Protection against early intestinal compromise by lipid-rich enteral nutrition through cholecystokinin receptors*

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Objective: **Early gut wall integrity loss and local intestinal inflammation are associated with the development of inflammatory complications in surgical and trauma patients. Prevention of these intestinal events is a potential target for therapies aimed to control systemic inflammation. Previously, we demonstrated in a rodent shock model that lipid-rich enteral nutrition attenuated systemic inflammation and prevented organ damage through a cholecystokinin receptor-dependent vagal pathway. The influence of lipid-rich nutrition on very early intestinal compromise as seen after shock is investigated. Next, the involvement of cholecystokinin receptors on the nutritional modulation of immediate gut integrity loss and intestinal inflammation is studied.**

Design: **Randomized controlled *in vivo* study.**

Setting: **University research unit.**

Subjects: **Male Sprague-Dawley rats.**

Interventions: **Liquid lipid-rich nutrition or control low-lipid feeding was administered per gavage before hemorrhagic shock. Cholecystokinin receptor antagonists were used to investigate involvement of the vagal antiinflammatory pathway.**

Measurements and Main Results: **Gut permeability to horseradish peroxidase increased as soon as 30 mins postshock and was prevented by lipid-rich nutrition compared with low-lipid ($p < .01$) and fasted controls ($p < .001$). Furthermore, lipid-rich nutrition reduced plasma levels of enterocyte damage marker ileal lipid binding protein at 60 mins ($p < .05$). Early gut barrier dysfunction correlated with rat mast cell protease plasma concentrations at 30 mins ($r_s = 0.67$; $p < .001$) and intestinal myeloperoxidase levels at 60 mins ($r_s = 0.58$; $p < .05$). Lipid-rich nutrition significantly reduced plasma rat mast cell protease ($p < .01$) and myeloperoxidase ($p < .05$) before systemic inflammation was detectable. Protective effects of lipid-rich nutrition were abrogated by cholecystokinin receptor antagonists (horseradish peroxidase; $p < .05$ and rat mast cell protease; $p < .05$).**

Conclusions: **Lipid-rich enteral nutrition prevents early gut barrier loss, enterocyte damage, and local intestinal inflammation before systemic inflammation develops in a cholecystokinin receptor-dependent manner. This study identifies activation of the vagal antiinflammatory pathway with lipid-rich nutrition as a potential therapy in patients prone to develop a compromised gut. (Crit Care Med 2010; 38:1592–1597)**

KEY WORDS: hemorrhagic shock; intestinal damage; lipids; enteral nutrition; intestinal integrity; cholinergic pathway

Loss of intestinal integrity has been implicated in the development of inflammatory complications, including respiratory dysfunction, organ damage, and sepsis (1–4). Based on these experimental findings, preservation of gut wall integrity is considered a potential target for therapies aimed at preventing excessive inflammation in surgical and critical care settings.

Increased gut wall permeability, enterocyte damage, and local intestinal inflammation are regarded as crucial interrelated events that transform the intestine into a proinflammatory organ (5). A growing number of studies demonstrate that a decrease in gut barrier function occurs also in several patient groups (6–10). Furthermore, the associations that were established between the level of enterocyte damage in septic patients and poor clinical outcome indicate that events in the gut wall may be of extraintestinal significance (11, 12). Recently, evidence was provided that intestinal epithelial damage is an early event in surgical and trauma patients that is related to the subsequently developing systemic inflammatory response and the occurrence of complications (13, 14). These clinical observations support the importance of preserving early intestinal integrity under certain surgical conditions as a potential target for antiinflammatory therapies. To test the direct effects of novel therapies on various aspects of intestinal integrity and local inflammation, animal models provide a straightforward approach.

A novel and promising means to control the acute inflammatory response is administration of lipid-rich enteral nutrition. Previously, we showed that lipid-rich nutrition activates the autonomic nervous system through activation of cholecystokinin-receptors (CCK-r) (15). Cytokine release is subsequently inhibited through activation of nicotinic receptors on inflammatory cells through the vagus nerve (15–17). Also, several organs, including the intestine, were strongly protected after either pre- or posttreatment with lipid-rich nutrition (15, 18, 19).

***See also p. 1608.**

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Drs. de Haan and Thuijls contributed equally to this study.

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The current study investigates the impact of lipid-rich enteral nutrition on the condition of the intestine early after hemorrhagic shock. For this, a rodent model was used in which previously early disruption of epithelial cell cytoskeleton and tight junctions was reported (20). Next, the involvement of the CCK-r-mediated vagal antiinflammatory pathway in the effects of lipid-rich nutrition on early intestinal compromise was determined.

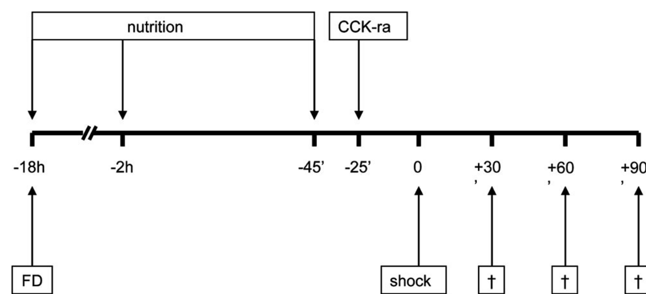

Figure 1. Experimental design. Rats were food-deprived (*FD*) 18 hrs before induction of shock and killed at 30, 60, or 90 mins postshock. A liquid lipid-rich or low-lipid enteral nutrition was administered at −18 hrs, −2 hrs, and −45 mins. Cholecystokinin receptor antagonists (*CCK-ra*) were given 25 mins before shock.

MATERIALS AND METHODS

Animals. Male Sprague-Dawley rats, weighing 300–350 g, were purchased from Charles River Laboratories (Maastricht, The Netherlands) and housed under controlled conditions of temperature and humidity. Before the experiments, rats were fed standard rodent chow *ad libitum* and had free access to water. The experimental protocols were approved by the Animal Ethics Committee of the Maastricht University Medical Center.

Experimental Design and Procedures. Nonlethal hemorrhagic shock was induced as previously described (18). In short, rats were anesthetized with isoflurane (induction 4%, maintenance 1.5% until kill) and bupivacaine was used for analgesia. Anesthetized animals were placed on a heating pad (Gaymar, New York, NY) to maintain body temperature at 37°C. The femoral artery was cannulated with polyethylene tubing (PE-10) containing heparinized saline (10 IU/mL), which was connected to a computer-assisted external pressure transducer (Kent Scientific, Torrington, CT). After 30 mins of acclimatization, 2.1 mL blood/100 g of body weight was withdrawn (representing 30–40% of the circulating volume) at a rate of 1 mL/min.

The severity of shock was reflected by profound alterations in mean arterial pressure (99 ± 4 mm Hg vs. 28 ± 2 mm Hg at 10 mins postshock) and heart rate (383 ± 11 beats/min vs. 240 ± 14 beats/min). These changes were comparable with our previous studies with the shock model (20, 21). No differences were observed between fasted animals and intervention groups. Animals were killed at 30, 60, or 90 mins after shock (Fig. 1). Each study group consisted of six animals. To determine preshock values of intestinal integrity and inflammation, fasted or fed groups were killed without operative procedures.

Before shock, rats were either fasted overnight or received liquid lipid-rich or low-lipid feeding (both 1.3 kcal/mL) per gavage at time points displayed in Figure 1. The lipid-rich diet contained 50.4 energy percent (en%) fat, of which 30% constituted of phospholipids, 8.7en% protein, and 40.9en% carbohydrates. The low-lipid control nutrition contained 16.0en% fat, 8.7en% proteins, and 75.3en% carbohydrates. The protein and carbohydrate composition of the two feedings was identical. The amount of fat in the control nutrition was isocaloric to that present in standard rodent chow and the lipid-rich nutrition was isocaloric and isonitrogenous to the control nutrition. In both feeding regimens, animals received a total of 5.9 kcal, which is equivalent to 10–12% of their daily caloric intake. The response to shock of animals with unrestricted access to standard rodent chow is comparable with animals receiving low-lipid nutrition per gavage (not shown).

To investigate CCK-r involvement in the nutritional effects on early intestinal compromise, antagonists to the CCK-1 receptor, Devazepide, and the CCK-2 receptor, L365,260 (both 500 μg/kg), were administered intraperitoneally 25 mins before shock induction in lipid-rich-fed animals. Devazepide and L365,260 (kind gifts from ML Laboratories PLC, Nottingham, UK) were dissolved in 90% saline, 5% Tween 20, and 5% DMSO.

Intestinal Permeability. Intestinal permeability was assessed by an ex vivo everted sac method. Segments of 8 cm terminal ileum (distal end is located at 5 cm of the ileocecal valve) were washed, everted, and filled with 1 mL of Tris buffer (125 mmol/L NaCl, 10 mmol/L fructose, 30 mmol/L Tris; pH 7.5) and ligated at both ends. The filled segments were incubated in Tris buffer containing 40 μg/mL of the 44 kD enzyme horseradish peroxidase (HRP) (Sigma, St Louis, MO). After incubation at room temperature for 45 mins, ileal content was carefully collected. HRP activity was measured spectrophotometrically at 450 nm after addition of tetramethylbenzidine as a substrate.

Western Blot. The amount of protein in extracts from isolated rat esophagus, stomach, jejunum, ileum, colon, liver, spleen, kidney, heart, and lung was determined with the Bradford method (Biorad, Hercules, CA). Next, aliquots with equal protein amounts were made. Aliquots were heated at 100°C for 5 mins in sodium dodecyl sulphate sample buffer, separated on sodium dodecyl sulphate–polyacrylamide gels, and transferred to polyvinylidene fluoride membrane (Immobilin P; Millipore, Bedford, MA). After transfer of proteins, a blocking step was performed in Tris-buffered saline with 5% nonfat dry milk and 0.05% Tween. Membranes were probed with 1 μg/mL rabbit antihuman ileal lipid-binding protein (ILBP) that crossreacts with rat (22) in Tris-buffered saline 0.05% Tween. After incubation with 0.1 μg/mL goat antirabbit HRP-conjugated secondary antibody (Hycult Biotech, Uden, The Netherlands), the signal was detected by chemiluminescence on film.

Immunohistochemistry. Localization of ILBP was investigated by immunohistochemistry performed on 3-μm paraffin sections of esophagus, stomach, jejunum, ileum, colon, liver, spleen, kidney, heart, and lung. Slides were deparaffinized and blocked for endogenous peroxidases. Nonspecific binding sites were blocked with 5% bovine serum albumin. All incubation steps were performed at room temperature. Sections were incubated for 50 mins with 1 μg/mL rabbit antimouse ILBP crossreacting with rat (Hycult Biotech). Thereafter, sections were incubated for 30 mins with 2 μg/mL biotin-labeled swine antirabbit IgG conjugate (Dako, Glostrup, Denmark) followed by 30 mins incubation with AB-complex and 3-amino-9-ethylcarbazole staining. Nuclear staining was performed with hematoxylin. Pictures were taken using the Metasystems Image Pro System (black and white charge-coupled device camera; Metasystems, Sandhausen, Germany) mounted on a Leica DM-RE microscope (Leica, Wetzler, Germany). Images were taken at equal time exposures after being normalized to negative control sections without primary antibody to exclude for nonspecific binding of the secondary antibody or autofluorescence. At least 25 microscopic fields for each tissue section were examined.

Enzyme-Linked Immunosorbent Assay. Intestinal cell damage was detected by measuring levels of ILBP (synonym, I-BABP) in arterial blood using a standard enzyme-linked immunosorbent assay (ELISA) for rat ILBP (Hycult Biotech). Mast cell degranulation was assessed in plasma with a Rat Mast Cell Protease II (RMCP II) ELISA (Moredun, Midlothian, UK). Myeloperoxidase (MPO) was assessed as described previously (18). Systemic inflammation was determined by measuring tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) concentrations in arterial blood using standard ELISA for rat TNF-α and rat

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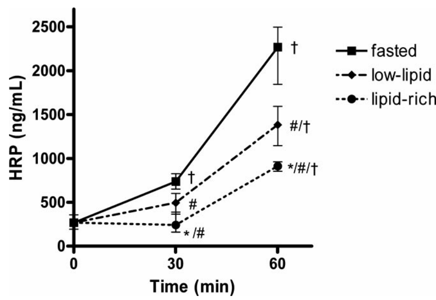

Figure 2. Intestinal barrier dysfunction develops rapidly after shock and is prevented by lipid-rich feeding. At 30 and 60 mins postshock, ileal permeability to horseradish peroxidase (*HRP*) was significantly elevated compared with preshock values. Pretreatment with lipid-rich nutrition significantly reduced HRP leakage compared with low-lipid and fasted animals at both time points. †$p < .01$ vs. preshock, *$p < .01$ vs. with low-lipid feeding, #$p < .05$ vs. fasting.

IL-6 (R&D Systems, Minneapolis, MN). Detection limits for TNF-α and IL-6 were 30 pg/mL and 10 pg/mL, respectively.

Statistical Analysis. For between-group comparisons, a two-tailed Mann-Whitney *U* test was used. Differences were considered statistically significant at $p \leq .05$. The results of the HRP permeability test and ILBP ELISA are represented as median, 25th percentile, and 75th percentile. For RMCP II and MPO concentrations and data obtained with CCK-r antagonists, also the range is displayed. The median, 25th percentile, and 75th percentile of TNF-α and IL-6 are given in the text. Spearman's correlation was used to assess the association between intestinal permeability and local intestinal inflammation. Prism 5.02 for Windows (GraphPad Software, San Diego, CA) was used for computations.

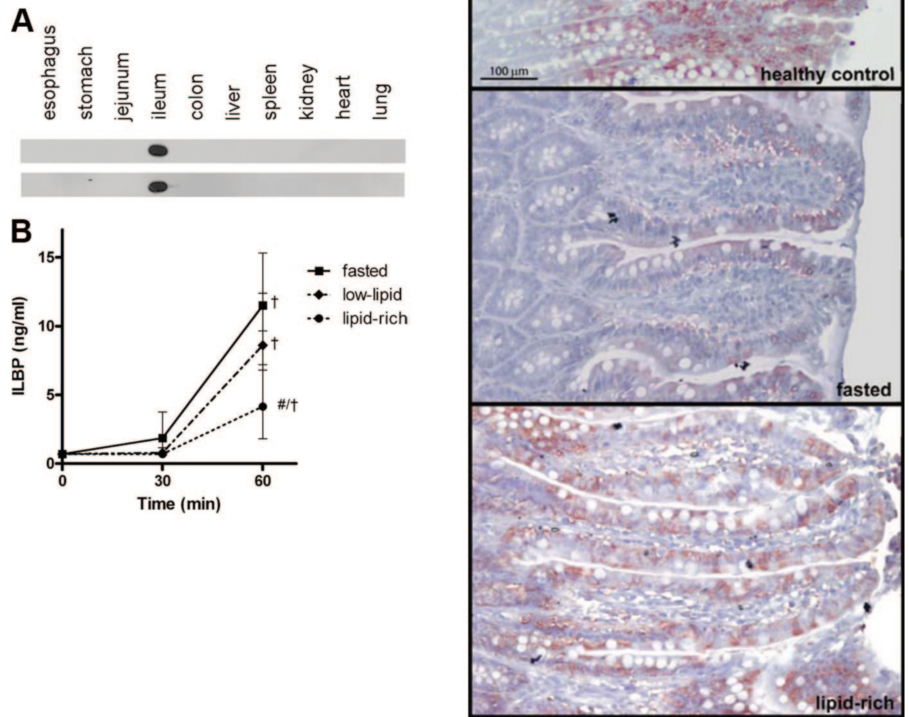

Figure 3. Early ileal cell damage is prevented by lipid-rich nutrition. *A,* Western blot revealed presence of ileal lipid binding protein (*ILBP*) in ileum and absence in other segments of the gastrointestinal tract. Furthermore, ILBP was not detected in liver, spleen, kidney, heart, or lung. *B,* Plasma ILBP levels representing epithelial damage in ileum were strongly increased at 60 mins after shock compared with preshock. Lipid-rich feeding significantly reduced circulatory ILBP levels compared with fasting. †$p < .01$ compared with preshock and #$p < .05$ vs. fasting. *C,* Staining of ILBP (*red*) in ileum of healthy animals indicated presence specifically at the location of matured enterocytes, whereas ILBP was not observed in crypts and submucosa. Nuclei were stained with hematoxylin (*blue*). Preserved enterocyte ILBP expression was observed in terminal ileum of lipid-rich-treated animals compared with fasted animals at 60 mins.

RESULTS

Rapid Increase of Ileal Permeability After Hemorrhagic Shock Is Prevented by Lipid-Rich Nutrition. As soon as 30 mins after shock, a significant increase of HRP leakage was observed compared with preshock conditions ($p < .01$; Fig. 2). Gut permeability further increased at 60 mins ($p < .01$). Lipid-rich nutrition reduced ileal leakage of HRP in comparison with low-lipid nutrition ($p < .01$) and fasted animals ($p < .001$) at 30 mins postshock. Also, low-lipid nutrition reduced ileal barrier loss compared with fasting ($p < .05$). In all intervention groups, gut wall permeability further increased at 60 mins after shock. Also at this time point, gut permeability to HRP was decreased in lipid-rich-treated animals compared with low-lipid ($p < .01$) and fasted controls ($p < .001$).

Lipid-Rich Nutrition Reduces Shock-Induced Enterocyte Damage. A specific marker for ileal cell damage in humans is ILBP (23). We investigated the expression of ILBP in the digestive tract, liver, spleen, kidneys, heart, and lungs of healthy rats. Western blot analysis showed selective presence of ILBP in ileum, whereas the protein was not detected in the other organs (Fig. 3*A*). The specific localization of ILBP in ileum was confirmed by immunohistochemistry (Fig. 3*C*; other organs not shown). The presence of ILBP was restricted to the upper part of the villi; no expression was observed in crypts or muscular layers. These findings identify ILBP as a specific marker of differentiated ileal enterocytes in rats.

After onset of shock, ILBP plasma concentrations remained close to preshock levels at 30 mins (Fig. 3*B*). A significant increase of ILBP in plasma was observed at 60 mins vs. preshock values ($p < .01$). Elevated plasma ILBP levels coincided with a decreased ILBP expression in rat ileal enterocytes (Fig. 3*B*–*C*).

Enterocyte damage was significantly reduced by lipid-rich nutrition at 60 mins postshock compared with fasted animals ($p < .05$) and a protective trend was seen in comparison with low-lipid feeding ($p = .07$; Fig. 3*B*). Immunohistochemistry showed that decreased ILBP plasma

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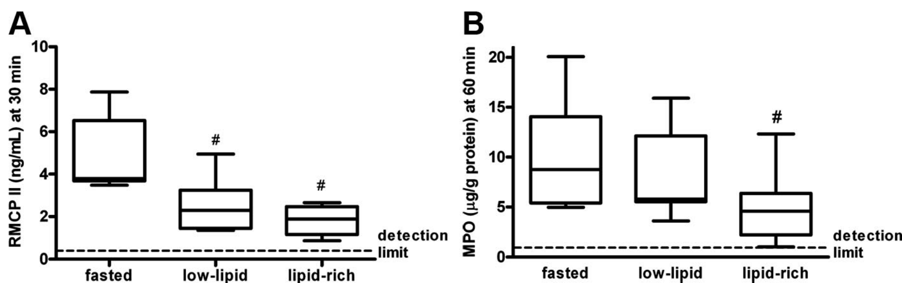

Figure 4. Mast cell degranulation and neutrophil influx occur early postshock and are suppressed by lipid-rich nutrition. *A*, Administration of lipid-rich feeding reduced mast cell degranulation assessed as plasma rat mast cell protease (*RMCP*) II at 30 mins compared with fasting. Also, low-lipid feeding significantly reduced mast cell degranulation. *B*, Tissue myeloperoxidase levels in ileum were significantly decreased at 60 mins after shock in lipid-rich treated animals compared to fasted controls. #$p < .05$ vs. fasting.

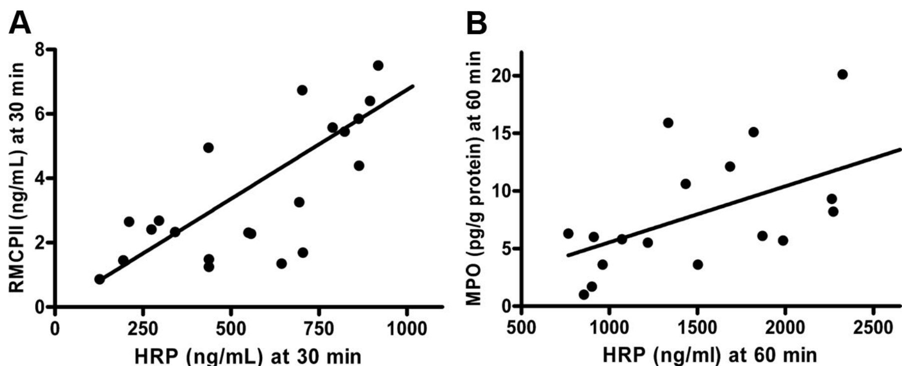

Figure 5. Early loss of gut barrier function correlates with development of local inflammation. *A*, Horseradish peroxidase (*HRP*) leakage through ileal wall and rat mast cell protease (*RMCP*) II levels in plasma correlate positively at 30 mins after shock ($r_s = 0.67$, $p < .001$). *B*, At 60 mins after hemorrhage, gut wall permeability correlates with myeloperoxidase concentrations in ileum ($r_s = 0.58$, $p < .05$).

values in lipid-rich treated rats paralleled the prevention of ILBP loss in ileal enterocytes in comparison with fasted controls (Fig. 3*C*).

Early Progress of Local Inflammation Is Reduced By Lipid-Rich Nutrition. Mast cell-derived RMCP II, a protease abundantly expressed in intestinal mucosal mast cells (24), is undetectable in plasma under physiological circumstances. As early as 30 mins after shock, enhanced RMCP II levels were detected in fasted animals (Fig. 4*A*). Treatment with lipid-rich feeding decreased RMCP II levels significantly ($p < .01$). Also low-lipid nutrition lowered mast cell degranulation compared with fasting ($p < .05$). At 60 mins, circulating RMCP II values of all groups had returned to preshock concentrations (data not shown).

Ileal tissue levels of MPO were used as a measure for neutrophilic granulocyte infiltration. Although traces of MPO can also be found in monocytes and specific resident macrophages (25), an increase of tissue MPO levels is considered representative of neutrophil influx (26). MPO concentrations were undetectable in healthy animals and at 30 mins (data not shown). At 60 mins, a strong increase of ileal MPO was observed in fasted animals (Fig. 4*B*). Treatment with lipid-rich feeding significantly reduced MPO levels compared with fasted animals ($p < .05$).

Gut Barrier Loss Early After Shock Is Related to the Development of Local Intestinal Inflammation. The crosstalk between loss of barrier integrity resulting in penetration of luminal contents and the early local inflammatory response is considered to contribute cumulatively to the development of systemic inflammation (5). We studied the relation between gut wall permeability to HRP and markers of local inflammation. At 30 mins, HRP leakage and RMCP II plasma levels correlated positively ($r_s = 0.67$, $p < .001$; Fig. 5*A*). In addition, a correlation was found between ileal permeability and MPO levels in ileum at 60 mins ($r_s = 0.58$, $p < .05$; Fig. 5*B*).

Systemic Inflammation Develops at a Later Stage. TNF-α and IL-6 were measured to confirm that early loss of intestinal compromise precedes the development of systemic inflammation. Whereas TNF-α and IL-6 could not be detected at 30 mins, concentrations surpassed the detection limit in 17% (four of 18) and 56% (ten of 18) of the animals at 60 mins, respectively. Conforming with previous findings, at 90 mins, lipid-rich nutrition significantly reduced inflammation compared with low-lipid (66 [range, 49–72] pg/mL vs. 101 [range, 83–124] pg/mL, $p < .05$) and fasted animals (272 [range, 214–315] pg/mL, $p < .01$) (15). Similar data were obtained with IL-6 (lipid-rich: 43 [range, 32–54] pg/mL vs. low-lipid: 104 [range, 89–119] pg/mL, $p < .05$ and fasted: 164 [range, 139–176] pg/mL, $p < .01$).

Cholecystokinin Receptors Mediate the Early Gut-Preserving Effects of Lipid-Rich Nutrition. Antagonists to CCK-r were administered to investigate the involvement of the vagal antiinflammatory pathway in the preservation of gut homeostasis in the early phase after shock. The protective effects of lipid-rich nutrition on intestinal permeability to HRP at 30 mins were abrogated by CCK-r antagonists ($p < .05$; Fig. 6*A*). In line, CCK-r blockage prevented the decrease of mast cell degranulation observed in lipid-rich-treated animals ($p < .05$; Fig. 6*B*).

DISCUSSION

Experimental and clinical findings identified preservation of intestinal integrity as a potential target for interventions directed at control of excessive inflammation and improvement of clinical outcome after major surgery or severe trauma (1–4, 13, 14). We provide evidence that lipid-rich enteral nutrition limits the development of enterocyte damage, ameliorates gut barrier function, and reduces local intestinal inflammation shortly after shock.

Splanchnic hypoperfusion is considered to be crucial in the development of intestinal compromise (11, 13, 27). Therefore, in the current study, a model of hemorrhagic shock was selected in which perfusion of mesenteric organs is known to be severely restricted (27, 28). Previously, in this model, early disruption of the enterocyte cytoskeleton and interconnecting tight junctions was shown (20). Because an intact epithelial lining is vital for gut barrier maintenance

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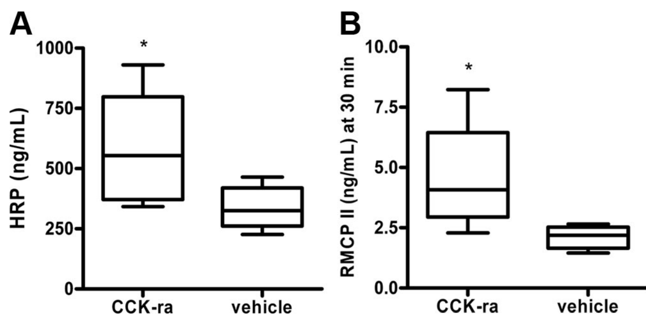

Figure 6. Cholecystokinin receptors mediate the protective effects of lipid-rich nutrition on early gut wall integrity and local inflammation. *A,* The prevention of intestinal barrier loss by lipid-rich nutrition at 30 mins was abrogated by cholecystokinin receptor antagonists. *B,* Blockage of cholecystokinin receptors blunted the decreased mast cell degranulation observed in lipid-rich-treated animals. $*p < .05$ vs. vehicle.

(29), gut wall integrity loss and intestinal inflammation were assumed to develop early after shock.

In line with clinical studies showing rapid development of intestinal cell damage after severe trauma and nonabdominal surgery (13, 14), in the current study, ileal cell damage was detected within 1 hr after shock. Enterocyte damage was defined as increased plasma levels of ILBP, an ileum-specific bile acid transporter confined to mature enterocytes (22, 23, 30). Next to epithelial cell damage, also gut wall permeability increased rapidly after shock. Loss of intestinal integrity may result in increased exposure of the immune apparatus to endogenous and exogenous proinflammatory signals, thus contributing to a local inflammatory response (1, 29). In accordance, we demonstrate a correlation between intestinal barrier dysfunction and increased levels of local inflammatory markers before systemic inflammation developed.

Lipid-rich nutrition significantly prevented the development of barrier dysfunction and enterocyte damage. Previously, lipid-rich nutrition was identified as a potent stimulator of the autonomic nervous system through activation of CCK-r (15). In accordance, the protective impact of lipid-rich nutrition can be mimicked by administration of pegylated CCK (31). We show, using CCK-r antagonists, that the vagus-mediated pathway underlies the effects of lipid-rich nutrition on early gut compromise before systemic inflammation develops. The current study indicates that the intestine may be an early and vital target organ for activation of the vagal pathway with lipid-rich nutrition.

Enhanced plasma levels of mast cell degranulation marker RMCP II were shown rapidly after shock. An important consequence of intestinal mucosal mast cell activation is increased gut wall permeability (24, 32–34). Vice versa, the influx of microbes and toxins as a result of increased intestinal permeability may induce mast cell activation (33). In line, the current study shows that plasma RMCP II levels correlate with early dysfunction of the intestinal barrier. Another important effect of mast cell degranulation is enhanced influx of neutrophils in damaged tissue by vascular leakage (35). In this study, neutrophil influx in ileum was observed 1 hr after shock. Administration of lipid-rich nutrition strongly decreased mast cell activation and ileal levels of MPO. Although mast cells are important regulators of neutrophil influx, in the current study, it could not be excluded that lipid-rich nutrition reduced neutrophil influx also in a nonmast cell-dependent manner. Apart from being a marker for neutrophil influx, MPO is a potent initiator and modulator of the local inflammatory response itself (25, 36). Local intestinal inflammation and gut barrier integrity are supposed to be interrelated (1, 5, 29), which conforms with the correlation between ileal MPO levels and gut wall permeability observed in this study.

Lipid-rich nutrition inhibited early shock-induced mast cell activation through CCK-r activation, implicating an important role for the vagal antiinflammatory pathway. This finding is supported by a previous study that showed CCK-r involvement in the protective effects of lipid-rich nutrition on postoperative ileus, a mast cell-dependent phenomenon (26). Several lines of evidence indicate that mast cell degranulation is regulated by the vagus nerve, including a close anatomic relation that was shown between vagal nerve endings and intestinal mucosal mast cells (37). A functional link between the vagus nerve and mast cells was provided by Stead et al (38), who demonstrated profound alterations in mast cell function after vagus stimulation or vagotomy. Furthermore, it was shown that nicotine and acetylcholine reduce degranulation of bone marrow-derived mast cells (39). Taken together, these studies support activation of the CCK-r-dependent vagal pathway as the underlying mechanism of the decreased mast cell activation reported here.

In the current study, nutritional intervention was installed before induction of shock. Previously, also postshock administration of lipid-rich nutrition was demonstrated to attenuate inflammation and preserve intestinal integrity (18), indicating that patients with ongoing inflammation or a compromised gut may benefit from intervention with enriched nutrition. Together, these data fit in the current tendency toward more liberal fasting guidelines preoperatively and rapid installation of enteral nutrition postoperatively (40–42). Because prevention of inflammation with lipid-rich nutrition yields stronger protective effects than posttreatment, in the clinical setting, nutritional interventions should preferably be oriented toward a pretreatment approach.

CONCLUSIONS

The present study demonstrates rapid development of gut barrier loss, enterocyte damage, and local intestinal inflammation after hemorrhagic shock. A small quantity of lipid-rich enteral nutrition strongly prevents early intestinal compromise before systemic inflammation develops in a CCK-r-dependent manner. This study identifies nutritional activation of the vagal antiinflammatory pathway with lipid-rich feeding as a potential therapy in patients prone to develop a compromised gut.

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