Differential effect of amino acid infusion route on net hepatic glucose uptake in the dog

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Moore, Mary Courtney, Po-Shiu Nan Hsieh, Paul J. Flakoll, Doss W. Neal, and Alan D. Cherrington. Differential effect of amino acid infusion route on net hepatic glucose uptake in the dog. Am. J. Physiol. 276 (Endocrinol. Metab. 39): E295–E302, 1999.—Concomitant portal infusion of gluconeogenic amino acids (GNGAA) and glucose significantly reduces net hepatic glucose uptake (NHGU), in comparison with NHGU during portal infusion of glucose alone. To determine whether this effect on NHGU is specific to the portal route of GNGAA delivery, somatostatin, intraportal insulin (3-fold basal) and glucagon (basal), and intraportal glucose (to increase the hepatic glucose load by ~50%) were infused for 240 min. GNGAA were infused peripherally into a group of dogs (PeAA), at a rate to match the hepatic GNGAA load in a group of dogs that were given the same GNGAA mixture intraportally (PoAA) at 7.6 μmol·kg⁻¹·min⁻¹ (9). The arterial blood glucose concentrations and hepatic glucose loads were the same in the two groups, but NHGU (~0.9 ± 0.2 PoAA and ~2.1 ± 0.5 mg·kg⁻¹·min⁻¹ in PeAA, P < 0.05) and net hepatic fractional extraction of glucose (2.6 ± 0.7% in PoAA vs. 5.9 ± 1.4% in PeAA, P < 0.05) differed. Neither the hepatic loads nor the net hepatic uptakes of GNGAA were significantly different in the two groups. Net hepatic glycogen synthesis was ~2.5-fold greater in PeAA than PoAA (P < 0.05). Intraportal, but not peripheral, amino acid infusion suppresses NHGU and net hepatic glycogen synthesis in response to intraportal glucose infusion.

NET HEPATIC GLUCOSE UPTAKE (NHGU) in conscious dogs receiving an intraportal glucose infusion was reduced by the concomitant intraportal delivery of a mixture of gluconeogenic amino acids (GNGAA) (9). This occurred in spite of the fact that insulin and glucagon concentrations and the load of glucose reaching the liver were controlled and kept equivalent in the presence and absence of amino acid infusion.

Abundant electrophysiological evidence indicates that nutrient sensors in the hepatoportal region play a role in modulating nutrient intake, pancreatic hormone secretion, and nutrient disposition. Gluconeceptors in the portal vein respond to stimulation by d-glucose but not by other monosaccharides or L-glucose (12). The afferent firing rate in the hepatic branch of the vagus nerve is inversely proportional to the portal vein glucose concentration (12). Moreover, sensors for >15 different amino acids have been identified in the hepatoportal region of the rat (13). Intraportal injection of these amino acids alters the afferent firing rate in the hepatic branch of the vagus nerve (13).

We now hypothesize that the reduction in NHGU occurring during concomitant intraportal delivery of glucose and a mixture of GNGAA is specific to the intraportal route of amino acid delivery. Presumably this effect is mediated by neural signals initiated by contact between hepatoportal sensors and the amino acids. To test this hypothesis, we studied a group of dogs under identical conditions to our previous studies (i.e., 3-fold basal insulin concentrations, basal glucagon concentrations, and hepatic glucose load 150% basal), except that the GNGAA mixture was delivered peripherally at a rate that would maintain the hepatic amino acid load equivalent to that evident in our previous study (9). If our hypothesis is correct, peripheral delivery of amino acids should not decrease the uptake of glucose by the liver or the rate of hepatic glycogen synthesis. We have demonstrated that a negative arterial-portal (A-P) glucose gradient (i.e., portal vein concentration greater than that in the artery, as occurs during intraportal glucose infusion or absorption of a meal) creates a “portal signal” that enhances NHGU (2, 10, 15). It may be that the production of a negative A-P gradient for one or more amino acids is responsible for the blunting of NHGU during concomitant intraportal infusion of glucose and amino acids.

MATERIALS AND METHODS

Animals, diets, and experimental preparation. This report describes studies carried out in seven conscious 42-h-fasted adult mongrel dogs of either sex with a mean weight of 21 ± 1 kg (group receiving amino acids via peripheral vein, PeAA) and compared with an identical group of seven dogs (group receiving amino acids via portal vein, PoAA) described in our previous report (9). Housing, diet, and protocol approval have been described previously (8). All dogs underwent a laparotomy under general anesthesia ~16 days before the 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, and the femoral artery as previously described (8, 9). 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. Prestudy assessment and preparation were performed as described previously (9).

Experimental design. At ~120 min, a primed (40 μCi), continuous (0.4 μCi/min) peripheral infusion of d-[3-3H]glucose and a continuous peripheral infusion of indocyanine green (ICG; Becton-Dickinson, Cockeysville, MD; 4 μg·kg⁻¹·min⁻¹) dye were begun. Each study consisted of an 80 min (~120 to 200 equilibration period, a 40 min (~40–0) control or basal period, and a 240 min (0–240) experimental
period. At time 0, constant infusions of several solutions were begun, and these infusions continued throughout the experimental period. Somatostatin (0.8 μg·kg⁻¹·min⁻¹; Bachem, Torrance, CA) was infused peripherally to suppress endogenous insulin and glucagon secretion. Insulin (1.2 mU·kg⁻¹·min⁻¹) and glucagon (both hormones obtained from Eli Lilly, Indianapolis, IN) were delivered into the portal circulation via the jejunal and splenic infusion catheters. In two dogs in both PeAA and PoAA, the rate of glucagon infusion was 0.65 ng·kg⁻¹·min⁻¹; when this rate resulted in circulating glucagon levels slightly higher than basal, the infusion rate was lowered to 0.5 ng·kg⁻¹·min⁻¹ in the remainder of the dogs. Dextrose (20% Baxter Healthcare, Deerfield, IL; 3.4 mg·kg⁻¹·min⁻¹) mixed with p-aminobenzoic acid (PAH; Sigma, St. Louis, MO; 0.4 mg·kg⁻¹·min⁻¹) was also infused intraportally. PAH was used to assess mixing of the infused glucose with the portal and hepatic veins (9). In PoAA, a mixture of GNGAA (L-isomers of glutamine, glutamate, threonine, serine, glycine, and alanine; molar ratio 1.0, 0.2, 0.5, 0.2, 0.4, 0.4, respectively) was infused intraportally at 7.6 μmol·kg⁻¹·min⁻¹. The amino acid mixture was prepared just before time 0 by dissolving the individual crystalline amino acids (Sigma) in deionized water (calculated osmolality 1,110 mosmol/kgH₂O, with the assumption of 100% dissociation). The PeAA group received the same amino acid mixture peripherally at a rate that would maintain the hepatic amino acid load equivalent to that in PoAA. (Although the data from PoAA have been published previously, the majority of the PoAA and PeAA studies were conducted concurrently, so that PeAA data are not being compared with historic data.) In addition to the constant infusions, a primed peripheral infusion of 50% dextrose was begun at time 0, and the infusion rate was adjusted as needed so that the hepatic glucose load could be clamped at a 1.5-fold basal throughout the experimental period (9). The collection, processing, and analysis of blood samples were carried out as in our previous report (9).

After completion of the experiment, each animal was killed with an overdose of pentobarbital, the liver was removed, and a tissue sample from each liver lobe was freeze-clamped immediately (9).

Calculations. The thoroughness of mixing of the infused glucose in the portal vein was assessed by comparing recovery of PAH in the portal and hepatic veins with the PAH infusion rate as previously described (9). An experiment was defined as having poor mixing (and was excluded from the database) if poor mixing was observed at at least three of the eight time points in the experimental period. Ten dogs were studied in the PeAA group; three were excluded because of poor mixing. In the PeAA group (as well as in the previously reported PoAA group), the ratios of recovered to infused PAH in both the portal and hepatic veins were 1.0 ± 0.1 (with a ratio of 1.0 representing ideal mixing).

Hepatic blood flow (HBF) was calculated by two methods, ultrasonic flow probes and dye extraction (8, 9), that yielded similar results. Calculations reported in this paper utilize HBF obtained from the flow probes when this was available. The flow probes did not function in two dogs in each group. In these animals, ICG-derived flows were used, and the portal vein was assumed to provide 80% of hepatic blood flow during the basal period and 74% during the experimental period (8, 9, 14).

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

\[
\text{load}_{\text{in}(d)} = ([S]_A \times \text{ABF}) + ([S]_P \times \text{PBF})
\]

where [S] is the substrate concentration, A and P refer to artery and portal veins, respectively, and BF refers to the rate of blood flow. To avoid any potential errors arising from either incomplete mixing of glucose during intraportal glucose infusion or lack of precise measurements of the distribution of hepatic blood flow, hepatic glucose load was also calculated by an indirect (i) method

\[
\text{load}_{\text{in}(i)} = (G_A \times \text{HBF}) + \text{GIR}_{Po} - \text{GUG}
\]

where G is the blood glucose concentration, \( \text{GIR}_{Po} \) 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 (14). The load of a substrate exiting the liver was calculated as

\[
\text{load}_{\text{out}} = [S]_H \times \text{HBF}
\]

where H represents the hepatic vein.

The direct calculation for net hepatic balance (NHB) was as follows: NHB = loadin - loadout. The indirect calculation was as follows: NHB = loadin - loadin(i). Both equations were used in calculation of net hepatic glucose and GNGAA loadin(d) and loadout in the peripheral arterial and portal venous input arteriovenous difference (8, 9).

Fig. 1. Arterial plasma insulin and glucagon concentrations in 42-h-fasted dogs in basal state and during infusions of somatostatin, intraportal insulin and glucagon (3-fold basal and basal rates, respectively), intraportal glucose, and a gluconeogenic amino acid mixture given intraportally (PoAA, n = 7) or peripherally (PeAA, n = 7). Data for PoAA (dotted lines) cover the range of mean ± 1 SEM. PoAA data have been published previously (9). No differences occurred between groups.
balance, and the results did not differ regardless of the method used in calculation. The direct calculation was employed for other substrates. The results given in this report are those obtained with the indirect calculation, as in our earlier studies (9, 14). Net fractional substrate extraction by the liver was calculated directly and indirectly as the ratio of \( NHB \) to \( \text{loadin} \). Tracer-determined hepatic glucose uptake (HGU) was calculated as the balance of \( [3-3\text{H}]\)glucose across the liver (9).

Net hepatic glycogen synthesis and contribution of the direct pathway of glycogen synthesis were calculated as previously described (9).

Data are presented as means ± SE. Time-course data were analyzed by repeated-measures ANOVA with SYSTAT (Evanston, IL). Independent sample t-tests were used for analysis of glycogen data. Results were considered statistically significant at \( P < 0.05 \).
In the basal period, the animals exhibited net hepatic glucose output at a rate of $1.8 \pm 0.2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (Fig. 3). During the infusion period, they shifted to NHGU, with a mean rate of $2.1 \pm 0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, more than twice that exhibited by PoAA ($0.9 \pm 0.2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $P < 0.05$). Similarly, the mean net hepatic fractional extraction of glucose during the infusion period was greater than two-fold that in PoAA ($5.9 \pm 1.4\%$ vs. $2.6 \pm 0.7\%$, $P < 0.05$; Fig. 3).

The rates of tracer-determined HGU in the basal period were the same in the two groups ($0.1 \pm 0.2$ and $0.1 \pm 0.04 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in PeAA and PoAA, respectively). During the infusion period, the mean rate of tracer-determined HGU in PeAA was $1.8 \pm 0.2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, greater than twofold the rate in PoAA ($0.8 \pm 0.3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $P < 0.05$).

The total glucose infusion rates (portal plus peripheral) in the two groups were the same, averaging $6.8 \pm 0.6$ and $6.6 \pm 1.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in PeAA and PoAA, respectively.

**GNGAA concentrations and metabolism.** The mean arterial concentration of the GNGAA was $1,944 \pm 87 \mu\text{mol/l}$ in the basal period and $2,433 \pm 275 \mu\text{mol/l}$ during the infusion period (Fig. 4). The portal vein concentrations during the basal and infusion periods were $1,930 \pm 73$ and $2,346 \pm 264 \mu\text{mol/l}$, respectively. The hepatic load of GNGAA did not change significantly between the basal and the infusion periods ($58 \pm 8$ and $66 \pm 12 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, respectively, NS). Furthermore, the GNGAA load was not different in the two protocols. The net hepatic uptake of GNGAA increased significantly ($P < 0.05$) during the infusion period in PeAA ($3 \pm 1$ vs. $11 \pm 1 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; Fig. 5; neither rate differed from that in the corresponding period of the PoAA study). Similarly, net hepatic fractional amino acid extraction increased from $0.08 \pm 0.02$ to $0.20 \pm 0.03$ ($P < 0.05$; not different from the rise in PoAA).

The arterial concentrations of the individual amino acids were significantly higher in PeAA than in PoAA (Fig. 4; Table 1). Neither the portal vein levels nor the...
Table 1. Arterial and portal blood concentrations, net hepatic uptake, and net hepatic fractional extractions of gluconeogenic amino acids in dogs in basal state and during peripheral or intraportal infusions of a gluconeogenic amino acid mixture

<table>
<thead>
<tr>
<th></th>
<th>Arterial Concentration, µmol/l</th>
<th>Portal Concentration, µmol/l</th>
<th>Net Hepatic Balance, µmol·kg⁻¹·min⁻¹</th>
<th>Fractional Extraction</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td><strong>Alanine</strong></td>
<td></td>
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</tr>
<tr>
<td>PeAA Basal</td>
<td>294 ± 33</td>
<td>340 ± 40</td>
<td>−2.9 ± 0.3</td>
<td>0.32 ± 0.05</td>
</tr>
<tr>
<td>PeAA Infusion</td>
<td>465 ± 71†</td>
<td>504 ± 70†</td>
<td>−4.0 ± 0.5†</td>
<td>0.32 ± 0.03†</td>
</tr>
<tr>
<td>PoAA Basal</td>
<td>297 ± 20</td>
<td>334 ± 19</td>
<td>−2.6 ± 0.4</td>
<td>0.26 ± 0.04</td>
</tr>
<tr>
<td>PoAA Infusion</td>
<td>302 ± 29†</td>
<td>428 ± 37†</td>
<td>−5.1 ± 0.7†</td>
<td>0.44 ± 0.04**</td>
</tr>
<tr>
<td><strong>Glutamate</strong></td>
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<tr>
<td>PeAA Basal</td>
<td>85 ± 8</td>
<td>95 ± 4</td>
<td>0.05 ± 0.2</td>
<td>−0.01 ± 0.08</td>
</tr>
<tr>
<td>PeAA Infusion</td>
<td>113 ± 12†</td>
<td>120 ± 12*</td>
<td>−0.3 ± 0.1†</td>
<td>0.12 ± 0.04*</td>
</tr>
<tr>
<td>PoAA Basal</td>
<td>77 ± 18</td>
<td>88 ± 14</td>
<td>−0.1 ± 0.1</td>
<td>0.02 ± 0.06</td>
</tr>
<tr>
<td>PoAA Infusion</td>
<td>83 ± 16†</td>
<td>138 ± 21*</td>
<td>−0.7 ± 0.1†</td>
<td>0.24 ± 0.08*</td>
</tr>
<tr>
<td><strong>Glycine</strong></td>
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<tr>
<td>PeAA Basal</td>
<td>921 ± 75†</td>
<td>833 ± 51</td>
<td>1.3 ± 0.8</td>
<td>−0.02 ± 0.04</td>
</tr>
<tr>
<td>PeAA Infusion</td>
<td>798 ± 87</td>
<td>680 ± 75*</td>
<td>−1.3 ± 0.2†</td>
<td>0.07 ± 0.01†</td>
</tr>
<tr>
<td>PoAA Basal</td>
<td>764 ± 65†</td>
<td>713 ± 70</td>
<td>0.4 ± 0.6</td>
<td>−0.01 ± 0.03</td>
</tr>
<tr>
<td>PoAA Infusion</td>
<td>566 ± 54†</td>
<td>617 ± 70</td>
<td>−2.4 ± 0.3†</td>
<td>0.14 ± 0.02†</td>
</tr>
<tr>
<td><strong>Serine</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PeAA Basal</td>
<td>233 ± 16</td>
<td>262 ± 21†</td>
<td>−1.1 ± 0.4</td>
<td>0.18 ± 0.05</td>
</tr>
<tr>
<td>PeAA Infusion</td>
<td>343 ± 51†</td>
<td>358 ± 48*</td>
<td>−2.5 ± 0.3†</td>
<td>0.28 ± 0.05*</td>
</tr>
<tr>
<td>PoAA Basal</td>
<td>185 ± 27</td>
<td>201 ± 21†</td>
<td>−0.8 ± 0.3</td>
<td>0.13 ± 0.05</td>
</tr>
<tr>
<td>PoAA Infusion</td>
<td>208 ± 24†</td>
<td>303 ± 37*</td>
<td>−2.7 ± 0.2†</td>
<td>0.34 ± 0.03*</td>
</tr>
<tr>
<td><strong>Threonine</strong></td>
<td></td>
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</tr>
<tr>
<td>PeAA Basal</td>
<td>161 ± 16†</td>
<td>167 ± 17</td>
<td>−0.8 ± 0.2</td>
<td>0.18 ± 0.05</td>
</tr>
<tr>
<td>PeAA Infusion</td>
<td>203 ± 32†</td>
<td>194 ± 30</td>
<td>−1.8 ± 0.2†</td>
<td>0.36 ± 0.04*</td>
</tr>
<tr>
<td>PoAA Basal</td>
<td>127 ± 15†</td>
<td>134 ± 16</td>
<td>−0.6 ± 0.2</td>
<td>0.17 ± 0.04</td>
</tr>
<tr>
<td>PoAA Infusion</td>
<td>134 ± 16†</td>
<td>171 ± 20*</td>
<td>−2.1 ± 0.2†</td>
<td>0.44 ± 0.04*</td>
</tr>
</tbody>
</table>

Negative values for net hepatic balance indicate uptake and negative values for net hepatic fractional extraction indicate net release by liver; n = 7 for dogs with peripheral infusion (PeAA) and intraportal infusion (PoAA) of gluconeogenic amino acid mixture. Basal and experimental period values are means of 2 and 7 determinations, respectively. Individual data were analyzed with ANOVA; data within each period were then averaged to simplify presentation. Values for PoAA have been published previously (9). *P < 0.05 for change from basal in same group; †P < 0.05 for differences between groups.

hepatic loads of GNGAA differed significantly in PeAA vs. PoAA. The net hepatic uptakes of alanine, glutamate, and glutamine were significantly (P < 0.05) greater in PoAA than in PeAA, and the net hepatic fractional extractions of alanine and glutamine were greater in PoAA than in PeAA (P < 0.05). However, there were no differences observed in net hepatic uptake and fractional extraction of glycine, serine, and threonine between the two groups. The net result was that the mean net hepatic uptake of the sum of the GNGAA was the same in the two groups.

Lactate and glycerol concentrations and metabolism. During the experimental period, arterial blood lactate concentrations in PoAA increased ~70% (432 ± 113 to 824 ± 118 µmol/l; Fig. 6). The liver exhibited net lactate uptake (7.9 ± 1.0 µmol·kg⁻¹·min⁻¹) during the basal period but shifted to net lactate release during the experimental period. Net hepatic lactate output peaked
at 7.3 ± 2.4 µmol·kg\(^{-1}\)·min\(^{-1}\) and then declined. Neither the arterial blood lactate concentrations nor net hepatic lactate output differed between the two groups at any time, but net hepatic lactate release (area under the curve) in PoAA was only 60% of that in PeAA (NS).

Arterial blood glycerol concentrations (data not shown) declined between the basal and experimental periods (91 ± 9 vs. 40 ± 7 µmol/l; \(P < 0.05\)). Net hepatic glycerol uptake declined from 1.4 ± 0.2 to 0.5 ± 0.1 µmol·kg\(^{-1}\)·min\(^{-1}\) (\(P < 0.05\)). These changes were not different from those in PoAA, where arterial glycerol concentrations declined from 87 ± 13 to 38 ± 8 µmol/l and net hepatic uptake declined from 1.6 ± 0.2 to 0.7 ± 0.2 µmol·kg\(^{-1}\)·min\(^{-1}\).

Net hepatic glycogen synthesis. The mean rate of net hepatic glycogen synthesis in PeAA was 3.5 ± 0.2 mg·kg\(^{-1}·min^{-1}\), >2.5-fold higher than the rate in PoAA (1.3 ± 0.3 mg·kg\(^{-1}·min^{-1}\); \(P < 0.05\)). Glycogen synthesis via the direct pathway, measured by deposition of tritiated glycogen, averaged 1.2 ± 0.2 and 0.6 ± 0.1 mg·kg\(^{-1}·min^{-1}\) in PeAA and PoAA, respectively (\(P < 0.05\)).

DISCUSSION

Concomitant intraportal delivery of GNGAA and glucose (in the presence of somatostatin and intraportal replacement of insulin and glucagon to achieve threefold basal and basal concentrations, respectively) resulted in ~50% reduction in the rate of NHGU, compared with dogs treated in an identical fashion except for the omission of the amino acid infusion (9). The present results clearly demonstrate, however, that amino acids administered peripherally do not reduce NHGU. Peripheral amino acid infusion was associated with significantly greater rates of net hepatic glycogen synthesis and of glycogen synthesis via the direct pathway than portal amino acid infusion, despite identical hepatic glucose loads and insulin and glucagon concentrations. Thus, during portal glucose delivery, NHGU and glycogen synthesis are reduced by the concomitant delivery of GNGAA via the portal vein but not a peripheral vein. This is consistent with the hypothesis that intraportal delivery of amino acids generates a signal that competes with or modulates the signal that enhances NHGU during portal glucose delivery (9).

The hepatic loads and net hepatic uptakes of the mixture of amino acids were not different, regardless of their route of delivery (Figs. 4 and 5), and thus there is no evidence that substrate competition was responsible for blunting NHGU in the PoAA group. Glycolytic flux appears to have been reduced in PoAA. The cumulative net hepatic lactate release, which reflects glycolytic flux, was 40% less in PoAA than in PeAA, paralleling the 50% reduction in the rate of NHGU in PoAA. Because the net hepatic fractional extractions of alanine and glutamine were enhanced in PoAA, without an increase in total net hepatic amino acid uptake, it is possible that one or both of these amino acids might have served as the signal to alter NHGU.

Two groups of amino acid sensors (exhibiting excitatory or inhibitory effects on the afferent firing rate in the hepatic branch of the vagus nerve) have been identified in the hepatoportal system in the rat, and >15 common dietary amino acids have been shown to interact with these sensors (13). Alanine and serine fall into the excitatory group, whereas glycine and threonine are inhibitory (13). No data are available regarding excitatory or inhibitory actions of glutamate and glutamine on afferent vagal signaling (although glutamate serves as a neurotransmitter in many sites, see Ref. 5). Sensors specific to α-glucose have also been identified in the hepatoporal region, and glucose injected into the portal vein has an inhibitory effect on the afferent firing rate (12). We have suggested that a suppression of afferent signaling in the vagus nerve stimulates efferent signals that enhance the magnitude of NHGU (2, 8). It is tempting to speculate that amino acids that stimulate the vagal afferent firing rate (e.g., alanine and serine) are responsible for initiating the signal that inhibits NHGU (and/or enhances the net hepatic fractional extraction of certain amino acids) during concomitant intraportal amino acid and glucose administration. In addition, as we have already stated, a negative A-P glucose gradient creates a portal signal that stimulates NHGU. If the situation with amino acids is analogous, a negative A-P amino acid gradient...
might also be responsible for creating a signal that alters net hepatic substrate uptake (in this case, blunting rather than stimulating NHGU). Of the amino acids in the excitatory category and those for which the excitatory or inhibitory effects on vagal signaling are unknown, both serine and glutamine exhibited a positive A-P gradient during peripheral amino acid infusion but a negative gradient during portal amino acid infusion. However, in a combined intestine-liver perfusion preparation, administration of glutamine into the intestine, but not into the superior mesenteric artery, was associated with enhancement of NHGU (6). Thus serine might play a signaling role.

In the PeAA group, the rates of net hepatic uptake of glucose and amino acids were very similar to net hepatic glycogen deposition and lactate output. In the PoAA group, however, only ~70% of the net hepatic substrate uptake could be accounted for by glycogen synthesis and lactate release. The fate of the remaining carbon remains unclear, although enhancement of hepatic protein synthesis in PoAA is one possibility. Amino acids stimulate protein synthesis and inhibit proteolysis (17), with the branched-chain amino acids (BCAA) being especially important mediators of these processes (7). Recent evidence has shown that amino acids, in particular the BCAA, are involved in key intracellular steps in the regulation of protein synthesis by insulin (16). The effects of BCAA on protein synthesis appear to be at least partially dependent on route of delivery. Intraportal delivery of a mixed amino acid solution (4) or of leucine alone (3) has been reported to stimulate hepatic protein synthesis significantly, in comparison with intravenous delivery of the same amino acids.

In our previous report, the arterial concentrations of amino acids were higher during portal amino acid and glucose infusion than during intraportal infusion of glucose alone (9). Thus there is a possibility that peripheral sensors for amino acids might have reflexively reduced NHGU or that the amino acids might have stimulated central nervous system sensors directly. The present data refute this possibility, because there was no impairment of NHGU in the PeAA group, despite the fact that they had the greater load of amino acids reaching the brain (Fig. 4; Table 1). Moreover, it is not simply the portal vein amino acid concentrations that serve as a signal that results in suppression of NHGU, because the portal concentrations of the amino acids did not differ during portal and peripheral amino acid delivery. In addition, although there are osmoreceptors in the portal vein (1), there is no evidence that they were responsible for the effects we observed. The portal serum osmolality was not different with the routes of delivery (296 and 299 mosmol/kgH2O in PeAA and PoAA, respectively), and the hepatoportal glucoreceptors have previously been shown to be distinct from the osmoreceptors (11).

In conclusion, these data demonstrate that concomitant intraportal delivery of glucose and GNGAA results in reduced rates of NHGU, compared with the rates exhibited during intraportal delivery of glucose without amino acids or intraportal glucose delivery with peripheral amino acid infusion. The portal route of amino acid delivery (and not merely the absolute concentration of GNGAA in the portal vein) blunts NHGU during intraportal glucose infusion. The current data are consistent with the hypothesis that not only glucose but also amino acids in the portal vein create neural signals that modulate hepatic nutrient uptake, and thus the supply of energy substrates available to the nonhepatic tissues.

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