

Protective effects of taurine against inflammation, apoptosis, and oxidative stress in brain injury

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Abstract. The protective effect of taurine against inflammation, apoptosis and oxidative stress in traumatic brain injury was investigated in the present study. Taurine is a non-proteogenic and essential amino acid in animals. It plays a critical nutritional role in brain cell growth, differentiation, and development. Taurine is involved in regeneration and neuroprotection in the injured nervous system, and is an effective antioxidant against lead-, cadmium-, and exercise-induced oxidative stress. Astrocytes and neuron cells were co-cultured and cells were treated with different concentrations of taurine (100, 200 and 300 mg/l) for 72 h, and the levels of reactive oxygen species, malondialdehyde, reduced glutathione, glutathione peroxidase, superoxide dismutase, catalase, acetylcholinesterase, tumor necrosis factor- α , interleukin-6, caspase-3, p53, B-cell lymphoma 2 and Bcl-2-associated X protein were determined. These inflammatory, apoptotic, and oxidative stress markers were substantially increased in injured cells, and returned to normal levels following taurine supplementation. Thus, taurine supplementation may be effective against oxidative stress, apoptosis, and inflammation in injured brain cells.

Introduction

Taurine is a non-proteogenic and essential amino acid in animals (1), and is known to play a critical nutritional role in brain cell growth, differentiation, and development (2). Huxtable (3) have reported on the functional role of taurine in the central nervous system, as well as its functions in cardiovascular and skeletal muscle. Rak *et al* (4) demonstrated that taurine plays a key role in regeneration and neuroprotection in the injured nervous system. Taurine is an effective antioxidant against lead-, cadmium-, and exercise-induced oxidative stress (5), and is known to reduce the secretion of lipids and

apolipoprotein B100 in liver cancer cells (6). Taurine is also involved in neurotransmission, detoxification, osmoregulation, calcium homeostasis, obesity prevention, excitotoxicity, osmotic shock recovery, and prevention of seizures (7-13).

Traumatic brain injury (TBI) leads to cognitive deficits, high mortality, and impaired movement (14). The most common cause of TBI is external force to the brain, and it can be classified as closed or penetrating head injury (15). Ischemia, oxidative stress, apoptosis, inflammation, excitotoxicity, and vascular and neuronal damage may also cause TBI (16,17). Lotocki *et al* (18) reported that inflammation is a well-known critical event in TBI, which may be mediated by the secretion of cytokines and activation of glial cells. Taurine supplementation may substantially reduce inflammatory cytokines, such as tumor necrosis factor (TNF)- α , interleukin (IL)-6, and IL-1 β , in spinal cord injury (19). Heidari *et al* (20) reported a protective effect of taurine against acute and chronic liver injuries. Recently, Wang *et al* (2) investigated the protective role of taurine against TBI. In the present study, we investigated the therapeutic effect of taurine on levels of ROS, malondialdehyde (MDA), reduced glutathione (GSH), glutathione peroxidase (Gpx), superoxide dismutase (SOD), catalase, acetylcholinesterase (AChE), TNF- α , IL-6, caspase-3, p53, bcl-2 and bax in injured brain cells.

Materials and methods

Animals. Twenty-four male albino Wistar strain neonatal rats were obtained from The Second Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China). The rats weighed 5-10 g and were allowed free access to water and food with a 12-h light and dark cycle. Rats were sacrificed by decapitation following intraperitoneal administration of ketamine hydrochloride (80 mg/kg) and xylazine (10 mg/kg). All experiments involving rats were monitored and approved by the ethics committee of The Second Affiliated Hospital of Xi'an Jiaotong University (Ref no. 2014/2Tx1221).

Cell culture. Cortical tissues were isolated from embryonic day 15 rats and dissociated. Separated cells were cultured at a density of 1.5×10^3 cells/ml on existing astrocyte cell cultures. Co-cultures of astrocytes and neuron cells were prepared as previously described (21). The co-culture was supplemented with standard growth medium containing 10% fetal bovine serum and Dulbecco's modified Eagle's medium.

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Experimental traumatic brain cell injury model. Experimental traumatic brain cell injury was induced according to Katano *et al.* (22). Traumatic model cells were supplemented with G5 (2%) for 12 h before the induction of injury. The mechanical injury was induced using a standard scratch method (23), and standard scratches were made in 6-well plates. Cells were supplemented with standard growth medium. After 24 h, cell survival was evaluated as lactate dehydrogenase activity (ab102526; Abcam, Cambridge, UK).

Taurine treatment and sample collection. Cells were treated with 100, 200, or 300 mg/l of taurine (ab141063; Abcam) for 72 h. Following treatment, the medium was removed carefully and the cells were washed with phosphate buffered saline. The cells were collected, centrifuged, and stored at -80°C .

Oxidative markers. ROS level was measured by the incubation of cells with dichloro-dihydro-fluorescein diacetate (DCFH-DA) for 30 min, and fluorescence was measured under a fluorescence plate reader (24). The MDA content in the cell supernatant was determined by measuring thiobarbituric acid reactive species (TBARS). Briefly, the reaction tube contained 0.1 ml of cell culture supernatant, thiobarbituric acid (1.5 ml), 0.2 ml of sodium dodecyl sulfate (SDS), and acetic acid (1.5 ml). The resultant upper layer product was measured at 534 nm (24). GSH levels were determined based on Ellman's reaction. The absorbance was measured at 412 nm (24). Gpx activity was measured by adding 0.2 ml of Tris-HCl buffer, 0.2 ml of GSH, 0.1 ml of H_2O_2 , 0.2 ml of homogenate, and sodium azide (0.1 ml) to the reaction tube. The reaction tube was centrifuged for 10 min at $3,000 \times g$. Then, cell culture supernatant (0.2 ml) and Ellman's reagent (0.1 ml) were added to the reaction tube, and the final absorbance was measured at 340 nm (25).

SOD activity was determined by adding cell culture supernatant (0.1 ml), nitro blue tetrazolium (0.3 ml), NADH (0.2 ml) and sodium phosphate buffer (1.2 ml). The final absorbance was measured at 560 nm (25). Catalase activity was determined by adding phosphate buffer (500 μl), cell culture supernatant (500 μl) and H_2O_2 (500 μl). Then, TiOSO_4 (500 μl) was added to the reaction tube, and the final absorbance was measured at 420 nm (25). AChE activity was determined by the addition of acetylcholine (0.02 ml), cell culture supernatant (0.02 ml), DTNB (0.1 ml) and phosphate buffer (3 ml) into the reaction tube. The final absorbance was measured at 410 nm (26).

Inflammatory markers. TNF- α and IL-6 levels were determined in the cell culture were determined by enzyme-linked immunosorbent assay (RAB0141-1KT, Mouse ELISA kit; Sigma-Aldrich China, Inc., Shanghai, China) (27-29).

Apoptosis markers. For the reverse transcription-quantitative polymerase chain reaction (RT-qPCR) assay, RNA was isolated from the cells and converted into cDNA using oligo (dT) primers. Then, qPCR was used to quantify the mRNA expression with primers specific for caspase-3, p53, bcl-2 and bax (Table I). Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as a qPCR internal control. The $2^{-\Delta\Delta\text{Ct}}$ method was used to calculate the relative ratios of expression (30). Caspase-3 protein expression was determined by immunofluorescence staining according to Lobos *et al.* (31)

and images were taken under fluorescence microscope (IX73 Inverted Microscope; Olympus Corporation, Tokyo, Japan).

Statistical analysis. Values are given as mean with standard deviations. Differences between the control and taurine groups were evaluated using the unpaired Student's t-test. One-way ANOVA was applied for statistical analysis of data and post hoc Tukey's test was used for multiple comparisons. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Effect of taurine on oxidative markers. The protective effect of taurine against inflammation, apoptosis, and oxidative stress in TBI was investigated in this study. Intracellular ROS levels were substantially increased to 234.52 relative fluorescence units (RFU) in injured brain cells. However, taurine supplementation significantly reduced ROS levels to 191.1 (100 mg/l), 135.24 (200 mg/l), and 44.72 RFU (300 mg/l) in injured brain cells ($P < 0.05$; Fig. 1). Lipid peroxidation was substantially increased to 155.32 nmol/g in injured brain cells. Taurine supplementation significantly reduced lipid peroxidation to 131.87 (100 mg/l), 94.61 (200 mg/l), and 47.3 nmol/g (300 mg/l) in injured brain cells ($P < 0.05$; Fig. 2). GSH content was substantially reduced to 29.25 mg/g in injured brain cells, while taurine supplementation significantly increased GSH content to 44.46 (100 mg/l), 62.63 (200 mg/l), and 83.56 mg/g (300 mg/l) in injured brain cells ($P < 0.05$; Fig. 2).

SOD activity was substantially reduced to 2.7 U/mg in injured brain cells. Taurine supplementation significantly increased SOD activity to 3.3 (100 mg/l), 4.5 (200 mg/l), and 5.1 U/mg (300 mg/l) in injured brain cells ($P < 0.05$; Fig. 3). Catalase activity was substantially reduced to 4.7 U/g in injured brain cells. Taurine supplementation significantly increased catalase activity to 6.2 (100 mg/l), 8.9 (200 mg/l), and 10.6 U/g (300 mg/l) in injured brain cells ($P < 0.05$; Fig. 3). Gpx activity was substantially reduced to 0.34 mg/protein in injured brain cells. Taurine supplementation significantly increased Gpx activity to 0.49 (100 mg/l), 0.62 (200 mg/l), and 0.84 mg/protein (300 mg/l) in injured brain cells ($P < 0.05$; Fig. 4). AChE activity was substantially reduced to 4.1 $\mu\text{mol}/\text{min}/\text{mg}$ of protein in injured brain cells. Taurine supplementation significantly increased AChE activity to 6.2 (100 mg/l), 8.4 (200 mg/l), and 10.9 $\mu\text{mol}/\text{min}/\text{mg}$ of protein (300 mg/l) in injured brain cells ($P < 0.05$; Fig. 4).

Effect of taurine on inflammatory markers. TNF- α and IL-6 levels were substantially reduced to 437.12 and 301.5 pg/mg of protein, respectively, in injured brain cells. Following taurine treatment, TNF- α levels were decreased [362.11 (100 mg/l), 287.45 (200 mg/l), and 127.25 pg/mg of protein (300 mg/l)], while IL-6 levels were increased [245.6 (100 mg/l), 186.5 (200 mg/l), and 87.5 pg/mg of protein (300 mg/l)] in injured brain cells ($P < 0.05$; Fig. 5).

Effect of taurine on apoptosis markers. Taurine supplementation significantly reduced p53, caspase-3, and bax mRNA expression and increased bcl-2 mRNA expression in injured brain cells ($P < 0.05$; Fig. 6). Protein expression of caspase-3

Table I. List of primers used in RT-qPCR for mRNA expression of p53, caspase-3, bax and Bcl-2.

Gene name	Sense primer	Anti-sense primer
p53	5'-TAACAGTTCCTGCATGGGCGGC-3'	5'-AGGACAGGCACAAACACGCACC-3'
Caspase-3	5'-TTAATAAAGGTATCCATGGAGAACACT-3'	5'-TTAGTGATAAAAATAGAGTTCTTTTGTGAG-3'
Bax	5'-TGGAGCTGCAGAGGATGATTG-3'	5'-GAAGTTGCCGTCAGAAAACATG-3'
GAPDH	5'-TCCCTCAAGATTGTCAGCAA-3'	5'-AGATCCACAACGGATACATT-3'
Bcl-2	5'-CACCCCTGGCATCTTCTCCTT-3'	5'-AGCGTCTTCAGAGACAGCCAG-3'

Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; RT-qPCR, reverse transcription-quantitative polymerase chain reaction.

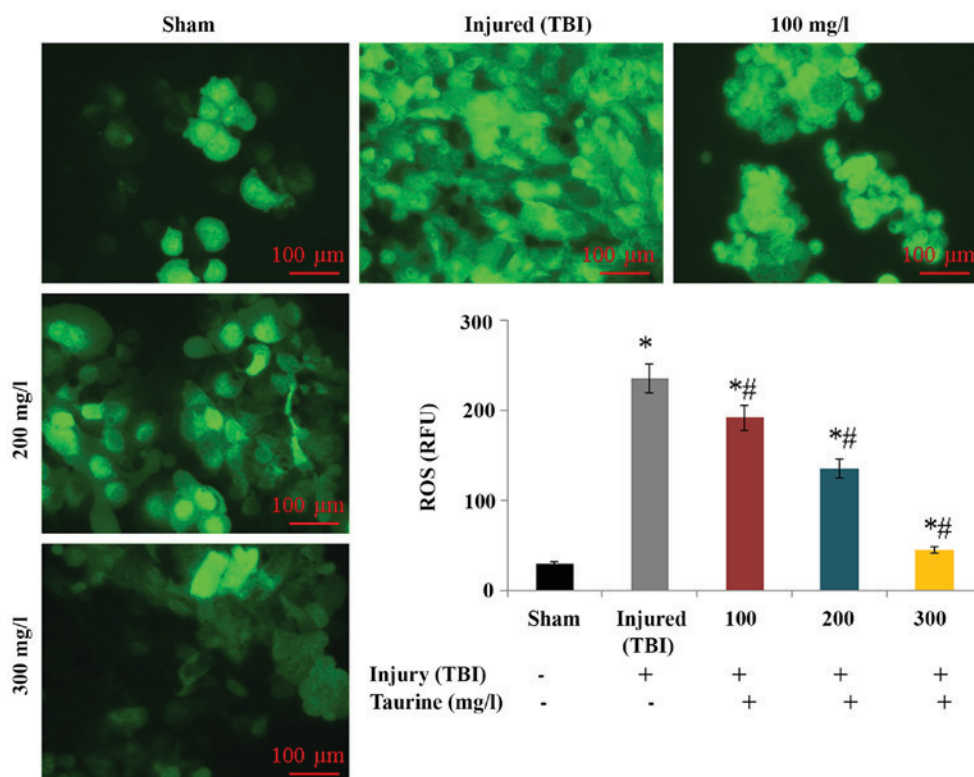


Figure 1. Effect of taurine supplementation on intracellular reactive oxygen species in injured brain cells. Data are expressed as mean \pm standard deviation. * $P < 0.05$ vs. sham and # $P < 0.05$ vs. injured (TBI). Magnification, $\times 40$. The scale bar is $100 \mu\text{m}$. TBI, traumatic brain injury.

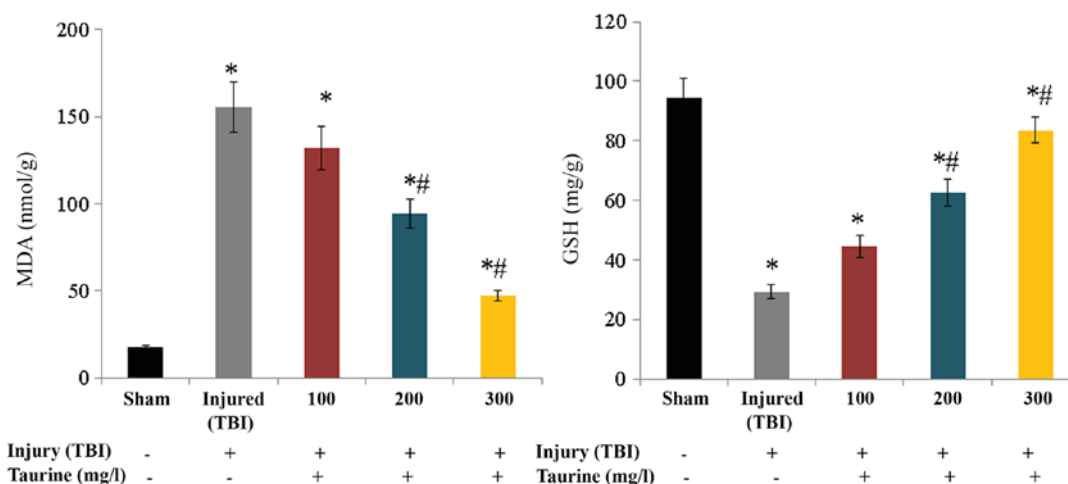


Figure 2. Effect of taurine supplementation on lipid peroxidation and reduced GSH levels in injured brain cells. Data are expressed as mean \pm standard deviation. * $P < 0.05$ vs. sham and # $P < 0.05$ vs. injured (TBI). TBI, traumatic brain injury; MDA, malondialdehyde; GSH, glutathione.

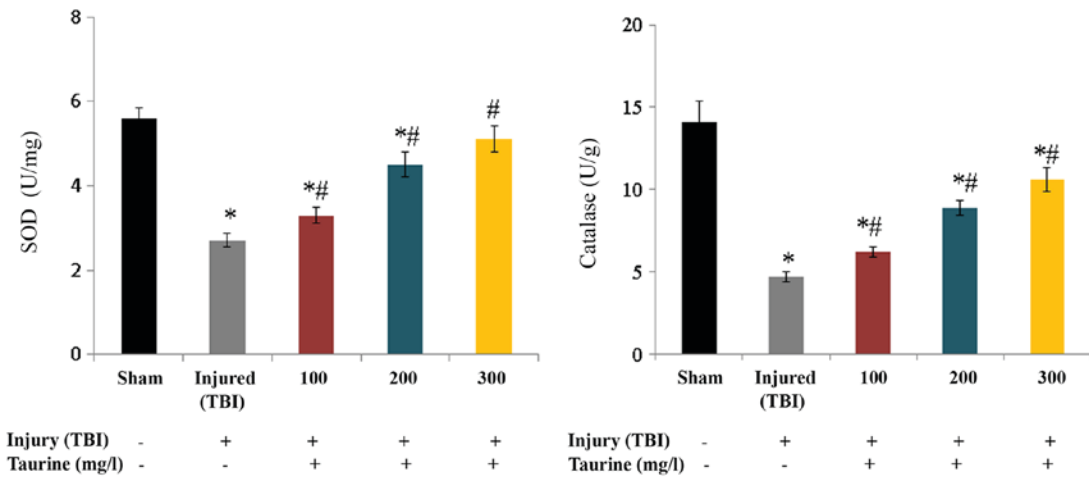


Figure 3. Effect of taurine supplementation on SOD and catalase activity in injured brain cells. Data are expressed as mean ± standard deviation. *P<0.05 vs. sham and #P<0.05 vs. injured (TBI). TBI, traumatic brain injury; SOD, superoxide dismutase.

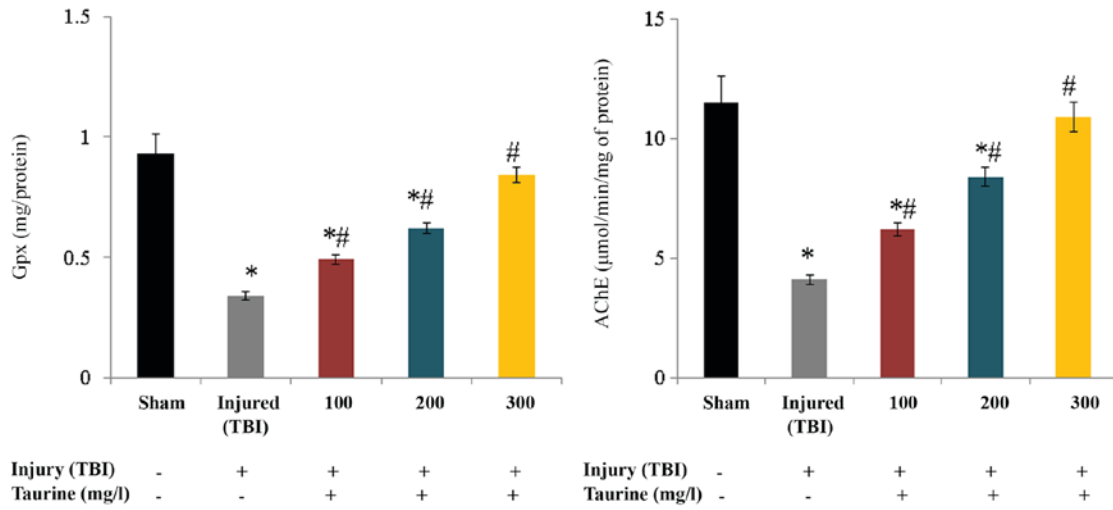


Figure 4. Effect of taurine supplementation on Gpx and AChE activity in injured brain cells. Data are expressed as mean ± standard deviation. *P<0.05 vs. sham and #P<0.05 vs. injured (TBI). TBI, traumatic brain injury; Gpx, glutathione peroxidase; AChE, acetylcholinesterase.

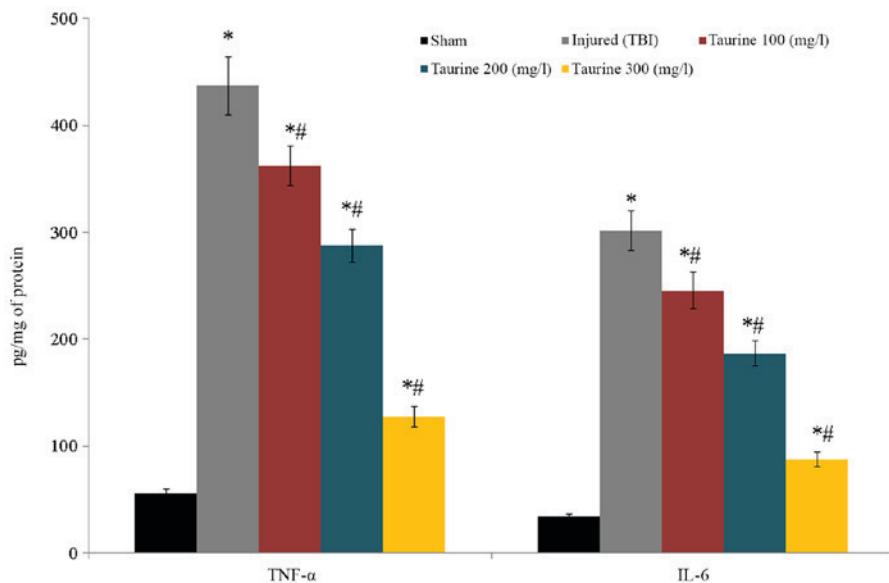


Figure 5. Effect of taurine supplementation on TNF-α and IL-6 levels in injured brain cells. Data are expressed as mean ± standard deviation. *P<0.05 vs. sham and #P<0.05 vs. injured (TBI). TBI, traumatic brain injury; TNF, tumor necrosis factor; IL, interleukin.

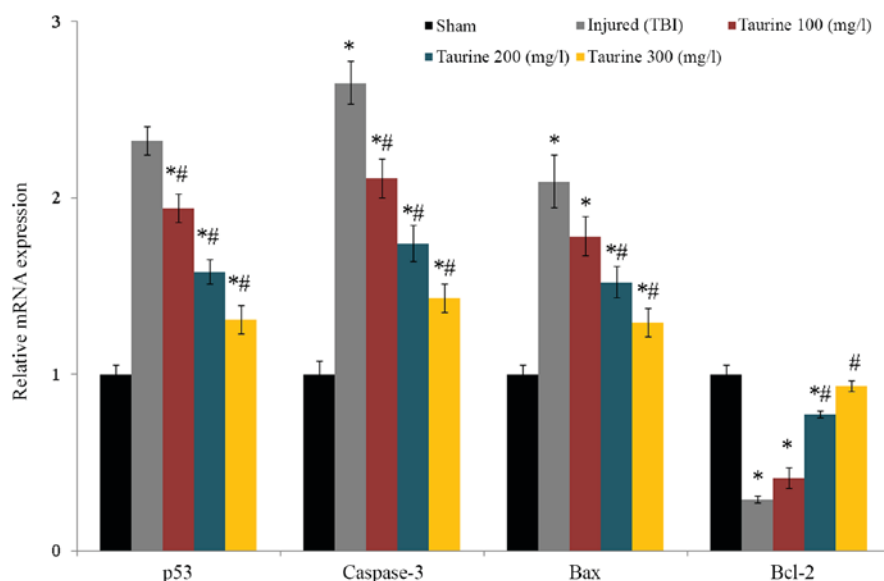


Figure 6. Effect of taurine supplementation on mRNA expression of p53, caspase-3, bax, and Bcl-2 in injured brain cells. Data are expressed as mean \pm standard deviation. * P <0.05 vs. sham and # P <0.05 vs. injured (TBI). TBI, traumatic brain injury; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2.

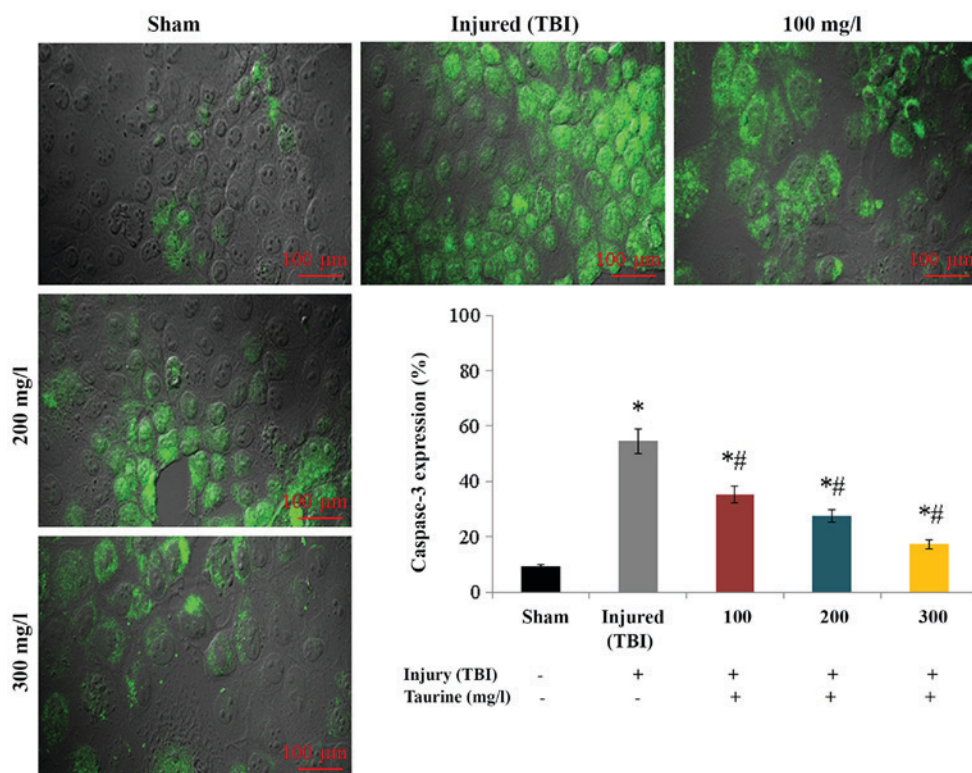


Figure 7. Effect of taurine supplementation on protein expression of caspase-3 in injured brain cells. Data are expressed as mean \pm standard deviation. * P <0.05 vs. sham and # P <0.05 vs. injured (TBI). Magnification, x40. The scale bar is 100 μ m. TBI, traumatic brain injury

increased to 54.51% in injured brain cells compared to normal brain cells. Taurine supplementation substantially reduced caspase-3 protein expression to 35.31 (100 mg/l), 27.48 (200 mg/l), and 17.3% (300 mg/l) (P <0.05; Fig. 7).

Discussion

This study investigated the protective effect of taurine against inflammation, apoptosis, and oxidative stress in TBI.

Taurine supplementation has been shown to substantially reduce infarct volume, brain swelling, cell death, and neurological deficits in a stroke-induced rat model (32). Taurine also significantly reduced apoptosis in cardiomyocytes of rats (33). Sun *et al* (34) also reported a protective effect of taurine against head injury. Several researchers have associated mitochondrial dysfunction with increased ROS and superoxide production, glutathione oxidation, and reduced antioxidant enzymes (2).

Taurine increases antioxidant activity by reducing superoxide production, which leads to improved mitochondrial function (35). Taurine also plays a crucial role in protein synthesis in mitochondria, and increases electron transport chain (ETC) activity (36). Our experimental results indicate that taurine increases antioxidant levels through increased mitochondrial ETC activity in TBI.

Mitochondrial dysfunction leads to increased production of oxidants, which leads to neuronal apoptosis and necrosis. Mitochondrial respiratory chains present on the inner mitochondrial membrane contain four transmembrane protein complexes. Chen and Chan (37) observed energy metabolism dysfunction associated with pathological changes in mitochondria following TBI. Several researchers have found that respiratory enzyme levels were decreased following traumatic and ischemic brain injury (38,39). Zhu *et al* (40) have illustrated the incidence of gastrointestinal dysfunction in TBI. Mitochondrial dysfunction can increase the production of oxidants, which play a crucial role in apoptosis and necrosis of neurons. Proapoptotic markers, such as bcl-2, increase in response to increased oxidants produced in brain injury. Apoptosis is induced through increased oxidants and misfolded proteins (41). Increased production of reactive oxygen species (ROS) and superoxide, glutathione oxidation, and reduced antioxidant enzymes have been associated with mitochondrial dysfunction (2,42-45). Vlodaysky *et al* (46) postulated that post-traumatic cytotoxic edema is associated with mitochondrial dysfunction. Sun *et al* (47,48) found that taurine increases respiratory chain complex activity and mitochondrial-mediated apoptosis and necrosis, and reduces free radical and oxidative stress.

The proapoptotic marker bcl-2 has been shown to increase following brain injury in response to increased oxidants, and apoptosis has been shown to be induced due to increased levels of oxidants and misfolded proteins. In this study, we investigated the expression of various anti-apoptotic markers including p53, caspase-3, and bax. Taurine supplementation substantially reduced expression of these markers *in vitro*. Several studies have reported that taurine is effective against calcium overload and oxidative stress (41). Lotocki *et al* (18) indicated that inflammation is a well-known critical event in TBI, and inflammation may be induced by the secretion of cytokines and activation of glial cells. Taurine supplementation has been shown to reduce inflammatory cytokines such as TNF- α , IL-6, IL-1 α , and IL-1 β in spinal cord injury and TBI (48). In this study, taurine significantly reduced TNF- α and IL-6 levels.

Taurine supplementation was found to be effective against oxidative stress, apoptosis, and inflammation in injured brain cells.

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Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XN, SZ, HL and SL were involved in the experimental design, data acquisition, data analysis and interpretation, and manuscript preparation. XN performed the experiments and SZ performed the review of the literature. HL conducted data analysis and SL was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All experiments involving rats were monitored and approved by the Ethics Committee of The Second Affiliated Hospital of Xi'an Jiaotong University (reference no. 2014/2Tx1221).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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