FEEDING STUDIES (7, 28) have shown that splanchnic removal of glucose is greater after oral glucose ingestion than after peripheral intravenous glucose administration. Moreover, Bergman et al. (3) and Adkins et al. (1) reported similar hepatic glucose uptake after intraportal glucose delivery as after oral glucose administration. Their data thus suggest that the enhanced net hepatic glucose uptake (NHGU) seen after oral glucose administration might occur as a result of the entry and trapping of glucose as after oral glucose administration. Moreover, Bergman et al. (3) and Adkins et al. (1) reported similar hepatic glucose uptake after intraportal glucose delivery as after oral glucose administration. Their data thus suggest that the enhanced net hepatic glucose uptake (NHGU) seen after oral glucose administration might occur as a result of the entry and trapping of glucose as after oral glucose administration.

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sonic flow probes (Transonic Systems, Ithaca, NY) were positioned around the portal vein and hepatic artery, and their proximal ends were placed in subcutaneous pockets. A second surgery was performed 8–9 days before each experiment. A ventral midline incision was made under general anesthesia, and Silastic catheters (Dow Corning, Midland, MI) were inserted into the vertebral and carotid arteries bilaterally (5). A catheter was also inserted into the left jugular vein to allow blood sampling so that the success of the head glucose clamp could be monitored. After insertion, the catheters were filled with glycerin-heparin (1,000 U/ml in a 1:1 ratio), their free ends were knotted, and they were placed in subcutaneous pockets.

Approximately 2 days before study, blood was drawn to determine the leukocyte count and the hematocrit of each animal. A dog was studied only with a leukocyte count <18,000/mm², a hematocrit >35%, normal stools, and if it had consumed all of its daily food ration. On the morning of the study, the proximal ends of the flow probes and surgically implanted catheters were exteriorized, the catheters were cleared, the dog was placed in a Pavlov harness, and intravenous access was established in three peripheral veins. At the end of the study, an autopsy was performed on each animal to verify the position of the carotid and vertebral catheter tips.

Experimental design. At ~120 min, a primed (36 µCi), continuous (0.3 µCi/min) peripheral infusion of D-[3-3H]glucose and a continuous peripheral infusion of indocyanine green dye (Becton-Dickinson, Cockeysville, MD; 4 µg·kg⁻¹·min⁻¹) were begun. The latter provided confirmation of hepatic vein catheter placement and a second measurement of hepatic blood flow. After 80 min (~120 to ~40) of dye equilibration, there was a 40-min (~40 to 0) basal period, followed by two 90-min experimental periods. At time 0, constant infusions of several solutions were begun, and these infusions were continued throughout the entire experiment. Somatostatin (0.8 µg·kg⁻¹·min⁻¹; Bachem, Torrance, CA) was infused to suppress endogenous insulin and glucagon secretion. Insulin (1.2 mU·kg⁻¹·min⁻¹; Bachem, Torrance, CA) and glucagon (0.6 ng·kg⁻¹·min⁻¹) were infused intraportally to raise the insulin level about three- to fourfold and to keep the glucagon level basal. In addition, at time 0, glucose (20% dextrose, Baxter Healthcare, Deerfield, IL) was infused intraportally (22 µmol·kg⁻¹·min⁻¹) to activate the portal signal. The portal signal was then present throughout both experimental periods in both protocols. At the same time, a primed, continuous peripheral infusion of 50% dextrose was begun so that the glucose load to the liver could quickly be doubled. At this time the dogs were begun on one of two protocols. In the first test period of protocol 1, glucose was infused into the four head arteries to eliminate the glucose gradient between arterial blood in the head and the portal vein. The peripheral glucose infusion rate was reduced as required to maintain the glucose load to the liver (HGL) at twofold basal. In the second test period, saline was infused into the head instead of glucose, and again the peripheral glucose infusion rate was adjusted to maintain a similar HGL to that seen in the previous period. The second protocol was identical to the first, except that the order of the two test periods was reversed. Para-aminomhippuric acid (PAH; Sigma Chemical, St. Louis, MO; delivered at 1.7 µmol·kg⁻¹·min⁻¹) was added to the portal vein infusate to assess mixing of the infused glucose with blood in the portal and hepatic veins, as described previously (2, 23).

Processing and analysis of samples. Plasma glucose was assayed using the glucose oxidase method with a Beckman Glucose Analyzer II (Fullerton, CA). Plasma insulin and glucagon concentrations were determined using radioimmunoassays (31). Blood glucose and blood lactate levels were determined from perchloric acid-treated samples according to the method of Lloyd et al. (16). PAH was also measured in perchloric acid-deproteinized blood as previously described (2, 19, 23).

Calculation. When substrates are infused intraportally, the possibility of poor mixing with the blood in the laminar flow of the portal circulation is of concern. Mixing of the infused glucose in the portal vein was assessed by comparing the recovery of PAH (which was mixed with the portal glucose infusate) in the portal and hepatic veins with the PAH infusion rate (2, 19, 23). Because of the magnitude of the coefficient of variation for the method used in assessing PAH balance, samples were considered statistically unmixed (i.e., 95% confidence that mixing did not occur) if hepatic or portal vein recovery of PAH was 40% greater or less than the actual amount of PAH infused (2, 19, 23). An experiment was defined as having poor mixing (and was excluded from the database) if a PAH recovery-to-infusion ratio of >1.4 or <0.6 was observed at less than one of the three time points in each test period. Twenty-two dogs were studied; 10 were not included because of poor mixing or unsuccessful glucose clamping. In the 12 dogs that were used (n = 6 protocol), the ratio of PAH recovery in the portal vein to the intraportal PAH infusion rate did not differ (0.8 ± 0.1 and 0.8 ± 0.1 vs. 0.9 ± 0.1 and 0.9 ± 0.1, respectively) in the two test periods of the two protocols. The ratio of PAH recovery in the hepatic vein to the PAH infusion rate were also similar (0.9 ± 0.1 and 0.8 ± 0.1 vs. 1.0 ± 0.1 and 1.0 ± 0.1) during the two test periods of protocols 1 and 2, respectively; a ratio of 1.0 would represent perfect mixing. When a dog was retained in the database, all of the points were used whether they were mixed or not, because mixing errors occur randomly.

Determination of the rate of glucose infusion into the carotid and vertebral arteries required to maintain the head arterial glucose level at a level similar to the portal glucose level was based on the following principle:

\[
\frac{\text{portal glucose infusion rate}}{\text{portal plasma flow}} = \frac{(\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})}{(\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})}
\]

\[
\frac{\text{carotid (or vertebral) glucose infusion rate}}{\text{carotid (or vertebral) plasma flow}} = \frac{(\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})}{(\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})}
\]

In the calculation of the cerebral glucose infusion rate, cardiac output (CO) was estimated to be 140 ml·kg⁻¹·min⁻¹ (26). Although estimates of CO in the dog range from 100 to 140 ml·kg⁻¹·min⁻¹, we choose the latter to ensure complete elimination of the glucose gradient between the head arteries and the portal vein. The carotid arterial blood flow was assumed to be 12% of CO; flow through the vertebral arteries was assumed to be 6% of CO (26). Because glucose was infused into the plasma compartment in both cases, carotid and vertebral arterial plasma flows were used in the glucose infusion calculation. In the study of Matsuhisa et al. (17), the carotid and vertebral blood flows measured by Doppler flow probes were ~12 and ~5%, respectively, of CO if we assume that the average CO was 100 ml·kg⁻¹·min⁻¹ and hematocrit was 40%. If the CO in our own dogs had averaged only 100 ml·kg⁻¹·min⁻¹, then we would have created a slightly higher glucose level in the head arteries (=10%) than in the portal vein, as our present data showed.
Hepatic blood flow (HBF) was calculated by two methods, ultrasonic flow probes and dye extraction (18). The results obtained with ultrasonic flow probes and dye were not significantly different, but the data shown in Figs. 1–4 are those obtained with the flow probes, because their measurement did not require an assumption regarding the distribution of the arterial and portal contributions to HBF.

The rate of substrate delivery to the liver, or hepatic substrate load, was calculated by a direct (D) method as

$$\text{load}_n(D) = ([S]_A \times \text{ABF}) + ([S]_P \times \text{PBF})$$

where [S] is the substrate concentration, A and P refer to artery and portal vein, respectively, and ABF and PBF refer to blood flow through the hepatic artery and portal vein, respectively. A similar method was used to calculate the hepatic sinusoidal insulin and glucagon concentrations

$$[H]_{HS} = ([H]_A \times \text{ABF}) + ([H]_P \times \text{PBF})/\text{ABF} + \text{PBF}$$

where [H] is the hormone concentration and HS refers to the hepatic sinusoids. To avoid any potential errors arising from either incomplete mixing of glucose during intraportal glucose infusion or a lack of precise measurement of the distribution of HBF, HGL was also calculated by an indirect (I) method during the portal glucose infusion period

$$\text{load}_n(I) = (G_A \times \text{HBF}) + \text{GIT}_P - \text{GUG}$$

where G is the blood glucose concentration, GIT_P is the intraportal glucose infusion rate, and GUG is the uptake of glucose by the gastrointestinal tract, calculated on the basis of the previously described relationship between the arterial blood glucose concentration and GUG (2, 19, 23). HGL did not differ whether measured using direct or indirect methods.

The load of a substrate exiting the liver was calculated as

$$\text{load}_n = [S]_H \times \text{HBF}$$

where H represents the hepatic vein.

Direct and indirect methods were used in calculation of net hepatic glucose balance (NHGB). The direct calculation was

$$\text{NHGB}_D = \text{load}_n(I) - \text{load}_n(D).$$

The indirect calculation was

$$\text{NHGB}_I = \text{load}_n(I) - \text{load}_n(I).$$

The glucose data in Figs. 1–4 represent those calculated with the indirect method, but the values were not significantly different from these calculations with the direct method. Lactate balance was calculated by the direct method. Net fractional glucose extraction by the liver was calculated as the ratio of NHGB (I) to load_n(I). Nonhepatic glucose uptake (non-HGU) was calculated by subtracting the rate of NHGU (I) from the total GIR. The net hepatic balance of glucose equivalents was calculated as the sum of the balances of NHGB (I) and lactate, once the latter had been converted to glucose equivalents. This calculation ignores carbon derived from gluconeogenic precursor uptake (= 2.5 \(\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\)) and glucose used for oxidation (= 1.5 \(\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\)), which tend to offset one another. Nevertheless, it provides an estimate of the carbon available for glycogen deposition in the liver.

To calculate glucose balance, plasma glucose values were converted to whole blood glucose values by using correction factors, as previously described (23). Use of whole blood glucose ensures accurate NHGB measurements regardless of the characteristics of glucose entry into the erythrocyte.

Data are presented as means ± SE. SYSTAT (Evanston, IL) was used for statistical analysis. The time course data were analyzed with repeated-measures ANOVA, with post hoc analysis by univariate F tests. Results were considered statistically significant at P < 0.05.

### RESULTS

Plasma insulin and glucagon concentrations.

Arterial and liver sinusoidal insulin concentrations rose similarly (≈ 3.5-fold) in both groups during the experimental periods (Table 1 and Fig. 1), thus mimicking the insulin concentrations seen in the postprandial state. Arterial and liver sinusoidal glucagon levels remained basal and did not differ between groups.

Blood glucose levels and HBF. Blood glucose levels in the femoral artery and portal vein were increased about twofold over basal and were not significantly different between the two groups at any time (Fig. 2). In the first test period, intraportal glucose infusion produced an arterial-portal blood glucose gradient of −0.55 ± 0.07 and −0.53 ± 0.08 \(\mu\text{mol} \cdot \text{kg}^{-1}\) in the presence of head glucose and head saline infusion, respectively (Fig. 2). Likewise, in the second test period, the arterial-portal glucose gradient was −0.62 ± 0.09 and −0.43 ± 0.05 \(\mu\text{mol} \cdot \text{kg}^{-1}\) in the presence of head glucose and head saline infusion, respectively (Fig. 2). Head glucose infusion, on the other hand, completely eliminated the negative blood glucose gradient between the head arteries (estimated) and the portal vein (0.23 ± 0.14 and 0.19 ± 0.20 \(\mu\text{mol} \cdot \text{kg}^{-1}\) in the first and second test periods of protocols 1 and 2, respectively).

HBF was not different (32 ± 1 and 33 ± 2 vs. 34 ± 3 and 38 ± 3 \(\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) in periods 1 and 2 of protocols 1 and 2, respectively) between test periods or between protocols.

HGL and NHGB. The HGLs increased twofold in both groups (150 ± 10 to 310 ± 14 and 338 ± 22 vs. 155 ± 9 to 328 ± 26 and 367 ± 27 \(\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\); basal to period 1 and period 2) in protocols 1 and 2, respectively (Fig. 3). NHGB changed from net outputs of 7 ± 2 and 11 ± 1 to net uptakes of 22 ± 3 and 21 ± 2 \(\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) during the first test period in the presence and absence, respectively, of head glucose infusion. Likewise, in the second test period, NHGU

<table>
<thead>
<tr>
<th>Item/Period</th>
<th>Protocol 1</th>
<th>Protocol 2</th>
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<tbody>
<tr>
<td>Arterial plasma insulin, (\mu\text{mol} / \text{l})</td>
<td>140 ± 11</td>
<td>148 ± 9</td>
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<tr>
<td>Arterial plasma glucagon, (\text{ng} / \text{ml})</td>
<td>40 ± 4</td>
<td>31 ± 1</td>
</tr>
<tr>
<td>TGI, (\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})</td>
<td>65 ± 8</td>
<td>85 ± 7</td>
</tr>
<tr>
<td>NHB, (\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})</td>
<td>4.7 ± 2.3</td>
<td>-1.2 ± 2.7</td>
</tr>
</tbody>
</table>

Values are means ± SE; the average of the test period represents the mean of 3 values taken between 60 and 90 min or between 150 and 180 min. \(H_{\text{Glucose}}\), head glucose infusion period; \(H_{\text{Saline}}\), head saline infusion period; \(TGI\), total glucose infusion rate; \(NHB\), net hepatic lactate balance. Each group period included 6 studies, except only 5 studies in the \(H_{\text{Saline}}\) period of protocol 1. A negative value indicates net hepatic uptake. No significant differences were observed between 2 groups in the same time period in these variables.
was 26 ± 3 and 29 ± 6 µmol·kg⁻¹·min⁻¹ in the presence and absence, respectively, of head glucose infusion. As expected, on the basis of these data, the net fractional extraction of glucose by the liver was not significantly different between groups (data not shown). If one compares data within each group (Fig. 3), it is also clear that head glucose infusion did not alter NHGU. Likewise, if the data from both periods of both groups are pooled, there was no effect of head glucose infusion on NHGU (24 ± 4 vs. 25 ± 5 µmol·kg⁻¹·min⁻¹) in the presence and absence, respectively, of head glucose infusion. When the direct method of calculation was used, NHGU was slightly but not significantly less than with the indirect method; however, again there was no difference between the presence (18 ± 2 µmol·kg⁻¹·min⁻¹) and absence (18 ± 3 µmol·kg⁻¹·min⁻¹) of head glucose infusion.

Non-HGU. Mean non-HGU increased to 43.6 ± 8.8 and 44.3 ± 7.0 µmol·kg⁻¹·min⁻¹ during the first test period in the presence and absence, respectively, of head glucose infusion (Fig. 4) and did not differ between the two groups. Similarly, in the second test period, non-HGU was 51.7 ± 7.9 and 47.4 ± 12.3 µmol·kg⁻¹·min⁻¹ in the presence and absence, respectively, of head glucose infusion. Likewise, if one examines the data within each protocol, one finds no difference. If the data from both groups are pooled, non-HGU was 46.1 ± 4.2 and 48.8 ± 7.0 µmol·kg⁻¹·min⁻¹ in the presence and absence, respectively, of head glucose infusion.

In the first test period, the rates of total glucose infusion were not different in the presence (65 ± 8 µmol·kg⁻¹·min⁻¹) and absence (65 ± 8 µmol·kg⁻¹·min⁻¹) of head glucose infusion. The glucose infusion rates rose modestly in the second period of each protocol [85 ± 7 and 78 ± 9 µmol·kg⁻¹·min⁻¹, nonsignificant (NS)], presumably as a result of the progressively increasing effect of insulin. When the data were pooled, there were no differences in the GIRs in the presence or absence of head glucose infusion (72 ± 5 and 73 ± 7 µmol·kg⁻¹·min⁻¹).

Net hepatic lactate balance. Net hepatic lactate balance switched to output (4.0 ± 3.0 vs. 5.5 ± 3.5 µmol·kg⁻¹·min⁻¹) in the first test period in the presence and absence, respectively, of head glucose (Table 1). In the second test period, net hepatic lactate output was slightly lower (−1.2 ± 2.7 vs. 5.0 ± 3.1 µmol·kg⁻¹·min⁻¹, P = 0.17) during head saline than head glucose infusion. When the data were pooled there was no difference in the net hepatic lactate balance in the presence or absence of head glucose infusion (4.8 ± 1.7 and 2.8 ± 1.2 µmol·kg⁻¹·min⁻¹).

The net balance of glucose equivalents across the liver, which represents the combination of glucose and lactate balance (after the latter is converted to glucose equivalents) serves as an estimate of the carbon used
for glycogen deposition. Net balance of glucose equivalents across the liver switched to uptake of 17.8 ± 3.5 and 19.1 ± 3.4 µmol·kg⁻¹·min⁻¹ (NS) during the first test period in the presence and absence, respectively, of head glucose infusion. Likewise, in the second test period, the net balance of glucose equivalents across the liver was 23.9 ± 3.4 vs. 29.2 ± 5.4 µmol·kg⁻¹·min⁻¹ (NS) in the presence and absence, respectively, of head glucose infusion. When all dogs are considered, the net balance of glucose equivalents across the liver was 21.5 ± 2.8 and 22.9 ± 3.5 µmol·kg⁻¹·min⁻¹ in the presence and absence, respectively, of head glucose infusion. Head glucose infusion thus had no effect on the amount of carbon available for glycogen deposition in response to portal glucose infusion.

**DISCUSSION**

Under postprandial conditions, the liver responds rapidly and uniquely to portal glucose delivery, suggesting that a signal in addition to insulin, which acts slowly, is involved in stimulating hepatic glucose uptake (4, 14, 15, 23) after feeding. Our previous studies (12, 13, 23) have demonstrated that a signal generated when the portal glucose level exceeds the arterial level plays such a role. Previous studies (10, 11, 17) have suggested that the two most likely reference sites for comparison of arterial and portal glucose levels are in the brain or liver. The present results suggest that the brain arterial glucose level is not used as a reference standard for comparison with the portal glucose level in generation of the portal signal and its effect on the liver. They leave open the possibility, as suggested by Garde- mann et al. (11) and Stumpel et al. (30), that under postprandial conditions it is the hepatic arterial glucose level that provides the required reference information.

Previous studies (1, 10, 12, 13, 23) have demonstrated that the portal signal not only enhances hepatic glucose uptake but also suppresses non-HGU. The potential mechanism by which the extrahepatic effect of portal glucose delivery occurs is still unknown. The present data clearly indicate that the brain arterial glucose level did not provide the reference information required to initiate the suppressive effect of portal glucose delivery on peripheral glucose uptake. Thus neither the effects of the portal signal on the liver nor those on muscle were altered by eliminating the glucose gradient between the brain and the portal vein. Xie et al. (32–37) have demonstrated that hepatic denervation per se can produce insulin resistance in the skeletal muscle of the cat and rat. Their data suggest that the signal that brings about the suppressive effect of portal glucose delivery on peripheral glucose uptake may originate within the liver itself. Our data thus are consistent with this hypothesis.

Although certain neurons in specific hypothalamic regions (21, 22, 29) appear to be sensitive to changes in local and/or plasma glucose concentrations, only one study by Matsuhisa et al. (17) has suggested that the brain arterial glucose level is involved in the effect of the portal signal on glucose uptake by the liver. Matsuhisa et al. utilized conscious dogs and infused somatostatin along with intraportal infusions of insulin (to create marked hyperinsulinemia) and glucagon (at basal rates). In one test period, glucose was infused intraportally (55.6 µmol·kg⁻¹·min⁻¹); in the next test period...
period, the portal glucose infusion was continued, and head glucose infusion was added through one carotid and one vertebral artery at a rate calculated to eliminate the portal vein-to-head arterial glucose gradient. Moderate hyperglycemia (8 mmol/l) was maintained throughout the experiment. Eliminating the gradient between the portal vein and the central nervous system diminished NHGU by ≈ 50% (42 ± 5 to 22 ± 3 μmol·kg⁻¹·min⁻¹) when the data from the last 30 min of each test period are considered, and the authors concluded that the brain was involved as a reference site for the portal portal signal. Caution should be used, however, in interpreting the findings of this study. First, although the authors infused the correct amount of glucose into the head, it was only given in one carotid and one vertebral artery, so that the extent of glucose mixing is unclear, and it seems likely that certain areas were above and others below the portal glucose level. Second, the quantitative accuracy of their balance data is not clear. Because the portal glucose infusion rate and the portal blood flow were the same in the presence and absence of the head glucose infusion, one would have expected the glucose gradient between the femoral artery and the portal vein to be the same in each period (Δ of 2 3 mmol/l). Instead, they were different (Δ of 2 1 vs. 1 .8 mmol/l), suggesting incomplete mixing of the infusion in portal blood. This random A-P glucose difference accounted for > 40% of the difference in NHGU in the two periods. Furthermore, if the indirect approach to calculating NHGU is used (which eliminates the need to use the portal glucose level), the difference in NHGU between the last two test periods is reduced to ≈ 15% and was probably not significant.

Although these authors assessed glucose mixing in the portal vein, they used the changes in glucose to do so, rather than an independent measurement such as PAH. The problem with this approach is that it does not allow the assessment of mixing in the hepatic vein. The latter is critical if the accuracy of both the direct and indirect estimates of NHGB is to be validated.

The effect of the portal signal on hepatic glucose uptake has been shown to turn on and off within 15 min (12, 13, 23). Knowing that is the case, one would have expected elimination of the brain-portal glucose gradient, if it were key to the initiation of the portal signal, to quickly reduce NHGU. On the contrary, in the study of Matsuhisa et al. (17) it took almost 1 h to see a diminution in NHGU. Finally, Matsuhisa et al. administered all treatments in the same order in each animal, and thus the lack of a time-matched control raises the issue of what would have happened over time in the absence of head glucose infusion. All of the above caveats weaken the conclusions that can be drawn from the study of Matsuhisa et al.

To maximize the mixing of glucose in the head in the present study, we infused glucose bilaterally through both carotid and both vertebral arteries (5, 9). We then assessed the head glucose clamp, using a catheter inserted into a jugular vein. With the assumption that 83% of the infused glucose escapes the head on first pass (5, 6), the estimated head arterial blood glucose levels were 11.0 ± 0.5 and 11.1 ± 0.2 mM in the presence of head glucose infusion in protocols 1 and 2, respectively. This confirms that we completely eliminated the negative glucose gradient between the head arteries and portal vein. According to the calculation we have shown, the head arterial glucose levels were 11 and 10% higher than the portal vein glucose levels in protocols 1 and 2, respectively. This was probably a result of the fact that we used a conservative estimate of CO in our studies. We assumed a CO of 140 ml·kg⁻¹·min⁻¹ to ensure complete elimination of the gradient in each dog. Some estimates of CO in the dog have been as low as 100 ml·kg⁻¹·min⁻¹ (44). It is unlikely that a slight excess of glucose in the brain would have had any effect, because cerebral glucose infusion itself is not thought to affect NHGU (17).

In summary, under hyperglycemic hyperinsulinemic conditions, the elimination of the negative glucose gradient between portal vein and head arteries did not alter the effect of the portal signal on hepatic or peripheral glucose uptake. This suggests that another reference site must play an important role in sensing the arterial glucose level and thereby triggering the response to portal glucose delivery.

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