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The effect of taurine on mesenteric blood flow and organ injury in sepsis

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Summary. Endotoxin decreases mesenteric blood flow and inflicts organ injury via free radicals. We investigated whether taurine, an endogenous antioxidant and vasodilator, could attenuate the deleterious effects of endotoxin in a mouse model of sepsis. Swiss albino mice were allocated into four groups and treated either with taurine (150 mg/kg, i.p. at 0^{th}, 8^{th}, 16^{th} h) or its solvent sterile saline (NaCl 0.9%, w/v) while *E. coli* endotoxin (20 mg/kg, i.p.) or its solvent saline were also given at 8^{th} h. At 24^{th} h the animals were anaesthetized and the mesenteric blood flow was measured by using perivascular ultrasonic Doppler-flowmeter. The animals were then exsanguinated, the spleen, liver, and kidneys were isolated for histopathological examination. Thiobarbituric acid-reacting substances (TBARS), glutathione, and myeloperoxidase activity were determined in the liver samples. Endotoxin significantly decreased the mesenteric blood flow and glutathione levels in liver while TBARS and myeloperoxidase activity were increased. However, taurine did not block the deleterious effects of endotoxin nor it did attenuate the histopathological injury. Therefore, we concluded that endotoxin-induced organ injury via free radicals is resistant to blockade by taurine.

Keywords: Endothelin – Taurine – Sepsis – Mesenteric ischemia – Doppler-flowmeter

1. Introduction

Sepsis is associated with oxidative stress (Tsai et al., 2000). Lipopolysaccharide (LPS) is known to enhance the formation of reactive oxygen species and lipid peroxidation products (Goode and Webster, 1993; Portoles et al., 1993; Novelli, 1997). During sepsis, there is overproduction of free oxygen radicals, while the natural scavenging mechanisms are weakened a process which lead to endothelial cell damage and multiorgan failure (Peralta et al., 1993). Previous work has shown that antioxidant therapy has the potential to protect against septic shock (Goode and Webster, 1993). On the other hand, LPS generates free radicals intracellulary through the ischemia-reperfusion syndrome secondary to the diminished blood flow (Portoles et al., 1993).

Septic shock is a systemic inflammatory response to an infection (Gullo et al., 2005) associated with systemic vasodilation, hyporesponsiveness to vasoconstrictors (Kavuklu et al., 2000), vasodilators (Guc et al., 1991) and hypoperfusion to vital organs that lead to multiple organ dysfunction (Parrillo, 1989; Bone, 1991). Particularly, diminished blood flow to the mesenteric vascular bed is related to multiple organ failure and exogenously applied endotoxin (ETX) reduces the mesenteric blood flow in experimental models (Baykal et al., 2000).

Taurine (2-aminoethane sulfonic acid) is a freely existing major intracellular amino acid that is normally present in most mammalian tissue (Chesney, 1985). A number of physiological functions have been attributed to taurine, including the osmoregulation, bile acid conjugation, cell proliferation, modulation of the central nervous system functions, viability and prevention of oxidant-induced injury in many tissues (Chesney, 1985; Huxtable, 1992), regulation of cardiovascular system and blood pressure (Trachtman et al., 1998). The beneficial effects of taurine as an antioxidant have been attributed to its ability to stabilize the biomembranes (Wright et al., 1986), to scavenge reactive oxygen species (Wright et al., 1985), and to reduce the production of malondialdehyde (Huxtable, 1992). Moreover, taurine protects tissues against attack by chlorinated oxidants, specifically hypochlorous acid (Wright et al., 1986; Trachtman et al., 1992) produced by the myeloperoxidase-hydrogen peroxide-chloride sys-

tem of monocyte and neutrophils. It is found in high concentrations in leukocytes, predominantly polymorphonuclear leukocytes and increases neutrophil phagocytic ability (Weiss, 1989).

On the other hand taurine is able to reduce contractile tone of rat aortic rings and consequently exerts powerful vasodilator effect in arteries contracted with either high potassium medium or noradrenaline (Ristori and Verdetti, 1991). Moreover, taurine reduces the basal tone of isolated vessels and plays a physiological role in the maintenance of vascular tone (Ristori and Verdetti, 1991) while sepsis causes blood flow to decrease into the mesenteric area due to vasoconstriction. Since taurine has a vasodilator effect and reduces free radicals, it could have beneficial effects in sepsis.

Thus, in the present study, we aimed to investigate the possible beneficial effects of taurine in sepsis produced by ETX with particular attention to the decrease in mesenteric blood flow, histopathological injury in target organs and reactive oxygen species generation in liver.

2. Materials and methods

2.1 Animals

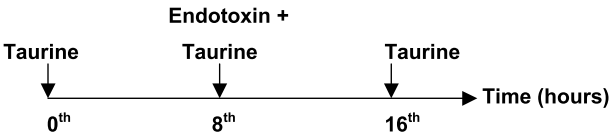
Swiss albino mice (25–35 g) were obtained from the Experimental Animals Breeding Unit of Refik Saydam Hygiene Center of The Turkish Republic Ministry of Health and housed in the Laboratory Animal Husbandry Facility of Hacettepe University Faculty of Medicine Department of Pharmacology until the experiments. All mice were acclimatized for two weeks prior to the experiments and kept under environmentally controlled conditions at $21 \pm 2\,^{\circ}C$ and 30–70% relative humidity with 12 h dark/12 h light illumination sequence (the lights were on between 07.00–19.00 h) with ad libitum access to tap water (drinking bottle) and standard pellet dairy chow (Dokuz Tug Yem Sanayii, Ankara, Turkey). The Guiding Principles in the Care and Use of Laboratory Animals together with The Recommendations from the Declaration of Helsinki were strictly adhered to during the execution of all the procedures described within this manuscript. This project was approved by the Institutional Experimental Animal Care and Use Ethics Committee of Hacettepe University (Approval Number: 2005/57-3) before the commencement of any intervention.

2.2 General procedures

Polymicrobial sepsis was induced in mice by ETX derived from *Escherichia coli* (lipopolysaccharide = LPS, O55:B5; 20 mg/kg, i.p.). After the ETX, the animals were placed in separate cages to recover from the interventions under the standard conditions of the Laboratory Animal Husbandry Facility of Hacettepe University Faculty of Medicine Department of Pharmacology.

2.3 Experimental protocol

Taurine (150 mg/kg, i.p.; in 1 ml) or non-pyrogenic sterile saline (NaCl 0.9%, w/v, dissolved in pyrogen-free distilled water; i.p., in 1 ml) was given at 0^{th}, 8^{th}, and 16^{th} h. *Escherichia coli* endotoxin or its solvent non-pyrogenic steril saline (in 1 ml) were given at 8^{th} h.



All drugs were prepared daily, dissolved in non-pyrogenic sterile saline and warmed to body temperature (approximately 37 °C) before the injections. Drug solutions were kept in dark containers until the injections in order to protect them from light-induced decomposition.

2.4 Surgical procedure and determination of blood flow

The mice were anaesthetized with chloralhydrate (400 mg/kg, i.p.) at 24^{th} h after ETX injection and then placed on a heat-insulated-cork-sheet-covered operating table. The animals were allowed to breathe room air spontaneously. Body temperatures of the mice were kept at $37.0 \pm 0.1\,^{\circ}C$ by a rectal thermistor probe-controlled incandescent lamp (100 W) placed approximately 30 cm above the animals.

A midline incision were made to the animal and a perivascular ultrasonic Doppler-flow probe, connected to a Transonic Small Animal Flowmeter System T106 (Transonic, Ithaca, New York, USA), was placed around the common mesenteric artery. The absolute blood flow values were measured in milliliters per minute for 15 min according to detailed guiding of our previous publication (Baykal et al., 2000). For standardization, these values were normalized for each mouse by dividing to the body weight of the individual animal and expressed as ml/min/kg body weight. The signals from the flowmeter were also recorded on a computer by using a MP35 Biopac data recording system (Goleta, CA, USA).

After the determination of the mesenteric blood flow for 15 min, the animals were exsanguinated by severing the common carotid artery and both kidneys were removed quickly together with the spleen and liver, placed on hydrophilic paper tissue in order to eliminate the remaining excess fluid. Approximately half of each liver was separated and stored at $-80\,^{\circ}C$ until the biochemical analyses while the rest of the organs were placed in formaldehyde fixation for conventional light microscopic examination. The whole procedure (beginning with the sacrification until the end of the tissue fixation) was completed within 2 min.

2.5 Histological examination

The right kidneys, spleen and half of the livers were fixed in 10% buffered formaldehyde and processed according to routine light microscopic tissue processing technique. 5 μm tissue sections stained with hematoxylen-eosin were examined and photographs were captured by Leica DM6000 microscope and image analyzing system.

2.6 Biochemical analyses

Thiobarbituric acid-reacting substances of lipid peroxidation, glutathione levels, and myeloperoxidase activities were determined in liver. Tissues were homogenized in 150 mM ice–cold potassium chloride (KCl) to make a 10% homogenate by using a glass Teflon homogenizer. All of the biochemical determinations were carried out on this homogenate. 2 ml of homogenate was immediately pipetted into a tube containing 2 ml of cold 8% (v/v) perchloric acid ($HClO_4$). The mixture was shaken vigorously and kept cold until centrifugation.

2.6.1 Determination of lipid peroxides

The levels of lipid peroxides in tissues, as an indicator of oxidative damage (stress), were determined by the method of Uchiama and Mihara (1977). 3 ml of 1% phosphoric acid (H_3PO_4) and 1 ml of thiobarbituric acid

solution were added to 0.5 ml of 10% tissue homogenate and pipetted into a tube. The mixture was heated in boiling water for 45 min. After cooling, the colored complex was extracted into 4 ml of *n*-butanol and the absorbance was measured at 532 nm ($\varepsilon = 1.56 \times 10^5/\mathrm{M/cm}$). The amount of lipid peroxides was calculated as thiobarbituric acid-reacting substance products of lipid peroxidation and expressed as nanomols per milligram of protein.

2.6.2 Determination of glutathione levels

Reduced glutathione, as an indicator of antioxidant capacity, was measured through total sulfhydryl groups by using Ellman Reagent (5,5′-dithio-bis 2-nitrobenzoic acid). Tissue homogenate was deproteinized as described above and neutralized by using 0.7 M K_3PO_4. The resulting precipitate was removed by centrifugation and the supernatant was used for glutathione determination as described earlier (Tietz, 1969). Glutathione levels were then calculated as millimoles per milligram of protein.

2.6.3 Determination of myeloperoxidases

Standard reaction mixture consisted of 500 µl detergent-containing buffer (160 mM potassium phosphate buffer, pH 5.4, 1% HETAP), 100 µl 3,3-5,5 Tetramethylbenzidine (TMB) (16 mM, dissolved in DMF (N, N-Dimethyl formamide), 50 µl sample homogenate and 300 µl water. The reaction was initiated by the addition of 50 µl H_2O_2 (diluted to 0.06% for tissue samples and 0.003% for leukocytes) at 37 °C. The rate of myeloperoxidases-catalyzed oxidation of TMB was followed by recording the increase of absorbance at 655 nm. Considering the initial and the linear phase of the reaction, we measured the absorbance change per minute and one enzyme unit was defined as the amount of enzyme producing one absorbance change per one minute under assay conditions. Enzyme activity, as an indicator of inflammation, was calculated as units per milligram of protein for tissue samples (Akbiyik et al., 2001).

2.6.4 Determination of protein levels

The biuret method was used for quantitative protein analysis of all samples where bovine serum albumine was used as a protein standard (Kingsley, 1942).

2.7 Statistical analyses

Statistical differences between mesenteric blood flows of groups were assessed by using two-way analysis of variance for repeated measures (Guc, 1992). Biochemical values were compared by using two-way ANOVA. All values were reported as the arithmetic mean ± standard error of the mean (S.E.M.) of number (n) of experiments. The differences were considered statistically significant when $P < 0.05$.

2.8 Drugs and reagents

Sodium chloride, hematoxylin (Merck, USA), chloralhydrate (Abbott, USA), lipopolysaccharide (*E.coli* endotoxin, serotype O55:B5, Sigma, USA), taurine, eosine (Sigma, USA), paraffin (Shandon, UK) and formaldehyde (Carlo Elba, Italy).

3. Results

3.1 The effect of taurine on mesenteric blood flow

Perivascular ultrasonic Doppler-flowmetric measurement indicated that ETX significantly reduced the mesenteric blood flow. But taurine treatment did not improve the blood flow (Fig. 1) and blood flow values of taurine group were not significantly different in ETX group. Interestingly, mesenteric blood flow curve of taurine-control group showed a decline in slope while it was stable at the beginning (Fig. 1).

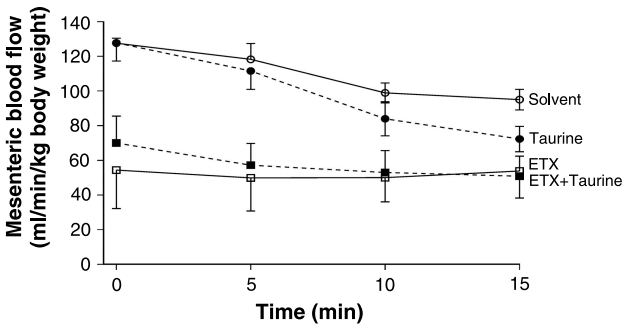


Fig. 1. Mesenteric arterial blood flow (ml/min per kg body weight) values of mice observed 24 h after endotoxin (ETX, 20 mg/kg, i.p.)-treatment which also received taurine (150 mg/kg at 0th, 8th, and 16th h, i.p.) or its solvent (saline, 1 ml/kg, i.p.). ETX or its solvent non-pyrogenic steril saline (in 1 ml) were given at 8th h. Values are mean ± standard error of the mean of number ($n = 5$–8) of experiments. Some error bars have been omitted for the sake of clarity. Two-way analysis of variance for repeated measures applied to "ENDOTOXIN (ETX = LPS)" vs. "SOLVENT (control)" curves indicated a significant difference between them ($P = 0.0086$). However, there was no significant difference between neither of the curves of "SOLVENT" vs. "TAURINE" nor "TAURINE" vs. "ETX + TAURINE" when pair-wise comparisons were performed by using two-way analysis of variance for repeated measures utilizing the "time" and "groups" as the two variables

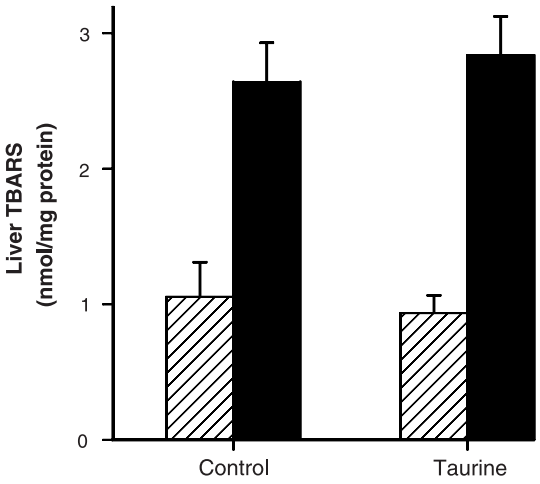


Fig. 2. The effect of taurine on liver thiobarbituric acid-reacting substances (TBARS) of lipid peroxidation in endotoxin (ETX = LPS, solid black columns) and in comparison to solvent (saline, hatched columns)-treated animals. Vertical bars indicate the standard error of the mean of number (n) of experiments. Two-way ANOVA applied to all four bars indicated that. The effect of ETX administration: $P < 0.0001$. The effect of taurine administration: not significant. Interaction between ETX and taurine: not significant

3.2 Biochemical analyses

Lipid peroxidation in liver, represented by the accumulation of thiobarbutiric acid-reacting substances, was significantly elevated by ETX (nmol/mg protein, control: 1.055 ± 0.255, $n = 6$; endotoxin: 2.644 ± 0.284, $n = 11$, $P < 0.0001$) but taurine has failed to reverse this increase (Fig. 2).

Liver glutathione levels, an indicator of the antioxidant capacity, were significantly decreased in ETX (Fig. 3) (mmol/mg protein, control: 0.045 ± 0.008, $n = 6$; ETX: 0.010 ± 0.001, $n = 12$; $P < 0.0001$ vs. control). Moreover, taurine did not elevate glutathione levels (Fig. 3).

Tissue myeloperoxidase activity, as an indicator of neutrophil accumulation in liver was also elevated by ETX, Taurine partly blocked this increase, although it was not significant (Fig. 4).

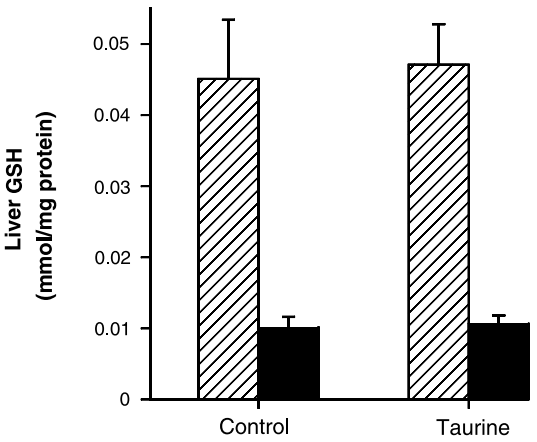


Fig. 3. The effect of taurine on liver glutathione (GSH) levels in endotoxin (ETX = LPS, solid black columns) and in comparison to solvent (saline, hatched columns)-treated animals. Vertical bars indicate the standard error of the mean of number (n) of experiments. Two-way ANOVA applied to all four bars indicated that: The effect of ETX administration: $P < 0.0001$. The effect of taurine administration: not significant. Interaction between ETX and taurine: not significant

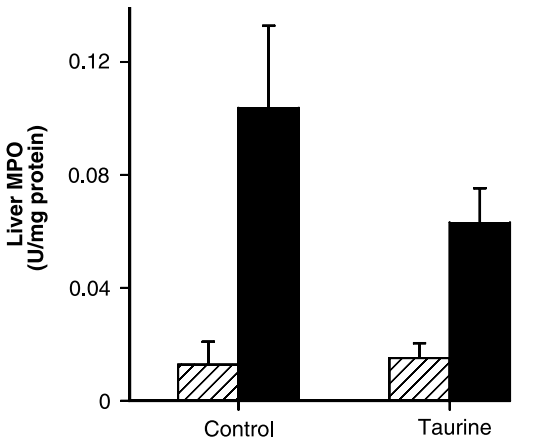


Fig. 4. The effect of taurine on liver myeloperoxidase (MPO) activity in endotoxin (ETX = LPS, solid black columns) and in comparison to solvent (saline, hatched columns)-treated animals. Vertical bars indicate the standard error of the mean of number (n) of experiments. Two-way ANOVA applied to all four bars indicated that: The effect of ETX administration: $P = 0.0023$. The effect of taurine administration: not significant. Interaction between ETX and taurine: not significant

3.3 Histopathological examination of liver, spleen and kidney

3.3.1 Liver

In all of the liver sections obtained from ETX group, hepatocytes showed ballooning degeneration and were swollen. Sinusoids were dilated and filled with blood as well as the central veins. Inflammatory cells were seen in the proximity of the central veins. In between the inflammatory cells hepatocytes were more degenerated (Fig. 5A). Taurine treatment has produced no significant histopathological alteration. Ballooning degeneration was also observed in all of the samples of this group like the sepsis group. Some of the hepatocytes were swollen and some were picnotic. Although the central veins were dilated, sinusoids between the hepatocytes were not visible because of the hydropic hepatocytes. In contrast to sepsis group inflammatory cells were not seen in the proximity of the central veins (Fig. 5D).

3.3.2 Spleen

Most striking histological changes were observed in the red pulp of the spleen in ETX group. Especially the venous sinuses were affected more with dilatation and stasis. There was increase in the number of giant cells also (Fig. 5B). Nevertheless, taurine treatment had no benefical effect. In all of the samples red pulp of the spleen was also affected severely. Venous sinuses were dilated with stasis. Many hemorrhagic foci were scattered all around the red pulp. Moreover, giant cells were observed in the red pulp as in the sepsis group (Fig. 5E).

3.3.3 Kidney

Some of the glomerules were affected with severe sclerosis whereas some of them had dilated capillaries with stasis in ETX group. Epithelial cell degeneration was prominent in the tubules and collecting tubules, being more severe in the proximal tubules. Proximal tubules had swollen and hydropic epithelial cells, but the cells of the collecting tubules were so degenerated that they

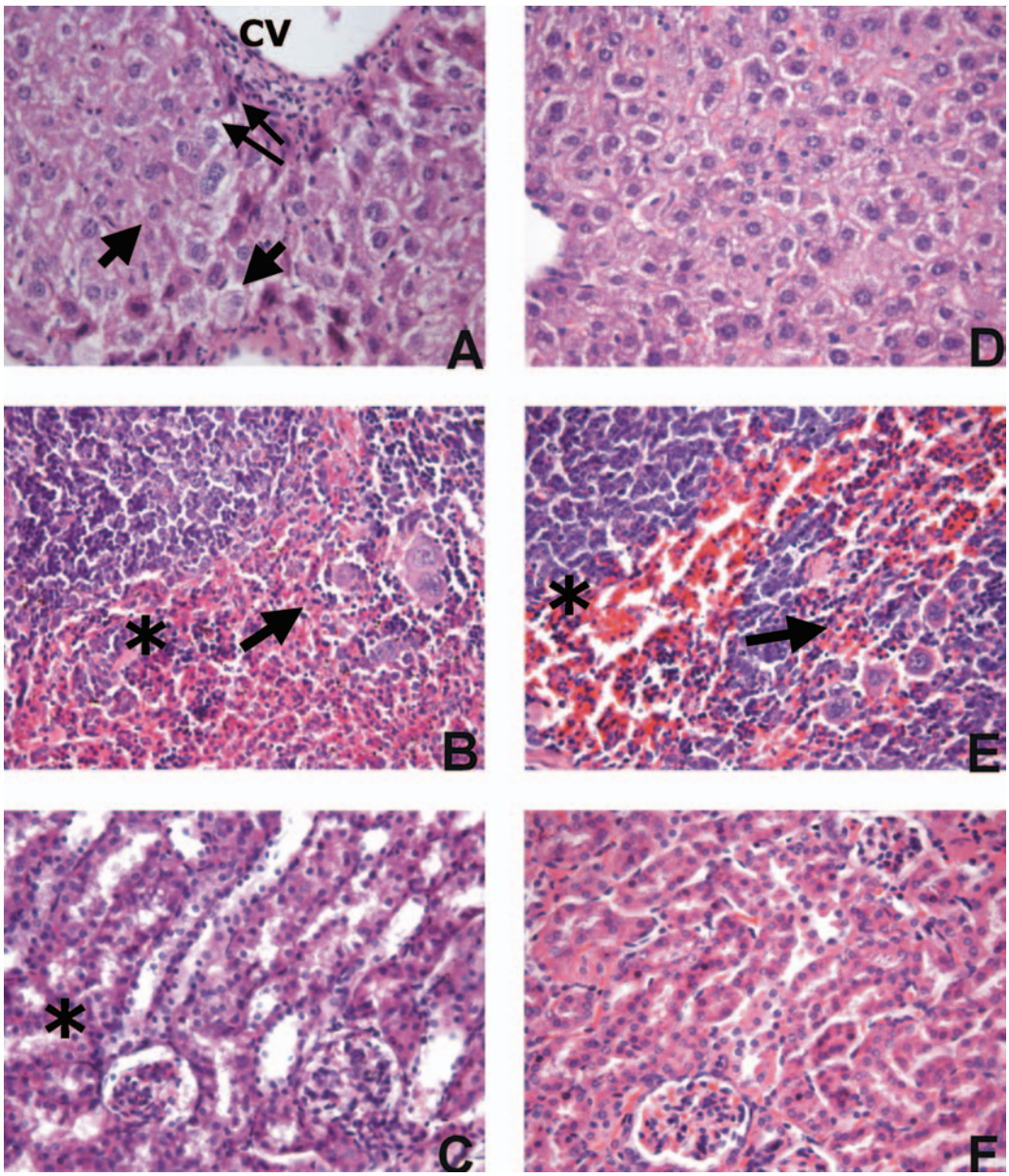


Fig. 5. The photographs on the left hand column depict the representative histological sections of liver (**A**), spleen (**B**), kidney (**C**) obtained from endotoxin (ETX 20 mg/kg, at 8th h, i.p.)-treated mice in comparison to those obtained from taurine-treated (150 mg/kg, at 0th, 8th and 16th h, i.p.) animals on the right-hand column (liver D, spleen E and kidney F). Hepatocytes with swollen cytoplasm (balloning degeneration) and inflammatory cells (*double arrows*) between more degenerated hepatocytes (*arrow*) were observed in the sepsis group (**A**) (*CV Central vein*). Inflammatory cells disappeared in the taurine group, but hepatocytes with swollen cytoplasm still persists (**D**). Taurine was not effectual on the spleen after sepsis. In both groups the red pulp (*) was affected severely with diffuse hemorrhage and many multinucleated giant cells (**B**, **E**) (*Arrow Giant cell*). Sclerotic changes in one of the glomerules (*) between proximal and collecting tubules with degenerated epithelial cells (**C**). Kidney tubules with almost normal structure prevented by taurine (**F**) Hematoxylen – Eosin X400 (For an interpretation of the reference to color in this figure, the reader is referred to the online version of this paper under www.springerlink.com)

were sloughed into the lumen. In the cortex and medulla interstitial blood vessels were dilated with stasis (Fig. 5C). As in the sepsis group, necrotic changes were observed in the glomerules of taurine treated group, except two cases with normal glomerules. In these two cases, the histological microarchitecture of the tubules was also normal. But, cells of the remaining proximal tubules were swollen and hydropic, whereas collecting tubules were dilated. On the other hand, epithelial degeneration was not so prominent in contrary to sepsis group (Fig. 5F).

4. Discussion

In the present investigation, we aimed to examine the effects of taurine on prevention of organ damage in mouse model of sepsis produced by ETX-administration. However taurine partly show protective effect on organ damage only in the kidney without improving the mesenteric blood flow and lipid peroxidation probably by stabilizing the cell membrane and reducing tissue hypoxia. We previously demonstrated that taurine reduced tissue lactate level which is an indicator of hypoxia (Erdem et al., 2000). Taurine might partly increases the endurance of cells by stabilizing cell membrane and lowering tissue hypoxia caused by reduced mesenteric blood flow.

Taurine is the major intracellular free sulfur-containing amino acid, and makes up over half the total amino acid pool in leukocytes (Fukuda et al., 1982). It has been shown that taurine protects the endothelium, increases polymorphonuclear activation, is a membrane stabilizer, and osmoregulator, participitates in antioxidant reactions, play a physiological role in the maintenance of vascular tone, exerts a vasodilator effect (Ristori and Verdetti, 1991; Huxtable, 1992; Watson et al., 1994). According the literature, it is known that, trauma, critical illness, surgery depletes taurine levels in human (Vente et al., 1989; Paauw and Davis, 1990; Gray et al., 1994). We, therefore, hypothesized that pre- and post-treatment with taurine would reduce the severity of organ injury in mice models of sepsis produced by ETX-administration.

Endotoxin is a product of the cell walls of Gram-negative bacteria that causes septic shock (Saluk-Juszczak and Wachowicz, 2005). LPS is known to enhance the formation of reactive oxygen species and lipid peroxidation products such as superoxide anions and peroxides and their secondary product, MDA and these molecules play an important role in the pathogenesis of sepsis and its complications (Ben-Saul et al., 2001; Bian and Murad, 2001; Koksal et al., 2004). Sepsis causes neutrophil-dependent oxidative tissue damage by increased lipid peroxidation and decreased glutathione levels (Sener et al., 2005). Also it has been shown that inflammatory cells such as neutrophils, macrophages or monocytes are activated during the sepsis and activated neutrophils secrete enzymes such as myeloperoxidase and liberate free oxygen radicals (Iseri et al., 2005) which increase the recruitment of neutrophils into the injured tissue (Zimmerman et al., 1990). Additionally, oxidative stress mediated by free oxygen radicals the overproduction of nitric oxide by endothelial and inducible isoforms of nitric oxide synthase due to ETX challenge further enhance the organ damage (Yilmaz et al., 2001). In the present study, we observed that ETX cause an increase in thiobarbutiric acid reacting substances and myeloperoxidase activity, and decrease in glutathione level which were taken as the indicators of lipid peroxidation, the extent neutrophil accumulation and the amount of antioxidant capacity, respectively. All of the biochemical results observed in the present study are similar with previous reports that ETX injection augments the formation of reactive oxygen species and increases the lipid production in liver (Portoles et al., 1993; Iseri et al., 2005). However, taurine had no effect on the lipid peroxidation and glutathione levels. Nevertheless, it has some beneficial effect on myeloperoxidase activity, although it was not significant. Egan et al. (2001) reported that taurine reduced pulmonary myeloperoxidase activity on endotoxin-induced acute lung injury in sheep. Treatment with taurine may have potential benefits to decrease neutrophil sequestration and tissue injury without altering the blood flow or antioxidant activity.

On the other hand, some vasoconstrictor mechanisms which include endothelin(s) release are also activated in response to endotoxin (Iskit et al., 1999; Kavuklu et al., 2000). This mechanism may help maintain the blood pressure and organ perfusion that are beneficial during the initial phase of septic shock, while excessive rises in plasma levels of endothelin for longer periods stimulate profound vasoconstriction in the mesenteric vascular bed which leads to organ damage (Iskit et al., 1999). Also, taurine exerts a vasorelaxant action which is neither depended on endothelium, nor mediated by adrenoceptors or muscarinic cholinoceptors (Ristori and Verdetti, 1991). Other investigators have shown that the vascular effect of chronic taurine treatment is partly dependent on the endothelium (Abebe and Mozaffari, 2000) and also taurine depletion alters the vascular reactivity in rats (Abebe and Mozaffari, 2003). Moreover, taurine has the direct inhibitory effect on norepinephrine-induced vascular contraction of the mesenteric artery of stroke-prone spontaneously hypertensive rats (Li et al., 1996). In the present study, we observed that ETX treatment reduced the mesenteric blood flow while taurine did not block this decrease. However, pretreatment with taurine significantly lessened the heamodynamic changes associated with endotoxin induced lung injury (Egan et al., 2001). Although our taurine results seem to disagree with these reports (Li et al., 1996; Egan et al., 2001; Abebe and Mozaffari, 2003), it may be related to species differences (rat and sheep vs. mice) or due to the technique used to measure mesenteric blood flow. In this study we monitored in vivo, but the other studies were done in vitro.

Knowledge on taurine indicates that taurine, has an antioxidant effect that scavenges oxygen free radicals and reduces lipid peroxidation which is increased in septic model. Furthermore, taurine plays a physiological role in the maintenance of vascular tone while sepsis causes blood flow to decrease into the mesenteric area due to vasoconstriction. Thus, we hypothesize that taurine may be beneficial in sepsis. But, we observe that there was almost no protective role of taurine on organ injury and lipid peroxidation with regard to the biochemical and histopathological results of the present study. Our findings are similar to the results of Niessen et al. (1998) that taurine had no beneficial effect on oxygen free radical production after haemorrhagic shock in rats. Also there are some studies showing the ineffectiveness of different antioxidant agents (including powerful *N*-acetylcysteine) in human and animal studies in sepsis (Broner et al., 1989; Spies et al., 1994).

During sepsis, severe sepsis, or septic shock, shunting of the systemic blood flow to peripheral tissues occurs (i.e. mesenteric blood is not perfused) resulting in increased venous admixture with a definable increased PvO_2 (Spronk et al., 2004). Although it becomes relevant to add a second definable outcome that stress the lack of response of taurine in increasing mesenteric blood flow, such the direct measurement of venous admixture, our current data strongly suggest that organ damage in septic states is expected to directly correlate with the scale of vasoconstriction. Preventing the organ injury is difficult without increasing the blood flow to the mesenteric circulation, thus preventing the ischemia. Therefore, increasing blood flow to mesenteric area appears to be the main exploitation for the prevention of organ injury, treatment of sepsis and endotoxin-induced organ injury via free radicals which is resistant to blockade by taurine. However, there are still some points that remain to be clarified by adding new series of experiments that confirm the reason of lack of the therapeutical benefit of taurine in the endotoxin-induced hypo-reactivity model in mouse.

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