Hepatic production and intestinal uptake of IGF-I: response to infection

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Lang, Charles H., Robert A. Frost, Joseph Ejiofor, D. Brooks Lacy, and Owen P. McGuinness. Hepatic production and intestinal uptake of IGF-I: response to infection. Am. J. Physiol. 275 (Gastrointest. Liver Physiol. 38): G1291–G1298, 1998.—The role of the liver and gut in contributing to the infection-induced fall in circulating insulin-like growth factor I (IGF-I) was examined in chronically catheterized conscious dogs. Two weeks before study, catheters and Doppler flow probes were implanted to assess hepatic and gut balance of IGF-I. To control nutrient intake, dogs were placed on total parenteral nutrition (TPN) as their sole caloric source. After dogs received TPN for 5 days, net hepatic and intestine IGF-I balances were assessed. A hypermetabolic infected state was then induced by the intraperitoneal implantation of a fibrin clot containing Escherichia coli. TPN was continued, and organ IGF-I balance was assessed 24 and 48 h after induction of infection. Arterial IGF-I levels were significantly decreased following infection (111 ± 18, 62 ± 10, and 63 ± 8 ng/ml before and 24 and 48 h after, respectively). Net hepatic IGF-I output decreased markedly (221 ± 73, to 73 ± 41 and 41 ± 17 ng·kg⁻¹·min⁻¹ before and 24 and 48 h after, respectively). The infection-induced decrease in hepatic IGF-I output could not be explained by concomitant alterations in plasma cortisol or insulin levels. The gut demonstrated a net uptake of IGF-I before infection (178 ± 29 ng·kg⁻¹·min⁻¹). However, after infection, intestinal IGF-I uptake was completely suppressed (−10 ± 15 and −8 ± 36 ng·kg⁻¹·min⁻¹). In summary, infection decreases net hepatic IGF-I release 65–80% and completely suppresses net IGF-I uptake by the intestine. As a consequence of these reciprocal changes in IGF-I balance across the liver and intestine, splanchnic production of IGF-I was unchanged by infection. These data suggest that changes in the clearance and/or production of IGF-I by extrasplanchnic tissues contribute to the infection-induced decrease in circulating IGF-I levels.

INSULIN-LIKE GROWTH FACTOR (IGF)-I is an important anabolic hormone that is essential for normal growth and development and the maintenance of lean body mass. A wide variety of tissues have the ability to synthesize IGF-I, and the expression of IGF-I mRNA and/or IGF-I protein content can be altered in a tissue-specific manner during certain pathophysiological conditions (6, 8, 15, 22). Hence, IGF-I is generally considered to function both as a classical hormone as well as in a paracrine and autocrine manner (14).

Despite the ability of numerous tissues to synthesize IGF-I, the liver is believed to be the primary production site for blood-borne IGF-I. This belief arises from studies conducted in rats demonstrating the ability of isolated perfused livers to secrete IGF-I at rates sufficient to account for estimated rates of IGF-I clearance from the circulation (7, 33). The direct measurement of hepatic IGF-I production under in vivo conditions has not been reported. However, studies by Müller et al. (25) have demonstrated a positive arterial hepatic venous IGF-I gradient across the splanchic organs (i.e., liver, intestine, spleen, pancreas, and so forth) in normal human volunteers. Although such data are consistent with the role of the liver in IGF-I production, interpretation of these data is complicated by the ability of nonhepatic splanchnic organs to both synthesize and remove IGF-I (5, 7, 20).

Bacterial infection has been previously demonstrated to decrease the circulating concentration of IGF-I (15, 16, 32), and the in vitro incubation of hepatocytes with inflammatory cytokines that are overproduced during sepsis can directly impair IGF-I secretion (37, 39). Furthermore, the injection of gram-negative endotoxin has also been shown to markedly impair intestinal uptake of 125I-labeled IGF-I from the circulation (7). However, the ability of sepsis to modulate hepatic secretion and/or intestinal uptake of IGF-I in vivo has not been quantitated.

The purpose of the present study was to directly quantitate the net output of IGF-I by the liver and the intestine under control conditions and following a septic insult. IGF-I balance for the liver and gut was determined in vivo by measuring organ blood flow and the arteriovenous (a-v) difference for IGF-I across each organ in chronically catheterized conscious dogs. Because infection decreases spontaneous food consumption (15) and caloric restriction is known to decrease IGF-I (15, 16, 32), and the in vitro incubation of hepatocytes with inflammatory cytokines that are overproduced during sepsis can directly impair IGF-I secretion (37, 39). Furthermore, the injection of gram-negative endotoxin has also been shown to markedly impair intestinal uptake of 125I-labeled IGF-I from the circulation (7). However, the ability of sepsis to modulate hepatic secretion and/or intestinal uptake of IGF-I in vivo has not been quantitated.

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MATERIALS AND METHODS

Animal preparation. Experiments were performed on eight conscious female nonpregnant mongrel dogs (20 ± 1 kg). Before the study, each dog received a diet consisting of Kal-Kan meat (Vernon, CA) and Purina dog chow (St. Louis, MO) once daily. The composition of the diet, made on the basis of dry weight, was 52% carbohydrate, 31% protein, 11% fat, and 6% fiber. The dogs were housed in a facility that met the
guidelines of the American Association for Accreditation of Laboratory Animal Care, and the protocol was approved by the Vanderbilt University Medical Center Animal Care Committee.

Fourteen to seventeen days before the study, a laparotomy was performed under general anesthesia using isoflurane. Infusion catheters were placed into the inferior vena cava for infusion of TPN. Sampling catheters (0.04 in. ID; Dow Corning, Midland, MI) were inserted into the portal vein and the left common hepatic vein for blood sampling. An additional catheter (0.04 in. ID) for blood sampling was inserted into the femoral artery following an incision in the left inguinal area. The catheters were then filled with saline containing heparin (200 U/ml). Doppler flow probes were placed around the 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 end of the inferior vena cava infusion catheter was exteriorized, tunneled subcutaneously, and placed under the skin between the Davides. The femoral artery catheter was placed under the skin in the inguinal region.

Experimental protocol. Two weeks after catheter implantation and immediately before the start of TPN, all animals had 1) a good appetite, consuming all of the daily food ration; 2) normal stools; 3) a hematocrit >35%; and 4) a total leukocyte count of <18,000 cells/mm³. At this time, dogs were switched to TPN as the sole exogenous calorie source for a 7-day period. The nutritional support was designed to match their calculated basal energy requirements (144 + 62.2 × BW kcal/day, where BW is body wt in kg; Ref. 35). Nitrogen (g protein/day) requirements were calculated according to the following formula: 1.5 × BW⁰.⁶⁷. This requirement was met by the infusion of Trasvelasol (10%, Clinetc Nutrition, Deerfield, IL). Twenty-five percent of the nonprotein energy requirements was derived from fat (Intralipid, Clinetc Nutrition) and 75% from dextrose (50%, Baxter, Toronto, ON, Canada). The TPN also included potassium phosphate (45 mM, 90 mg potassium-kg⁻¹-day⁻¹) and sodium chloride (0.9%, 2.9 ml-kg⁻¹-day⁻¹) as well as a multivitamin infusion (MVI-12, Astra USA, Westborough, MA). The dogs had free access to water.

Parenteral nutrients were given via two catheters placed into the inferior vena cava at the time of surgery. Each dog was placed in a jacket (Alice King Chatham, Los Angeles, CA) containing a pocket into which two portable infusion pumps were placed (INFUMED, Medfusion Systems, Norcross, GA). The nutritional support was given continuously over the 7-day period. TPN was prepared under sterile conditions and changed once daily.

After 5 days of TPN, dogs were anesthetized with a short-acting anesthetic agent (thiampyl sodium; 15 mg/kg). In six animals, a sterile fibrinogen clot containing Escherichia coli was placed into the peritoneum (24). The remaining two animals served as time-matched controls and had a sterile clot implanted. Dogs received 500 ml of saline resuscitation immediately after clot implantation. An additional 1,000 ml of saline was given on day 1.

This model of infection has been previously demonstrated to be hypermetabolic and hyperdynamic (24). Bacterial cultures of the peritoneal cavity are routinely positive in all infected dogs, whereas single time-point blood cultures are positive in 40% of the animals (24). No viable bacteria have been detected in nonseptic dogs. Bacterial cultures were not performed in the current study. However, the presence of an infective state was confirmed by the febrile response and the increase in plasma glucagon concentration and hepatic arterial plasma flow (data presented below), all of which are consistent characteristics of the septic condition.

Before and at 24 and 48 h after clot implantation, the blood-sampling catheters and Doppler flow probe leads were removed from subcutaneous pockets under local anesthesia (2% lidocaine), and dogs were placed into Pavlov harnesses. Animals rested quietly for 60–90 min before blood samples were taken. Thereafter, serial blood samples from the femoral artery, portal vein, and hepatic vein were obtained at 0, 30, and 60 min. During each sampling period, artery and portal vein samples were taken simultaneously, 30 s before collection of the hepatic venous blood sample. Rectal temperature was determined daily using a Yellow Springs (Yellow Springs, OH) telethermometer.

Fibrinogen clot preparation. A 1% bovine fibrinogen solution (10 mg/kg) was prepared in sterile saline and filtered through a sterile 0.45-µm filter (Corning, Corning, NY). E. coli (25922, American Type Culture Collection, Manassas, VA) was added to the fibrinogen solution (2 × 10⁹ colony-forming organisms/kg). Thrombin was then added (1,000 units), and 30 min were allowed for clot formation (24).

Analytical methods. To determine IGF-I levels, plasma was extracted using a modified acid-ethanol (0.25 N, 87.5% ethanol) procedure with overnight cryoprecipitation (15, 16). This method has been previously shown to remove >99% of all IGF binding proteins in plasma (9). The IGF-I concentration in samples was determined in quadruplicate by RIA, as previously described (15, 16).

The plasma concentration of IGF binding protein-3 (IGFBP-3) was determined by Western ligand blot analysis, as described by Hossenlopp et al. (12). Briefly, samples were subjected to SDS-PAGE without reduction of disulfide bonds. The electrophoresed proteins were transferred onto nitrocellulose in Tris-methanol-glycine buffer using a semidry blotter (Bio-Rad, Hercules, CA) for 25 min at a constant voltage of 21 V. Nitrocellulose sheets were washed and then incubated overnight with radiolabeled IGF-I with and without excess unlabeled IGF-I. The nitrocellulose sheets were washed extensively in Tween 20, dried, and autoradiographed with a phosphor screen (DuPont, Wilmington, DE) at −70°C. Band intensities were determined by scanning the autoradiogram and performing densitometry with NIH Image Software (ScionCorp, Frederick, MD).

IGFBP-3 proteolysis was measured by incubating ¹²⁵I-labeled IGFBP-3 (30,000 counts/min, Diagnostic Systems Laboratory, Webster, TX) with 4 µl of plasma in 0.1 M sodium phosphate buffer (pH 7.4) for 4 h at 37°C. The reaction was stopped by boiling in electrophoresis sample buffer, and the reaction products were separated by SDS-PAGE. ¹²⁵I-labeled IGFBP-3 proteolysis was assayed in paired samples before and after induction of infection and compared with the proteolytic activity present in serum from a pediatric AIDS patient as previously described (10).

The plasma concentrations of insulin, cortisol, and glucagon (known mediators of the IGF system) were determined by RIA; characteristics of each assay have been previously described (15, 16). Alanine aminotransferase (ALT; EC 2.6.1.2) and aspartate aminotransferase (AST; EC 2.6.1.1) activities in plasma were determined colorimetrically (Sigma, St. Louis, MO).

Hepatic artery and portal vein blood flows were assessed using Transonic flow probes (Transonic Systems, Ithaca, NY). Blood flow was converted to plasma flow by multiplying by 1 – hematocrit ratio.
Calculations and statistics. Net hepatic IGF-I output was calculated using the formula 
\[H - (F_A \times A + F_P \times P)] \times HPF,\]
where H, A, and P are the plasma IGF-I concentrations in the hepatic vein, femoral artery, and portal vein, respectively, and Fa and Fp represent the fractional contribution of the hepatic artery and portal vein, respectively, to total hepatic plasma flow (HPF). Net intestinal output was calculated using the formula \((P - A) \times PPF,\) where P and A are portal vein and femoral artery IGF-I concentrations, respectively, and PPF is portal plasma flow. Because the intestine was a net consumer (i.e., negative output) of IGF-I, data are presented as positive values and denote net IGF-I uptake. Net intestinal fractional IGF-I extraction was calculated using the following formula: \((A - P)/A.\) Finally, net splanchnic IGF-I output was calculated using \((A - H) \times HPF.\)

The data reported represent means ± SE (n = 6, where n is no. of animals) of the average IGF-I concentration at each of the three different time points. Statistical comparisons were made using repeated ANOVA followed by Student-Newman-Keuls test.

RESULTS

The arterial plasma IGF-I concentration averaged 111 ± 18 ng/ml during the control period and was significantly decreased by 45% at 24 and 48 h after induction of infection (Fig. 1). A similar infection-induced reduction in IGF-I was detected in blood obtained from the portal and hepatic veins (data not shown). Net hepatic IGF-I output by the liver averaged 221 ± 73 ng·kg body wt⁻¹·min⁻¹ during the control period (Fig. 2). After infection, net hepatic IGF-I output was decreased by 67 and 81% (24 and 48 h, respectively) compared with control values. In contrast, the intestine demonstrated a net uptake of IGF-I during the control period (178 ± 29 ng·kg⁻¹·min⁻¹; Fig. 3, top). Intestinal IGF-I uptake was completely eliminated at both 24 and 48 h after infection. The net fractional extraction of IGF-I by the intestine decreased markedly by 95% (Fig. 3, bottom). Finally, in contrast to the above observations, although dogs demonstrated a net splanchnic output of IGF-I under basal conditions, no change in this parameter could be detected at either time point after infection (basal, 47.8 ± 18.6 ng·kg⁻¹·min⁻¹; 24 h, 78.2 ± 21.5 ng·kg⁻¹·min⁻¹; and 48 h, 49.1 ± 14.0 ng·kg⁻¹·min⁻¹).

In the present study, two dogs were also used as time-matched controls and were treated similarly to infected animals, except that a sterile fibrin clot was implanted intraperitoneally. Variables were determined during the basal period and then again 48 h after implantation of the sterile clot. In noninfected control dogs, mean values for arterial plasma IGF-I (157 and 163 ng/ml), hepatic IGF-I output (305 and 336 ng·kg⁻¹·min⁻¹), and intestinal IGF-I uptake (152 and 250 ng·kg⁻¹·min⁻¹) were similar to those observed in infected animals. In addition, no change in these parameters could be detected at any time point after implantation of the sterile clot.
201 ng·kg\(^{-1}\)·min\(^{-1}\) for control and 48-h groups, respectively, were similar at both time points. These data indicate that alterations in these variables observed in the experimental group were produced by the resulting infection and were not simply a result of the surgical stress imposed by implantation of the fibrin clot.

Figure 4 illustrates hepatic arterial, portal vein, and hepatic vein plasma flow under control and septic conditions. On the first day after induction of infection, hepatic arterial plasma flow was increased almost fourfold, resulting in a significant increase in hepatic vein plasma flow. By the second day of infection, plasma flow in the hepatic artery and vein had decreased to levels intermediate between those observed during the control period and those on day 1 of infection. No significant change in portal (intestinal) vein plasma flow was detected following infection.

The concentration of IGFBP-3 in samples from the hepatic artery, portal vein, and hepatic vein 1 day after induction of infection was decreased 40–60% compared with control values (Fig. 5). This reduction in plasma IGFBP-3 was still observed on day 2. We were unable to detect a significant transhepatic flux of IGFBP-3 under either control or septic conditions using ligand blot analysis. We also were unable to detect the presence of significant proteolysis of IGFBP-3 under either control or infected conditions (data not shown).

The concentrations of several hormones known to modulate the IGF system were also determined. Plasma insulin levels on day 1 of infection were increased more than threefold, compared with control values (Fig. 6, top). However, by day 2 of infection, insulin levels were not significantly different from control values. Plasma glucagon levels were also increased on the first day of infection (3.5-fold) and returned to near control values by day 2 (Fig. 6, bottom). As a result of these concomitant changes, the molar ratio of insulin to glucagon was not significantly altered in infected dogs infused with TPN compared with nonseptic values (basal, 10.8 ± 2.4; 24 h, 11.5 ± 2.0; and 48 h, 11.5 ± 1.6). There was no infection-induced increase in cortisol levels observed in these animals (Fig. 6, middle).

There was no significant difference between the activity of AST and ALT in plasma from infected dogs infused with TPN, compared with similarly treated time-matched control animals (Table 1). Moreover, the basal (i.e., time 0) values for both groups of dogs are not elevated, compared with naive, orally fed dogs (19). Hence, no overt hepatic toxicity was noted in either

![Fig. 4. Plasma flow determined in the hepatic artery, portal vein, and hepatic vein in dogs under control conditions and after induction of infection. Values are means ± SE; n = 6. Groups with different letters are significantly different from each other (P < 0.05). Groups with the same letters are not statistically different.](#)

![Fig. 5. Representative Western ligand blot of plasma samples from the hepatic artery (HA), portal vein (PV), and hepatic vein (HV). Samples were obtained either during control conditions (time 0) or at 24 or 48 h after induction of infection. The 2 bands in each lane represent IGF binding protein-3 (BP-3), which is glycosylated to a different extent.](#)

![Fig. 6. Arterial plasma concentrations of insulin (top), cortisol (middle), and glucagon (bottom) during control conditions and after the induction of infection. Values are means ± SE; n = 6. Groups with different letters are significantly different from each other (P < 0.05). Groups with the same letters are not statistically different.](#)
control or septic dogs as a result of the 7-day infusion of TPN.

Rectal temperature was determined for infected animals each day before the start of the experimental protocol. Compared with basal values (100.6 ± 0.3°F), infection produced a marked febrile response at both 24 and 48 h (103.5 ± 0.5 and 103.0 ± 0.2°F, respectively). Temperature data were not obtained on the two nonseptic control animals.

**DISCUSSION**

The central role of the liver in maintaining circulating IGF-I levels is based on studies demonstrating a relatively high IGF-I mRNA expression in liver (21) and the ability of the isolated perfused liver to secrete IGF-I (7, 33). However, the most convincing data in support of this hypothesis are from experiments that show a net IGF-I output by splanchnic organs in healthy human volunteers (25). Unfortunately, the relative contribution of the liver and intestinal organs to this splanchnic production cannot be ascertained from previous studies because the venous outflow of numerous nonhepatic organs is included when determining a-v differences between the artery and hepatic vein. Our results extend these earlier observations and clearly indicate a net output of IGF-I by the liver under noninfected conditions in well-nourished dogs receiving TPN. In contrast, in the basal state the intestine exhibits a net uptake of IGF-I, which is equivalent to 80% of the IGF-I released by the liver under basal conditions. Hence, measured rates of splanchnic production underestimated the actual rate of hepatic IGF-I output under basal, noninfected conditions.

A potential caveat to these conclusions and those described below is that our measurements were made in dogs infused with TPN. Animals were provided intravenous nutritional support in this study because infection is known to alter intestinal structure and the absorptive capacity of the gut (34). Thus any differences in nutrient availability between the basal and infected conditions are minimized by this experimental paradigm. Moreover, although the current trend is to provide nutrition to the septic patient via the enteral route, the effectiveness and safety of this route of administration, compared with TPN, is still controversial (18). However, we cannot exclude the possibility that hepatic output and intestinal uptake of IGF-I might differ in animals fed enterally. Furthermore, the infusion of excessive TPN can induce hepatotoxicity (26), which might also impair hepatic function, resulting in a decreased output of IGF-I. However, circulating levels of the liver enzymes ALT and AST were not elevated in either control or infected dogs by the infusion of TPN. Moreover, there was no increase in the molar ratio of insulin to glucagon, which is often associated with steatosis (26), in TPN-infused infected dogs. Therefore, we have no evidence to suggest that the observed changes in IGF-I balance are the result of TPN-induced hepatic dysfunction.

The a-v difference techniques, such as the one used in the present study, provide estimates of net rates of uptake or output for a particular substance and do not exclude the possibility that tissues both synthesize and remove IGF-I. Therefore, our present data are not inconsistent with previous studies indicating the ability of the liver to remove 125I-labeled IGF-I from the circulation (7). Conversely, the net uptake of IGF-I by the intestine is also not contradictory to studies demonstrating the ability of the gut to synthesize IGF-I (5, 30). The relative importance of the various cell types within these two heterogenous organs for bidirectional IGF-I flux remains to be elucidated.

The present study also indicates that hemorrhagic shock markedly decreases hepatic IGF-I output and that this reduction persists for at least 48 h. This reduction was due to the infection, since it was not seen in time-matched control animals that were implanted with a sterile clot. These data extend previous observations that demonstrated that sepsis and inflammation decrease plasma IGF-I levels and hepatic IGF-I mRNA expression (6, 8, 15). IGF-I synthesis is exquisitely sensitive to the nutritional status of the host, and its synthesis is downregulated by protein-calorie malnutrition (36). In the present study, animals received TPN for 5 days before and for the 2-day period after infection to minimize the differences in nutrient intake as a cause for the infection-induced decrease in hepatic IGF-I output. However, this septic insult has previously been demonstrated to produce a hypermetabolic condition and, hence, the animals would be expected to have an elevated caloric requirement. Studies in rats have reported that restriction of food intake to 60% of normal for as long as 21 days failed to significantly decrease plasma IGF-I, hepatic IGF-I mRNA expression, or plasma IGFBP-3 levels (27). Therefore, it seems unlikely that the relatively mild caloric deficiency present in the infected dogs can account for the entire decrease in plasma IGF-I, the hepatic IGF-I output, or the marked reduction in IGFBP-3 in these animals.

Elevated glucocorticoid levels have also been shown to impair hepatic IGF-I synthesis (17, 29). In previous studies, we have shown that this infectious challenge is sufficient to increase plasma cortisol levels (24). However, in this particular study, infection failed to significantly increase circulating cortisol. The reason why
cortisol was not increased is not known, but this lack of response effectively eliminates this hormone as a mediator of the decrease in hepatic IGF-I output. Conversely, decreases in insulin can impair IGF-I synthesis. However, again, the infection-induced decrease in hepatic IGF-I output was not associated with insulinopenia. Various proinflammatory cytokines, such as tumor necrosis factor-α, interleukin-1, and interleukin-6, are also known to decrease plasma IGF-I levels in vivo (4, 6, 8) and to directly impair growth hormone-mediated synthesis of IGF-I in cultured hepatocytes (37, 39). Moreover, treatment of rats with neutralizing agents to these cytokines can attenuate the decreases in plasma IGF-I induced by various catabolic insults (4, 6, 8). At this time, the overproduction of one or more of these inflammatory cytokines would appear to be the most likely cause for the infection-induced reduction in IGF-I output by the liver.

Our current study also indicates that infection completely prevents the uptake of IGF-I by the intestine observed under basal, control conditions. The decrease in intestinal IGF-I uptake was not solely due to a fall in IGF-I delivery to the intestine. IGF-I levels only decreased by 50%, and portal vein blood flow was not decreased. In contrast, both the uptake and fractional extraction of IGF-I by the intestine were completely suppressed. These data are consistent with the decreased 125I-labeled IGF-I uptake by the small intestine previously reported in rats following injection of endotoxin (7). The physiological consequences of this decreased uptake are unknown. However, exogenous administration of IGF-I does attenuate the mucosal atrophy that accompanies catabolic conditions produced by the injection of dexamethasone or burn injury (13, 31). Moreover, IGF-I also increases mucosal cellularity and mucosal growth after intestinal resection or transplantation (23). Hence, the decrease in intestinal IGF-I uptake may be partially responsible for some of the impairment in intestinal immune and absorptive function observed during infection (28, 34). It is noteworthy that, because of the reciprocal changes in IGF-I balance by the liver and intestine, alterations in splanchnic IGF-I release cannot solely explain the infection-induced fall in arterial IGF-I levels. Hence, in vivo determination of splanchnic IGF-I balance, during at least this particular catabolic condition, does not provide an accurate assessment of hepatic IGF-I output. Moreover, these data suggest that the infection-induced decrease in arterial IGF-I results in part from an enhanced clearance and/or decreased production of IGF-I by extraplanchnic tissues. At this time, an increased clearance of IGF-I would appear to be the most likely of these possibilities. We speculate that the infection-induced decrease in circulating IGFBP-3 reduces the binding capacity of the plasma for IGF-I, leading to a generalized increased clearance of IGF-I. Alternatively, or in addition to, tissues such as the kidney and/or lung may be primarily responsible for the enhanced uptake, since an increased removal of 125I-labeled IGF-I by these tissues has been demonstrated during endotoxemia (7).

Unlike insulin, which circulates in the free form, IGF-I in the blood is bound to several high-affinity binding proteins. Although the exact physiological functions of the various IGF binding proteins are not known, they do possess the ability to alter the bioavailability and bioactivity of IGF-I (14). The majority of the IGF-I in the circulation is bound to IGFBP-3 and the acid-labile subunit to form a ternary complex. Because of its large molecular mass (e.g., 150 kDa), the IGF-I bound in this complex is effectively restricted to the vascular compartment. Decreased IGFBP-3 levels in blood have been reported in patients following surgical trauma, infection, and thermal injury (3, 10, 11, 38) and may result from an increased proteolytic activity in the blood (3, 10) and/or a decrease in hepatic IGFBP-3 mRNA expression (32). In the present study, plasma IGFBP-3 levels were markedly decreased within 24 h after induction of infection and remained reduced for at least 48 h. Furthermore, this decrease could not be attributed to an increase in IGFBP-3 protease activity, suggesting a decreased rate of synthesis. Net transsplanchnic flux of IGFBP-3 could not be detected under basal or septic conditions using ligand blot analysis. We did attempt to quantitate plasma IGFBP-3 levels using a commercially available RIA for human IGFBP-3 (DSL, Webster, TX) but were unsuccessful. However, using the same RIA, other investigators have also been unable to detect a net splanchnic production of IGFBP-3 in humans (2). Hence, the primary site of IGFBP-3 synthesis remains to be determined. Although IGFBP-3 is thought to restrict the transendothelial transport of IGF-I when it is present as a ternary complex, free IGFBP-3 and IGF-I exhibit a rapid movement to tissues. IGFBP-3 has been shown to accumulate in the intestines and the stomach (1). IGF-BP-3 may, therefore, deliver IGF-I to the intestine in healthy subjects. Conversely, decreased blood levels of IGFBP-3 during infection may partially account for the suppressed uptake of IGF-I by the intestine during infection.

In summary, in TPN-fed dogs, the liver demonstrates a net output of IGF-I, whereas the intestine is a major site of net IGF-I disposal. Induction of hypermetabolic infection leads to a major reduction in hepatic IGF-I secretion. However, splanchnic IGF-I production does not decrease because infection essentially eliminates IGF-I uptake by the intestine. Thus the infection-induced fall in circulating IGF-I levels appears to be due in part to an enhanced IGF-I clearance or production by nonsplanchnic tissues in the dog. IGFBP-3 levels are also decreased by infection, but transsplanchnic flux for this binding protein could not be detected. Hence, infection leads to marked alterations in hepatic, intestinal, and extraplanchnic IGF-I balance, all of which might be expected to modulate tissue anabolic responses both via classical endocrine mechanisms as well as via autocrine-paracrine mechanisms.

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