Amino Acids (2010) 38:237–245
DOI 10.1007/s00726-009-0233-z

ORIGINAL ARTICLE

Protective effects of taurine against endotoxin-induced acute liver injury after hepatic ischemia reperfusion

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Received: 20 October 2008 / Accepted: 5 January 2009 / Published online: 5 March 2009

Abstract Hepatic ischemia reperfusion (HIR) not only results in liver injury, but also leads to endotoxemia, which aggravates HIR-induced liver injury and dysfunction, or even causes liver failure. Taurine has been shown to protect organs from ischemia reperfusion or endotoxin by its anti-oxidant and anti-inflammatory activities. The aim of this study was to investigate whether taurine could attenuate endotoxin-induced acute liver injury after HIR. Wistar rats subjected to 30 min of hepatic ischemia followed by reperfusion and lipopolysaccharide (LPS) (0.5 mg/kg) administration, exhibited liver dysfunction (elevated serum levels of ALT, AST and LDH) and hepatic histopathological alteration. The serum levels of TNF-α and production of myeloperoxidase (MPO) and malondialdehyde (MDA) in liver tissues and apoptosis of hepatocytes were also increased after the combination of HIR and LPS. However, pre-administration of taurine protected livers from injury induced by the combination of HIR + LPS as the histological score, apoptotic index, MPO activity and production of MDA in liver tissues, and serum levels of AST, ALT, LDH and TNF-α, were significantly reduced. The expression of caspase-3, Fas and Fas ligand was upregulated in homogenates of livers from rats subjected to HIR and LPS, and this elevated expression could be inhibited by taurine. In summary, the results further emphasize the potential utilization of taurine in protecting livers against endotoxin-induced injury especially after HIR, by its anti-inflammatory, anti-oxidative and anti-apoptotic activities.

Keywords Ischemia reperfusion · Endotoxemia · Taurine · Liver · Myeloperoxidase · Inflammatory cytokine · Apoptosis

Introduction

Hepatic ischemia reperfusion (HIR) injury is common in major liver surgery including liver transplantation and hepatectomy. During HIR, the release of proinflammatory cytokines and generation of reactive oxygen species (ROS) cause liver tissue damage and organ dysfunction (Selzner et al. 2000). Despite improvement in surgical techniques and perioperative management, liver failure remains one of the major complications. Moreover, occlusion of portal vein interrupts the flow of mesenteric blood, leading to intestinal ischemia, stagnation, and damage to the intestinal barriers, thus accelerates the release of endotoxin into liver via portal vein (Xing et al. 2005; Watanabe et al. 2000), which complicates HIR-induced injury (Fernandez et al. 2000). Post-operative infections after major liver surgery may also cause endotoxemia, which aggravates damage to liver tissues induced by HIR. The role of endotoxin in HIR injury has been supported by one study where endotoxin tolerance

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protects organ against HIR injury in rats (Fernandez et al. 2000). Endotoxin has been shown to induce release of oxidative stress (Kono et al. 2001), free radical formation (Suzuki et al. 1996), inflammatory mediators (Seki et al. 2000; Deutschman et al. 1996) including tumor necrotic factor (TNF)-α (Bellezzo et al. 1996).

As a non-toxic endogenous antioxidant, taurine has become an attractive candidate for attenuating ischemia reperfusion (IR) injury (Kingston et al. 2004). Taurine is present high concentration in mammal tissues (Huxtable 1992) but dramatically drops after trauma, critical illness and surgery (O'Flaherty and Bouchier-Hayes 1999; Franconi et al. 1995). Taurine plays a very important role for the majority of homeostatic functions (Rakotoambinina et al. 2004). Taurine has shown protective effects for liver (Wettstein and Häussinger 1997; Wettstein and Haussinger 2000), kidney (Licht et al. 1998), skeletal muscle (McLaughlin et al. 2000), heart (Raschke et al. 1995) and brain (Zhang and Niu 1994) against IR injury. We have previously reported that taurine attenuated HIR injury in rabbits (Tong et al. 2005), and multiple organ damage induced by intestinal IR in rats (Zhang et al. 2008). Taurine has also shown beneficial effects in endotoxemia by decreasing MPO activity, levels of NO_2^- and TauCl in polymorphonuclear leukocytes (Erdamar et al. 2007). These studies indicate that taurine may also have the protective effects on aggravated HIR injury by endotoxin. To test this hypothesis, we established the liver injury model of rats by subjecting them to the combination of HIR and endotoxin, and investigated whether administration of taurine could attenuate liver injury.

Materials and methods

Animals and experiment design

Male Wistar rats, 200–250 g in weight, were supplied by the Animal Research Center at the First Clinical Medical School of Harbin Medical University, Harbin, China. The animals maintained under standard conditions were fed rodent chow and water. All surgical procedures and care administered to the animals have been approved by the institutional ethic committee. The procedures for inducing HIR and administration of taurine have been described previously (Zhang et al. 2008; Jiang et al. 2007). Briefly, taurine (Sigma-Aldrich, China) solution was injected into rats (200 mg/kg weight) via penis vein 30 min before HIR. After laparotomy, hepatic ischemia was induced by occluding portal vein andhepatic artery with a vascular clamp, reperfusion was initiated by removal of the clamp 30 min later, and lipopolysaccharide (LPS) (Sigma-Aldrich, China) was intravenously injected (1 mg/kg weight) right afterward. At the indicated time points, the rats were randomly sacrificed, and blood and liver samples were collected. Blood samples were centrifuged at $3{,}000 \times g$ for 10 min to collect serum and stored at −80°C.

Biochemical assay

The levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) in sera were measured with an auto-biochemical analyzer (Toshiba, Japan).

Histological examination

Liver specimens were fixed in 10% buffered formalin, embedded in paraffin, stained with hematoxylin/eosin and examined by light microscope. The histopathological scoring analysis was performed blindly according to previously described methods (Tang et al. 2007). The assessment was expressed as the sum of the individual score grades from 0 (no findings), 1 (mild), 2 (moderate), to 3 (severe) for each of the following six parameters: cytoplasmic color fading, vacuolization, nuclear condensation, nuclear fragmentation, nuclear fading and erythrocyte stasis.

Terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL) assay

Serial sections of 5 μm thickness were prepared from livers. The TUNEL (Roche, Shanghai, China) staining of sections was performed according to manufacturer's instruction, and examined by light microscopy. The apoptotic index was calculated as the percentage of stained cells, namely, number of apoptotic cells × 100/total number of nucleated cells.

Myeloperoxidase (MPO) activity

The methodology of measuring activity of MPO in liver tissues has been described in our previous report (Jiang et al. 2007).

Malondialdehyde (MDA) levels

The levels of MDA in liver tissues were measured to assess lipid peroxidation. Samples of liver tissues were homogenized with ice-cold 150 mM potassium chloride, and the MDA levels were measured spectrophotometrically. Results were expressed as nmol of MDA per gram tissue (Buege and Aust 1978).

ELISA

Levels of TNF-α were measured with a TNF-α ELISA kit (Jingmei Biotech Co. Ltd, Shenzhen, China) according to the manufacturer's instruction, as described previously (Zhang et al. 2008; Jiang et al. 2007).

Western blotting

The methodology to detect protein expression by Western blot analysis has been described previously (Zhang et al. 2008; Tang et al. 2007). Briefly, tissues were homogenized in protein lysate buffer. The homogenates were resolved on polyacrylamide SDS gels, and electrophoretically transferred to polyvinylidene difluoride (PVDF) membranes. The membranes were blocked with 3% BSA, incubated with Abs against active caspase-3, Fas and Fas ligand (Fas L) (Santa Cruz Biotechnology, Inc. Santa Cruz, CA), and subsequently with alkaline phosphatase-conjugated secondary Abs. They were developed by 5-bromo-4-chloro-3-indolyl phosphate (BCIP)/nitro blue tetrazolium (NBT) (Tiangen Biotech Co. Ltd, Beijing, China). Blots were stained with an anti-tubulin Ab to confirm that each lane contained similar amounts of proteins, and the levels of proteins were normalized with respect to tubulin band density.

Statistical methods

Results were expressed as mean values ± standard deviation (SD), and a Student's *t* test was used to evaluate statistical significance. $P < 0.05$ was considered to be statistically significant.

Results

LPS aggravates HIR injury

Firstly, we performed a preliminary experiment to confirm that endotoxin aggravates liver injury induced by HIR. Twenty-four rats were randomly assigned to four groups (each group had six rats): Sham, HIR, LPS and HIR + LPS. Rats in the HIR or LPS group were subjected to HIR or LPS injection, respectively, as described in "Material and methods". The rats in the HIR + LPS group were subjected to HIR, followed by LPS injection. Rats in the sham group underwent laparotomy and the abdominal cavity was closed without HIR or LPS injection. The sera and liver tissues were collected 6 h later when the rats were killed. As shown in Fig. 1a–c, the serum levels of AST, ALT and LDH were significantly (all $P < 0.01$) increased in HIR or LPS-treated rats, compared with sham-operated rats. The combination of HIR + LPS further increased the serum levels of AST, ALT and LDH, which were highly significantly different from that in sham-operated rats, and significantly higher than that in HIR or LPS-treated rats (all $P < 0.05$). The histological analysis further confirmed the serological changes. As shown in Fig. 1d, the liver injury scores in HIR or LPS-treated rats were significantly greater than that in sham-operated rats, and the combination of HIR + LPS further elevated the liver injury scores compared with HIR or LPS treatment.

Taurine attenuates liver injury

Next, we investigated whether taurine could attenuate liver injury induced by the combination of HIR and LPS.

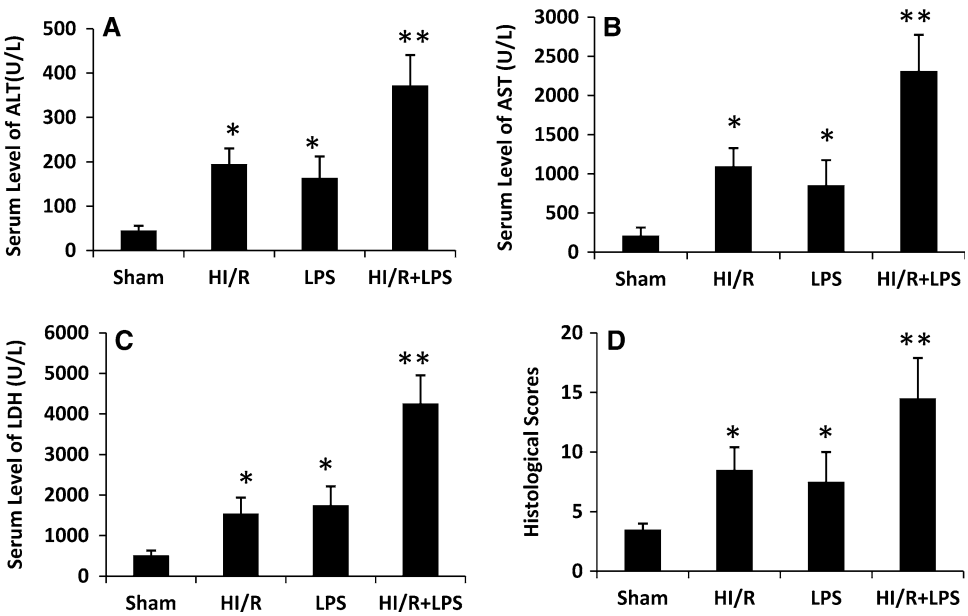

Fig. 1 LPS aggravates HIR injury. Rats were assigned to four groups: Sham, HIR, LPS, HIR + LPS. The rats were killed 6 h later, blood samples were collected and livers removed. The serum levels of ALT (**a**), AST (**b**) and LDH (**c**) were measured. **d** Histological scoring of hepatic injury was performed as described in "Materials and methods". Results are expressed as mean ± SD ($n = 6$). A significant difference from sham-operated rats is denoted by "*asterisk*" ($P < 0.01$), and from HIR or LPS-treated rats by "*double asterisks*" ($P < 0.05$)

Seventy-two rats were randomly assigned into three groups as follows (each group had 24 rats): Sham, Saline and Taurine. The rats in the saline or taurine group received intravenous injection of 1 ml physiological saline or equal volume of taurine via penis vein 30 min before HIR, respectively. Thirty minutes after occlusion of blood vessels, reperfusion was initiated and LPS was injected. Rats in the sham group underwent laparotomy and the abdominal cavity was closed without HIR or LPS injection. At each of the indicated time points (1, 3, 6, 9 h after HIR), the rats (six per group) were randomly sacrificed, and blood and liver samples were collected. As shown in Fig. 2, the serum levels of AST (Fig. 2a), ALT (Fig. 2b) and LDH (Fig. 2c) were significantly higher in the saline group than that in sham-operated rats, at all the indicated time points (all $P < 0.001$). These increases were significantly reduced by pre-administration of taurine at most of the time points (Fig. 2a–c). The results suggest that taurine can attenuate the cellular damage that occurs as a result of hepatic damage by HIR + LPS. The serological changes were further confirmed by histological analysis. Sham operation did not show any effects on liver histology as the HE stained liver sections exhibited normal morphology (Fig. 3a). Histological alteration of the liver from saline-treated rats was characterized as inflammatory cell infiltration, hemorrhagic change and focal necrosis in the midzone and periportal regions of the liver 6 h after HIR + LPS (Fig. 3b, c). In contrast, pre-treatment of taurine markedly attenuated the pathological changes (Fig. 3d). The liver injury scores in the saline-treated rats were significantly greater than that in the sham-operated rats at all the indicated time points (all $P < 0.001$), and pre-treatment with taurine significantly decreased the histological scores compared with saline (all $P < 0.01$) (Fig. 3e).

Inflammatory reaction and lipid peroxidation

The combination of HIR + LPS dramatically increased liver MPO activity compared with sham control at all the indicated time points (all $P < 0.001$) (Fig. 4a). These increases were significantly diminished by pre-treatment of taurine at the time points of 1, 3, 6 h after HIR + LPS (all $P < 0.05$). Although the level of MPO was slightly reduced in taurine-treated rats compared with saline-treated rats 9 h after perfusion, the difference did not reach significance (Fig. 4a). We have previously demonstrated that HIR elevated the serum level of TNF-α, a main factor involved in inflammatory injury caused by IR (Zhang et al. 2008; Jiang et al. 2007). Here we could also show that the combination of HIR + PLS dramatically ($P < 0.001$) increased the serum level of TNF-α (78.5 ± 19.6 pg/ml) in saline-treated rats 6 h after reperfusion, and this increase was significantly ($P < 0.05$) diminished by pre-administration of taurine, as the level of TNF-α was only 42.8 ± 14.2 pg/ml 6 h after reperfusion. Similarly, the level of MDA in liver tissues were significantly ($P < 0.001$) increased in saline-treated rats 6 h after reperfusion, compared to sham-operated rats, but pre-administration of taurine significantly ($P < 0.05$) decreased the level of MDA (Fig. 4c).

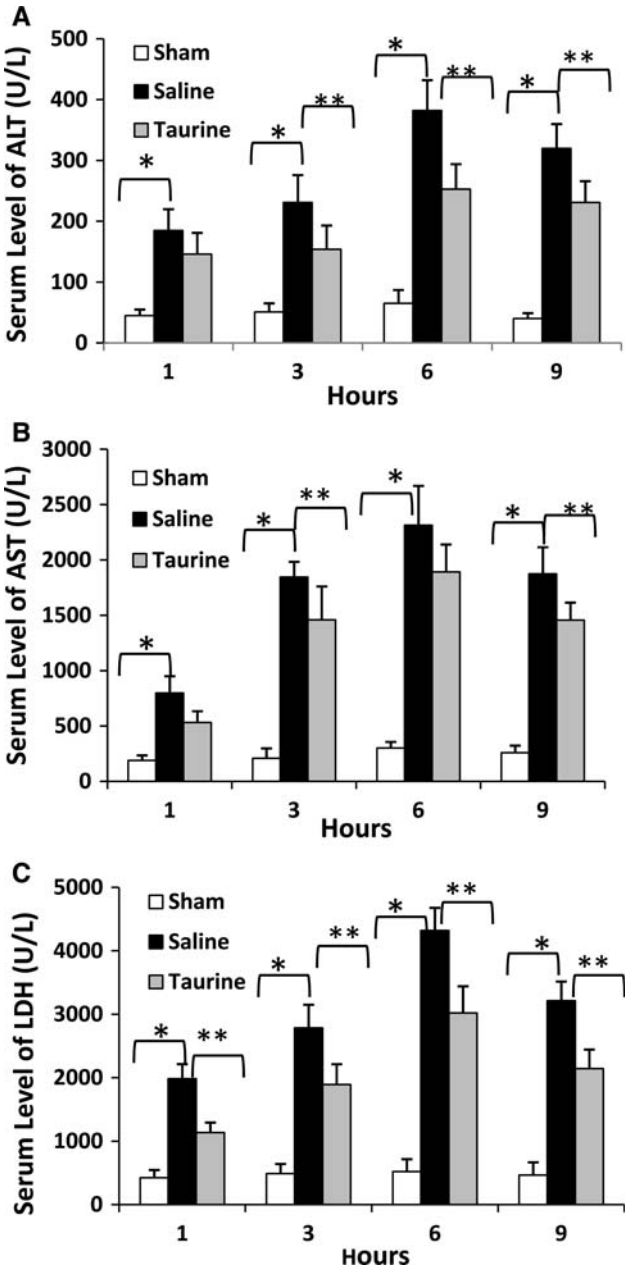

Fig. 2 Taurine attenuates liver dysfunction induced by HIR + LPS. Blood samples were taken from rats 1, 3, 6 and 9 h after HIR, pre-treated with saline or taurine, respectively. The sham-operated rats served as control. The serum levels of ALT (**a**), AST (**b**) and LDH (**c**) were measured. Results are expressed as mean ± SD ($n = 6$). Significant difference between the sham and saline groups is denoted by "*asterisk*"($P < 0.001$), and between the saline and taurine groups by "*double asterisks*"($P < 0.01$)

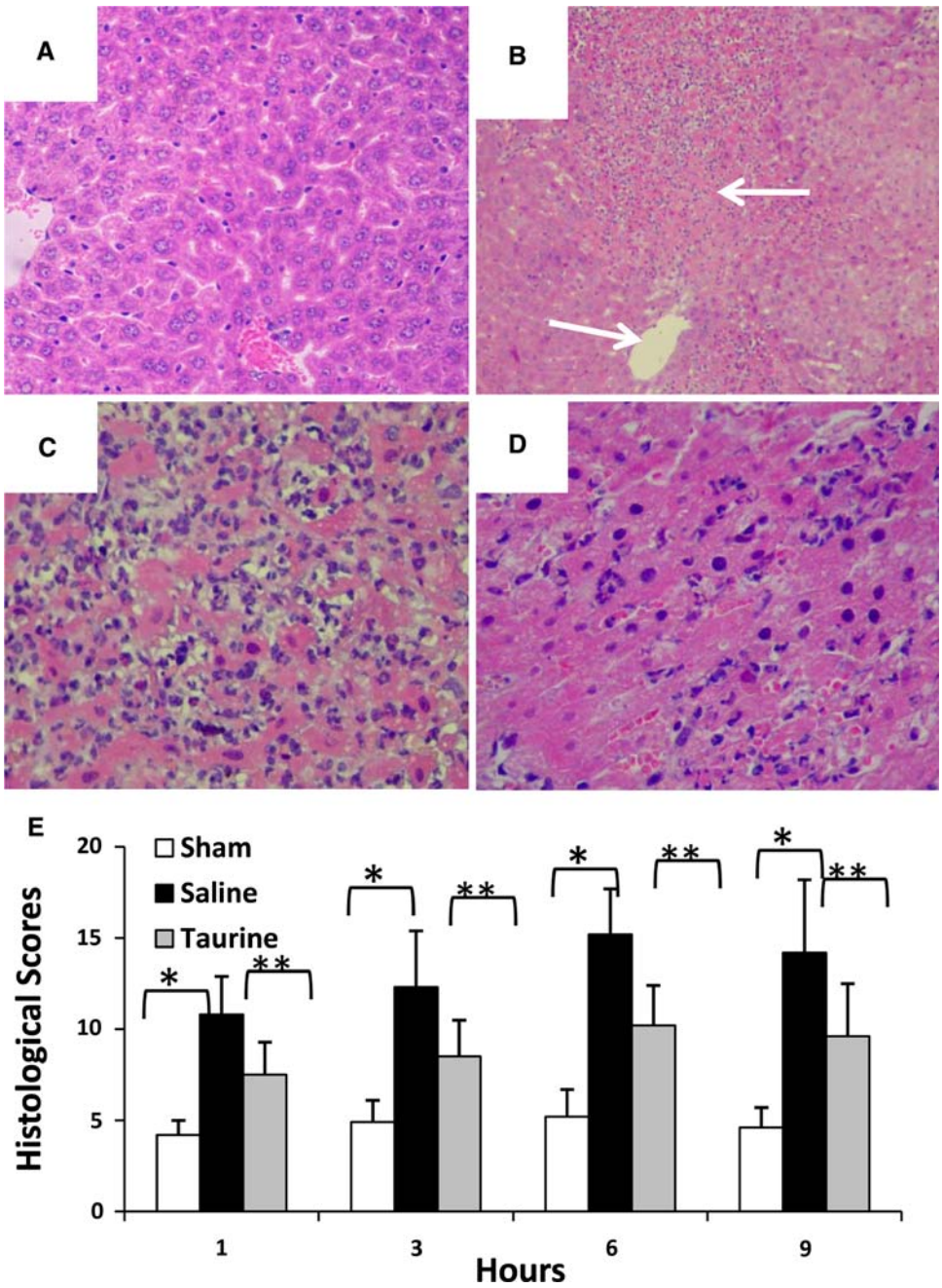

Fig. 3 Taurine attenuates histological alteration of livers induced by HIR + LPS. The rats in Fig. 2 were killed at the indicated time points and livers removed. Representative photographs (×400 magnification) of liver sections stained with HE were taken from sham-operated rats (**a**) or rats 6 h after HIR, treated with saline (**c**) or taurine (**d**). A representative photograph (×100 magnification) was from rats 6 h after HIR treated with saline (**b**). *Arrows* point to the midzone (*upper*) or periportal region (*lower*). (**e**) Histopathological scoring of hepatic injury was performed. Results are expressed as mean ± SD ($n = 6$). A significant difference between the sham and saline groups is denoted by "*asterisk*" ($P < 0.001$), and between the taurine and saline groups, by "*double asterisks*" ($P < 0.01$)

Apoptosis of hepatocytes

There were very few apoptotic cells sparsely in the liver sections taken from sham-operated rats 6 h after operation (data not shown), whereas the combination of HIR + LPS dramatically increased apoptosis of hepatocytes in saline-treated rats 6 h after reperfusion (Fig. 5a). Pre-treatment of taurine reduced the development of apoptosis of hepatocytes induced by HIR + LPS (Fig. 5b). The apoptosis indexes in the livers from saline-treated rats were significantly ($P < 0.01$) increased, compared with sham-operated rats, and pre-treatment of taurine significantly ($P < 0.05$) reduced AIs elevated by HIR + LPS in livers by 34% 6 h after perfusion (Fig. 5c).

We further investigated the molecular pathways involved in the apoptosis by Western blotting analysis of liver homogenates, which demonstrated that HIR + LPS upregulated expression of activated caspase-3, Fas and Fas L in liver tissues compared with the sham control, and pre-treatment of taurine inhibited the elevated expression of

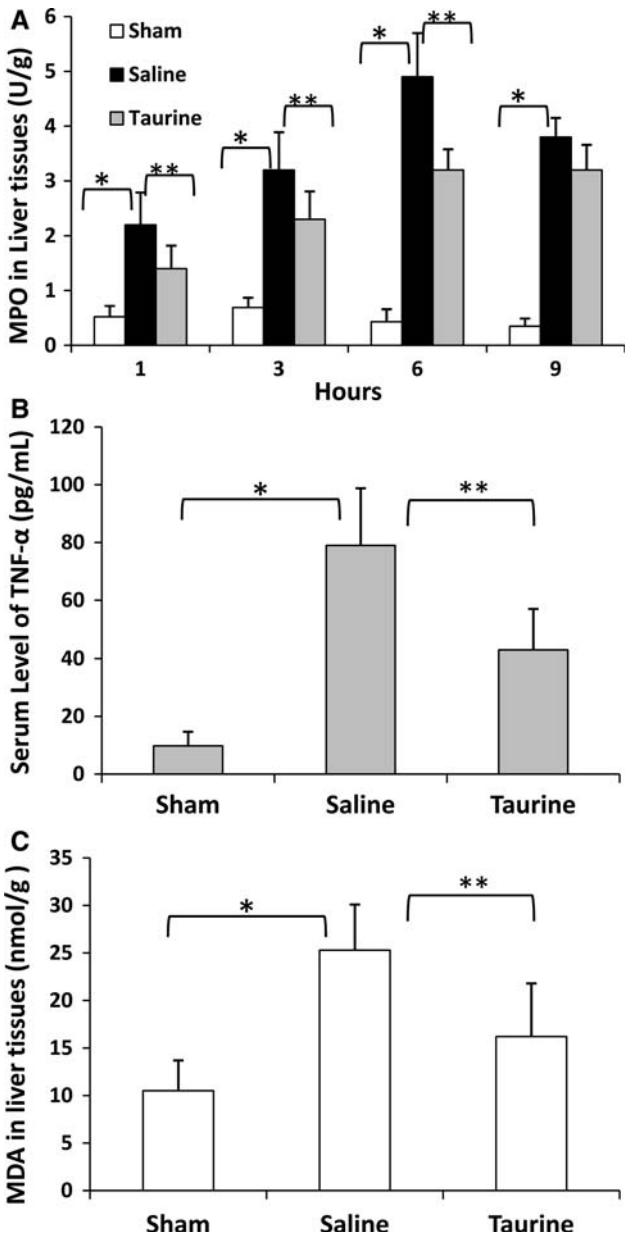

Fig. 4 Taurine inhibits production of MPO, TNF-α and MDA. Liver tissues and blood samples were taken from the rats in Fig. 2. The levels of MPO (**a**), TNF-α (**b**) and MDA (**c**) were assessed as described in "Materials and methods". Results are expressed as mean ± SD ($n = 6$). A significant difference between the sham and saline groups is denoted by "*asterisk*" ($P < 0.001$), and between the taurine and saline groups, by "*double asterisks*" ($P < 0.05$)

these apoptosis related proteins by HIR + LPS (Fig. 5d). Quantification of the densities of bands on the blot indicated that there were significant differences in the levels of caspase-3, Fas and Fas L in rat liver homogenates from the sham and saline groups. The expression of caspase-3 and Fas L in the saline group was significantly lower than that in the saline group, but the difference in Fas expression between these two groups did not reach significance (Fig. 5d).

Discussion

The present study has demonstrated that LPS aggravates liver injury induced by HIR evidenced by the elevated serum levels of AST, ALT and LDH, and increased histological scores. The cytotoxic sensitivity to endotoxin is increased after major liver surgery such as hepatectomy (Tsuji et al. 2005), and the increased sensitivity is partly associated with the reduced phagocytic function of reticuloendothelial system (Arii et al. 1985). Several studies have demonstrated that the HIR-induced liver injury was increased by LPS (Fernandez et al. 2000; Kaibori et al. 2004; Colletti and Green 2001). HIR not only causes systemic and portal endotoxemia (Fernandez et al. 2000), but also activates LPS signaling pathways, initiating a cascade of complications of septic shock and multiple organ failure (Tsoulfas et al. 2002). Thus, endotoxemia represents one of the main causes of death after massive liver surgery. The results presented here is promising as administration of taurine attenuates endotoxin-aggravated liver injury induced by HIR, evidenced by the reduction of serum levels of AST, ALT and LDH, attenuation of histopathological alterations, and inhibition of cell apoptosis.

Taurine has displayed many aspects in protecting livers from this injury by anti-oxidation, anti-inflammation and anti-apoptosis. Taurine, the most abundant free amino acid in mammalian cells, presents in particularly high concentrations in neutrophils by active transport across a taurine-sodium symport (Redmond et al. 1998). The roles of taurine so far elucidated include membrane stabilization, osmoregulation, bile salt formation, growth regulation, calcium homeostasis, and apoptosis modulation (Redmond et al. 1998), all of which contribute to a cyto-protective effect against a variety of mechanisms of cell damage (Schaffer et al. 2003), including IR and endotoxin-induced injury. Taurine has been applied in several animal models to protect livers from HIR injury (Wettstein and Häussinger 1997; Tong et al. 2005), and protect livers in alcoholic liver disease (Wu et al. 2008). Recently dietary taurine has been shown to ameliorate liver injury in chronic hepatitis patients (Hu et al. 2007). Reduction of liver taurine in rats by beta-alanine treatment has increased carbon tetrachloride induced hepatotoxicity, indicating taurine might have a direct protective effect against toxic compound, carbon tetrachloride (Waterfield et al. 1993). Recently it has been shown that taurine reduced production of MPO, NO_2^- and TauCl in PMN leukocytes elevated by endotoxin in guinea pigs (Erdamar et al. 2007). In accord, the present study has demonstrated that pre-administration of taurine attenuated liver injury induced by the combination of HIR and LPS, by reducing the production of MPO, MDA and TNF-α. However, Erdem et al. (2008) has reported that taurine was

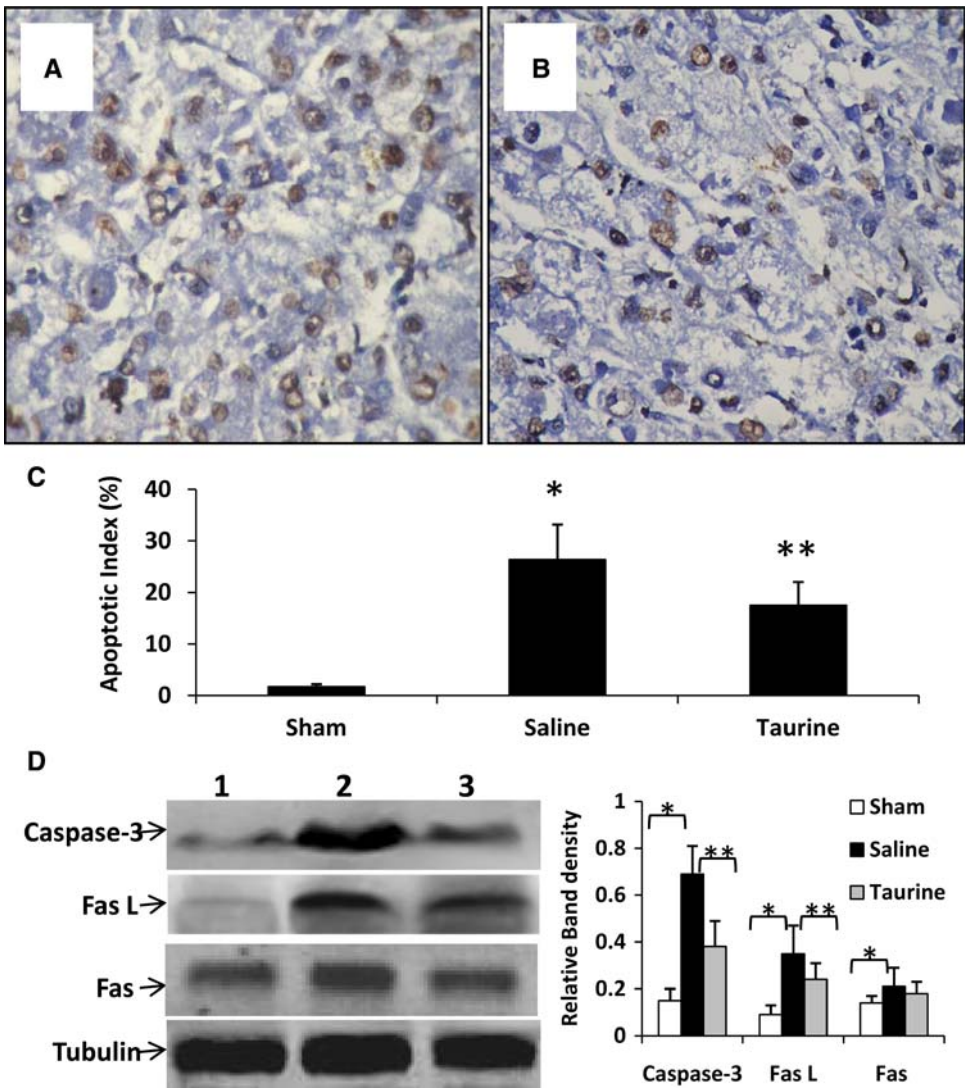

Fig. 5 Anti-apoptotic effects of taurine. Illustrated are liver sections stained by TUNEL for apoptotic cells. Representative photographs (×400 magnification) were taken rats subjected to HIR and LPS 6 h earlier, which were treated with saline (**a**) or taurine (**b**). **c** TUNEL-positive cells were counted to record the apoptosis index. **d** Western blot analysis of caspase-3, Fas and Fas L in liver homogenates from rats above (six rats per group). Representative blots were from the sham-operated rats (*lane 1*), and rats subjected to HIR and LPS, which were treated with saline (*lane 2*) or taurine (*lane 3*). The density of each band was measured and compared to that of the internal control, tubulin. Results are expressed as mean ± SD ($n = 6$). A significant difference between sham and saline-treated rats is denoted by "*asterisk*" ($P < 0.01$), and between the saline- and taurine-treated rats by "*double asterisks*" ($P < 0.05$)

unable to block endotoxin-induced reduction of mesenteric blood flow and organ injury in mice. The different results may result from different animal species used in these studies, as Erdem et al. (2008) used mice in their study, while larger animals including rats and guinea pigs were used in the other studies including the present one. Therefore, future investigation is required to clarfiy whether taurine has the protect effects on endotoxin-induced hepatic injury in rats in the future.

During endotoxemia, inflammatory cytokines including TNF-α and neutrophil infiltration play important roles in the liver injury (Sakaguchi et al. 1999). MPO, an enzyme present in neutrophils, is a widely used marker of neutrophil infiltration (Jiang et al. 2005). By producing oxidative stress, neutrophils activate Kupffer cells, and contribute to microvascular dysfunction and edema formation (Jaeschke 2000). We have previously reported that HIR increased the MPO activity in livers (Jiang et al. 2007), here the combination of HIR + LPS further increased MPO activity when the results in the two studies were compared, suggesting that neutrophils also contribute to liver damage induced by LPS. However, pre-administration of taurine decreases MPO activity, thus inhibits neutrophil infiltration and ameliorates the injury to livers.

We have previously reported that HIR increased release of TNF-α (Jiang et al. 2007), and later reported that LPS-induced acute liver injury after partial hepatectomy by promoting translocation of nuclear factor-kappa B (NF-κB) into the nuclei and release of TNF-α (Tang et al. 2007). In accord, the present study has also showed that the combination of HIR + LPS markedly increased the serum levels of TNF-α. TNF-α is a key mediator of the cytokine cascade and tissue injury in sepsis (Suzuki et al. 1996), and is involved in the pathogenesis of LPS-induced liver injury (Sakaguchi et al. 1999). LPS triggers sepsis syndrome by activating monocytes to produce proinflammatory cytokines, which potently stimulate the activation of neutrophils. LPS binds to LPS-binding protein, and interacts with CD14

to form a ternary complex, which transfers LPS to the toll-like receptor 4 (TLR4) accessory protein MD2 complex, leading to activation of TLR4 and subsequent activation of NF-κB (Dauphinee and Karsan 2006). Once activated, NF-κB is dissociated from its inhibitor, I-κB, and translocated into nuclei, where it induces transcriptional up-regulation of various proinflammatory mediators such as TNF-α (Su 2002). In the present study, taurine reduced the levels of TNF-α, thus was able to inhibit inflammation and hepatocyte apoptosis via the death domain receptor pathway.

We have previously reported that the apoptosis of hepatocytes was observed in damaged livers induced by HIR (Jiang et al. 2007; Jiang et al. 2005), and also by LPS (Tang et al. 2007). Cellular apoptosis is initiated through two alternative pathways: death receptors and intrinsic mitochondrial pathways. The first pathway involves ligand-induced activation of death receptors including Fas/Fas L and TNF-R1, which leads to activation of caspase-8 (Green 2000). Activated caspase-8 cleaves procaspase-3, resulting in activation and development of the apoptotic process (Krammer 2000). In the mitochondrial pathway, mitochondria are induced to release cytochrome c, which binds to Apaf-1 and procaspase-9. Active caspase-9 in turn directly activates pro-caspase-3, initiating a cascade of additional caspase activation that culminates in apoptosis (Li et al. 1997). Thus, caspase-3, the "effector" protease in the apoptotic cascade, plays a key role in cell apoptosis. The present study has demonstrated that the combination of HIR + LPS upregulated expression of caspase-3, Fas and Fas L in liver tissues, whereas pre-administration of taurine inhibited the upregulation, indicating the inhibitory activity of apoptosis by taurine depends at least on downregulation of the three apoptosis related molecules, in accordance with our previous reports (Zhang et al. 2008; Jiang et al. 2005).

In conclusion, the present study has for the first time demonstrated the protective activity of taurine on acute liver injury induced by the combination of HIR and LPS. Its protective mechanisms may be attributable to its anti-inflammatory activity by inhibiting release of proinflammatory mediators and neutrophil accumulation, and anti-oxidative activity by reducing the production of lipid peroxidation. Taurine also exhibits anti-apoptotic activity, probably relying on downregulation of caspase-3 and Fas/Fas L. The results further emphasize the potential utilization of taurine in protecting livers against endotoxin-induced injury especially after HIR.

Acknowledgments The work was supported by the National Natural Scientific Foundation of China (30571808, 30571753, 30872987), a Collaborative Fund for Oversea Scholars from The Science and Technology Bureau of Heilongjiang Province, China (WH05C02), and the Creative Foundation of Daqing High-tech Industrial Development Zone, China (DQCX06YF001).

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