Route-dependent effect of nutritional support on liver glucose uptake

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The liver is a major site of glucose disposal during chronic (5 day) total parenteral (TPN) and enteral (TEN) nutrition. Net hepatic glucose uptake (NHGU) is dependent on the route of delivery when only glucose is delivered acutely; however, the hepatic response to chronic TPN and TEN is very similar. We aimed to determine whether the route of nutrient delivery altered the acute (first 8 h) response of the liver and whether chronic enteral delivery of glucose alone could augment the adaptive response to TPN. Chronically catheterized conscious dogs received either TPN or TEN containing glucose, Intralipid, and Travasol for either 8 or 5 days. Another group received TPN for 5 days, but ~50% of the glucose in the nutrition was given via the enteral route (TPN + EG). Hepatic metabolism was assessed with tracer and arteriovenous difference techniques. In the presence of similar arterial plasma glucose levels (~6 mM), NHGU and net hepatic lactate release increased approximately twofold between 8 h and 5 days in TPN and TEN. NHGU (26 ± 1 vs. 23 ± 3 μmol·kg⁻¹·min⁻¹) and net hepatic lactate release (44 ± 1 vs. 34 ± 6 μmol·kg⁻¹·min⁻¹) in TPN+EG were similar to results for TPN, despite lower insulin levels (96 ± 6 vs. 58 ± 16 pmol·l⁻¹) in TPN vs. TPN+EG. TEN does not acutely enhance NHGU or disposition above that seen with TPN. However, partial delivery of enteral glucose is effective in decreasing the insulin requirement during chronic TPN.

IN STRESSED STATES (trauma, injury, or infection) nutritional support is often provided to patients either via the parenteral (TPN) or enteral (TEN) route. Prior studies suggest that when the nutrition (either TPN or TEN) is given continuously for 5 days liver glucose uptake is markedly augmented; the liver removes ~45% of the exogenous glucose (1). Even more surprisingly, substantial liver glucose uptake occurred in the absence of hyperglycemia (~6.7 mmol/l) and in only mild hyperinsulinemia (102 pmol/l) (1). Recently, our group (3) observed that the enhancement in the capacity of the liver to take up glucose (i.e., adaptive response) begins within 5 h after initiation of TPN and is nearly fully manifest by 24 h.

The enteral route is the preferred route for delivery of exogenous nutrients (12, 14). In postsurgical and stressed patients, isocaloric enteral nutrition can be given without significant accompanying hyperglycemia (22, 23) compared with that shown with TPN. A potential benefit of the enteral route is that when only glucose is delivered via the enteral route in the acute setting it enhances net hepatic glucose uptake (NHGU) to a greater extent than when glucose is delivered via a peripheral route; this route-dependent effect has been termed the “portal signal” (7, 20). The portal signal can rapidly (<15 min) augment NHGU; it does not require the presence of hyperglycemia or hyperinsulinemia (11). Surprisingly, when TEN is administered chronically in unstressed animals, which should activate the portal signal, NHGU is not any greater than that seen with TPN alone (1). This suggests that the portal signal is not effective chronically.

One explanation for the failure of TEN to further enhance NHGU is that the portal signal is time dependent and may only be effective when TEN is initiated. All of the studies that have demonstrated an enhancement of NHGU by the enteral route have been done in <4 h. Because the portal signal is very fast in enhancing NHGU (10), the beneficial effect of enteral glucose delivery may subside over time. A second possibility is that the unique metabolic fate of glucose (i.e., hepatic lactate release rather than hepatic glycogen deposition) during chronic nutritional support (TPN or TEN) diminishes the effectiveness of the portal signal. The primary fate enhanced by acute enteral glucose delivery is glycogen synthesis (20). In contrast, the primary metabolic fate of NHGU in the adapted state is lactate release (1). It is possible that continued benefit of the portal signal requires further activation of glycolysis, which is not a target of the portal signal. A third possibility is that other nutrients in the nutritional support block the effect of the portal signal. Acute delivery of amino acids into the portal vein, but not into a peripheral vein, impairs the effect of the portal signal (15).

The dependency of the time course of hepatic adaptation on the route of nutrient delivery is unknown. Because enteral delivery of nonglucose nutrients can impair the portal signal, this may explain the failure of chronic TEN to further enhance NHGU. It is possible that if chronic enteral glucose delivery (i.e., portal signal activation) is combined with parenteral delivery of the remaining nutrients it will be more effective than chronic parenteral delivery of all nutrients. The aims of the study were 1) to examine the influence of the route of nutrient delivery on the time course of the hepatic adaptation during the first 8 h of nutrient delivery and 2) to determine whether chronic activation of the portal signal can enhance the adaptive response to TPN.

METHODS

Animal Preparation

Twenty-seven female nonpregnant mongrel dogs (22 ± 1 kg) were fed standard Kal-Kan meat (Vernon, CA) and Purina Lab canine diet 5006 (Purina Mills, St. Louis, MO) once daily and were allowed free access to water. The composition of the diet based on dry weight was...

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52% carbohydrate, 31% protein, 11% fat, and 6% fiber. Dogs were housed in a facility that met American Association for the Accreditation of Laboratory Animal Care International guidelines. The Vanderbilt University Medical Center Animal Care Committee approved the protocols. The health of the animals was determined before surgery and before administration of nutritional support as having a good appetite (i.e., consumed at least three-fourths of the daily ration), normal stools, hematocrit >35%, and leukocyte count <18,000 mm\(^{-3}\).

**Experimental Preparation**

Fourteen to seventeen days before initiation of nutritional support, blood sampling catheters were positioned in the left common iliac, portal, and left common hepatic veins and the iliac artery (1). Two infusion catheters were placed in the inferior vena cava (IVC) for TPN, and an infusion catheter was inserted into the duodenum for TEN. Flow probes (Transonic Systems, Ithaca, NY) were positioned about the portal vein, hepatic artery, and right external iliac artery.

**Experimental Protocol**

The first group of studies was performed on 42-h-fasted dogs in random order. The free ends of all catheters were exteriorized under local anesthesia (2% lidocaine), and their contents were aspirated and flushed with saline. The free ends of the flow probes were also exteriorized and connected to a flow meter (Transonic Systems). The dog was placed in a Pavlov harness for the duration of the study. The study consisted of a 90-min equilibration period, a 30-min basal sampling (−30 to 0 min) period, and an 8-h nutrition infusion period. During the 30-min basal sampling period, blood samples were taken from the four sampling catheters (iliac artery, portal vein, hepatic vein, and iliac vein) at −30, −15, and 0 min. TPN (n = 6 dogs) or TEN (n = 5 dog) was then infused via IVC or duodenal catheter for 8 h; the blood samples were taken hourly for the first 4 h and every 30 min for the remaining 4 h. Primed (44 and 27 μCi) constant infusions (0.4 and 0.3 μCi/min) of [3-\(^{3}H\)]glucose and [U-\(^{14}C\)]glucose (New England Nuclear, Wilmington, DE), respectively, were infused into the IVC beginning 120 min after initiation of TPN or TEN. At the end of the study, the animals were killed with an overdose of pentobarbital sodium (Veterinary Lab, Lenexa, KS). Tissue samples from each of the seven liver lobes and a muscle (adductor magnus et brevis) were freeze-clamped with Wallenberg clamps precooled in liquid nitrogen and were stored at −70°C until analyses. The entire liver was removed and weighed. TPN results have been reported (3).

In a second group of studies, animals were placed on nutritional support for 5 days. Animals received either TPN (n = 6), TEN (n = 6), or a modified TPN (TPN+EG; n = 4). In TPN+EG, a portion (27.8 μmol·kg\(^{-1}\)·min\(^{-1}\)) of the glucose requirements given in TPN was given enterally, and all nonglucose nutrients and the remaining portion of the glucose requirements (25 μmol·kg\(^{-1}\)·min\(^{-1}\)) were given parenterally. All three groups were performed in random order, and the total amounts of glucose infused were equal (52.8 μmol·kg\(^{-1}\)·min\(^{-1}\)). The results of TEN and TPN have been reported (1). On the morning of day 5, the catheters and flow probes were exteriorized as described above. After a 90-min equilibration period, five samples were taken at 15-min intervals from each of the four sampling catheters. Biopsies were not taken because dogs were used for other studies.

**Nutritional Support**

During the studies, the sole caloric source was that infused either parenterally and/or enterally. The TPN or TEN was designed to be isocaloric, based on predicted resting energy expenditure (19). The components in the TPN and TEN were glucose, lipids, amino acids, saline (2.9 ml·kg\(^{-1}\)·min\(^{-1}\)), potassium phosphate (90 mg·kg\(^{-1}\)·min\(^{-1}\)), and a multivitamin supplement (MVI-12; Astra USA, Westborough, MA). Glucose (50% dextrose; Abbott) made up 75% of the nonprotein calories, and a fat emulsion (20% Intralipid; Baxter Healthcare, Deerfield, IL) constituted the remaining 25% of the energy requirements. Travasol (Baxter) was infused to supply basal nitrogen requirements (~12 g protein/day), calculated with the formula 1.5 × body wt\(^{0.67}\) (in kg). Nutrition solutions were prepared under sterile conditions. TPN or TEN was infused with calibrated infusion pumps (Harvard Apparatus, Holliston, MA; Dakmed, Buffalo, NY).

**Sample Processing**

Blood samples were placed in chilled tubes containing potassium EDTA (15 mg). The collection and immediate processing of blood samples have been described previously (1, 4).

**Analysis**

Immunoassay and glucagon levels were assayed with modification of a radioimmunoassay kit from Linco Research (St. Louis, MO; intra-assay coefficient of variation of 11 and 10%, respectively). Cortisol was assayed with Diagnostic Products (Los Angeles, CA) RIA kit (coefficient of variation of 12%).

Analysis of plasma lipids, including triglycerides and total cholesterol, was performed on a Beckman instrument (Fullerton, CA) by using commercial kits. Free fatty acids (FFA) were determined with a modification of the method of Renard et al. (13). The concentration of nonesterified fatty acids (NEFA) was determined spectrophotometrically (Wako Chemicals, Richmond, VA).

**Calculations**

Blood flow in the hepatic artery and portal vein, respectively. Similarly, the substrate load leaving the liver was the product of HVs and HBF, in which HVs and HBF represent the hepatic vein blood substrate concentration and total hepatic blood flow (HVF + PVF) or plasma flow. Net hepatic substrate uptake was the difference between hepatic substrate load and substrate load leaving the liver. Net hepatic substrate fractional extraction was calculated as the ratio of net hepatic substrate uptake and hepatic substrate load. Net splanchnic substrate fractional extraction was calculated as the ratio of net hepatic substrate uptake and hepatic substrate load. Net splanchnic substrate uptake was calculated as (HBF × PVF) × (A\(_H\) − H\(_I\)), where A\(_H\) represents the blood substrate concentration in the hepatic vein. Plasma glucose was converted to blood glucose by a correction factor of 0.73 (18). These equations were used to calculate net hepatic glucose, \(^{14}CO\(_2\), lactate, alanine, glycerol, amino acid, and NEFA balances. To calculate organ NEFA balance, plasma flow rather than blood flow was used; plasma flow was calculated by multiplying blood flow (hepatic artery, portal vein, and total hepatic blood flow) by (1 − hematocrit ratio).

Net hindlimb glucose uptake was calculated with the formula (A\(_H\) − V\(_P\)) × ABF, where A\(_H\) and V\(_P\) represent blood glucose concentrations in the iliac artery and iliac vein and ABF represents blood flow in the iliac vein. Net intestinal glucose uptake was calculated with the formula (A\(_V\) − V\(_P\)) × PVF, where V\(_P\) represents blood glucose concentrations in the portal vein. In TPN and TPN+EG, net non-splanchnic glucose uptake (Non-SGU) was calculated as the difference between exogenous glucose infusion rate given parenterally and net splanchnic glucose uptake. Because the splanchnic bed is the sole source of glucose for the peripheral tissues in TEN, net Non-SGU was equal to net splanchnic glucose output.

Unidirectional intestinal glucose uptake was calculated as the ratio of intestinal \(^{14}H\)glucose uptake divided by the corresponding arterial \(^{14}H\)glucose specific activity. Intestinal glucose production (i.e., absorption) was equal to the sum of net intestinal glucose output [PV\(_V\) − A\(_H\)] × PVF] and unidirectional intestinal glucose uptake.
Table 1. Hepatic artery, portal vein, and total hepatic blood flow in dogs receiving nutritional support either for 8 h or 5 days

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>60</th>
<th>120</th>
<th>240</th>
<th>300</th>
<th>420</th>
<th>480</th>
<th>5-Day Infusion</th>
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<td><strong>Hepatic artery flow, ml·kg⁻¹·min⁻¹</strong></td>
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<tr>
<td>TEN</td>
<td>6.0±1.1</td>
<td>5.5±1.4</td>
<td>6.1±1.1</td>
<td>6.1±1.3</td>
<td>5.7±1.1</td>
<td>6.4±1.4</td>
<td>6.0±1.3</td>
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<td>TPN</td>
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<td>6.6±2.0</td>
<td>8.1±1.5</td>
<td>6.5±1.4</td>
<td>6.7±1.0</td>
<td>6.2±1.1</td>
<td>5.5±1.1</td>
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<tr>
<td>TPN + EG</td>
<td>3.0±1.1</td>
<td>3.1±2.0</td>
<td>2.7±1.5</td>
<td>3.0±2.0</td>
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<td>2.7±1.0</td>
<td>2.5±0.9</td>
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<tr>
<td><strong>Portal vein flow, ml·kg⁻¹·min⁻¹</strong></td>
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<tr>
<td>TEN</td>
<td>25.1±1.8</td>
<td>31.6±0.7*</td>
<td>28.7±1.5*</td>
<td>28.4±1.4</td>
<td>26.5±1.4</td>
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<td><strong>Total hepatic flow, ml·kg⁻¹·min⁻¹</strong></td>
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<tr>
<td>TEN</td>
<td>31.1±2.8</td>
<td>37.1±2.0</td>
<td>34.8±2.5</td>
<td>34.5±2.2</td>
<td>32.2±2.1</td>
<td>33.8±2.6</td>
<td>31.4±2.1</td>
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<td>27.3±4.6</td>
<td>28.4±3.1</td>
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<td>28.0±3.4</td>
<td>26.8±3.8</td>
<td>30.6±1.8</td>
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<tr>
<td>TPN + EG</td>
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<td>31.7±1.0</td>
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</table>

Values are means ± SE. Data are from 42-h-fasted dogs during a basal period and during a 480-min period of isocaloric nutrition infusion given enterally (TEN; n = 5) or parenterally (TPN; n = 6). A separate group of animals received TPN, TEN, or TPN with a portion of the glucose given via the enteral route (TPN + EG) for 5 days. Data are means of all the sampling times on the 5th day of infusion. *Significantly different from basal period of TEN group (P < 0.05).

Hepatic conversion of glucose to CO₂ (hepatic glucose oxidation) was calculated as the net hepatic [¹⁴C]glucose precursor specific activity (SA). The hepatic [¹⁴C]glucose precursor SA was considered to be the [¹⁴C]glucose SA in the blood flowing to the liver. Hepatic glucose storage was the sum of NHGU and total net gluconeogenic precursor uptake (lactate, amino acids, and glycerol). Hepatic glycogen content in 42-h-fasted dogs was assumed to equal 18 mg/g liver (8). Net deposition of glycogen from [¹⁴C]glucose in liver was calculated by dividing hepatic [¹⁴C]glucose precursor SA (dpm/g) by the average inflowing [¹⁴C]glucose SA (dpm/mg).

Statistics

All values for the basal period are the average of data obtained at −30, −15, and 0 min. Unless otherwise stated, data for the experimental period are the mean of 7, 7.5, and 8 h. In the 5-day studies, mean data are the means of the five samples taken on the day of the study. Statistical comparisons were made with two-way ANOVA followed by an F test (SYSTA, Evanston, IL) and one-way ANOVA when comparing groups. P < 0.05 was regarded as significant.

RESULTS

Response to an 8-h Nutrient Infusion

Blood flow and hormone concentrations. During the 8-h nutrient infusion, portal vein blood flow increased (P < 0.05) in TEN but not in TPN (Table 1). Hepatic arterial blood flow did not change in either group. Arterial plasma insulin concentrations increased to a greater extent (P < 0.05) in TPN (44 ± 8 to 234 ± 35 pM) than in TEN (37 ± 7 to 170 ± 38 pM) 1 h after initiation of nutrient infusion. However, these results were similar by 8 h (Fig. 1). The arterial plasma glucagon concentration decreased at the onset of nutritional support and remained suppressed for the duration of the study in both groups (33 ± 4 to 23 ± 10 vs. 30 ± 8 to 21 ± 3 ng/l; basal to 8 h; TPN vs. TEN).

Hepatic metabolism. The arterial blood glucose concentrations (Fig. 2) were similar during the basal period. During the first 8 h of TPN or TEN, they increased to a similar extent. Glucose infusion rate was similar in both groups (52.4 ± 0.3 vs. 54.3 ± 0.2 μmol·kg⁻¹·min⁻¹, TPN vs. TEN).

Net hepatic glucose output (Fig. 3) was similar in the two groups during the basal period. During the nutrition infusion, the liver rapidly switched to a net glucose consumer. A stable rate of NHGU was reached for 4 h, after which NHGU gradually increased for the duration of the study. At 8 h, NHGU increased by 50 ± 16 and 46 ± 35% in TPN and TEN groups, respectively, compared with NHGU seen at 4 h. Despite a lower hepatic glucose load because of the lower portal vein glucose concentration (Fig. 2) in the TPN group, the NHGU was similar in the two groups. The net fractional hepatic glucose extraction in the two groups had a similar pattern to NHGU. Hepatic glucose oxidation between 6 and 8 h was similar in the two groups (0.25 ± 0.01 vs. 0.23 ± 0.09 mg·kg⁻¹·min⁻¹, TPN vs. TEN).

Fig. 1. Arterial plasma insulin concentrations in 42-h-fasted dogs during the basal period and an infusion period of total enteral (TEN) and parenteral (TPN) nutrition for 8 h. Data are expressed as means ± SE.
The arterial blood lactate levels (Fig. 4) were similar during the basal period and increased after initiation of nutritional support. During the basal period, the liver was a consumer of lactate in both groups. However, with the onset of nutritional support, a brisk but transient increase in net hepatic lactate release occurred. After 3 h, net hepatic lactate release increased progressively for the duration of the study. At 8 h, 33/110069 and 30/110066% of NHGU could be accounted for as lactate release (TPN and TEN).

Arterial blood alanine levels (Fig. 5) gradually increased to a similar extent in both groups during 8 h of nutritional support. Net fractional hepatic alanine extraction remained unaltered for the first 4 h of nutrient infusion and then gradually decreased for the duration of the study. Arterial blood glycerol levels (79/110068 to 45/110067 µM) and net hepatic glycerol uptake (1.8 ± 0.2 to 1.2 ± 0.2 µmol·kg⁻¹·min⁻¹) decreased in TEN but were unaltered in TPN (85 ± 9 to 90 ± 29 µM and 1.8 ± 0.2 to 1.6 ± 0.4 µmol·kg⁻¹·min⁻¹, respectively). Net fractional hepatic glycerol extraction (0.63 ± 0.02 to 0.64 ± 0.02 vs. 0.61 ± 0.01 to 0.58 ± 0.02) did not change and was similar in both groups.

Arterial NEFA levels decreased markedly during TPN and TEN (962 ± 65 to 256 ± 48 vs. 799 ± 100 to 200 ± 31 µM). Because net fractional hepatic NEFA extraction did not change, net hepatic NEFA uptake decreased (3.5 ± 0.9 to 0.5 ± 0.1 vs. 3.4 ± 1.6 to 0.7 ± 0.2 µmol·kg⁻¹·min⁻¹).

The net retention of glucose carbon in the liver during 8 h of nutritional support assuming a baseline of 18 mg/g liver increased to similar extents in both groups (48 ± 8 and 42 ± 5 mg/g liver, TPN and TEN). Consistent with this, both terminal liver glycogen content (54 ± 5 vs. 58 ± 1 mg/g liver, TPN vs. TEN) and 13C-determined glycogen synthesis (23 ± 5 vs. 22 ± 1 mg/g liver, TPN vs. TEN) were similar.

**Intestinal metabolism.** The intestine was a net consumer of glucose before initiation of nutrient infusion and remained a consumer during the 8-h TPN infusion (Table 2). The intestine was a net producer of glucose (i.e., net glucose absorption) during TEN (Table 2). The net production of glucose by the intestine during the 8-h TEN could account for 67 ± 5% of the infused glucose during the first hour and 47 ± 3% at 8 h.

Between 4 and 8 h, unidirectional intestinal glucose uptake was higher (P < 0.05) in the TPN group (4.3 ± 0.7 vs. –0.1 ± 0.0 µmol·kg⁻¹·min⁻¹, TPN vs. TEN). However, intestinal glucose production (i.e., absorption) was elevated (P < 0.05) in TEN and was not different from zero in TPN (1 ± 1 vs. 27 ± 2 µmol·kg⁻¹·min⁻¹, TPN vs. TEN).

The release of lactate by the intestine during the basal period gradually decreased during the 8-h infusion. The intestine (Table 2) was a greater producer of alanine during the 8-h TEN infusion.

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**Fig. 2.** Arterial blood glucose concentrations and hepatic glucose load in 42-h-fasted dogs during the basal period and an infusion period of TEN and TPN for 8 h. Data are expressed as means ± SE.

**Fig. 3.** Net hepatic glucose uptake and net fractional hepatic glucose extraction in 42-h-fasted dogs during the basal period and an infusion period of TEN and TPN for 8 h. Data are expressed as means ± SE.
infusion; the increase could account for nearly all of the enterally delivered alanine (0.89 μmol·kg⁻¹·min⁻¹).

**Nonsplanchnic and hindlimb metabolism.** Non-SGU increased during nutrient infusion in both groups. However, Non-SGU was significantly lower in TEN (Fig. 6). Consistent with the rise in Non-SGU, net hindlimb glucose uptake increased in TPN (8.4 to 58 ± 10 μmol/min) and TEN (10 ± 4 to 45 ± 11 μmol/min). However, we could not detect a blunted rise in hindlimb glucose uptake in TEN. Net fractional hindlimb glucose extraction increased similarly in the two groups (0.03 ± 0.01 to 0.07 ± 0.01 vs. 0.02 ± 0.01 to 0.06 ± 0.01, TPN vs. TEN). However, net fractional hindlimb lactate extraction decreased (0.16 ± 0.04 to 0.04 ± 0.03 vs. 0.07 ± 0.03 to 0.01 ± 0.03, TPN vs. TEN) in the two groups.

**Response to 5 Days of Nutrient Infusion**

**Blood flow and hormone concentrations.** In animals receiving 5 days of nutritional support, hepatic artery and portal vein blood flow were not significantly different among TPN, TEN, and TPN+EG (Table 1). Arterial insulin concentrations were higher in TEN (P < 0.05 vs. TPN) and lower (P < 0.05 vs. TPN) in TPN+EG (96 ± 6, 144 ± 30, and 58 ± 14 pM for TPN, TEN, and TPN+EG, respectively). Arterial glucagon levels were higher (P < 0.05) in TEN than in TPN (28 ± 5, 44 ± 4, and 30 ± 8 ng/l).

**Hepatic metabolism.** After 5 days of nutritional support, NHGU was higher (~2-fold) in all groups than results seen after 8 h of nutritional support. Arterial glucose concentration and NHGU were not significantly influenced by the route of nutrient delivery. However, net hepatic fractional glucose extraction was lower in TEN than in TPN, and this decrease was absent when only glucose was given by the enteral route (TPN+EG; Fig. 7).

After 5 days of nutritional support, arterial blood lactate concentrations were 1.5 ± 0.2, 1.3 ± 0.2, and 1.3 ± 0.2 mM
Table 2. Net intestinal glucose, lactate, and alanine output in dogs receiving nutritional support either for 480 min or 5 days

<table>
<thead>
<tr>
<th>TEN or TPN Infusion, min</th>
<th>5-Day Infusion</th>
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<tr>
<td></td>
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<tr>
<td>Basal</td>
<td>60</td>
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<tr>
<td>Glucose output, μmol·kg⁻¹·min⁻¹</td>
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</tr>
<tr>
<td>TEN</td>
<td>−1.0±0.7</td>
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<tr>
<td>TPN</td>
<td>−2.1±0.8</td>
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<tr>
<td>TPN + EG</td>
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<tr>
<td>Lactate output, μmol·kg⁻¹·min⁻¹</td>
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<tr>
<td>TEN</td>
<td>1.3±0.5</td>
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<tr>
<td>TPN</td>
<td>2.4±0.3</td>
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<td>TPN + EG</td>
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<td>Alanine output, μmol·kg⁻¹·min⁻¹</td>
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<tr>
<td>TEN</td>
<td>0.8±0.2</td>
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<tr>
<td>TPN</td>
<td>0.9±0.2</td>
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<tr>
<td>TPN + EG</td>
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</table>

Values are means ± SE. Data are from 42-h-fasted dogs during a basal period and during a 480-min period of TEN (n = 5) or TPN (n = 6). A separate group of animals received TPN, TEN, or TPN + EG for 5 days. Data are means of all the sampling times on the 5th day of infusion. *Significantly different from TPN group (P < 0.05).

In TEN, TPN, and TPN+EG, respectively. Net hepatic lactate release was markedly increased (34 ± 6, 31 ± 4, and 44 ± 1 μmol·kg⁻¹·min⁻¹; ~3-fold; P < 0.05) compared with that seen after 8 h. Net hepatic lactate release accounted for 75 ± 12, 71 ± 9, and 89 ± 5% (TPN, TEN, and TPN+EG) of NHGU. Arterial blood alanine concentrations (509 ± 51, 532 ± 55, and 616 ± 46 μM) were higher (P < 0.05) than that seen 8 h of nutritional support. Net hepatic alanine uptake (1.4 ± 0.3, 1.4 ± 0.4, and 1.2 ± 0.5 μmol·kg⁻¹·min⁻¹) and fractional extraction (0.08 ± 0.02, 0.08 ± 0.03, and 0.06 ± 0.03) were not affected by the route of nutrient delivery but were lower (P < 0.05) that that seen after 8 h of nutritional support.

After 5 days of nutritional support, arterial glycerol concentrations (81 ± 20, 46 ± 3, and 49 ± 3 μM) and net hepatic glycerol uptakes (1.4 ± 0.4, 0.8 ± 0.1, and 1.0 ± 0.1 μmol·kg⁻¹·min⁻¹) were lower when nutrients were given enterally. Net hepatic fractional glycerol extraction (0.53 ± 0.06, 0.54 ± 0.02, and 0.64 ± 0.03) was higher in TPN+EG. NEFA concentration (322 ± 57, 215 ± 26, and 244 ± 36 μM) and net hepatic NEFA uptake (0.7 ± 0.5, 0.2 ± 0.1, and 0.4 ± 0.4 μmol·kg⁻¹·min⁻¹) remained suppressed in all groups.

Intestinal metabolism. The intestine was a net consumer of glucose after 5 days of TPN infusion (Table 2). The intestine was a net producer of glucose during TEN and TPN+EG infusion (Table 2). After 5 days of TEN and TPN+EG, net intestinal glucose output could account for 72 ± 9 and 65 ± 8% (TEN and TPN+EG) of the glucose infused via the enteral route. The intestine (Table 2) was a greater producer of alanine after TEN than TPN; the increase could account for nearly all of the enteral delivered alanine (0.89 μmol·kg⁻¹·min⁻¹).

Nonplanchnic metabolism. Non-SGU increased during nutrient infusion in all groups. Non-SGU was significantly lower in TEN and TPN+EG (25.9 ± 3.3, 16.1 ± 3.9, and 19.1 ± 0.4 μmol·kg⁻¹·min⁻¹ for TPN, TEN, and TPN+EG, respectively).

DISCUSSION

The liver undergoes a profound adaptation to TPN to become a major site of glucose disposal during chronic (>5 days) nutritional support (1). Interestingly the majority (75%) of the glucose carbon removed by the liver is released as lactate, and the route of nutrient delivery does not influence the long-term adaptive response (1). Our studies compared the early time course of this response to TPN and TEN. After 4 h of TPN, the liver switched to a more efficient consumer of glucose, and, by 8 h of TPN and TEN, ~30% of the glucose taken up was released as lactate. Although the efficiency of glucose disposal by the liver increased progressively, the rate of glycogen accretion remained constant over the 8-h study. Surprisingly, TEN did not enhance the speed of this adaptation or alter the metabolic fate of glucose. Interestingly, delivery of a portion of the glucose requirements during chronic TPN via the enteral route did not alter NHGU but decreased overall insulin requirements.
During the first 3 h, NHGU was not greater during TEN than during TPN. Previous work suggested that NHGU should be higher because portal glucose delivery activates the portal signal (20). In TPN, the hepatic response was consistent with previous studies when only glucose was infused. Moore et al. (16) demonstrated that, after 3 h of a continuous infusion of glucose (55.6 \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)), NHGU (6.1 ± 0.2 \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)) and net hepatic fractional glucose extraction (0.03 ± 0.01) were similar to results seen in our study (5.8 ± 2.2 \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) and 0.03 ± 0.01, respectively) at 3 h. Although NHGU increased progressively during the 8-h infusion of TEN, NHGU (8.6 ± 3.9 \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)) and fractional glucose extraction (0.03 ± 0.01) were not greater than results shown with infusion of TPN. Based on previous work (16) and the higher hepatic glucose load, NHGU and fractional extraction should have been much higher (≈14 \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) and ≈0.07) in TEN. One possible explanation for the failure of the portal signal to enhance NHGU is that amino acids in the TEN impaired the ability of the portal signal to augment NHGU. Interestingly, portal, but not peripheral, delivery of gluconeogenic amino acids impairs the portal signal (15). This would explain why amino acids in TPN did not impair NHGU. An additional explanation is that the capacity of the liver to take up and phosphorylate glucose has reached a maximum. This could explain why the portal signal may not be able to augment NHGU further. However, both fructose-induced translocation of glucokinase and acute increases in glucose can markedly increase NHGU in the adapted setting (2, 5). Thus it is unlikely that the glucose phosphorylation capacity is limited.

The time course of hepatic adaptation to nutritional support was not influenced by the route of nutrient delivery. Within 5 h of initiation of nutritional support, the efficiency of NHGU began to progressively increase for the remaining 3 h irrespective of the route of nutrient delivery. Net hepatic fractional extraction of glucose increased gradually from 0.03 to 0.08 over the 3-h period, despite gradual decreases in arterial glucose concentration and hepatic glucose load. A similar response was seen in TEN, for which fractional extraction rose from 0.04 to 0.07 over the same time period.

The hepatic adaptation to nutritional support is not complete after 8 h. After 8 h of nutritional support, net hepatic fractional glucose extraction was 0.08 and 30% of the glucose taken up by the liver was released as lactate. On the basis of our 5-day studies, net hepatic fractional extraction of glucose can be >0.15, a twofold increase over that seen at 8 h (1). Moreover, >75% of the glucose is converted to lactate after 5 days, a threefold increase over that seen at 8 h. Our recent work (3) suggests it takes <24 h to achieve the high efficiency of NHGU and fractional glucose extraction seen after 5 days of TPN.

The fraction of NHGU diverted to glycogen gradually decreased as the duration of TPN and TEN infusion increased. Despite glycogen synthesis being the primary fate of glucose disposal during the first 4 h of TPN and TEN, its rate of accretion did not increase as NHGU increased. In fact, the slope of the relationship between accumulated net carbohydrate storage and time is linear for nearly 6 h. Thus any additional carbon taken up was diverted to alternative pathways such as lactate release. Interestingly, TEN did not augment the rate of accumulation of glycogen; total hepatic glycogen content was identical after TPN and TEN. The gradual shift of glucose carbon to other metabolic pathways occurred before a stable glycogen level was reached. This suggests that either the controller of glucose entry (presumably glucokinase) is gradually augmented to exceed glycogen synthetic capacity or pathways downstream of glucose-6-phosphate (e.g., phosphofructokinase) are gradually activated to facilitate glucose-6-phosphate metabolism, thus lowering the total resistance for glucose entry.

Chronic activation of the portal signal decreased insulin requirements during TPN. NHGU and net hepatic fractional glucose extraction were not higher with TPN+EG than with TPN; however, arterial insulin levels were 40% lower with...
TPN+EG. The arterial-portal glucose gradient shown with TPN+EG was large enough to maximally activate the portal signal (1.0 ± 0.1 mM) (21). As long as insulin is present at concentrations at or above basal, the ability of the portal signal to augment NHGU acutely (more than ~2 mg·kg⁻¹·min⁻¹) is independent of insulin levels (18). If the portal signal can persist chronically to sustain NHGU, the insulin concentration required to dispose of the entire exogenous glucose load can be lowered. Generally with enteral glucose delivery, hepatic glucose load is higher than when the same amount of glucose is delivered into a peripheral vein, thus favoring an increase in NHGU. Given the comparable net hepatic fractional extraction of glucose in TPN and TPN+EG, an increase in NHGU was expected in TPN+EG. However, the slightly lower arterial glucose levels during TPN+EG offset the higher portal vein glucose levels, equating the hepatic glucose loads and therefore NHGU.

Acute activation of the portal signal is known to enhance insulin secretion (6), yet chronic activation of the portal vein lowered insulin levels. The lower arterial glucose levels likely contributed to the lower insulin levels. Consistent with previous studies, only ~70% of the glucose given enterally is absorbed as glucose (8, 17); the remaining 30% is metabolized by the intestine. A failure to absorb 100% of the enterally delivered glucose as glucose is likely not the sole explanation for the lower insulin concentration in TPN+EG. In TEN, 70% of the glucose is absorbed and insulin levels are higher than with TPN and TPN+EG. As already discussed, the portal signal was ineffective in facilitating NHGU in TEN; it is likely that activation of the portal signal diminished the overall insulin requirements in TPN+EG. Interestingly, in head trauma patients (23), insulin requirements are lower when patients are given TEN compared with TPN; however, this decrease may be due to enhanced endogenous insulin secretion.

The ability of the portal signal to limit Non-SGU persists in TEN. During TPN, Non-SGU remained elevated for the duration of the study. In contrast, in TEN, Non-SGU gradually decreased during the 8-h infusion, despite similar glucose and insulin concentrations to those in TPN. Even after 5 days of TEN and TPN+EG, Non-SGU was decreased. This is consistent with the known inhibitory effect of the portal signal on glucose uptake by peripheral tissues (9, 20). Muscle is one of the targets (9). However, we were unable to detect a corresponding decrease in hindlimb glucose uptake. The lower glucose disposal by peripheral tissues during TEN or TPN+EG is not due to differences in fatty acid availability. NEFA were markedly suppressed in all groups. It is interesting that delivery of amino acids into the portal vein impaired the ability of the portal signal to facilitate NHGU but is unable to impair its ability to restrain peripheral glucose uptake (15). This amino acid effect on the portal signal is consistent with the persistent attenuation of Non-SGU in TEN despite an apparent defect in the portal signal’s ability to facilitate NHGU.

In summary, irrespective of the route of nutrient delivery, the adaptation to nutritional support by the liver begins within 8 h. However, it does not attain the highly efficient glucose-consuming ability seen after 5 days of nutritional support. This gradual shift to a more efficient glucose-consuming state begins ~5 h after initiation of nutritional support. Surprisingly, although TEN does not enhance the adaptive response to TPN, chronic activation of the portal signal by delivering a portion of the glucose requirements enterally markedly decreased the insulin requirements during TPN. It is thus possible that, in patients receiving TPN, if a small portion of the glucose were given enterally this would limit the insulin requirement and the risk of hyperglycemia that is commonly seen with stressed patients.

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