Hepatic and muscle glucose metabolism during total parenteral nutrition: impact of infection

Owen P. McGuinness, Christine Donmoyer, Joseph Ejiofor, Suzanne McElligott, and D. Brooks Lacy
Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, TN 37232-0615

McGuinness, Owen P., Christine Donmoyer, Joseph Ejiofor, Suzanne McElligott, and D. Brooks Lacy. Hepatic and muscle glucose metabolism during total parenteral nutrition: impact of infection. Am. J. Physiol. 275 (Endocrinol. Metab. 38): E763–E769, 1998.—We examined the impact of infection on hepatic and muscle glucose metabolism in dogs adapted to chronic total parenteral nutrition (TPN). Studies were done in five conscious chronically catheterized dogs, in which sampling (artery, portal and hepatic vein, and iliac vein), infusion catheters (inferior vena cava), and Transonic flow probes (hepatic artery, portal vein, and iliac artery) were implanted. Fourteen days after surgery, dogs were placed on TPN. After 5 days of TPN, an infection was induced, and the TPN was continued. The balance of substrates across the liver and limb was assessed on the day before infection (day 0) and 18 (day 1) and 42 h (day 2) after infection. On day 0, the liver was a marked net consumer of glucose (4.3 ± 0.6 mg·kg⁻¹·min⁻¹) despite near normoglycemia (117 ± 5 mg/dl) and only mild hyperinsulinemia (16 ± 2 µU/ml). In addition, the majority (79 ± 13%) of the glucose taken up by the liver was released as lactate (34 ± 6 µmol·kg⁻¹·min⁻¹). After infection, net hepatic glucose uptake decreased markedly on day 1 (1.6 ± 0.9 mg·kg⁻¹·min⁻¹) and remained suppressed on day 2 (2.4 ± 0.5 mg·kg⁻¹·min⁻¹). Net hepatic lactate output also decreased on days 1 and 2 (15 ± 5 and 12 ± 3 µmol·kg⁻¹·min⁻¹, respectively). This occurred despite increases in arterial plasma glucose on days 1 and 2 (135 ± 9 and 144 ± 9 mg/dl, respectively) and insulin levels on days 1 and 2 (57 ± 14 and 34 ± 9 µU/ml, respectively). In summary, the liver undergoes a profound adaptation to TPN, making it a major site of glucose disposal and conversion to lactate. Infection impairs hepatic glucose uptake, forcing TPN-derived glucose to be removed by peripheral tissues. 

Liver blood flow; lactate; intestine 

Infection leads to marked alterations in whole body glucose metabolism, characterized by an acceleration in glucose production and utilization (17). The increase in glucose production is derived from an increase in gluconeogenesis, driven by the elevated counterregulatory hormone environment (17).

In this environment of elevated glucose flux, the ability of infected individuals to dispose of exogenous glucose is impaired, as evidenced by exaggerated hyperglycemia during glucose-based parenteral nutrition (15, 19). Peripheral insulin resistance and impaired suppression of hepatic glucose production contribute to the glucose intolerance (12). The peripheral insulin resistance is marked; insulin-stimulated whole body glucose utilization is decreased by ~50% (11, 26).

An impairment in net hepatic glucose uptake also contributes to the abnormal glucose tolerance seen during an acute infusion of glucose. During a 180-min intravenous glucose infusion, net hepatic glucose uptake was 25% of normal in infected animals (19). Consistent with previous reports (28), a failure to suppress endogenous glucose production contributed ~40% of the impairment in net hepaptic glucose uptake. The remaining 60% was due to a failure to increase unidirectional hepatic glucose uptake despite marked hyperinsulinemia.

The majority of stressed patients are not given glucose alone; rather glucose is given in combination with specific fats and amino acids. In addition, nutrients are administered on a chronic basis. The response of the liver to chronic nutritional support and its interaction with infection have not been examined. In the present study, we examined the balance of glucose and substrates across the liver and muscle in chronically catheterized conscious dogs receiving continuous total parenteral nutrition (TPN). In addition, we assessed the impact of infection on the TPN-adapted liver.

Materials and Methods

Animal preparation. Experiments were carried out on five conscious female mongrel dogs (20 ± 1 kg). Before being studied, they received a diet consisting of Kalkan meat (Vernon, CA) and Purina dog chow (St. Louis, MO) once daily. The composition of the diet was 52% carbohydrate, 31% protein, 11% fat, and 6% fiber based on dry weight. The dogs were housed in a facility that met American Association for Accreditation of Laboratory Animal Care guidelines, and the experimental protocols were approved by the Vanderbilt University Animal Care Subcommittee.

Experimental preparation. Fourteen to seventeen days before a study, a laparotomy was performed under general anesthesia (isoflurane). Infusion catheters were placed into the inferior vena cava for infusion of TPN. Sampling catheters (0.04 inch ID) were inserted into the portal vein and the left common hepatic vein for blood sampling. Additional catheters (0.04 inch ID) for blood sampling were inserted into the femoral artery after an incision was made in the left inguinal area, and into the common iliac vein after an incision was made in the right inguinal region. The catheters were then filled with saline containing heparin (200 U/ml). Doppler flow probes were placed about the external iliac artery, portal vein, and hepatic artery after the gastroduodenal vein was ligated. The portal and hepatic vein sampling catheters and the Doppler flow probe leads were exteriorized and placed in a subcutaneous pocket in the abdominal area. The free ends of

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

0193-1849/98 $5.00 Copyright © 1998 the American Physiological Society E763
were calculated according to the formula (1.5 kg·day⁻¹·m⁻²). Nitrogen (grams of protein/day) requirements were determined with the method of Lloyd et al. (14) on a Monarch 2000 centrifugal analyzer (Instrumentation Laboratories, Lexington, MA). Plasma glucose was assayed immediately with a Beckman GlucoseAnalyzer II (Beckman Instruments, Fullerton, CA). Plasma nonesterified fatty acids were determined spectrophotometrically (Wako Chemicals, Richmond, VA); intra-assay coefficient of variation (CV) of 11%. Plasma treated with 500 kallikrein-inhibitor units of Trasylol (Miles, Kankakee, IL) was assayed for immunoreactive glucagon (1) with a procedure similar to that for insulin (intra-assay CV of 8%). Plasma cortisol (6) was assayed with Clinical Assays Gamma Coat radioimmunoassay kit (intra-assay CV of 6%). Plasma catecholamines were measured by HPLC techniques (CV of 14%) (16), as modified by Davis et al. (5). Hepatic artery, iliac artery, and portal vein blood flow were assessed with Transonic flow probes (Transonic Systems, Ithaca, NY). Blood flow was converted to plasma flow by multiplying by 1 – hematocrit ratio.

Calculations. Net hepatic glucose uptake was calculated with the formula [\(\frac{I}{P} \times (A + F_a \times P) \times \frac{1}{HBF}\)], where \(H\), \(A\), and \(P\) are the blood glucose concentrations in the hepatic vein, femoral artery, and portal vein, respectively, and \(F_a\) and \(F_p\) represent the fractional contributions of the hepatic artery and portal vein, respectively, to total hepatic blood flow (HBF). Net fractional hepatic glucose extraction was calculated as the ratio of net hepatic glucose uptake and hepatic glucose load. Hepatic glucose load was calculated with the formula \(\left(\frac{F_a \times A + F_p \times P}{HBF}\right)\). Plasma glucose concentrations were converted to whole blood concentrations with a correction factor of 0.73 (23). The above equations were used to calculate net hepatic lactate, alanine, nonesterified free fatty acid (NEFA), and glycerol uptake and fractional extraction as well. However, because the liver was a net producer (i.e., negative uptake) of lactate, the lactate data are presented as positive values and denoted as net output. Plasma flow was used instead of blood flow to calculate net hepatic NEFA uptake. In an analogous way, net limb substrate uptake was calculated with the formula \(\left[\frac{A - V}{LBF}\right]\), where \(V\) is the blood substrate concentrations in the iliac vein and \(LBF\) is blood flow in the iliac artery.

Statistics. Hepatic blood flow and substrate flux are expressed on a per kilogram body weight basis. Statistical comparisons were made with ANOVA (Systat for Windows; Systat, Evanston, IL). A univariate post hoc F-test was used when a significant F ratio was found. Statistical significance was accepted at \(P < 0.05\).

RESULTS

Liver and limb blood flow. On day 0 before induction of infection, hepatic artery blood flow and portal vein blood flow were 5.9 ± 1.3 and 26.5 ± 2.7 ml·kg⁻¹·min⁻¹, respectively (Table 1). After the induction of infection, hepatic artery blood flow increased to 20.3 ± 4.6 and 11.6 ± 3.0 ml·kg⁻¹·min⁻¹ on days 1 and 2 (\(P < 0.05\)). Portal vein blood flow was unaltered by infection.
Table 1. Blood flow in hepatic artery, portal vein, and iliac artery in chronically catheterized conscious dogs receiving chronic TPN before induction of infection and 18 and 42 h after infection

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic artery</td>
<td>5.9 ± 1.3</td>
<td>20.3 ± 4.6</td>
<td>11.6 ± 3.0</td>
</tr>
<tr>
<td>Portal vein</td>
<td>26.5 ± 2.7</td>
<td>30.7 ± 5.1</td>
<td>25.7 ± 3.4</td>
</tr>
<tr>
<td>Iliac artery</td>
<td>9.9 ± 1.6</td>
<td>12.7 ± 2.1</td>
<td>11.7 ± 2.1</td>
</tr>
</tbody>
</table>

Data are means ± SE (ml·kg⁻¹·min⁻¹) of 5 dogs. Day 0, before infection; days 1 and 2, 18 and 42 h after infection, respectively. TPN, total parenteral nutrition. *Significantly different from day 0.

Consequently, total hepatic blood flow increased from 32 ± 2 ml·kg⁻¹·min⁻¹ to 51 ± 8.8 ml·kg⁻¹·min⁻¹ on day 1 (P < 0.05) and 37.3 ± 3.9 ml·kg⁻¹·min⁻¹ on day 2. Thus the contribution of the hepatic artery to total hepatic blood flow increased from 19 ± 5% on day 0 to 40 ± 6 and 31 ± 8% on days 1 and 2, respectively (P < 0.05). Iliac vein blood flow was not significantly increased by infection (Table 1).

Hormone levels. Arterial insulin levels were 16 ± 2 µU/ml on day 0 and increased to 57 ± 14 µU/ml on day 1 and 34 ± 9 µU/ml on day 2 (Table 2; P < 0.05). Arterial plasma glucagon levels increased from 30 ± 6 pg/ml to 132 ± 22 (P < 0.05) and 80 ± 28 pg/ml on days 1 and 2, respectively. Arterial cortisol levels were 3 ± 1, 5 ± 2, and 4 ± 1 µg/dl on days 0, 1, and 2, respectively. Respective arterial plasma epinephrine levels were 199 ± 46, 271 ± 96, and 203 ± 103 pg/ml, and those for arterial plasma norepinephrine were 276 ± 81, 423 ± 121, and 477 ± 123 pg/ml.

Hepatic metabolism. Arterial plasma glucose levels increased from 117 ± 5 mg/dl on day 0 to 135 ± 9 and 144 ± 9 mg/dl on days 1 and 2, respectively (P < 0.05; Fig. 1). On day 0, the liver was a net consumer of glucose (4.3 ± 0.6 mg·kg⁻¹·min⁻¹). On days 1 and 2, despite hyperglycemia and hyperinsulinemia, net hepatic glucose uptake decreased to 1.6 ± 0.9 and 2.4 ± 0.5 mg·kg⁻¹·min⁻¹ (P < 0.05). Net fractional hepatic glucose extraction was markedly elevated with TPN and decreased markedly after infection. The fraction of TPN-infused glucose (9.5 ± 0.1 mg·kg⁻¹·min⁻¹) removed by the liver was 45 ± 6% on day 0 and decreased markedly to 16 ± 9 and 25 ± 5% (Fig. 2) on days 1 and 2.

Table 2. Arterial plasma insulin, glucagon, cortisol, epinephrine, and norepinephrine in chronically catheterized conscious dogs receiving chronic TPN before induction of infection and 18 and 42 h after infection

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin, µU/ml</td>
<td>16 ± 2</td>
<td>57 ± 14</td>
<td>34 ± 9</td>
</tr>
<tr>
<td>Glucagon, pg/ml</td>
<td>30 ± 6</td>
<td>132 ± 22</td>
<td>80 ± 28</td>
</tr>
<tr>
<td>Cortisol, µg/dl</td>
<td>3 ± 1</td>
<td>5 ± 2</td>
<td>4 ± 1</td>
</tr>
<tr>
<td>Epinephrine, pg/ml</td>
<td>199 ± 46</td>
<td>271 ± 96</td>
<td>203 ± 103</td>
</tr>
<tr>
<td>Norepinephrine, pg/ml</td>
<td>276 ± 81</td>
<td>423 ± 121</td>
<td>477 ± 123</td>
</tr>
</tbody>
</table>

Data are means ± SE of 5 dogs. Day 0, before infection; days 1 and 2, 18 and 42 h after infection, respectively. TPN, total parenteral nutrition. *Significantly different from day 0.

Arterial lactate levels were 1.5 ± 0.1 mM on day 0, were not altered on day 1 (1.5 ± 0.2 mM), and were decreased on day 2 (P < 0.05; 1.0 ± 0.1 mM; Fig. 3). The liver was a marked producer of lactate on day 0 (34 ± 6 µmol·kg⁻¹·min⁻¹). After infection, net hepatic lactate release decreased to 15 ± 5 and 12 ± 3 µmol·kg⁻¹·min⁻¹ on days 1 and 2 (P < 0.05). On day 0, 79 ± 13% of the glucose taken up by the liver was converted to lactate. After infection, this percentage did not decrease on day 1 (84 ± 51%). However, on day 2, it was decreased (44 ± 14%; P < 0.05).

Arterial alanine levels fell from 509 ± 51 µM on day 0 to 273 ± 23 and 342 ± 46 µM on days 1 and 2 (P < 0.05;
Fig. 4. Net hepatic alanine uptake increased (P < 0.05) from 1.4 ± 0.3 µmol·kg⁻¹·min⁻¹ to 2.7 ± 0.4 on day 1 and tended to return toward normal by day 2 (1.9 ± 0.3 µmol·kg⁻¹·min⁻¹). A parallel rise in net fractional hepatic alanine extraction also occurred (0.08 ± 0.2 to 0.21 ± 0.03 to 0.16 ± 0.02 on days 0, 1, and 2, respectively).

Agorcal glycerol levels were not altered by infection (Table 3). Net hepatic glycerol uptake was increased on days 1 and 2. Net fractional hepatic glycerol extraction was not altered.

Arterial NEFA levels were not altered by infection (Table 3). However, both net hepatic NEFA uptake and fractional hepatic extraction were increased on day 1. On day 2, net hepatic NEFA uptake was not significantly elevated, although net fractional hepatic NEFA extraction remained elevated.

Gut metabolism. On day 0, net gut glucose uptake was 0.6 ± 0.1 mg·kg⁻¹·min⁻¹. After the induction of an infection, net gut glucose uptake increased to 1.2 ± 0.3
mg kg\(^{-1}\)·min\(^{-1}\) on day 1, and on day 2 it returned to the basal rate, 0.7 ± 0.1 mg kg\(^{-1}\)·min\(^{-1}\). The intestine was a net consumer of lactate on day 0 (2.5 ± 0.9 µmol·kg\(^{-1}\)·min\(^{-1}\)). On days 1 and 2, the gut lactate uptake decreased to 0.8 ± 0.4 and 0.7 ± 0.8 µmol·kg\(^{-1}\)·min\(^{-1}\), respectively. The gut was a net producer of alanine (0.7 ± 0.1 µmol·kg\(^{-1}\)·min\(^{-1}\)) on day 0, and net gut alanine release was not altered on days 1 and 2 (0.6 ± 0.2 and 0.3 ± 0.2 µmol·kg\(^{-1}\)·min\(^{-1}\)).

Limb metabolism. On day 0, limb glucose uptake and fractional glucose extraction were 6 ± 1 mg/min and 0.04 ± 0.01, respectively (Fig. 5). On day 1, after the induction of infection, limb glucose uptake increased (18 ± 8 mg/min) and returned toward normal on day 2 (10 ± 3 mg/min). Limb glucose fractional extraction was 0.08 ± 0.04 and 0.05 ± 0.01 on days 1 and 2, respectively.

On day 0, limb lactate uptake and limb lactate fractional extraction were 34 ± 5 µmol/min and 0.18 ± 0.04, respectively. On day 1, limb lactate uptake and fractional extraction were decreased (−3 ± 17 µmol/min and 0.0 ± 0.04, respectively). They remained decreased on day 2 (2 ± 8 µmol/min and 0.05 ± 0.04).

The limb increased its release of glycerol from 0.2 ± 1.1 µmol/min on day 0 to 5.3 ± 1.6 and 4.1 ± 1.9 µmol/min on days 1 and 2, respectively. The limb release of NEFA was unaltered (0.4 ± 2.7 to 3.5 ± 6.8 to 2.9 ± 6.6 µmol/min on days 0, 1, and 2).

**Discussion**

These studies demonstrate that the liver has a remarkable ability to adapt to chronic (5 days) total parenteral nutrition. In the presence of mild hyperinsulinemia and normoglycemia, the liver became a marked consumer of glucose (~45% of exogenous glucose infusion). Surprisingly, the liver did not retain the glucose carbon. Rather, it converted ~80% of the glucose to lactate, which was consumed by peripheral tissues such as those of the limb (i.e., muscle). After the induction of infection, net hepatic glucose uptake and lactate release decreased markedly. A parallel rise in limb glucose uptake and a fall in limb lactate uptake were observed. Thus the adaptation of the liver to TPN is essential in limiting the hyperglycemia and hyperinsulinemia that would otherwise be seen. Infection attenuates this adaptation, forcing peripheral tissues to consume a greater portion of the glucose, which results in hyperglycemia and hyperinsulinemia.

The most surprising finding of the study was that the liver could take up substantial quantities of glucose (4.3 mg·kg\(^{-1}\)·min\(^{-1}\)) in the absence of hyperglycemia (117 mg/dl) and only mild hyperinsulinemia (17 µU/ml). The substantial uptake of glucose by the liver after TPN (45% of the exogenous glucose) is greater than that which would have been predicted on the basis of acute studies (4). The three factors that regulate net hepatic glucose uptake are the hepatic glucose load (flow × level), the hormonal milieu (insulin and glucagon levels), and the route of glucose delivery. Physiological increases in glucose alone will not induce net hepatic glucose uptake. However, in the presence of elevated glucose levels, net hepatic glucose uptake increases in a dose-dependent manner with a rise in insulin. This is further enhanced if the glucose is administered into the portal vein (which activates the

**Table 3. Arterial concentration, net hepatic uptake, and net fractional hepatic extraction of glycerol and NEFA in chronically catheterized conscious dogs receiving chronic TPN before induction of infection and 18 and 42 h after infection**

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glycerol</td>
<td>81 ± 19</td>
<td>101 ± 17</td>
<td>86 ± 8</td>
</tr>
<tr>
<td>Net hepatic uptake, µmol·kg(^{-1})·min(^{-1})</td>
<td>1.4 ± 0.4</td>
<td>2.5 ± 0.1*</td>
<td>2.0 ± 0.2*</td>
</tr>
<tr>
<td>Net fractional hepatic extraction</td>
<td>0.53 ± 0.06</td>
<td>0.57 ± 0.02</td>
<td>0.63 ± 0.03</td>
</tr>
<tr>
<td>Plasma NEFA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level, µM</td>
<td>322 ± 57</td>
<td>484 ± 59</td>
<td>384 ± 20</td>
</tr>
<tr>
<td>Net hepatic uptake, µmol·kg(^{-1})·min(^{-1})</td>
<td>1.0 ± 0.7</td>
<td>3.7 ± 0.9*</td>
<td>2.0 ± 0.4</td>
</tr>
<tr>
<td>Net fractional hepatic extraction</td>
<td>0.09 ± 0.05</td>
<td>0.21 ± 0.04*</td>
<td>0.18 ± 0.04*</td>
</tr>
</tbody>
</table>

Data are means ± SE of 5 dogs. Day 0, before infection; days 1 and 2, 18 and 42 h after infection. TPN, total parenteral nutrition, NEFA, nonesterified free fatty acid. *Significantly different from day 0.

**Fig. 5.** Net limb glucose uptake (A) and net limb lactate uptake (B) in dogs receiving a continuous TPN infusion before induction of infection (day 0) and 18 (day 1) and 42 h (day 2) after induction of infection. Data are means ± SE. *Significantly different from day 0.
“portal” signal) (23, 25). To acutely increase net hepatic glucose uptake to \( \sim 4.3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \), the arterial plasma glucose levels would have to be greater than 200 mg/dl, and the arterial insulin levels would have to exceed 40 \( \mu \text{U/ml} \) (23). In addition, the glucose would have to be infused into the portal vein. Thus TPN has increased the capacity of the liver to consume glucose. This response is similar to but somewhat greater than those responses seen in malnourished humans receiving TPN in which the splanchnic bed removed \( \sim 20\% \) of the TPN-derived glucose (9). The lower glucose uptake in the human may be due, in part, to the fact that the subjects were not healthy and they had elevated glucagon levels. One likely explanation for the enhancement in liver glucose uptake is an increase in glucokinase activity (2, 24), possibly initiated by the mild hyperinsulinemia and the very low glucagon levels seen in the normal dog receiving TPN. Other glycolytic enzymes must also be involved, because activation of glucokinase alone cannot explain the marked increase in hepatic glycolysis observed (29).

The major fate of glucose taken up by the liver of TPN-adapted dogs was conversion to lactate and subsequent release. If a liver is acutely induced to consume \( \sim 4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) of glucose by exposure to combined hyperinsulinemia and hyperglycemia, only a small fraction (\( \sim 10\% \)) of the glucose is released as lactate. The majority of the consumed glucose is converted to glycogen. In response to chronic TPN, however, a large fraction (\( \sim 80\% \)) of the glucose was converted to lactate. As is the case for the high rate of glucose uptake, the mechanism is unclear.

The hepatic conversion of glucose to lactate allows the peripheral tissues to consume \( \sim 90\% \) of the exogenous carbohydrate without marked hyperinsulinemia in the normal TPN-adapted dog. Insulin levels were only increased twofold over those seen in overnight-fasted dogs (4). Consistent with this, limb fractional extraction and uptake of glucose were elevated compared with normal overnight-fasted dogs (32). Whereas the limb was consuming more glucose than in a fasted state, nearly 50% of the limb carbohydrate uptake was supplied as lactate. The increased dependency on lactate allows the muscle to utilize large quantities of carbohydrate without exaggerated hyperinsulinemia.

Infection led to a marked inhibition of liver glucose uptake. The mechanism for the infection-induced decrease in net hepatic glucose uptake is unknown. A fall in net hepatic glucose uptake could be due to either a decrease in the entry of glucose into the liver and/or a corresponding increase in hepatic glucose production. In response to an acute infusion of glucose into a peripheral vein, infection decreases net hepatic glucose uptake because of an impaired entry of glucose as well as an impaired suppression of hepatic glucose production (19). In septic patients receiving overnight glucose infusion, endogenous glucose production and alanine gluconeogenesis are not completely suppressed (27). Because the response of the liver to acute glucose infusion and chronic TPN infusion is markedly different, it is uncertain whether a similar explanation would apply to an infected animal receiving nutritional support. The factors responsible for the alterations in net hepatic glucose uptake are unclear. However, it is likely that the infection-induced hyperglucagonemia plays a central role. Hyperglucagonemia when combined with the available nutrients (amino acids and lipid supplied by the TPN) can increase the rate of gluconeogenesis (15, 18, 19).

After infection, the peripheral tissues were forced to dispose of the TPN-derived glucose directly, because liver glucose uptake was markedly decreased. Extrahepatic glucose uptake (exogenous glucose infusion rate – net hepatic glucose uptake) increased by 52 and 37% on days 1 and 2. Some of this increase occurred in muscle, because limb glucose uptake increased markedly on day 1 and remained somewhat elevated on day 2 (the hindlimb in the dog is \( \sim 65\% \) skeletal muscle by weight). The decrease in net hepatic lactate release was paralleled by a near-complete cessation of net limb lactate uptake on days 1 and 2. The prevailing hyperinsulinemia likely contributed to the increase in limb glucose uptake. However, because infection also increases insulin-independent glucose uptake (10), this may also contribute to the increase.

Arterial alanine levels were likely altered by infection because of the infection-induced rise in glucagon. On day 0, both arterial glucagon levels and net fractional hepatic alanine extraction were markedly lower than in overnight-fasted dogs (30 vs. 50 pg/ml and 0.08 vs. 0.30). After infection, arterial alanine levels fell because of the rise in net hepatic alanine fractional extraction. The rise in net fractional hepatic alanine extraction is consistent with the known potent effects of glucagon on this parameter (21).

The liver became more reliant on fatty acids after infection. Nonesterified fatty acid uptake and extraction were increased during infection. In addition, net hepatic glycerol uptake was increased. These data are consistent with the known acceleration of lipolysis during infection. Because the levels of these substrates did not increase, the primary mechanism for the increase in uptake is an increase in hepatic blood flow and fractional extraction of these precursors.

Infection leads to a marked increase in liver blood flow, predominantly by enhancing hepatic artery blood flow. This increase has been reported in the rat (8). The mechanism is unclear. However, because liver energy demands increase after infection, it may activate the hepatic artery buffer response (13) or possibly an infection-induced increase in local release of vasodilators, such as nitric oxide (22).

In summary, after adaptation to TPN, the liver becomes a major site of glucose disposal. However, the liver does not retain the glucose skeleton; rather, it converts it to lactate, which is subsequently released and consumed by peripheral tissues. This adaptation allows peripheral tissues to remove large amounts of carbohydrate while minimizing the insulin requirements. After infection, this cycle is disrupted. Net hepatic glucose uptake is markedly inhibited, and the conversion to lactate is diminished. The result is that
the peripheral tissues must directly remove a greater fraction of the TPN-derived glucose. Because infection also leads to peripheral insulin resistance, the insulin requirements are further amplified, resulting in hyperglycemia.

We are grateful for the technical assistance of Pamela Venson and Eric Allen from the hormone core laboratory of the Vanderbilt University Diabetes Research and Training Center. This study was supported by National Institute of Diabetes and Digestive and Kidney Diseases Grant DK-43748 (principal investigator: O. P. McGuinness) and Diabetes Research and Training Center Grant P60-DK-20593.

Address for reprint requests: O. P. McGuinness, 702 Light Hall, Dept. of Molecular Physiology and Biophysics, Vanderbilt Univ., Nashville, TN 37232–0615.

Received 17 April 1998; accepted in final form 3 August 1998.

REFERENCES