptake was significantly greater after oral and intraportal glucose compared with peripheral glucose administration. Furthermore, in the experiments in which portal vein glucose was kept constant by a peripheral and then portal infusion of glucose, the arterial glucose value was lower after portal vein glucose infusion, yet the net hepatic glucose uptake increased significantly. The results of that experiment also suggested that net hepatic glucose uptake was not primarily regulated by either the portal vein glucose concentration or the amount of glucose reaching the liver. Thus, despite constant portal vein glucose concentration and the amount of glucose presented to the liver, net hepatic glucose uptake was significantly increased when glucose was infused into the portal vein. These results suggest that the portal-arterial glucose difference might generate an important signal for hepatic glucose uptake. Since an augmented hepatic glucose uptake would decrease arterial glucose concentrations, it is difficult to know which phenomenon comes first. In experiments in which atropine was administered before and during oral glucose absorption, the majority of the glucose was removed by the liver, despite portal vein glucose levels that were less than those obtained after peripheral glucose infusion (unpublished observations). While Abumrad et al. (8) reported a correlation between net hepatic glucose uptake and the peak blood glucose level after oral glucose, no similar correlation existed with the glucose or insulin area under the curve.

**FIGURE 6** The plasma glucagon concentration in the portal vein, hepatic vein and artery (*left* panel) and total glucagon balance across the liver (nanograms per minute) (*right* panel) during the three different routes of glucose administration. Oral glucose (*upper* panel), intraportal glucose (*middle* panel), and peripheral intravenous glucose (*lower* panel). ◆, ◇, and ▲ as in Fig. 1.
The permissive effect of insulin on hepatic glucose uptake has also been demonstrated in vitro studies (30, 31). Bergman and Bucolo (30) reported that addition of insulin to glucose increased hepatic glucose uptake by 45%. They concluded that although glucose is a more important regulator of hepatic glucose uptake, insulin

Abumrad et al. (8) concluded that the peak insulin level after glucose was an important factor regulating augmented hepatic glucose uptake after oral glucose. Cherrington et al. (9) demonstrated that physiologic increments in plasma insulin have a marked effect on the ability of hyperglycemia induced by intravenous glucose infusion to stimulate net hepatic glucose uptake in somatostatin-treated conscious dogs.
potentiates the effect of the portal vein glucose level. Furthermore, Bergman (31) suggested that glucose exerts a rapid moment-to-moment influence on the rate of uptake of glucose by the liver, while insulin is very effective in optimizing the amount of glycogen the liver stores during food ingestion.

However, our results do not indicate that the arterial insulin level is a major determinant of hepatic glucose uptake, since the arterial insulin concentrations were equivalent after all three routes of glucose administration, although net hepatic glucose uptake after oral and intraportal glucose was significantly greater than after peripheral glucose infusion. Arterial insulin concentrations were similar during the experiments in which glucose was infused peripherally and then portal, but net hepatic glucose was greater during the latter period. It is also unlikely that the portal vein insulin concentration modulates the increased net hepatic glucose uptake. Thus, during the sequential infusion of glucose into a peripheral and the portal vein, portal vein insulin levels and the amount of insulin presented to the liver were similar. However, net hepatic glucose uptake was greater during portal vein infusion of glucose. The portal vein insulin concentrations were also similar in the two experimental groups receiving intraportal and peripheral glucose infusion, but the former had significantly greater net hepatic glucose uptake. If the amount of insulin reaching the liver during intraportal glucose infusion were saturating for the process of increasing net hepatic glucose uptake, one would expect the same net hepatic glucose uptake after peripheral glucose administration as after intraportal glucose. Finally, in experiments in which atropine and glucose (oral) were given, the portal vein insulin concentration was actually lower than after peripheral glucose infusion, but the net hepatic glucose uptake was greater in the former (unpublished observations). Since net hepatic glucose uptake increased equally after oral and intraportal glucose, but fractional hepatic extraction of insulin increased only after the former, such augmented insulin extraction is not necessary for this effect.

The basal fractional extraction of \( \sim 45\% \) of insulin presented to the liver during a single transhepatic passage in conscious dogs confirms our previous results in conscious (14, 15) and in anesthetized dogs (10–13, 16, 18), as well as those of others (17, 32–34). The significant increase of hepatic extraction of insulin to a peak of 61% after oral glucose is consistent with our results (16) and others (17). In contrast, Faber et al. (35) reported decreased hepatic extraction of insulin after oral glucose but no change after peripheral intravenous glucose infusion in normal human subjects. Such results were based on an analysis of the relationship between peripheral insulin and C-peptide levels. Waldhausl et al. (36) reported that the basal hepatic extraction of insulin was 75% in normal humans and was not altered after oral glucose. Hepatic extraction of insulin was calculated as the difference between pancreatic insulin secretion (C-peptide measurement) and the splanchic output of insulin. Bittner et al. (37) suggested hepatic extraction of insulin was unchanged in conscious humans during oral glucose tolerance, based on measurement of the portal and peripheral vein insulin concentrations. The explanations for these discrepancies are not apparent, but it should be emphasized that different techniques and experimental models have been used and hepatic extraction of insulin was assessed by indirect measurements. In conscious pancreatectomized dogs, Goriya et al. (38) reported greater hepatic insulin extraction after ingestion of a mixed meal and intraportal insulin infusion compared with peripheral intravenous insulin infusion. They attributed the difference to the higher portal vein insulin and glucose levels.

In contrast to our results after oral glucose, the fractional hepatic extraction of insulin was unchanged during intraportal and peripheral intravenous glucose infusions. Camu (33) and Fisher et al. (39) reported increased hepatic extraction of insulin during peripheral intravenous glucose infusion in anesthetized dogs, using an experimental model similar to ours. The reason for this discrepancy is not clear. On the other hand, Tranberg and Thorell (40, 41) reported that hepatic insulin extraction was markedly decreased during intraportal, but not peripheral, insulin infusion in man, regardless of the amount of insulin infused into portal vein.

The factors responsible for the augmented hepatic extraction of insulin after oral glucose are not known. It does not reflect the increased portal vein plasma flow after oral glucose, since the portal vein plasma flow is significantly greater in conscious dogs compared with anesthetized ones, although the basal fractional hepatic extraction of insulin is similar (14). In the isolated perfused liver, controversy exists as to whether changes in flow itself can modify hepatic extraction of insulin (42–44). The increased portal vein plasma glucose level and/or increased amount of glucose presented to the liver is not solely responsible for the increased hepatic extraction of insulin after oral glucose. It is also unlikely that the portal vein insulin concentration regulates fractional hepatic insulin extraction, since intraportal insulin infusion (13, 18) or increased endogenous insulin secretion induced by tolbutamide (18) did not increase fractional hepatic insulin extraction. It is possible that gut or neurogenic factors stimulated by oral glucose are important in the augmented
extraction of insulin. Atropine infusion inhibited the increased fractional hepatic insulin extraction after oral glucose (unpublished observations). However, this might reflect inhibition of parasympathetic innervation, release of gut factors, and/or delayed glucose absorption. The present study demonstrated similar plasma glucagon responses after the three different routes of glucose administration, suggesting that glucagon does not mediate the increased hepatic insulin extraction after oral glucose. However, the effect of glucagon on hepatic insulin extraction is controversial. We have shown that infusion of pharmacological (10, 12) but not physiological (14) amounts of glucagon and insulin decreased hepatic extraction of insulin. Such results suggest that the amount of glucagon presented to the liver as well as the types of stimulation might be important. On the other hand, no effect of glucagon on the hepatic extraction of insulin was observed in in vitro studies (45).

Pancreatic glucagon secretion is influenced by the blood glucose concentration (46, 47) and was decreased equivalently by the three different routes of glucose administration. Hepatic extraction of glucagon of 13–22% was similar to our previous results (10–15) and was unchanged by any of the experimental procedures, including the rebound in glucagon secretion after hyperglycemia. Although we did not determine the heterogeneity of plasma glucagon in the present studies, it is unlikely that the low basal and the unchanged extraction of glucagon after hyperglycemia reflects the heterogeneity of circulating plasma glucagon immunoreactivity (11, 12, 48).

In conclusion, the present study has demonstrated that hepatic glucose uptake is significantly greater after oral and intraportal glucose administration than after peripheral intravenous glucose infusion. This did not appear to be related to the portal vein plasma flow or the amount of glucose or insulin presented to the liver. The increased hepatic glucose uptake did not depend upon augmented fractional hepatic insulin extraction, which was seen only after oral glucose. These results indicate that hepatic glucose uptake and hepatic insulin extraction are regulated independently.

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