

Taurine alleviates lipopolysaccharide-induced liver injury by anti-inflammation and antioxidants in rats

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Abstract. The aim of the present study was to investigate the protective effect of taurine on lipopolysaccharide (LPS)-induced liver injury and its mechanisms. Male rats were randomly divided into three groups: Normal saline, LPS model and taurine treatment. Experimental animals were treated with saline or taurine (dissolved in saline, 200 mg/kg/day) via intravenous injection. After 2 h, saline or LPS (0.5 mg/kg) was administrated via intraperitoneal injection. Markers of liver injury, pro-inflammatory cytokines and superoxide dismutase (SOD) activity were determined in plasma. Liver tissues were removed for morphological analysis and determination by western blot analysis. Taurine significantly reduced the elevation in the levels of LPS-induced aspartate transaminase and alanine transaminase and decreased the concentrations of LPS-induced inflammatory factors including tumor necrosis factor- α and interleukin-6. Taurine also increased the activity of SOD in serum and the expression of heme oxygenase-1 protein in liver tissue. Taurine pretreatment also reduced the elevated expression levels of LPS-induced cyclooxygenase-2, nuclear factor κ B and extracellular regulated protein kinase. The results from the present study demonstrated that taurine alleviates LPS-induced liver injury. The beneficial role of taurine may be associated with its reduction of pro-inflammatory response and oxidative stress.

Introduction

Hepatic disorder has become a major disease endangering human health and exhibits a high morbidity and fatality rate (1). As the mechanisms of severe hepatic failure are poorly understood, there remains a lack of effective treatment. An increasing number of studies have suggested that the production of

inflammatory cytokines serves important roles in various types of liver damage (2,3). Lipopolysaccharide (LPS), a component of Gram-negative bacteria, can activate liver macrophages, which produce inflammatory cytokines including tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β and IL-6 (4-6). In addition, LPS possesses pro-oxidative action via the induction of excessive production of reactive oxygen species (ROS). ROS are the major cause of damage to macromolecules, including protein and DNA, and to the cell membrane, which leads to mitochondrial dysfunction (7,8). A further study demonstrated that ROS are involved in modulation of the inflammatory response (9). Various types of liver damage, including ischemia-reperfusion and liver cancer, are associated with LPS (10,11). Therefore, LPS-induced liver injury is used as an animal model of liver disorder.

Taurine, a sulfur-containing β -amino acid, is a metabolic product of L-cysteine and is abundant in a number of mammalian tissues. Taurine is not involved in the synthesis of protein; however, considerable evidence has demonstrated that taurine serves a number of vital roles in physiological processes, including regulation of calcium concentration (12), stabilization of the cell membrane (13), regulation of blood pressure and protection of endothelial cells (14). The antioxidant properties of taurine have been confirmed by a number of results, although taurine itself is not able to scavenge ROS. Taurine exerts its antioxidant action by inhibiting the production of ROS, which result from the increasing activities of antioxidantases (15). Certain studies have indicated that taurine protects cells against oxidative stress (16,17). Taurine is changed into taurine chloramine (TauCl) *in vivo*, which inhibits secretion of pro-inflammatory cytokines including IL-6, IL-1 β , TNF- α and IL-8 (18,19). It is suggested that taurine is a potent anti-inflammatory factor.

The present study examined the beneficial effects of taurine on LPS-induced liver injury in rats. The results suggested that administration of taurine may be beneficial for patients with hepatopathy.

Materials and methods

Animals and experimental design. A total of 30 healthy male Sprague-Dawley rats (weighing 280 \pm 20 g) were obtained from the Animal Center at West Anhui Health Vocational College and housed in a standard facility at 22°C and 50-70% humidity

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with a 12-h light/dark cycle. Experimental rats received a standard pellet diet and water *ad libitum*. The study was approved by the Ethics Committee of West Anhui Health Vocational College (Lu'an, China). After a week, the animals were randomly divided into three groups (n=10 per group): i) Normal saline group (NS), ii) LPS control group (LPS) and iii) taurine + LPS group (TL). Rats from NS and LPS were treated with sterile saline by intravenous injection and animals from TL were intravenously injected with taurine (100 mg/kg body weight, dissolved in sterile saline; Sigma-Aldrich; Merck KGaA, Darmstadt, Germany). After 4 h, rats from LPS and TL groups were intraperitoneally injected with LPS (10 mg/kg body weight, dissolved in sterile saline; Sigma-Aldrich; Merck KGaA) and NS rats received sterile saline. At 6 h following administration of LPS, the animals were anesthetized with sodium pentobarbital (50 mg/kg, i.p.; Sigma-Aldrich; Merck KGaA) to collect blood samples prior to animal sacrifice. Fasting blood samples were collected by artery catheterization for biochemical analyses and liver tissues were obtained for histological analyses.

Determination of liver function. Fasting blood samples were centrifuged at 3,000 x g to separate the serum. Markers of liver function, serum aspartate transaminase (AST) and alanine transaminase (ALT) were determined using an enzymatic colorimetric method (Diagnostica Stago S.A.S., Paris, France) according to the manufacturer's protocols and analyzed by a semi-automatic analyzer, with the results being expressed as U/l.

Measurement of inflammatory cytokines. Serum levels of TNF- α , procalcitonin (PCT) and IL-6 were detected with rat TNF- α (cat. no. ELS-2855-1), PCT (cat. no. ELS-3485-1) and IL-6 (cat. no. ELS-2866-1) specific ELISA kits (Hefei Bomei Biotechnology Co., Ltd., Hefei, China) according to manufacturer's protocol. The levels of TNF- α and IL-6 were expressed as ng/l.

Estimation of antioxidant effects. To estimate changes in antioxidant effects, the activity of the antioxidant, superoxide dismutase (SOD) was determined using xanthine oxidase methods, and the content of lipid peroxidation production, malonaldehyde (MDA), was measured using thiobarbituric acid methods, according to the manufacturer's protocol (both from Nanjing Jiancheng Bioengineering Institute, Nanjing, China).

Histological analysis. Liver tissues were harvested and fixed in 4% phosphate-buffered formalin for pathological analysis. Fixed tissues were dehydrated in ethanol, embedded in paraffin and 5 μ m sections were cut. After drying overnight, sections were dewaxed, rehydrated and stained with hematoxylin and eosin (H&E) for histomorphological observation under a light microscope.

Western blot analysis. Liver tissues (0.2 g) were harvested, lysed and homogenized in 2 ml lysis buffer with 10 mM Tris-buffered saline, 1 mM EDTA, 1 mM EGTA, 2 mM PMSF and 1% Triton X-100 (v/v) for 20 min. Lysates were centrifuged at 13,000 x g for 15 min at 4°C. Protein concentration was measured using a Quick Start™ Bradford protein assay

(Bio-Rad Laboratories, Inc., Hercules, CA, USA). Denatured proteins in supernatants were separated by 10% SDS-PAGE and transferred onto nitrocellulose membranes. The membranes were blocked with 5% non-fat milk in TBS with Tween-20 (10 mM Tris-HCl, 150 mM NaCl and 1% Tween-20) for 2 h. The membranes were subsequently incubated with primary polyclonal antibodies against β -actin (1:1,000), heme oxygenase-1 (HO-1; 1:1,000), cyclooxygenase-2 (COX-2), nuclear factor (NF)- κ B, phosphorylated (p)-NF- κ B, extracellular signal-regulated kinase (ERK) and p-ERK1/2 (Bio Basic Inc., Markham, ON, Canada) overnight at 4°C. Following an extensive wash with TBST, the membranes were incubated with a horseradish peroxidase-conjugated goat anti-rabbit secondary antibody (1:10,000; cat. no. A9169; Sigma-Aldrich; Merck KGaA) for 2 h at room temperature. The membranes were washed three times and visualized with 3,3'-diaminobenzidine (Bio Basic Inc.).

Statistical analysis. All values are expressed as mean \pm standard deviation. The data were analyzed using SPSS version 16.0 (SPSS, Inc., Chicago, IL, USA). Statistical difference was determined by Tukey's test for unpaired data or one-way analysis of variance with least significant difference-t and/or Tamhane's T₂ post hoc tests for multiple comparisons. P<0.05 was considered statistically to indicate a statistically significant difference.

Results

Ameliorative effects of taurine on liver damage. To examine liver function, serum AST and ALT transaminases were determined. The result demonstrated a significant increase in activity of AST and ALT in LPS rats compared with NS rats (P<0.01; Fig. 1). Administration of taurine reduced the increase in activity of AST and ALT (P<0.01; Fig. 1).

Change of antioxidant effects. The activity of serum SOD, an antioxidant, was reduced and the content of serum MDA, a product of lipid peroxidation, was increased in LPS-treated rats compared with NS rats (P<0.01; Fig. 2). Taurine significantly enhanced SOD activity and decreased the concentration of MDA (P<0.01; Fig. 2).

Effects of taurine on pro-inflammatory cytokines. The levels of TNF- α and IL-6 in serum were significantly increased in LPS rats (P<0.01; Fig. 3A and B) and an increased level of PCT was determined (P<0.05; Fig. 3C). Taurine treatment prior to LPS significantly reduced the levels of TNF- α and IL-6 (P<0.01; Fig. 3A and B) and decreased the concentration of PCT (P<0.05; Fig. 3C).

Effects of taurine on hepatic histopathology. Liver sections stained with H&E were observed under a light microscope for hepatic morphology. Recruitment of inflammatory cells and release of inflammatory factors in liver are involved in liver injury (20). Exposure to LPS resulted in an increase in the infiltration of inflammatory cells and hepatocyte edema (Fig. 4). Administration of taurine prior to LPS attenuated congestion in liver tissues, abated the number of the infiltration of inflammatory cells and intact lobular structure was observed (Fig. 4).

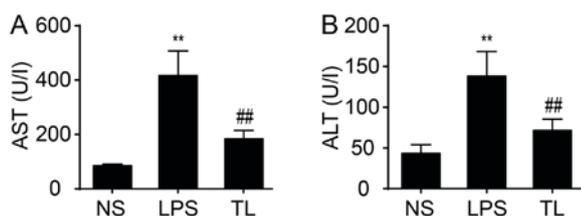


Figure 1. Effects of taurine on the levels of (A) AST and (B) ALT. Data are presented as the mean \pm standard deviation (n=10). **P<0.01 vs. NS group and ##P<0.01 vs. LPS group. AST, aspartate transaminase; ALT, alanine transaminase; NS, normal saline group; LPS, lipopolysaccharide control group; TL, taurine + LPS group.

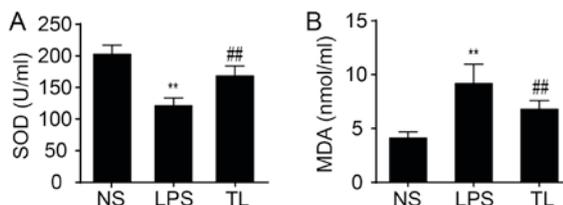


Figure 2. Effects of taurine on the levels of (A)SOD and (B) MDA. Data are presented as the mean \pm standard deviation (n=10). **P<0.01 vs. NS group and ##P<0.01 vs. LPS group. SOD, superoxide dismutase; MDA, malonaldehyde; NS, normal saline group; LPS, lipopolysaccharide control group; TL, taurine + LPS group.

Effects of taurine on liver ERK1/2, COX-2, HO-1 and NF- κ B protein expression. Antioxidant alterations were examined; taurine pretreatment elevated HO-1 protein expression (Fig. 5A). Furthermore, the protein expression levels of COX-2 (Fig. 5B), NF- κ B (Fig. 5C) and p-ERK (Fig. 5D) were investigated to evaluate inflammation signaling. Taurine pretreatment reduced the protein expression of NF- κ B, COX-2 and p-ERK.

Discussion

It is well-known that activation of macrophages and release of inflammatory cytokines serve important roles in organ damage, including acute and chronic liver injury (21,22). The present study aimed to investigate effects of taurine pretreatment on LPS-induced liver injury. The results demonstrated that taurine pretreatment by intravenous injection reduced the activity of plasma AST and ALT, and decreased the level of serum inflammatory cytokines including TNF- α , IL-6 and MDA. Serum SOD activity and HO-1 protein expression in liver was significantly increased in taurine-pretreated rats, while COX-2, pNF- κ B (E) and p-ERK protein expression levels in liver were reduced. In addition, taurine pretreatment alleviated the infiltration of inflammatory cells in liver tissues and hepatic congestion. The present study suggested that taurine pretreatment protected the liver against LPS-induced injury.

LPS-induced tissue injury results from an increase in the release of cytokines, oxidative stress and impairment of mitochondrial function (23). LPS induces excessive release of pro-inflammatory cytokines including TNF- α and IL-6 and the production of ROS by binding with Toll-like receptor 4 on the surface of K \ddot{u} pffer cells (24,25), stimulating the apoptosis of hepatic cells and necrosis (26).

Oxidative stress results from excessive generation of ROS and/or deletion of antioxidants including reduced activities of the antioxidant enzymes, imbalance of glutathione redox status (27) and increased products of lipid peroxidation (28), which damages cells via macromolecules and mitochondrial dysfunction, further harming various tissues including the liver (7,29). Release of ROS is a mechanism of LPS-induced hepatic injury, therefore reduction of ROS signaling relieves such damage (30). Studies have indicated that treatment with antioxidant and anti-inflammatory agents is beneficial in LPS-induced hepatic injury (31,32), and that taurine can reduce oxidative stress (33,34) and relieve tissue injuries by its antioxidative properties (35,36). The results of the present study indicated that administration of LPS resulted increased ALT and AST activities in serum, considered as markers of liver injury. Taurine pretreatment reduced the increases of ALT and AST, and decreased the concentration of MDA, a marker of lipid peroxidation; it also elevated the activity of SOD and the protein expression of antioxidant enzyme HO-1.

Inflammatory response serves an important role in various liver disorders. LPS initiates inflammation by recruiting neutrophils to the liver and subsequently stimulating the expression of inflammatory factors, including TNF- α , which provoke the release of ROS (37). The results of the present study demonstrated that LPS elevated the levels of TNF- α and IL-6 in serum and expression of COX-2 and NF- κ B protein. Taurine pretreatment reduced the expression of pro-inflammatory proteins including COX-2 and NF- κ B.

It is reported that taurine is converted into taurine chloramine *in vivo* and that this reduces the inflammatory response (38). Taurine increases its antioxidative effects by increasing the expression of HO-1 protein (39), which is reported to inhibit expression of COX-2 (40). COX-2 induces the production of prostaglandin, which is involved in inflammation and pain and results in cellular injury (41,42). HO-1, an inducible rate-limiting enzyme, catalyzes heme into equimolar amounts of carbon monoxide (CO), biliverdin and free iron. Induction of HO-1 may protect against oxidative stress-related cell and tissue injury (40,43). Biliverdin has been confirmed to be a potent antioxidant (44). CO, a catalytic product of HO-1, exerts antioxidative, anti-inflammatory and anti-apoptotic effects (45). Increasing evidence has confirmed that the HO/CO signaling exerts a vital role in regulation of anti-inflammation and cytoprotection (46-48).

NF- κ B is involved in LPS signaling. Activation of NF- κ B by LPS upregulates the expression of COX-2 (49). It is reported that the anti-inflammatory effect of CO is associated with its regulation on transcription factors including NF- κ B (50,51). A previous study demonstrated that CO alleviates LPS-induced inflammation by suppression of NF- κ B (48). The results suggested that taurine inhibited NF- κ B/COX-2 signaling via induction of HO-1. In addition, the mitogen-activated protein kinase (MAPK)/ERK pathway is implicated in LPS-induced inflammation (52) and is an upstream mediator of NF- κ B nuclear translocation (53,54). Another study demonstrated that reduced MAPK/ERK1/2 signaling downregulates NF- κ B in LPS-activated hepatocytes (54). Recent studies have indicated that increased levels of phosphorylated ERK and c-Jun N-terminal kinases promote COX-2 protein expression (55,56).

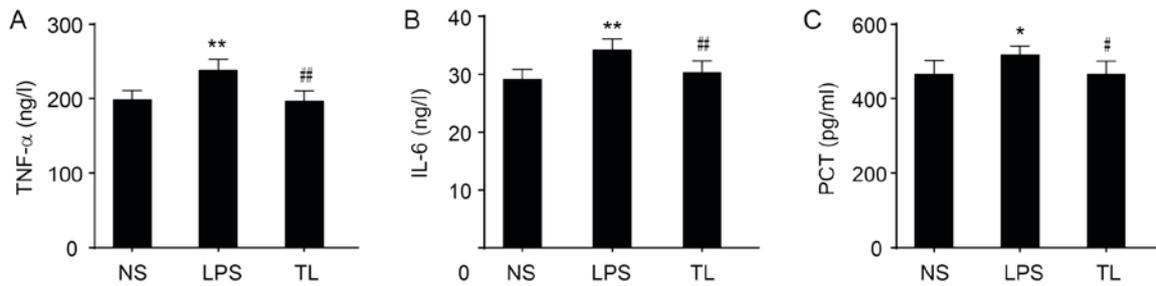


Figure 3. Effects of taurine on the levels of (A) IL-6, (B) TNF- α and (C) PCT. Data are presented as the mean \pm standard deviation (n=10). *P<0.05 vs. NS group, **P<0.01 vs. NS group, #P<0.05 vs. LPS group and ##P<0.01 vs. LPS group. IL-6, interleukin 6; TNF- α , tumor necrosis factor- α ; PCT, procalcitonin; NS, normal saline group; LPS, lipopolysaccharide control group; TL, taurine + LPS group.

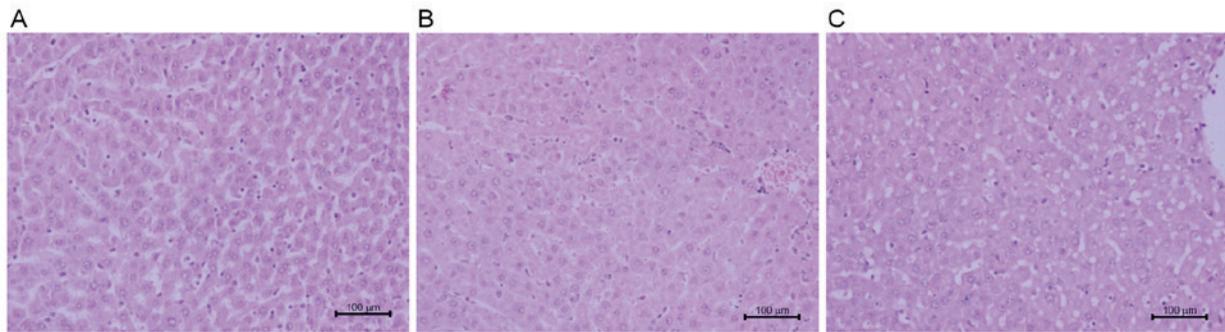


Figure 4. Photomicrographs of hematoxylin and eosin staining in the liver tissue of each group. (A) NS group, (B) LPS group and (C) TL group. Scale bar, 100 μ m. NS, normal saline group; LPS, lipopolysaccharide control group; TL, taurine + LPS group.

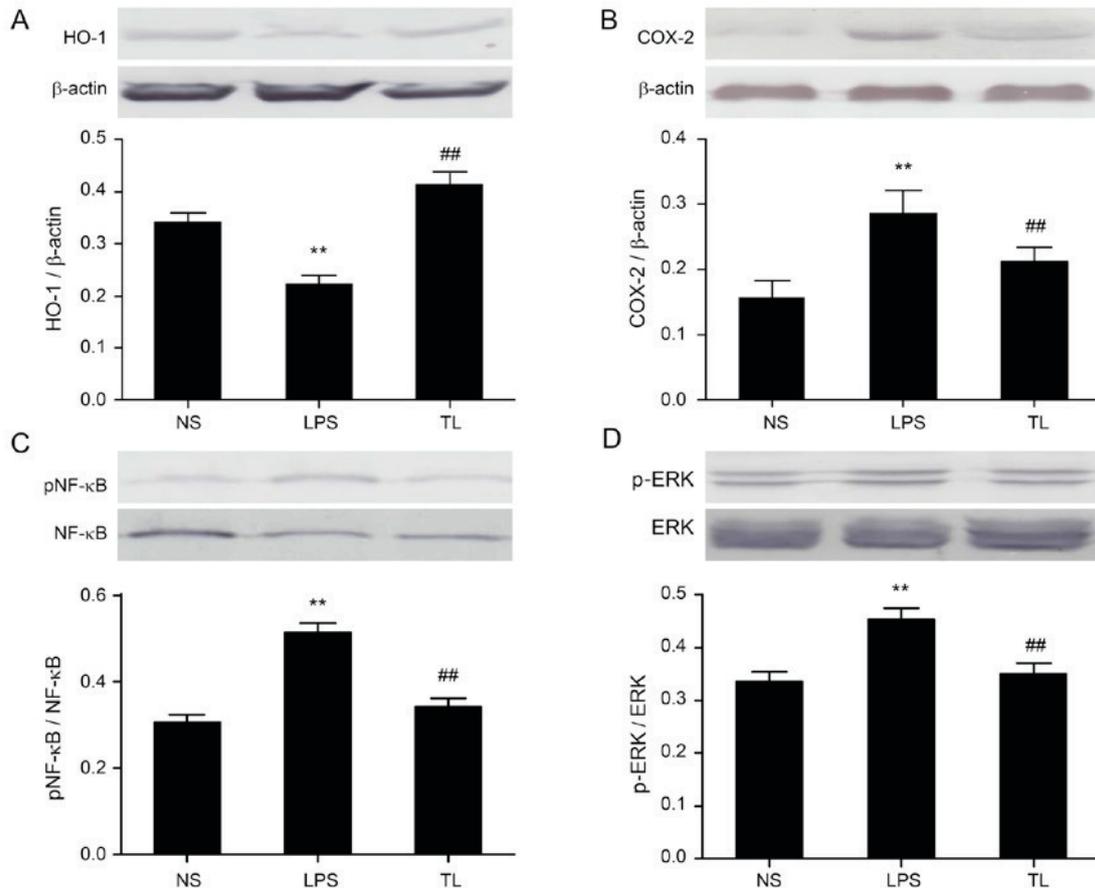


Figure 5. Effects of taurine on the expression levels of HO-1, COX-2, pNF- κ B and p-ERK protein. Representative western blot images and quantification of (A) HO-1, (B) COX-2, (C) pNF- κ B and (D) p-ERK. Data are presented as the mean \pm standard deviation. **P<0.01 vs. NS group and ##P<0.01 vs. TL group; n=6 per group. HO-1, heme oxygenase-1; COX-2, cyclooxygenase-2; NF- κ B, nuclear factor- κ B; ERK, extracellular signal-regulated kinase; p-, phosphorylated.

In conclusion, the results of the present study indicated that taurine pretreatment protected the liver against LPS-induced injury by increasing its antioxidation and anti-inflammation ability, which were associated with the increased expression of HO-1 protein and reduced expression levels of NF- κ B, COX-2 and p-ERK proteins. The findings suggested that taurine reduced NF- κ B/COX-2 signaling by activation of HO-1/CO.

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