Intestinal preconditioning prevents inflammatory response by modulating heme oxygenase-1 expression in endotoxic shock model

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A COMPROMISED GUT BARRIER function may be associated with systemic inflammatory response syndrome, sepsis, and multiple organ dysfunction syndrome (8, 14, 32). Splanchnic hyperperfusion is associated with increased intestinal permeability and an exaggerated acute phase response (25, 40, 45). Gut hyperpermeability has often suggested to be one of the essential factors in the pathogenesis of multiple organ failure. Theisen et al. (39) reported alterations in microvascular blood flow to the gut mucosa in a porcine model of hyperdynamic endotoxic shock (ES). Gut alterations, including ileal mucosal acidosis (3), increased mucosal permeability (31), and gut ischemia (15), have often been reported after administration of lipopolysaccharide (LPS) or live bacteria. Clinical and laboratory research indicates that gut ischemia may be a pivotal initiating event in the secretion of numerous proinflammatory mediators that causes multiple organ failure (14). However, further study will be required to better understand and really demonstrate the role of gut ischemia in multiple organ failure after LPS challenge.

One possible approach for this specific evaluation is by assaying the effect on the systemic inflammatory response of interventions that selectively prevent gut injury. Among the known anti-ischemic interventions, preconditioning with brief transient episodes of ischemia is considered as one of the most potent, at least at the level of the heart. Thus, intestinal preconditioning (PC) may be used as a tool to assess the role of mucosal intestinal damage induced by ischemia-reperfusion in inflammatory response (7, 20). Our laboratory has previously demonstrated that PC reduces significantly systemic inflammatory response after hemorrhagic shock (37).

The mechanisms of the protective effects of preconditioning involve the production of one or more protective proteins, including antioxidant enzymes, nitric oxide synthase (5, 21), and various heat-shock proteins (34), especially heme oxygenase-1 (HO-1). Indeed, HO-1 is highly regulated by stress and injury in many organ systems and may exert marked protective effects in ischemia-reperfusion, oxidant injury, or ES (13, 27, 43). Furthermore, we have shown that induction of HO-1 (by hemoglobin) induces a delayed (24 h) prevention of the inflammatory responses to hemorrhagic shock (36). Thus HO-1 may be one of the endogenous enzymes involved in the protective effects of preconditioning, as we already demonstrated in the context of hemorrhagic shock (37).

Thus the purposes of the present study were 1) to assess the role of gut ischemia, using PC, in the cascade of events leading to multiple organ failure after LPS challenge; 2) to evaluate the effect of intestinal HO-1 induction in the anti-inflammatory and cytoprotective effects; and 3) to better understand the molecular mechanisms link between gut and multiple organ failure. It would seem that this relation between gut injury and organ failure should to be answered before clinical preventive strategies can be proposed.

MATERIALS AND METHODS

Surgical Procedure: Induction of PC and ES

Adult male Wistar rats, weighing 300–320 g, were used. On day 1, they were anesthetized with 25 mg/kg pentobarbital sodium intraperitoneally. A laparotomy was performed and the superior mesenteric artery was exposed. The abdominal area was covered with gauze soaked in saline at 37°C and a plastic remnant to minimize dehydration and evaporative heat loss of exposed tissues. The University of
Rouen Institutional Animal Care and Use Committee approved the protocol.

Preconditioning was induced by four cycles of 1 min mesenteric artery occlusion (special arterial clamp) separated by 4 min of reperfusion (day 1). Hepatic ischemia was not observed in these conditions and no animals died after this procedure. After induction of preconditioning, the occluder was removed and the abdominal area was closed with polyester sutures. The animals were allowed to recover from anesthesia (usually within 30 min), after which they were returned to their cage for 24 h. Sham-operated animals were subjected to the same protocol, except that the mesenteric artery was not occluded.

Twenty-four hours after preconditioning or sham surgery (day 2), rats were reanesthetized with 25 mg/kg sodium pentobarbital intraperitoneally for anesthesia and sedation. The carotid arteries were cannulated with a 20-gauge polyethylene catheter and connected to a pressure transducer to enable continuous recording of mean arterial pressure (MAP). Another catheter (22-gauge polyethylene catheter) was placed in the jugular vein for fluid resuscitation. The animals were allowed to recover for 30 min before the experimental protocol was started. To induce ES, rats received an injection of LPS 10 mg/kg (LPS; Escherichia coli) at 25 ml/kg (H9262; Sigma Chemical, St. Louis, MO), intravenously suspended in pyrogen-free saline and administered over 3 min (38). The onset of ES was defined as the time at which MAP decreased below 65 mmHg (i.e., 150 min after injection of LPS). At this point, the animals were resuscitated with 0.9% NaCl at 15 ml/h to maintain MAP under 65 mmHg (38). Fluid resuscitation was continued to the end of experiment to maintain MAP under 65 mmHg, and cumulative fluid requirements were used as an indirect indicator of microvascular injury.

Hemodynamic measurements were obtained at baseline and every 30 min up to 6 h (360 min) after LPS or vehicle administration. At the end of the experiment, carotid and mesenteric blood samples were collected in syringes containing 5 U heparin. Samples were immediately centrifuged at 10,000 g for 20 min, and plasma was stored at −80°C until it was used for measurement of TNF-α. The plasma was thawed and backtitrated to pH 7 with 0.2 mol/l NaOH. Two separate measurements were performed: total GSH and the oxidized glutathione (GSSG). The reduced GSH level was calculated as the difference between total GSH and the oxidized form. Total GSH concentration was determined by using 10 mmol/l 5'-dithio-bis-2-nitrobenzoic acid, after reduction of GSSG by GSSG reductase (derived from baker's yeast, Sigma Chemical). The resulting amount of GSH was determined from a standard curve (0–2.5 nmol GSH), measured spectrophotometrically at 412 nm and expressed as a change in absorbance per minute during reduction with GSH reductase. To measure tissue GSSG content, alkylation of the SH groups of glutathione was carried out with freshly prepared 10 mmol/l 5'-dithio-bis-2-nitrobenzoic acid. The resulting GSSG fraction was measured spectrophotometrically at 412 nm.

Protein Extraction TNF-α and ICAM and Protein Expression (Western Blot Analysis)

Protein Extraction

The protein fraction was isolated by homogenization using Tissue-Tearor (Bel-Art Products, NJ) according to the manufacturer's manual. The homogenate was centrifuged at 90,000 g for 60 min. The resulting pellet was taken to be the membrane fraction. Protein concentration was determined by use of a bicinchoninic acid assay kit with BSA as the standard (Pierce).

Protein (50 μg/lane) was separated on 7.5% (for ICAM-1) or 15% (for TNF-α) SDS-polyacrylamide slab gel under denaturing conditions and was electroblotted to nitrocellulose membrane (Bio-Rad). Bio-Rad protein molecular weight markers were used as standards. After incubation in 5% dry milk in PBS containing 0.05% Tween-20 at room temperature for 2 h, the membrane was immunoblotted to the following antibodies (Abs) at room temperature for 1 h in separate experiments: anti-rat ICAM-1 monoclonal Ab (G-5; Santa Cruz Biotechnology, Santa Cruz, CA), and anti-TNF polyclonal Ab (Santa Cruz Biotechnology). The secondary Abs were horseradish peroxidase-conjugated goat anti-mouse, monkey anti-goat, or horse anti-rabbit Abs. Peroxidase labeling was detected with the ECL Western blotting detection system (Amersham). Western blot bands were quantified by densitometry, and data are presented as optical density units.

Systemic and mesenteric TNF-α production. Plasma TNF-α concentration was measured with an immunoassay kit (Biosource International Cytoscreen Rat TNF-α Ultraseensitive ELISA). Systemic and mesenteric blood samples were collected in syringes containing 5 U heparin. Samples were immediately centrifuged at 10,000 g for 20 min, and plasma was stored at −80°C until it was used for measurement of TNF-α. The plasma was thawed and backtitrated to pH 7 with 0.2 mol/l NaOH. Two separate measurements were performed: total GSH and the oxidized glutathione (GSSG). The reduced GSH level was calculated as the difference between total GSH and the oxidized form. Total GSH concentration was determined by using 10 mmol/l 5'-dithio-bis-2-nitrobenzoic acid, after reduction of GSSG by GSSG reductase (derived from baker's yeast, Sigma Chemical). The resulting amount of GSH was determined from a standard curve (0–2.5 nmol GSSG), measured spectrophotometrically at 412 nm and expressed as a change in absorbance per minute during reduction with GSH reductase. To measure tissue GSSG content, alkylation of the SH groups of glutathione was carried out with freshly prepared 10 mmol/l N-ethylmaleimide.

Organ Dysfunction

Mucosal intestinal injury. Proximal ileum was immersed in 4% formalin for at least 24 h and then embedded in paraffin blocks; transverse sections of 5 μm were cut and placed on glass microscope slides. Slides were stained with hematoxylin and eosin. Tissues were examined under light microscopy by a blinded observer and scored with a system described by Chiu et al. (9): grade 0 = normal mucosa; grade 1 = subepithelial space developing at the tip of the villus; grade 2 = lifting of the epithelial layer from the lamina propria and moderate extension of the subepithelial space; grade 3 = some denuded tips of the villi and massive lifting of the epithelial layer; grade 4 = dilated and exposed capillaries and denuded villi; and grade 5 = hemorrhage, ulceration, and disintegrated lamina propria.
**Intestinal lactate production.** Intestinal lactate was assessed in samples homogenized in 2 ml of water and acetone. The homogenates were centrifuged at 15,000 g for 10 min, and the supernatants were vacuum evaporated and lyophilized. The resulting dried residues were suspended in 1 ml of water for subsequent analysis. Lactate content was determined enzymatically.

**Pulmonary injury.** The lung wet weight-to-dry weight ratio was used as an index of pulmonary edema and microvascular injury (35). Lung tissues samples were dried at 80°C for 24 h. The dry tissue was then determined and wet-to-dry weight ratio was calculated.

**Experimental Protocol**

In the first part of the study, the animals were randomized to four groups of animals (n = 10 per group): 1) sham rats, which were subjected to anesthesia and sham surgery on day 1 and received serum saline administration on day 2; 2) untreated ES, in which the animals were subjected to sham surgery on day 1 and LPS on day 2; 3) preconditioning (PC + ES), in which the animals were subjected to PC on day 1 and LPS on day 2 (i.e., 24 h after preconditioning); and 4) preconditioning + HO-1 inhibition activity, in which the animals were subjected to the same protocol as group 3 but received the inhibitor of HO-1 activity: zinc-protoporphyrin (Zn-PP, 20 μmol/kg) administered subcutaneously 3 h before LPS (14) (PC + Zn-PP + ES).

In pilot experiments (n = 10 per group), we found that Zn-PP did not affect the effects on hemodynamic parameters and inflammatory response in the absence of preconditioning (data not shown). Copper-protoporphyrin (Cu-PP) exhibits no inhibitory activity of HO-1 and was used as a negative control for nonspecific effects of the protoporphyrin compounds. Negative control group were subjected to the same protocol as group 3 but received Cu-PP (20 μmol/kg) administered subcutaneously 3 h before LPS (PC + Cu-PP + ES) to evaluate TNF and ICAM gene expression compared with the PC + Zn-PP + ES group. The other parameters were not evaluated with Cu-PP.

In a fifth group, 5) bilirubin + ES (Bili + ES), the animals were subjected to the same protocol as group 2 (ES) but received bilirubin (40 μmol/kg) administered intraperitoneally 3 h before LPS challenge. Bilirubin (Logan, UT) was dissolved in 0.1 N NaOH and adjusted to a final pH of 7.4 with HCl.

To study the selective intestinal effect of preconditioning on HO-1 induction, tissues samples (lung and intestine) were isolated for the measurement of HO-1 mRNA expression on day 2 either at baseline (H0) or 6 h (H6) after LPS challenge in sham, ES, and PC + ES groups.

The PC + Zn-PP + ES group was not evaluated because Zn-PP affects only HO-1 activity expression.

**Statistics**

Data are presented as means ± SD. Results were compared by t-test or ANOVA when appropriate, and a P value <0.05 was considered statistically significant.

**RESULTS**

**Hemodynamic Parameters**

We measured MAP in the four groups challenged after LPS or saline administration. In the sham group, MAP was maintained at ~110 ± 10 mmHg throughout all the experiment. After LPS administration (Fig. 1), MAP began to decrease at 120 min. In most rats, MAP decreased to 65 ± 10 mmHg 150 min after LPS injection (defined as the onset of ES). The lowest blood pressure values were obtained ~210 min after injection and averaged 55 ± 10 mmHg. MAP remained significantly lower than sham values at the end of the experiment (H6), despite the saline resuscitation. In PC + ES rats, MAP decreased to 65 ± 9 mmHg and MAP was without significant difference from that of the ES group (P < 0.05). In the Zn-PP group, MAP was similar than in other groups (ES or PC + ES). These data suggest that HO-1 induction was not associated with recovery of LPS-induced hypotension.
Intestinal and lung TNF and ICAM-1 gene expression. TNF-α and ICAM-1 mRNA expression were considerably higher in the ES group than in the sham group ($P < 0.05$) (Fig. 2). PC markedly reduced the expression of both TNF-α and ICAM, and this was abolished by Zn-PP ($P < 0.05$) (Fig. 2). The effect of PC on TNF-α and ICAM gene expression could be mimicked by bilirubin pretreatment. Using Cu-PP administration as negative control, we observed no effect on TNF and ICAM gene mRNA expression (Fig. 2).

Intestinal and lung TNF and ICAM-1 protein expression. We compared ICAM-1 and TNF protein levels in tissue homogenates (lungs and intestine) from sham animals, rats challenged with LPS for 6 h, rats pretreated with PC for 24 h before LPS challenge with or without Zn-PP, a specific HO-1 inhibitor activity, and rats that received bilirubin before LPS administration. TNF-α and ICAM-1 proteins were detectable in sham homogenates but LPS was a potent stimulus resulting in a significant increase in intestine and lungs TNF-α and ICAM-1 proteins (Fig. 3). Pretreatment with PC significantly limited the expression of these proteins, although the response was variable (Fig. 3). Suppression by PC of LPS-induced expression of these proteins showed organ dependency. Bilirubin treatment significantly reduced the induction of TNF-α and ICAM-1.

Systemic and mesenteric plasma levels of TNF-α. TNF-α was not detectable in the sham group at any time. ES led to a marked increase in systemic and mesenteric plasma TNF-α (Fig. 4). Mesenteric plasma TNF-α was significantly higher compared with values in systemic plasma ($P < 0.05$). PC significantly reduced systemic and mesenteric concentrations of TNF-α. Zn-PP abolished significantly the effect of PC on plasma TNF-α, and treatment with bilirubin of the LPS animals prevented sepsis-induced TNF-α production, bringing the concentration back to near the basal concentration.

Intestinal and lung oxidative stress: GSH/GSSG ratio. Bilirubin has known antioxidant properties; to investigate this possibility, we performed GSH/GSSG ratio analysis (Fig. 5). ES led to a significant decrease in GSH/GSSG ratio compared with sham rats (intestine: 14 ± 7.2 vs. 42 ± 17 nmol·mmol−1·mg−1; lung: 13 ± 4.08 vs. 28 ± 10.2 nmol·mmol−1·mg−1, $P < 0.05$). PC significantly increased this ratio, compared with ES animals (intestine: 31 ± 10.4 vs. 14 ± 7.2 nmol·mmol−1·mg−1; lung: 21 ± 12.2 vs. 13 ± 4.08 nmol·mmol−1·mg−1, $P < 0.05$), and the effect of PC was significantly abolished by ZN-PP pretreatment ($P < 0.05$). GSH/GSSG ratio of distant organs from the bilirubin-injected animals was not significantly greater compared with the PC animals.

Organ Dysfunction

Intestinal lactate production. Compared with sham rats, intestinal lactate accumulation increased in ES rats (6.7 ± 2 vs. 2.1 ± 0.2 mmol/mg protein), and this increase was prevented by PC (2.2 ± 0.3 mmol/mg protein), whereas the effect of PC was prevented by Zn-PP (6.9 ± 3 mmol/mg protein) (Fig. 6A).
Lung injury. ES significantly increased lung wet weight-to-dry weight ratio (8.25 ± 0.3 vs. 4.15 ± 0.2; P < 0.05). This ES-induced lung edema was reduced by PC (6.55 ± 0.3, P < 0.05), and it was abolished by Zn-PP (P < 0.05) (Fig. 6B). The effect of PC on fluid requirement was diminished by Zn-PP (P < 0.05).

Mucosal intestine damage. Sham-operated rats presented normal histology (score 0) (Fig. 6C). Mucosal injury was significantly increased by ES (score 3) compared with sham animals, but this was significantly decreased by PC (score 1). The beneficial effect of PC was abolished by Zn-PP, which tended to increase injury compared with ES alone (score 4).

Fluid requirements. At the end of the experiment (H6), the cumulative volume of fluids required to maintain MAP to a value of under 90 mmHg were significantly lower after PC than after ES alone (ES: 96 ± 3 ml, PC+ES: 65 ± 2 ml; P < 0.05) (Fig. 6D). The effect of PC on fluid requirement was diminished by Zn-PP (P < 0.05).

Treatment with bilirubin of the LPS animals prevented sepsis-induced organ dysfunction.

Intestinal and Lung HO-1 mRNA Induction After Intestinal PC

Compared with sham rats, ES induced a significant increase in HO-1 mRNA levels in intestine and lung (Fig. 7). Compared with the values obtained after ES, PC induced a significant increase in HO-1 mRNA in intestine that was present before baseline and did not further decrease during the experiment. However, PC selectively increased HO-1 mRNA in intestine in contrast to the lung (Fig. 7).

DISCUSSION

Splanchnic hypoperfusion alters local and systemic immune function, supporting the hypothesis that the gut has a central role in the immune inflammatory response (42). The gut, regarded as initiating multiple organ failure and its potential pathogenicity, has been given more attention. The gut became a “cytokine-releasing organ” and can amplify the early systemic inflammatory response syndrome. This early gut injury has been considered to be the “motor” that drives sepsis-induced multiple organ failure. Also, gut injury is likely harmful, but is it the motor of inflammatory response and multiple organ failure in septic shock?

The major findings of the present study are that prevention of LPS-induced intestinal injury, achieved by PC, markedly reduced the systemic consequences of ES, including systemic inflammatory responses, oxidative stress, and distant organ injury.

The protective effects induced by PC were accompanied by a specific marked intestinal expression of HO-1. These protec-

Fig. 6. Effect of PC on lactate production, vascular and lung injury, and intestinal mucosal injury (Chiu score) induced by ES. A: intestinal lactate concentration (mmol/mg protein) in the intestine 6 h after LPS challenge or saline in the ES, PC+ES, PC+Zn-PP+ES, and Bili+ES groups. B: wet weight-to-dry weight ratio in the lungs isolated from the 4 groups of rats. C: intestinal mucosal injury 6 h after LPS challenge or saline in the ES, PC+ES, PC+Zn-PP+ES, and Bili+ES groups. D: cumulative fluid resuscitation volumes 6 h after LPS or saline serum challenge from 4 groups of rats. Data are means ± SD of 10 animals per group. *P < 0.05 vs. sham; #P < 0.05 PC+ES/Bili+ES compared with ES/PC+Zn-PP+ES.

Fig. 7. Effect of PC on HO-1 mRNA expression in intestine and lung. HO-1 mRNA expression in intestine and lung in control sham rats and from rats subjected to ES without PC, or with PC. One group was subjected to sham surgery on day 1 and serum saline on day 2, whereas the other groups received LPS 24 h after preconditioning or sham surgery. Data are mean ± SD; n = 10 per group. *P < 0.05 sham vs. ES; #P < 0.05 vs. PC+ES/ES.
tive effects were blocked by an HO-1 inhibitor (Zn-PP) and mimicked by bilirubin treatment, suggesting that they are mediated at least in part by HO-1 or its end metabolites. One study reported that Zn-PP may inhibit iNOS expression (17). Thus, if Zn-PP inhibits iNOS in our experiments, this would probably be associated with a protective effect, whereas we found Zn-PP to be deleterious (i.e., by abolishing the beneficial effect of preconditioning). We thus believe that either Zn-PP does not inhibit iNOS in the present setting or that this possible beneficial effect is totally offset by the marked deleterious effect of HO-1 inhibition and that this does not change the major conclusion of our paper regarding the role of HO-1.

Our results have demonstrated that intestinal HO-1 expression aimed at reducing systemic inflammatory response and oxidative injury in target organs although this strategy contributes to sustained hypotension.

Our observations that LPS induce mucosal intestine damage agree with the results from other studies (41). For example, in hyperdynamic acute endotoxemia, skeletal muscle PO2 and systemic O2 consumption are well maintained, but blood flow within the gut is significantly disturbed with severe mucosal hypoxia (31). Moreover, a high dose of LPS (20 mg/kg) led to a morphological damage to both segments of the intestinal epithelium and suggest that the gut injury may be a target during endotoxemia (12). The selective prevention of mucosal intestinal ischemia by PC demonstrates that gut ischemia may be a major event for systemic inflammatory response and multiple organ injury in endotoxemia. Using a cecal ligation and puncture model, Overhaus et al. (29) have observed that bilirubin attenuates sepsis-induced morbidity to the intestine by selectively modulating the proinflammatory cascade and intestinal motility. These observations are consistent with our findings that the gastrointestinal tract plays a major role in sepsis, not only because it produces various pathogens but also because it is a major target of intestinal inflammatory response.

PC appears to target effector molecules that modulate the inflammatory response and oxidative stress involved in ischemia-reperfusion injury. Indeed, PC attenuated morphological alterations and mucosal apoptosis partly by inhibiting the reactive oxygen species-mediated mitochondria-dependent pathway in the rat small intestine (19). Moreover, several studies showed that PC prevents intestinal ischemia-reperfusion injury by inhibiting leukocyte-endothelial cell interactions (2, 33, 47). The role of cell adhesion molecules like ICAM-1 and transmigration of neutrophils through the endothelial barrier is probably essential in gut barrier dysfunction (11). Previously, our laboratory has demonstrated that PC prevented reoxygenation-induced, free radical-mediated expression of ICAM-1 and transmigration of neutrophils within the endothelial barrier is probably essential in gut barrier dysfunction (11). Previously, our laboratory has demonstrated that PC prevented reoxygenation-induced, free radical-mediated expression of ICAM-1, and this is associated with a lesser adhesion of neutrophils to endothelial cells (6). In agreement with these previous observations, we have observed that PC reduces expression of ICAM-1 after LPS administration in distant organs. Our findings and others indicate that protective effect of PC on intestinal damage, resulting in reduced systemic inflammatory response and distant organ damage, may be related to a reduction of leukocyte-dependent injury (46).

Accumulating evidence suggests that HO-1 is an important stress response protein (7, 10, 13) that plays a major role in the endogenous defense against oxidative stress. HO-1 is the rate-limiting enzyme in the catabolism of heme, followed by production of biliverdin, free iron, and carbon monoxide (16, 23, 40). Importantly, HO-1 may act as an endogenous defensive mechanism to reduce inflammation and tissue injury in the intestinal tract (4, 24, 26) and also may be protective against lethal endotoxemia (28). Our results indicate that PC leads to a selective HO-1 expression in the intestine and significantly limits intestine injury and distant organ injury by this specific HO-1 induction. PC mechanisms explain this HO-1 induction only in the intestine and the absence of HO-1 induction (mRNA, protein, and activity) in distant organs such as in lung. Bilirubin reduces the severity of the inflammatory response to LPS challenge. Our results encouraged us to hypothesize that bilirubin would act to protect against oxidative stress, in a manner similar to what has been observed with HO-1 induction. Bilirubin appears to act via the downregulation of proinflammatory mediators with a subsequent reduction in vascular injury and organ failure. Bilirubin or HO-1 overexpression could provide new effective treatment to decrease systemic inflammatory response syndrome and multiple organ failure.

However, recent studies have suggested that, in addition to the effects of hypoperfusion on endotoxin-induced gut injury, LPS may induce alterations in gastrointestinal oxygen metabolism (17). Cellular alterations referred to as “cytopathic hypoxia” may be implicated in multiple organ failure, in which case production of ATP may be decreased despite normal PO2 values in the vicinity of mitochondria within cells. PC and specific anti-ischemic interventions limit selectively mucosal intestinal damage induced by ischemia-reperfusion, and it would be interesting in the future to evaluate the effect of HO-1 induction in this cytopathic hypoxia.

In summary, the data presented in this study suggest that PC may protect against systemic inflammatory response and limit end-organ injury in ES via enhanced intestinal HO-1 overexpression. Thus the protective effects of early intestinal HO-1 expression occur by targeting selective elements with proinflammatory pathways. Together, interventions to induce intestinal HO-1 expression leads to an attenuation of the sepsis-induced organ injury. Furthermore, identification of the exact molecular mechanisms responsible for HO-1 induction during PC may lead to the development of new pharmacological interventions that mimic this potent endogenous protective pathway and could be protective in situations in which gut injury has been implicated as a major cause for multiple organ failure.

GRANTS

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