Nonhepatic response to portal glucose delivery in conscious dogs

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Moore, Mary Courtney, Po-Shiuan Hsieh, Doss W. Neal, and Alan D. Cherrington. Nonhepatic response to portal glucose delivery in conscious dogs. Am J Physiol Endocrinol Metab 279: E1271–E1277, 2000.—The glycemic and hormonal responses and net hepatic and nonhepatic glucose uptakes were quantified in conscious 42-h-fasted dogs during a 180-min infusion of glucose at 10 mg·kg⁻¹·min⁻¹ via a peripheral (Pe10, n = 5) or the portal (Po10, n = 6) vein. Arterial plasma insulin concentrations were not different during the glucose infusion in Pe10 and Po10 (37 ± 6 and 35 ± 12 μU/ml, respectively), and glucagon concentrations declined similarly throughout the two studies. Arterial blood glucose concentrations during glucose infusion were not different between groups (125 ± 13 and 120 ± 6 mg/dl in Pe10 and Po10, respectively). Portal glucose delivery made the hepatic glucose load significantly greater (36 ± 3 vs. 46 ± 5 mg·kg⁻¹·min⁻¹ in Pe10 vs. Po10, respectively, P < 0.05). Net hepatic glucose uptake (NHGU; 1.1 ± 0.4 vs. 3.1 ± 0.4 mg·kg⁻¹·min⁻¹) and fractional extraction (0.03 ± 0.01 vs. 0.07 ± 0.01) were smaller (P < 0.05) in Pe10 than in Po10. Nonhepatic (primarily muscle) glucose uptake was correspondingly increased in Pe10 compared with Po10 (8.9 ± 0.4 vs. 6.9 ± 0.4 mg·kg⁻¹·min⁻¹, P < 0.05). Approximately one-half of the difference in NHGU between groups could be accounted for by the difference in hepatic glucose load, with the remainder attributable to the effect of the portal signal itself. Even in the absence of somatostatin and fixed hormone concentrations, the portal signal acts to alter partitioning of a glucose load among the tissues, stimulating NHGU and reducing peripheral glucose uptake.

portal vein; liver; insulin sensitivity; glucose load

The rate of net hepatic glucose uptake (NHGU) is two to three times greater when glucose is infused via the portal vein, compared with a peripheral vein, under conditions in which insulin and glucagon concentrations and the hepatic glucose load are fixed at similar values with the two routes of delivery (1, 15, 16, 20). Evidence suggests that the enhancement of NHGU during portal glucose delivery results from a neurally mediated signal (the “portal signal”) induced by the presence of a negative arterial-portal gradient, i.e., the portal vein glucose concentration is greater than the arterial concentration (1, 2, 21). The effect of this portal signal is not restricted to the liver. Nonhepatic tissues, particularly skeletal muscle, reduce their net glucose uptake in response to the portal signal (5). Thus it appears that the portal signal provides a mechanism for coordinating the disposition of glucose entering the body via the portal vein.

We have never quantified the effect of the portal signal when insulin and glucagon were free to change. Ishida et al. (6) infused glucose into the jugular or portal veins of dogs for 120 min at rates varying from 3 to 13 mg·kg⁻¹·min⁻¹ (identical for the two routes of glucose infusion) and found that the arterial, portal, and hepatic vein insulin responses did not differ significantly with the two glucose infusion routes. Moreover, the arterial glucose concentrations were the same with the two routes of delivery. Nevertheless, NHGU was nearly threefold greater during portal vs. peripheral glucose infusion. Ishida et al., however, were interested primarily in the insulin response to glucose infusion and therefore did not attempt to confirm that mixing of the glucose infusate with the blood in the portal vein had occurred. Thus it was not clear that their hepatic balance data were completely reliable. Moreover, they did not report the rate of nonhepatic glucose uptake. Therefore the first purpose of the current studies was to assess the glycemic and hormonal responses to glucose delivered at the same rate via the peripheral and portal routes. We designed the study to use data only from dogs in which we could confirm that mixing of the portal infusate with the portal vein blood had occurred. Our second goal was to quantify the hepatic and the nonhepatic contributions to glucose disposal. These studies provide a quantitative assessment of any glycemic advantage inherent in the presence of the portal signaling mechanism.

MATERIALS AND METHODS

Animals, diets, and experimental preparation. Studies were carried out in conscious 42-h-fasted adult dogs of either sex with a mean weight of 25 ± 1 kg. Housing and diet have been described previously (12). The protocol was approved by

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the Vanderbilt University Medical Center Animal Care Sub-
committee, and animals were housed according to American
Association for the Accreditation of Laboratory Animal Care
International guidelines. All dogs underwent a laparotomy
under general anesthesia ~16 days before the initial study,
and silicone rubber catheters (Dow Corning, Midland, MI)
were inserted in the portal and left common hepatic veins,
a splenic and a jejunal vein, the inferior cava, and the femoral
artery, as previously described (12, 13). Ultrasonic flow
probes (Transonic Systems, Ithaca, NY) were positioned
around the portal vein and hepatic artery, and their proximal
ends were placed in subcutaneous pockets. Criteria for use of
an animal in an experiment were as previously published
(13).

Experimental design. At ~90 min, a continuous peripheral
infusion of indocyanine green dye (ICG; Sigma, St. Louis,
MO; 4 μg·kg⁻¹·min⁻¹) was begun. The latter provided con-
firmation of hepatic vein catheter placement and a second
measurement of hepatic blood flow. After 70 min (~100 to
~30) of dye equilibration, there was a 30-min (~30 to 0)
control or basal period, followed by a 180-min (0–180 min)
period of continuous glucose infusion (Dextrose 20%, Baxter
Healthcare, Deerfield, IL). There were two different proto-
cols, based on the route of glucose infusion: glucose via
periportal vein (inferior vena cava) at 10 mg·kg⁻¹·min⁻¹
(Pe10, n = 5) or glucose via portal vein (i.e., jejunal and
splenic infusion catheters) at 10 mg·kg⁻¹·min⁻¹ (Po10, n =
6). The dogs received glucose at 3.3 mg·kg⁻¹·min⁻¹ for
the first 15 min of the glucose infusion period, 6.7
mg·kg⁻¹·min⁻¹ for the next 15 min, and 10 mg·kg⁻¹·min⁻¹
thereafter. For the Po10 protocol, p-aminohippuric acid
(PAH; Sigma) was mixed with the glucose so that it was
delivered at 0.4 mg·kg⁻¹·min⁻¹. PAH was used to assess
mixing of the infused glucose with blood in the portal and
hepatic veins, as described previously (13). In both protocols,
blood samples (3–9 ml each) were obtained from the artery
every 15–30 min and from the portal and hepatic veins (to
allow calculation of hepatic balance via the arteriovenous
difference technique) every 30–60 min throughout the basal
and glucose infusion periods. The collection, processing, and
analysis of blood samples have been described in detail else-
where (14, 20).

Processing and analysis of samples. Hematocrit; blood glu-
cose, lactate, alanine, and glycerol; and plasma glucose, in-
sulin, and glucagon concentrations were determined as
described previously (12, 13). Plasma nonesterified fatty acid
(NEFA C kit, Wako Chemicals, Richmond, VA).

Calculations. Hepatic blood flow (HBF) was calculated by
two methods, ultrasonic flow probes and ICG dye extraction
(12, 13). The results obtained with the two methods were not
significantly different. Because the flow probes make it pos-
sible to determine the relative proportions of the HBF pro-
vided by the hepatic artery and the portal vein, the results
reported in this paper utilize HBF obtained from the flow
probes.

In the Po10 group, the recovery of PAH in the portal and
hepatic veins was compared with the PAH infusion rate as
previously described to determine the adequacy of mixing
of the glucose infused with the blood in the portal vein (13).
Because the portal glucose infusion rate in these studies was
so high, making up nearly one-half of the increase in the
hepatic glucose load during the glucose infusion period, ade-
quate mixing was both more difficult to achieve than in
studies with lower infusion rates and also more crucial to
obtaining reliable data. Ten Po10 studies were performed;
four were excluded because of poor mixing. PAH recovery
was calculated with both Transonic and dye-derived hepatic
blood flow measurements, and all dogs retained in the data-
base exhibited acceptable mixing of the infusate with both
blood flow measurements. In the six dogs included in this
report, the recovery ratios for PAH in both the portal and
hepatic veins were 0.8 ± 0.1 with Transonic flows. When ICG
flows were used, the recovery ratios were 0.9 ± 0.1 in both
veins. A ratio of 1.0 would represent ideal mixing. Because
mixing errors, when they occur, are random, individual data
points were not excluded if the experiment as a whole was
included.

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

\[
load_{in(D)} = ([S]_A \times ABF) + ([S]_P \times PBF)
\]

where [S] is the substrate concentration, A and P refer to
artery and portal vein, respectively, and ABF and PBF refer
to blood or plasma flow (as appropriate) through the hepatic
artery and portal vein, respectively. Hepatic sinusoidal insulin
concentrations were calculated in a manner similar to
load_in, with plasma flows, and the results were divided by the
total hepatic plasma flow.

To avoid any potential errors arising from either incom-
plete mixing of glucose during intraportal glucose infusion or
lack of precise measurements of the distribution of HBF,
hepatic glucose load was also calculated by an indirect (I)
method

\[
load_{in(I)} = (G_A \times HBF) + GIRQ_P - GUG
\]

where \( G \) is the blood glucose concentration, GIRQ_P is the
intraportal glucose infusion rate (corrected for any incom-
plete recovery of the PAH in the portal vein), 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 (15, 16).

The load of a substrate exiting the liver was calculated as

\[
load_{out} = [S]_H \times HBF
\]

where \( H \) represents the hepatic vein.

Direct and indirect methods were used in calculation of
hepatic net balance (NHB). The direct calculation (used for sub-
strates other than glucose) was

\[
NHB = load_{out} - load_{in(D)}
\]

The indirect calculation (used for glucose, because this
method minimizes any errors introduced by inadequacies of
mixing) was

\[
NHB = load_{out} - load_{in(I)}
\]

A negative value indicates net uptake. Net fractional glucose extraction by the
liver was calculated as the ratio of NHB to load_in. Net
nonhepatic glucose extraction was calculated as glucose infused
minus NHGU.

The trapezoidal rule was used to determine the area under
the curve. Both positive and negative excursions (i.e., net
balance) were included in the calculations for net hepatic
disposition of substrates.

Data are presented as means ± SE. SYSTAT (Evanston,
IL) was used for statistical analysis. Time-course data were
analyzed with repeated-measures ANOVA, and individual
pieces of data (e.g., area under the curve) were analyzed with
independent t-tests. Results were considered statistically sig-
ificant at \( P < 0.05 \).

RESULTS

Insulin and glucagon concentrations. The mean basal arterial plasma insulin concentrations in Pe10
and Po10 were 8 ± 2 and 11 ± 3 μU/ml, respectively
\( (P = 0.5; \) Fig. 1). The arterial insulin concentrations
PORTAL VS. PERIPHERAL GLUCOSE INFUSION

Fig. 1. Arterial plasma insulin (A) and glucagon (B) concentrations in 42-h-fasted conscious dogs in the basal condition and during the peripheral iv (Pe10, n = 5) or portal (Po10, n = 6) infusion of glucose at 10 mg·kg⁻¹·min⁻¹. Glucose was infused at 3.3 mg·kg⁻¹·min⁻¹ from 0 to 15 min, 6.7 mg·kg⁻¹·min⁻¹ from 15 to 30 min, and 10 mg·kg⁻¹·min⁻¹ for the remainder of the infusion period. There are no significant differences between groups.

during the glucose infusion period (0–180 min) did not differ significantly between Pe10 and Po10 (mean values 37 ± 6 and 43 ± 12 μU/ml, respectively; P = 0.4). On the other hand, the portal vein insulin concentrations (data not shown; 72 ± 13 and 112 ± 23 μU/ml during the last 2 h of the studies in Pe10 and Po10, respectively) and the estimated hepatic sinusoidal insulin concentrations (Table 1) were only about two-thirds as great in Pe10 as the corresponding concentrations in Po10, although these findings did not reach significance (P = 0.3).

The mean basal arterial plasma glucagon concentrations in Pe10 and Po10 were 40 ± 7 and 44 ± 7 pg/ml, respectively (P = 0.6). The glucagon concentrations showed a progressive and significant decline during glucose infusion but were not different (P = 0.8) between the groups at any time (final concentrations 31 ± 5 and 31 ± 6, respectively, P < 0.05 vs. basal concentrations).

HBF. HBF did not change between the basal and the infusion periods, and it was not different between the treatments (data not shown). The mean HBF’s during the last 2 h were 30 ± 1 and 32 ± 3 ml·kg⁻¹·min⁻¹ in Pe10 and Po10, respectively.

Glucose concentrations and balance data. The arterial blood glucose concentrations in the basal period were not different in the two groups [80 ± 2 (Pe10) and 78 ± 2 (Po10) mg/dl; Fig. 2]. During the glucose infusion period, the arterial blood glucose concentrations were indistinguishable in Pe10 and Po10 (mean during the last 2 h, when the glucose infusion rate was 10 mg·kg⁻¹·min⁻¹: 125 ± 13 and 120 ± 6 mg/dl, respectively). The portal blood glucose concentration during the infusion period was lower in Pe10 than in Po10 (121 ± 13 and 146 ± 4 mg/dl during the last 2 h; P < 0.05). The hepatic glucose loads did not differ between the groups during the basal period, but during glucose infusion, the hepatic glucose load was lower in Pe10 than in Po10 (36 ± 3 vs. 45 ± 5 mg·kg⁻¹·min⁻¹, respectively, P < 0.05).

During the basal period, the livers exhibited net release of glucose at a similar rate in both groups (1.6 ± 0.2 and 1.8 ± 0.2 mg·kg⁻¹·min⁻¹ in Pe10 and Po10, respectively; Fig. 3). The rate of NHGU during the glucose infusion period was almost threefold larger in Po10 than in Pe10 (3.1 ± 0.4 vs. 1.1 ± 0.4 mg·kg⁻¹·min⁻¹ during the last 2 h; P < 0.05) was used. NHGU in Po10 was slightly less (2.5 ± 0.2 mg·kg⁻¹·min⁻¹) when the direct calculation was used. Net hepatic fractional extraction of glucose (NHFEG) was also over twofold higher in Po10 than in Pe10 (0.07 ± 0.01 vs. 0.03 ± 0.01; P < 0.05). The rate of nonhepatic glucose uptake (indirect calculation) was 6.9 ± 0.4 vs. 8.9 ± 0.4 mg·kg⁻¹·min⁻¹ in Pe10 and Po10 respectively, P < 0.05.

Lactate concentrations and balance data. The arterial blood lactate concentrations and net hepatic lactate balances were very similar in the two groups throughout the basal and glucose infusion periods (Fig. 4). During the basal period, the dogs exhibited net hepatic lactate uptake. After the beginning of the glucose infusion, the livers shifted to net hepatic lactate output, with a peak rate of −13 μmol·kg⁻¹·min⁻¹ in both groups.

Table 1. Estimated sinusoidal insulin concentrations in dogs receiving glucose at 10 mg·kg⁻¹·min⁻¹ via a peripheral or the portal vein

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Basal Period</th>
<th>30 min</th>
<th>60 min</th>
<th>120 min</th>
<th>150 min</th>
<th>180 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pe10</td>
<td>5</td>
<td>19 ± 7</td>
<td>88 ± 18</td>
<td>79 ± 18</td>
<td>57 ± 11</td>
<td>67 ± 12</td>
<td>64 ± 10</td>
</tr>
<tr>
<td>Po10</td>
<td>6</td>
<td>21 ± 4</td>
<td>79 ± 20</td>
<td>129 ± 36</td>
<td>103 ± 29</td>
<td>82 ± 27</td>
<td>90 ± 26</td>
</tr>
</tbody>
</table>

Data are means ± SE expressed in μU/ml; n, no of dogs. Pe10, glucose via a peripheral vein; Po10, via the portal vein. Basal period values are the means of 2 sampling times before glucose infusion began. See MATERIALS AND METHODS for calculation of sinusoidal concentrations. P = 0.3 for repeated-measures ANOVA and P = 0.2 for t-test of area under the curve.
Subtraction of the cumulative net hepatic lactate output from the cumulative NHGU yields an estimate of the carbon available for glycogen synthesis. In Pe10, the net hepatic uptake of carbon was only

\[ \frac{195}{6} \text{ mg glucose equivalents/kg} \]

whereas in Po10, it was

\[ \frac{395}{6} \text{ mg glucose equivalents/kg} \]  

\( P = 0.05 \). Glucose oxidation rates during hyperinsulinemic, hyperglycemic clamps (with similar insulinemia and glycemia as in the current studies) are only

\[ \frac{0.07}{6} \text{ mg/kg} \cdot \text{min}^{-1} \]  

(S. Satake, M. C. Moore, and A. D. Cherrington, unpublished observations). At that rate, glucose oxidation over the course of these studies would total <13 mg/kg.

**Glycerol and NEFA data.** Arterial blood glycerol concentrations tended to be higher in Po10 during the basal period (86 ± 5 and 107 ± 23 µmol/l in Pe10 and Po10, respectively; \( P = 0.2 \)), but they decreased similarly with both routes of glucose infusion (Δ from basal to lowest value: -56 ± 5 and -56 ± 15 µmol/l in Pe10 and Po10, respectively, \( P = 0.7 \); Table 2). The nadir of the glycerol concentrations tended to be lower in Pe10 than in Po10 (30 ± 8 vs. 51 ± 18 µmol/l, \( P = 0.3 \)). The basal and nadir rates of net hepatic glycerol uptake were 1.6 ± 0.1 and 0.4 ± 0.1 µmol·kg⁻¹·min⁻¹ in Pe10 and 1.7 ± 0.2 and 0.1 ± 0.3 µmol·kg⁻¹·min⁻¹ in Po10 (\( P = 1.0 \) between groups). Net hepatic fractional ex-

![Fig. 3. Net hepatic glucose balance, net hepatic fractional extraction of glucose, and nonhepatic glucose uptake in 42-h-fasted conscious dogs in the basal condition and during the peripheral iv (Pe10, n = 5) or portal (Po10, n = 6) infusion of glucose at 10 mg·kg⁻¹·min⁻¹. Glucose was infused at 3.3 mg·kg⁻¹·min⁻¹ from 0 to 15 min, 6.7 mg·kg⁻¹·min⁻¹ from 15 to 30 min, and 10 mg·kg⁻¹·min⁻¹ for the remainder of the infusion period. *P < 0.05 vs. Pe10.](http://ajpendo.physiology.org/doi)
traction of glycerol did not differ among groups \([0.6 \pm 0.1 \text{ (basal)} \text{ to } 0.4 \pm 0.1 \text{ (nadir)} \text{ in Po10 and } 0.5 \pm 0.1 \text{ to } 0.3 \pm 0.1 \text{ in Po10; data not shown}].

Plasma NEFA concentrations and net hepatic uptakes also declined in both groups. Both the basal values \([635 \pm 30 \text{ (Pe10) vs. } 884 \pm 112 \text{ (Po10)} \mumol/l, P = 0.06]\) and the change from basal concentrations during glucose infusion \([-538 \pm 26 \text{ (Pe10) and } -797 \pm 113 \text{ (Po10)} \mumol/l; P = 0.05]\) tended to be greater in Po10. The net hepatic NEFA uptake rates fell from \(2.5 \pm 0.3 \text{ to } 0.0 \pm 0.0 \mu mol \cdot kg^{-1} \cdot min^{-1}\) in Pe10 and from \(2.9 \pm 0.2 \text{ to } 0.0 \pm 0.1 \mu mol \cdot kg^{-1} \cdot min^{-1}\) in Po10 \((P = 0.8 \text{ between groups}). \) NHFEG fell from \(0.2 \pm 0.0 \text{ to } 0.0 \pm 0.0 \) in both groups (data not shown).

**DISCUSSION**

We have previously demonstrated that NHGU is about two- to threefold greater with portal vs. peripheral glucose infusion, when somatostatin is infused and the insulin and glucagon concentrations and the hepatic glucose load are kept the same between the two infusion routes (1, 15, 16). The present experiments were the first in which we assessed the impact of the portal signal in a model in which we did not infuse somatostatin or fix the insulin and glucagon levels and the hepatic glucose load. Nevertheless, NHGU was \(~2.5\text{-fold (~2 mg \cdot kg}^{-1} \cdot \text{min}^{-1}\) greater during portal infusion of glucose at \(10 \mu mol \cdot kg^{-1} \cdot min^{-1}\) than during peripheral infusion of glucose at the same rate. Approximately one-half of the difference in NHGU between the groups can be accounted for by the larger hepatic glucose load in Po10 than in Pe10 (15), and the remainder represents a portal signal effect. This conclusion is reinforced by the NHFEGs, which take into account differences in hepatic glucose load. The NHFEG in Po10 was approximately twofold greater than that evident in Pe10. Because more glucose entered the general circulation in Pe10 than in Po10, it might be expected that the arterial blood glucose concentrations would be higher during peripheral glucose delivery. Glucose uptake by the nonhepatic tissues was \(~29\%\) greater in Pe10 than in Po10, however, resulting in a virtually identical arterial blood glucose response in the two protocols.

The difference in nonhepatic glucose uptake was remarkable in that the circulating insulin concentrations were very similar between groups, and in fact tended to be higher in Po10, particularly at 60 min (Fig. 1). The portal and hepatic sinusoidal insulin concentrations were \(~50\%\) greater in Po10 than in Pe10, although the responses in both groups were highly variable and were not significantly different (Table 1). There are two potential explanations for the insulin data in these studies. First, it is possible that the portal delivery of glucose enhanced insulin secretion. It is well established that hyperglycemia resulting from oral glucose consumption stimulates insulin secretion more than equivalent hyperglycemia resulting from peripheral glucose infusion (19). This “incretin effect” has been largely attributed to the actions of gut hormons.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Arterial blood glucose, (\mu mol/l)</th>
<th>Net hepatic glycerol uptake, (\mu mol \cdot kg^{-1} \cdot min^{-1})</th>
<th>Arterial plasma NEFA, (\mu mol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Period</td>
<td>60 min</td>
<td>120 min</td>
<td>180 min</td>
</tr>
<tr>
<td>Pe10</td>
<td>86 ± 5</td>
<td>32 ± 6</td>
<td>34 ± 6</td>
</tr>
<tr>
<td>Po10</td>
<td>107 ± 23</td>
<td>64 ± 16</td>
<td>59 ± 17</td>
</tr>
<tr>
<td>Pe10</td>
<td>1.6 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>Po10</td>
<td>1.7 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.1 ± 0.3</td>
</tr>
<tr>
<td>Pe10</td>
<td>635 ± 30</td>
<td>109 ± 14</td>
<td>102 ± 20</td>
</tr>
<tr>
<td>Po10</td>
<td>884 ± 112</td>
<td>144 ± 20</td>
<td>115 ± 17</td>
</tr>
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</table>

Data are means ± SE for 5 (Pe10) or 6 (Po10) dogs. Basal period values are the means of 2 sampling times before glucose infusion began. There are no significant differences between groups. NEFA, nonesterified fatty acid.
mones, such as gastric inhibitory peptide and glucagon-like peptide 1 (17, 18). However, Dunning et al. (4) in our laboratory demonstrated that portal glucose delivery also enhances insulin secretion over that observed with peripheral glucose infusion. These investigators achieved identical hyperglycemia (∼150 mg/dl) in two groups of dogs by infusing glucose either peripherally or portally. The arterial insulin concentrations and pancreatic output of insulin increased ∼75% more with portal vs. peripheral glucose infusion, and these effects were determined to be neurally mediated (4). The arterial insulin concentrations were only 15% greater (∼6 μU/ml; nonsignificant) in Po10 than in Pe10, compared with the 75% difference noted in our previous study. Because portal insulin concentrations were ∼50% greater (∼30 μU/ml; nonsignificant) in Po10 than in Pe10, clearance of insulin may have been enhanced by portal glucose delivery, thus causing arterial insulin to reflect insulin secretion less precisely. However, Ishida et al. (6) found no difference in fractional hepatic extraction of insulin after portal vs. peripheral glucose infusion. An alternative explanation for the discrepancy in the percent increase in the arterial and portal vein insulin in the current studies is that the tendency for the portal and sinusoidal concentrations to be higher in Po10 was a random event resulting from incomplete mixing of the pancreatic hormones with the portal vein blood. This would mean that the dogs experienced only a small increase in insulin secretion with portal vs. peripheral glucose delivery. As mentioned above, this explanation is supported by the findings of Ishida et al., who also infused glucose at identical rates via the portal and peripheral routes and found no difference in arterial, portal, or hepatic vein insulin concentrations with the two routes of delivery.

Clearly the portal signal by itself enhances NHGU in the presence of fixed hormone concentrations (1, 13, 15, 20). When hormones are free to change, however, the stimulation of insulin secretion may be an important component of the action of the portal signal. Even if an increase in insulin secretion was responsible for a portion of the enhancement of NHGU during portal glucose delivery in these studies, the insulin response cannot explain the impact of portal glucose delivery on peripheral glucose uptake. Despite the tendency for arterial insulin concentrations to be higher in Po10 than in Pe10, there was significantly less glucose uptake by the nonhepatic tissues in Po10, implying that some factor in addition to insulin was involved in regulation of peripheral glucose uptake. The similarity in the circulating insulin concentrations confirms the findings of Ishida et al. (6), who also infused identical amounts of glucose via the peripheral and portal routes in conscious dogs. The reduction in glucose uptake by the nonhepatic tissues (primarily skeletal muscle) during portal glucose delivery in the current studies was consistent with previous observations from our laboratory (1, 20). Recently we have been able to demonstrate, by direct measurement of glucose uptake across the canine hindlimb, that the suppression of nonhepatic glucose uptake in response to portal glucose delivery is due primarily to a decrease in skeletal muscle glucose uptake (5). It is not known how this suppression of skeletal muscle glucose uptake is mediated, but either neural (8, 10, 11, 24) or humoral (26, 27) mechanisms, or both, might serve to allow communication between the hepatoportal region and the muscle.

The basal arterial concentrations of glycerol and NEFA tended to be higher in Po10 than in Pe10. This was a chance finding, because all of the dogs were managed and fasted in the same manner before study and were randomly assigned to their treatment groups. Despite this, the net hepatic uptakes of glycerol and NEFA were no different basally, indicating that there was no systematic difference in hepatic substrate uptake between groups. When NEFA and glycerol concentrations are maintained at basal concentrations, rather than being allowed to fall in the presence of hyperglycemia and hyperinsulinemia, hepatic glucose output is not suppressed as it normally would be by insulin (7, 9, 22, 23, 25). High levels of NEFA are associated with decreases in glucose disappearance, glucose oxidation, muscle glycogen synthase activity, and glycogen synthesis (3). Thus differences in NEFA during glucose administration in the current studies would have been expected to minimize differences in NHGU and accentuate the differences in nonhepatic uptake. However, during the administration of glucose, the blood glycerol and plasma NEFA concentrations decreased by similar percentages in the two groups (50–60% decrease in glycerol, 84–87% decrease in NEFA), making the availability of these substrates to the livers very similar (Table 2). In absolute terms, NEFA concentrations were decreased more in Po10 than in Pe10, suggesting that lipolysis may have been reduced more by portal than by peripheral glucose delivery. If this were the case, then our findings would be consistent with a simultaneous increase in insulin responsiveness in adipose tissue and decrease in insulin responsiveness in skeletal muscle during portal glucose delivery. This suggests a very high degree of tissue specificity in the response to the portal signal.

Net hepatic uptake of carbon (net glucose uptake – net lactate output) was about twofold greater in Po10 than in Pe10. The likely major fate of this carbon was glycogen synthesis. We have previously shown that the portal signal, in the absence of a rise in insulin concentration, enhances glycogen synthase activity and net hepatic glycogen synthesis (20), but whether the enhancement of glycogen synthase is the primary effect of the portal signal on the liver is unknown. Glycogen synthase is allosterically regulated by glucose 6-phosphate, and it may be that the portal signal stimulates glycogen synthase secondarily by enhancing the hepatic uptake or phosphorylation of glucose. Glycogen synthase activity would also be stimulated if there were enhancement of insulin secretion in Po10.

In conclusion, the current data and other recent data from our laboratory indicate that the portal signal impacts upon the liver but also upon nonhepatic tissues, particularly skeletal muscle (5). Portal glucose
delivery in the current study enhanced NHGU nearly threefold. This could be attributed, in approximately equal proportions, to the difference in the hepatic glucose loads during peripheral and portal glucose infusion and to portal signal effects, possibly including a stimulation of insulin secretion. The portal signal also suppressed glucose uptake in nonhepatic tissues. This is evident because the arterial blood glucose concentrations plateaued at a similar level with the two infusion routes, whereas circulating insulin levels were virtually identical in the two groups during the final 2 h of study. Because the liver’s role in glucose removal was enhanced in Po10 compared with Pe10, the circulating glucose concentrations would have been expected to be lower in Po10 if the nonhepatic tissues had not displayed a reduction in glucose uptake. Thus, even in the absence of somatostatin and fixed insulin and glucagon concentrations, the portal signal impacted upon the distribution of a glucose load between the hepatic and nonhepatic tissues and stimulated the hepatic storage of carbon.

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