Gut-derived norepinephrine plays a critical role in producing hepatocellular dysfunction during early sepsis

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Gut-derived norepinephrine plays a critical role in producing hepatocellular dysfunction during early sepsis. Am J Physiol Gastrointest Liver Physiol 279: G1274–G1281, 2000.—Although plasma norepinephrine (NE) increases and hepatocellular function is depressed during early sepsis, it is unknown whether gut is a significant source of NE and, if so, whether gut-derived NE helps produce hepatocellular dysfunction. We subjected rats to sepsis by cecal ligation and puncture (CLP), and 2 h later (i.e., early sepsis) portal and systemic blood samples were collected and plasma levels of NE were assayed. Other rats were enterectomized before CLP. Hepatocellular function was assessed with an in vivo indocyanine green (ICG) clearance technique, systemic levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 were determined, and the effect of NE on hepatic ICG clearance capacity was assessed in an isolated, perfused liver preparation. Portal levels of NE were significantly higher than systemic levels at 2 h after CLP. Prior enterectomy reduced NE levels in septic animals. Thus gut appears to be the major source of NE release during sepsis. Enterectomy before sepsis also attenuated hepatocellular dysfunction and downregulated TNF-α, IL-1β, and IL-6. Perfusion of the isolated livers with 20 nM NE (similar to that observed in sepsis) significantly reduced ICG clearance capacity. These results suggest that gut-derived NE plays a significant role in hepatocellular dysfunction and upregulating inflammatory cytokines. Modulation of NE release and/or hepatic responsiveness to NE should provide a novel approach for maintaining hepatocellular function in sepsis.

indocyanine green clearance; enterectomy; isolated, perfused rat liver; cecal ligation and puncture; inflammatory cytokines

DESPITE REFINEMENTS in the management of septic patients, sepsis, septic shock, and multiple organ failure remain major causes of death in surgical intensive care units (3, 23). It is possible that the subtle alterations in cellular functions that occur early after the onset of sepsis are not identified and are consequently missed, leading to inadequate or delayed treatment of the septic patient (40). The animal model of polymicrobial sepsis induced by cecal ligation and puncture (CLP) has been extensively used to study the pathophysiology of sepsis. This model of sepsis is characterized by an early, hyperdynamic phase (which includes increased cardiac output, tissue perfusion, and oxygen delivery, decreased vascular resistance, hyperglycemia, and hyperinsulinemia) followed by a late, hypodynamic phase (which includes reduced cardiac output, tissue perfusion, and oxygen delivery, hypoglycemia, and hypoinsulinemia) (6, 10, 40, 44). Although hepatic failure during sepsis is generally thought to be a late complication following pulmonary and renal failures (2), our studies have indicated that hepatocellular dysfunction occurs early after the onset of sepsis (36) and is further depressed with the progression of sepsis (34). Furthermore, the depression in hepatocellular function does not appear to be due to a disturbance of hepatic perfusion or microcirculatory failure (34, 35, 42). In this regard, proinflammatory cytokines such as tumor necrosis factor (TNF)-α have been implicated as important mediators responsible for producing cellular dysfunction and metabolic alteration during sepsis (30, 32).

It has been suggested that the gastrointestinal tract may be the “motor” for initiating multiple organ dysfunction following injury (25). Although the gut is capable of producing inflammatory cytokines, it appears that organs other than the gut, such as the liver, are responsible for the upregulated proinflammatory cytokines during polymicrobial sepsis (19). However, the gut may play a crucial role during sepsis through the release of other mediators, such as norepinephrine (NE), that stimulate Kupffer cells (KC) and increase inflammatory cytokine release. To this end, studies from our laboratory (12), as well as by Kovarik et al. (20), have indicated that systemic levels of NE increase significantly during sepsis. Moreover, Spengler et al. (29) have demonstrated that stimulation of α2-adrenoceptors augments the production of macrophage-derived TNF-α. In this regard, KC are known to be a major source of proinflammatory cytokine release during sepsis as well as under other adverse circulatory conditions (4, 17, 27). However, the mechanism by

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which KC are upregulated to produce increased proinflammatory cytokines remains unknown. We therefore hypothesize that the gut is a significant source of NE during sepsis and that increased gut-derived NE is responsible for depressing hepatocellular function via upregulating inflammatory cytokine production by KC during the early stage of sepsis.

MATERIALS AND METHODS

Experimental model of polymicrobial sepsis. Polymicrobial sepsis was induced by CLP as described in detail previously (6). Male Sprague-Dawley rats (275–325 g) were fasted overnight but allowed water ad libitum. The animals were then anesthetized with methoxyflurane inhalation, and a 4-cm midline incision was performed. The cecum was exposed, ligated just distal to the ileocecal valve to avoid intestinal obstruction, and then punctured twice with an 18-gauge needle. The punctured cecum was squeezed to expel a small amount of fecal material and returned to the abdominal cavity, and the abdominal incision was closed in two layers. Sham-operated rats underwent the same surgical procedure except that the cecum was neither ligated nor punctured. All animals received normal saline (3 ml/100 g body wt) subcutaneously immediately after operation (i.e., fluid resuscitation). The animals were divided into four groups: 1) sham operation, 2) enterectomy before sham operation, 3) CLP, and 4) enterectomy before CLP (see Experimental model of enterectomy for details). The four groups of animals were randomly selected and were studied at 2 h after CLP or sham operation. We have previously demonstrated that 2 h after CLP is the time point that is representative of the early stage of polymicrobial sepsis (39). The experiments described here were performed in adherence to the National Institute of Health guidelines for the use of experimental animals. This project was approved by the Institutional Animal Care and Use Committee of Rhode Island Hospital, Providence, RI.

Experimental model of enterectomy. Enterectomy was performed in animals immediately before CLP or sham operation in which the entire intestine from the third part of duodenum to the anus was excised (45). The first and second parts of duodenum were kept intact to maintain the normal bile and pancreatic fluid drainage. The ends of the duodenum and anus were ligated securely and cleaned with iodine, 75% ethyl alcohol, and normal saline one after another. The end of duodenum was then buried by a purse string suture, and the end of the anus was closed by suture. In animals undergoing CLP, the cecum was excised from the removed gut, stitched to the posterior peritoneum, and then punctured twice with an 18-gauge needle. The punctured cecum was squeezed to expel a small amount of fecal material, and the abdominal incision was closed in two layers. Sham-operated animals only underwent a total enterectomy.

Measurement of plasma levels of NE. At 2 h after CLP, portal and systemic blood samples were simultaneously collected into tubes containing EGTA and reduced glutathione to prevent blood clotting and NE degradation. Plasma was immediately separated and stored at −70°C until assayed. Plasma levels of NE in both portal and systemic samples were determined radioenzymatically, as previously described by us (12), using a commercially available assay (CAT-A-KIT; Amersham, Piscataway, NJ).

Assessment of hepatocellular function. Hepatocellular function was assessed using an in vivo indocyanine green (ICG) clearance technique as previously described by us (39). It should be noted that the maximal velocity of ICG clearance ($V_{\text{max}}$) represents the number of functional ICG receptors or carriers of the active hepatocellular ICG transport system and that the kinetic constant ($K_{\text{a}}$) represents the efficiency of the active transport process (39).

Determination of inflammatory cytokines. Following the determination of hepatocellular function, blood samples were withdrawn by cardiac puncture. The blood samples were put on ice for 10 min and then centrifuged at 1,200 g for 10 min, and the serum was stored at −70°C until assay. The levels of TNF-α, interleukin (IL)-1β, and IL-6 were measured with enzyme-linked immunosorbent assay kits (BioSource International, Camarillo, CA) according to the manufacturer's instructions.

Isolated, perfused liver preparation and in vitro ICG clearance. We used an isolated, perfused rat liver preparation similar to that described and characterized previously by Wolkoff et al. (43) with modifications. In brief, rats were anesthetized with methoxyflurane inhalation, and longitudinal midline and transverse subcostal incisions were made to expose the liver. The common bile duct was isolated and cannulated with polyethylene-10 tubing for the collection and determination of bile production throughout the experiment. Sutures were then loosely placed around the inferior vena cava above and below the right renal vein, around the portal vein above the splenic vein, and around the portal vein and hepatic artery. The distal renal vein and distal vena cava were then ligated. The portal vein was then immediately cannulated with a 16-gauge silicon catheter, and perfusion was begun within 1 min. This catheter was connected to a three-limb tube that was attached to a perfusion pump and to a syringe filled with 3 ml of normal saline with heparin (20 U/ml). A blood pressure analyzer (Micro-Med, Louisville, KY) was connected to the portal vein catheter using polyethylene-50 tubing for the monitoring of perfusion pressure. While the portal vein catheter was being secured, heparin saline was injected into the liver and the perfusion was started. A 12-gauge silicone tube was inserted into the inferior vena cava toward the heart, and the vena cava was ligated suprahepatically. The liver was perfused at a rate of 36 ml/min for 60 min with Krebs-Henseleit buffer with 0.1% glucose and 0.5% bovine serum albumin (fraction V) that was gassed with 95% O₂-5% CO₂. NE (20 nM) was added to the perfusate and was present throughout the entire period of perfusion. Temperature (37°C), perfusion pressure (≥14 cmH₂O), perfusate pH (7.3–7.4), and P⁰₂ (≥500 mmHg) were monitored and maintained. Before ICG clearance determination, the liver was perfused for 30 min with Krebs-Henseleit buffer without recirculation. The liver was then perfused with an additional 400 ml of perfusate containing 8 mg ICG with recirculation for an additional 30 min. Samples of effluent (1 ml each) were collected every 5 min for 30 min after ICG administration. The ICG concentration in the effluent was determined by a spectrophotometer (U-3210; Hitachi) at a wavelength of 800 nm (33) followed by interpolation against a standard curve. The difference in ICG content between different time points was the amount of ICG taken up by the liver. Samples of effluent were assayed for alanine aminotransferase (ALT) with Sigma assay kits according to the manufacturer's instructions. The bile production was also recorded. At the end of the experiment, the liver was harvested for determination of dry weight. Hepatic ICG clearance was expressed as micrograms per gram dry tissue.

Histology of the isolated, perfused liver. The alterations in liver morphology were examined at 60 min after perfusion. Hepatic tissue was harvested and fixed in 10% neutral buffered formalin (Sigma, St. Louis, MO) and later embedded in paraffin. The tissue was then sectioned at a thickness of 5 μm
and stained with hematoxylin and eosin. Slides were evaluated by light microscopy and documented by photographs.

Statistical analysis. Data are presented as means ± SE. One-way ANOVA and Tukey’s test were employed for comparison among different groups of animals. The differences were considered significant at \( P < 0.05 \).

RESULTS

Portal and systemic levels of NE and the effect of enterectomy on circulating NE. As shown in Fig. 1, the portal NE level was 74% higher than the systemic level in sham-operated animals despite the fact that statistical analysis did not show significant difference. Although both systemic and portal levels of NE increased significantly at 2 h after CLP, the levels of NE in portal blood were significantly higher than NE in systemic blood (Fig. 1). Enteroectomy before the onset of sepsis, however, reduced systemic NE levels by 51% (\( P < 0.05 \)) at 2 h after CLP (Fig. 1). To determine whether prior enterectomy causes liver injury, plasma levels of ALT were measured. The results in Table 1 indicate that enterectomy does not significantly increase ALT levels at 2 h after operation.

Alterations in in vivo ICG clearance. As indicated in Fig. 2A, enterectomy in sham-operated animals did not significantly affect the \( V_{\text{max}} \) values of in vivo ICG clearance. In contrast, \( V_{\text{max}} \) decreased by 67% (\( P < 0.05 \)) at 2 h after CLP compared with sham-operated animals (Fig. 2A). Enteroectomy before the onset of sepsis, however, partially prevented the reduction in \( V_{\text{max}} \) (Fig. 2A). Similar to \( V_{\text{max}} \) values of ICG clearance, enterectomy in sham-operated animals did not alter \( K_m \) (Fig. 2B). \( K_m \) values of ICG clearance, however, were reduced by 69% (\( P < 0.05 \)) at 2 h after CLP, which was prevented by enterectomy immediately before the onset of sepsis (Fig. 2B).

Alterations in ICG clearance in isolated, perfused liver preparation. The perfused livers isolated from sham-operated animals demonstrated effective ICG clearance (Fig. 3). In contrast, in vitro ICG clearance decreased significantly in the livers isolated from those

Table 1. Alterations in plasma levels of alanine aminotransferase at 2 h after operation

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<th>Sham</th>
<th>CLP</th>
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<td>ALT (SF units/ml)</td>
<td>18.5 ± 3.7</td>
<td>24.3 ± 2.1</td>
<td>27.0 ± 1.0</td>
<td>24.8 ± 0.6</td>
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Values are means ± SE; \( n = 6 \) group; ALT, alanine aminotransferase; CLP, cecal ligation and puncture; ER, enterectomy; SF, Sigma-Frankel. Comparison by 1-way ANOVA indicates that there was no significant difference between sham and other groups.
animals that underwent sepsis for 2 h. Similarly, perfusion with 20 nM NE also caused a significant decrease of ICG clearance in the livers isolated from sham-operated animals (Fig. 3). Determination of ALT levels present in the effluent demonstrated no significant change throughout the 60-min perfusion period in sham-operated animals (Fig. 4A). Additionally, bile production was not different between livers isolated from sham-operated animals, septic animals, and those perfused with NE throughout the perfusion period (Fig. 4B). The morphological findings indicate that compared with livers from normal rats (Fig. 5A), the isolated, perfused rat liver at 60 min after perfusion shows normal liver histology, with the exception of moderate sinusoidal dilation (Fig. 5B). The normal hepatic morphology, effective ICG clearance, and normal liver enzyme and bile formation suggest that the viability of the isolated livers were maintained throughout the 60-min perfusion.

**Alterations in inflammatory cytokines.** The results in Fig. 6 indicate that circulating levels of the measured cytokines (i.e., TNF-α, IL-1β, and IL-6) increased by 520–869% (P < 0.05) at 2 h after CLP. Prior enterectomy, however, significantly attenuated the increase of these cytokines during early sepsis. Enterectomy in sham-operated animals did not significantly affect sham levels of plasma TNF-α, IL-1β, and IL-6 (Fig. 6).

**DISCUSSION**

Because of its important role in metabolism and host defense mechanisms, the liver has been extensively studied during sepsis and septic shock and is thought to be a major organ in the development of multiple organ failure under such conditions (39). Although hepatic failure is generally thought to be a late complication following pulmonary and renal failures (2), our studies have indicated that hepatocellular function is depressed early after the onset of sepsis and that this depression does not appear to be due to a reduction in...
hepatic perfusion (34–36, 42). Thus it is important to determine the mediators (which are released early after the onset of sepsis) responsible for producing hepatocellular dysfunction. In this regard, studies have indicated that levels of NE increase significantly during early sepsis (12, 20). Additionally, mesenteric organs (primarily the gut) are thought to contribute substantially to total body NE production (~50% of the NE formed in the body under normal conditions) (1, 7). Therefore, the present study was conducted to determine whether the gut is a significant source of NE during early sepsis and, if so, whether gut-derived NE plays any role in producing hepatocellular dysfunction under such conditions.

Our results indicate that both portal and systemic levels of NE were markedly elevated at 2 h after the onset of sepsis. The portal levels of NE, however, were significantly higher than systemic levels in septic animals. Although the fact that levels of NE in portal blood were significantly higher than those in systemic blood indicated that the gut is a major source of NE during early sepsis, the strong piece of evidence supporting this comes from animals that were enterectomized before the induction of sepsis. The results from this group of animals demonstrate that removal of gut before the CLP prevents the increase in NE seen after the onset of sepsis. Thus the gut appears to be the major source of NE production during the early stage of sepsis. The data also indicate that hepatocellular function was markedly depressed at 2 h after CLP. Prior enterectomy, however, attenuated hepatocellular dysfunction during early sepsis, as evidenced by increased $V_{max}$ and $K_m$ of in vivo ICG clearance. Furthermore, the increased levels of TNF-α, IL-1β, and IL-6 observed at 2 h after CLP were significantly reduced in animals undergoing enterectomy immediately before the onset of sepsis. To further confirm the role of gut-derived NE in hepatocellular dysfunction, we used an isolated, perfused liver preparation for determining in vitro ICG clearance. The isolated, perfused rat liver preparation permits one to study hepatic function in a system that approaches normal physiological conditions in which alterations in blood flow, blood pressure, or hormonal milieu can be minimized (43). Our results have demonstrated that the ICG clearance was significantly reduced in livers isolated at 2 h after CLP compared with livers isolated from sham-operated animals. Moreover, perfusion of the isolated liver with 20 nM NE, similar to that observed during sepsis (12), reduced ICG clearance capacity to a level similar to that seen at 2 h after the onset of sepsis. Together, these results indicate that the gut is a major source of NE release during the early stage of sepsis and that gut-derived NE appears to play a significant role in producing hepatocellular dysfunction, which may be mediated via the upregulation of inflammatory cytokine production.

Previous studies have suggested that the occurrence of hepatocellular dysfunction during the early stage of sepsis appears to be due to upregulation of inflammatory cytokines such as TNF-α (37). It has been demonstrated that infusion of TNF-α at a dose that does not decrease cardiac output and hepatic perfusion produces hepatocellular dysfunction similar to that observed during the early stage of sepsis (32). Studies have also indicated that inhibition of TNF-α biological activity by its monoclonal antibodies or reduction of its synthesis by pharmacological agents such as pentoxifylline is beneficial during sepsis (24, 31). Thus cellular dysfunctions such as hepatocellular dysfunction observed early after the onset of sepsis may be a consequence of upregulated proinflammatory cytokines such as TNF-α (37, 39). Although the gut is indeed capable of being a cytokine-producing organ (26) and although inflammatory cytokines such as TNF-α, IL-1β, and IL-6 are upregulated during early sepsis (9), our recent studies have indicated that organs other than the gut appear to be responsible for the upregulated proinflammatory cytokine release during sepsis (19). In this regard, studies have demonstrated that KC are the major source of inflammatory cytokine release during sepsis or under other adverse circulatory conditions (4, 17, 27, 37). Because of their position in splanchnic circulation, KC are among the first cells to come into
contact with gut-derived products. Since KC constitute 80–90% of the fixed macrophage population, their activation and subsequent release of inflammatory cytokines have great effects on the systemic response during sepsis (21). Previous studies have indicated that upregulation of KC proinflammatory cytokine gene expression occurs early after the onset of sepsis, with increased circulating levels shortly thereafter (37). Moreover, the increased gene expression and plasma inflammatory cytokines occur before the depression in hepatocellular function during early sepsis. Furthermore, our studies indicate that the reduction and blockade of phagocytic activity in vivo by gadolinium chloride prevents the increase in inflammatory cytokines and prevents hepatocellular dysfunction during early sepsis (17). Thus it appears that KC are the major source of inflammatory cytokine release during early sepsis. Because of the anatomic relationship between the gut and liver via portal circulation, gut-derived mediators such as NE should play an important role in stimulating KC and releasing proinflammatory cytokines under pathophysiological conditions. Although gut-derived NE appears to be responsible for producing hepatocellular dysfunction via an upregulation of TNF-α release by KC, endotoxin also plays an important role in upregulating proinflammatory cytokines and depressing hepatocellular function during polymicrobial sepsis. Thus further studies are necessary to determine the individual roles of NE and endotoxin in producing hepatocellular dysfunction as well as the synergistic effects that these factors may possess.

Although the increase in intracellular cAMP levels following stimulation of β2-adrenoceptors by epinephrine (epinephrine has much higher selectivity for β2-adrenoceptors than NE) downregulates TNF-α gene expression and its release (11, 28), studies by Spengler et al. (29) have demonstrated that the α2-adrenergic agonists NE and UK-14304 increase endotoxin-stimulated TNF-α production by peritoneal macrophages. In this regard, NE production and release have been found to be significantly correlated with the spontaneous secretion of TNF-α by alveolar macrophages (16). The presence of macrophage α2-adrenergic receptors has previously been confirmed (13, 29). Moreover, α2-adrenergic agonists increase TNF-α mRNA accumulation at the transcriptional level that can be blocked with the α2-adrenergic antagonist yohimbine (29). In vivo studies indicate that α2-adrenergic antagonists inhibit TNF-α production following endotoxemia (8, 14). Thus gut-derived NE appears to play a major role in upregulating proinflammatory cytokines, such as TNF-α, by KC through an α2-adrenoceptor pathway. The findings that enterectomy before the onset of sepsis reduces gut-derived NE production and circulating levels of inflammatory cytokines in the present study support this notion. Since we (32) have previously demonstrated that administration of a low dose of recombinant TNF-α, which does not reduce cardiac output and hepatic perfusion, produces hepatocellular dysfunction, it is likely that NE depresses hepatocellular function through the increase in TNF-α production by KC during the early stage of sepsis.

Although the findings of this study support the notion that the increase in gut-derived NE plays a major role in hepatocellular dysfunction, the results of our preliminary experiments using α2-adrenoceptor antagonists both in vivo and with perfusion experiments in relation to hepatocellular function and inflammatory cytokine production and release strongly support this hypothesis. These preliminary findings show that administration of NE via the portal vein upregulates KC TNF-α gene expression as well as KC and plasma levels of this cytokine. However, the coadministration of NE and the α2-adrenergic antagonist yohimbine prevented the increase of TNF-α in KC and in plasma (46). Moreover, in vivo administration of the α2-adrenergic antagonist rauwolscine protects hepatocellular function and attenuates the upregulation in TNF-α during early sepsis (preliminary data). In isolated, perfused liver experiments, administration of NE in combination with the α2-adrenergic antagonist rauwolscine prevented the depression of ICG clearance and attenuated the NE-induced upregulation of TNF-α (preliminary data). These results, together and in combination with the findings of the present study, suggest that the increased gut-derived NE release during the early stage of sepsis is responsible for depressing hepatocellular function through upregulation of KC TNF-α production, which is mediated through an α2-adrenoceptor pathway.

It could be argued that the enterectomy procedure may significantly alter hepatic hemodynamics. Although it is evident that portal blood flow decreases markedly following enterectomy, our recent study indicates that oxygen delivery to the liver is well maintained (45). In that study, enterectomy reduced portal blood flow by 85%, which was accompanied by an increase in hepatic arterial blood flow by 367%, resulting in no significant changes in hepatic oxygen delivery and consumption (45). Furthermore, the results of this study indicate that enterectomy alone in sham-operated animals did not alter hepatocellular function or cytokine release. It can also be argued that the addition of erythrocytes to the perfusate of the isolated liver preparation is necessary to maintain hepatic viability. However, the monitoring of PO2 in our preparation indicates a significant reduction in effluent PO2 compared with that in the perfusate (data not shown), demonstrating that oxygen use is maintained despite an absence of erythrocytes in the perfusate. Morphological observations also support the viability of the isolated livers after 60 min of perfusion. It could also be argued that since NE is known to be a vasoconstrictor, its effects on portal circulation may be of concern. In the isolated, perfused liver preparations, we determined portal pressure throughout the experiment. These results show that portal pressure was not altered as a result of NE perfusion through the isolated liver. Moreover, we have performed preliminary studies of NE infusion via the portal vein and these results show that NE infusion does not alter mean arterial...
pressure. Together, these results suggest that NE does not significantly affect portal circulation.

ICG clearance technique assesses the cholephilic organic anion transport function of the hepatocyte (22), which is an important aspect of hepatocellular function, and ICG clearance has been shown to be an extremely sensitive and early indicator of alterations in hepatocellular function during sepsis and other adverse circulatory conditions (5, 15, 36, 41). This technique remains distinct from the assessment of plasma liver enzymes because it measures hepatocellular function rather than hepatocellular damage. Moreover, the decrease in the hepatic clearance of this dye occurs as early as 1.5 h after the onset of sepsis and is followed by a decrease in the hepatic clearance of this dye occurs as early as 1.5 h after the onset of sepsis and is followed by a decrease in the hepatic clearance of this dye occurs as early as 1.5 h after the onset of sepsis and is followed by a decrease in the hepatic clearance of this dye occurs as early as 1.5 h after the onset of sepsis and is followed by an increase in circulating levels of α-glutathione S-transferase at 5 h (18) and liver transaminases at 10 h after CLP (38). Therefore, it appears that ICG clearance is an important and sensitive technique for detecting alterations in hepatocellular function, which was not significantly affected by enterectomy at 2 h after the procedure.

In summary, our results indicate that portal levels of NE are significantly higher than systemic levels during early sepsis and that enterectomy before the onset of sepsis significantly reduced circulating NE levels under such conditions. Thus the gut appears to be the major source of NE release during sepsis. Enterectomy before CLP significantly attenuated hepatocellular dysfunction and downregulated inflammatory cytokine release. Moreover, perfusion of the isolated livers with NE significantly reduced circulating NE levels un- der such conditions. Thus the gut appears to be the major source of NE release during sepsis. Enterectomy before CLP significantly attenuated hepatocellular dysfunction and downregulated inflammatory cytokine release. Moreover, perfusion of the isolated livers with NE significantly reduced ICG clearance capacity. Therefore, it appears that gut-derived NE during early sepsis plays an important role in upregulating proinflammatory cytokine release and depressing hepatocellular function. Since it has been shown that NE upregulates proinflammatory cytokines, modulation of NE release and/or tissue responsiveness to NE should provide a novel approach for attenuating cell and organ dysfunction during sepsis.

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A portion of the data presented in this study has been published as an abstract (Shock 13: 9A–10A, 2000) and presented at the 20th Annual Meeting of the Surgical Infection Society, Providence, RI, April 27–29, 2000.

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