



Hepatoprotective Effects of Taurine Against Cadmium-Induced Liver Injury in Female Mice

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Abstract

Cadmium (Cd), a heavy metal contaminant, seriously threatens human and animal health. Taurine (Tau) has been used against hepatotoxicity caused by different environmental toxins. However, it has not been elucidated whether Tau exerts its protective function against Cd-induced hepatotoxicity. The aim of this study was thus to evaluate the ameliorative function of Tau (500 mg/kg body weight intraperitoneally) on Cd-induced (2 mg/kg body weight intraperitoneally) liver toxicity in mice for 14 days. The histopathologic and ultrastructure changes as well as alterations in indexes related to liver function, antioxidant biomarkers, inflammatory, and apoptosis were evaluated. The results showed that Tau alleviated the vacuolar degeneration, nuclear condensation, mitochondria swelling, and cristae lysis of hepatocytes induced by Cd. In addition, Tau treatment significantly reduced the ALT, AST levels in serum, and inflammatory factor TNF- α and IL-1 β in liver tissue. Furthermore, Tau treatment decreased the Bax/Bcl-2 ratio and cleaved caspase-3 protein expression levels. Taken together, these observations demonstrate that Tau has an important hepatic protective function against the inflammation and apoptosis induced by Cd.

Keywords Cadmium · Taurine · Inflammation · Apoptosis · Hepatotoxicity

Introduction

Cadmium (Cd) is a ubiquitous environmental and industrial contaminant, which seriously threatens the health of animals and human beings due to its long metabolism rate [1, 2]. China is the largest producer of Cd worldwide, with an annual Cd production of approximately 8200 tons, accounting for one-third of the total global production (<https://www.usgs.gov/centers/nmic/cadmium-statistics-and-information>). Recently, the rapid increase in Cd contamination incidents

has raised public concerns about its potential hazards. The general population is exposed to Cd primarily by inhalation of contaminated air and consumption of grains and vegetables produced from irrigated agricultural fields containing Cd wastewater [3]. As the primary organ for detoxification and metabolism, hence, liver is extremely susceptible to Cd exposure [1, 4]. Environmental Cd exposure was associated with, hepatic necroinflammation, non-alcoholic fatty liver disease, and liver fibrosis [5–8]. In addition, growing evidence reported potential relationships between Cd exposure and inflammation, oxidative stress, and apoptosis [9–11]. It is thus crucial to find the supplements or drugs to protect against hepatotoxicity resulted from Cd.

Antioxidants exist in many natural dietary sources, and daily consumption of antioxidants has a vital role in human and animal health [12, 13]. Taurine (Tau) is a semi-essential amino acid present in mammalian muscles, liver, brain, retina, adrenal gland, and other tissues. It is involved in several essential biological events, including the formation of bile salts, detoxification, biological membrane stabilization, osmoregulation, and regulation of intracellular Ca²⁺ concentration [14–19]. Tau has protective effects on various organ system diseases, such as cardiovascular [20,

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21], integumentary [22], skeletal muscle [23], and endocrine systems [24]. Recent studies showed that Tau has functions against oxidative stress and inflammatory reactions, thus preventing apoptosis and necrotic cell death [25–27]. Oral administration of Tau prevented Cd-induced the decreases in antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), glutathione S-transferase (GST), and glutathione reductase (GR) [28]. In addition, Tau significantly decreased inflammatory cytokines including tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) in lipopolysaccharide-induced liver injury [29]. Most importantly, Tau has a strong potency in inhibiting apoptosis by increasing Bcl-2 levels and decreasing Bax and caspase-3 levels in hypoxic-ischemic brain injury in neonatal rats [30, 31].

Recently, Tau has been reported to ameliorate hepatotoxicity induced by various toxicants in the liver [26, 32]. However, the exact mechanism of Tau on Cd-induced liver disease has not been elucidated. Therefore, the purpose of this study was to explore the potential effects of Tau against Cd poisoning and elucidate the possible mechanisms in female mice. In addition, this study may provide a clue to the therapeutic application of Tau in Cd-induced hepatotoxicity.

Materials and Methods

Materials

Cadmium chloride was purchased from Sigma-Aldrich (St. Louis, MO, USA). Assay kits including total protein (TP), lactate dehydrogenase (LDH), alanine transaminase (ALT), and aspartate aminotransferase (AST) were purchased from Beijing Xinchuangyuan Bioengineering Institute (Beijing, China). Glutathione (GSH), superoxide dismutase (SOD), and malondialdehyde (MDA) were purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, Jiangsu, China). The bicinchoninic acid (BCA) protein assay kit was purchased from the Beyotime Institute of Biotechnology (Shanghai, China). Antibody against Bcl-2 (ab32124) was procured from Abcam (Cambridge, MA, USA). Antibodies against cleaved caspase-3 (9664), Bax (14796), and Horseradish Peroxidase (HRP)-conjugated goat anti-rabbit immunoglobulin G (IgG) were purchased from Cell Signaling Technology (Boston, MA, USA). Other chemicals used in this work were purchased from Shenggong Bioengineering Ltd. Company (Shanghai, China).

Experimental Animals

Twenty-four five-week-old ICR female mice were purchased from the Laboratory Animal Center of Yangzhou University. All animals were housed in an animal facility with a 12-/12-h light/dark cycle temperature of 20–22 °C,

and humidity of $55 \pm 5\%$. The mice had free access to water and food. All procedures were approved by the Animal Care and Use Committee at Yangzhou University (approval ID: SYXK (Su) 2017–0044). The animals were acclimatized for 1 week before starting the experiments.

Experimental Design

Both Cd and Tau solutions were prepared by dissolving in sterile saline. The concentrations of Cd solution and Tau solution were 0.4 mg/ml and 100 mg/ml, respectively. The doses of Cd and Tau were 2 and 500 mg/kg, respectively, according to the earlier literature [9, 33]. The animals were divided into 4 groups as (1) control group: received an equal volume of normal saline; (2) Tau group: received Tau intraperitoneally at a dose of 500 mg/kg body weight for 14 days, once daily; (3) Cd group: received Cd intraperitoneally at a dose of 2 mg/kg body weight for 14 days, once daily; and (4) Cd + Tau group: received Tau one hour prior to Cd injection for 14 days, once daily. The flow diagram of animal grouping and treatment is shown in Fig. S2.

Collection of Samples

The body weights of the mice were weighed from the beginning of the experiment and then every 2 days until day 14. After the end of the experiment, the mice were anesthetized with sodium pentobarbital (50 mg/kg). Blood samples were collected by excise the eyeballs and centrifuged at 3000 rpm for 10 min at 4 °C to obtain the serum. The livers were quickly isolated and weighed. Part of the liver was taken then fixed in 4% paraformaldehyde solution for histological analysis. The remained part of the liver was immediately frozen in liquid nitrogen and stored at –80 °C. The relative weight liver was calculated as: Relative liver weight = (liver weight/body weight) \times 100.

Histopathological Analysis

Liver samples were embedded in paraffin after gradient dehydration and xylene transparency. Sections were cut into 5 μ m thickness, deparaffinized with xylene, and stained with hematoxylin and eosin (H&E) according to previous literature [9]. The sections were analyzed by light microscope (IX71; Olympus, Tokyo, Japan).

Electron Microscopic Investigations

Electron microscopic investigations protocol was according to previous literature [32]. In brief, the fresh liver tissues were cut into 1 mm³ sections and being fixed with 2.5% glutaraldehyde at 4 °C overnight. After fixed with osmium tetroxide, the samples were washed with 0.1M PBS and

dehydrated by ethanol gradient and embedded in the resin to prepare ultrathin sections. After being stained in uranyl acetate and lead citrate, sections were observed under a transmission electron microscope (TEM) (H7800, Hitachi, Japan).

Measurement of Liver Function Biomarkers

Serum alanine transaminase (ALT), aspartate aminotransferase (AST), serum lactic dehydrogenase (LDH), and total protein (TP) levels were measured by commercial kits according to the manufacturer's instructions.

Determination of GSH, MDA, and SOD Levels in the Liver

Liver tissues were homogenized in normal saline and centrifuged to obtain the supernatant. The contents of GSH, MDA, and the activities of SOD were detected by using commercial kits following the manufacturer's instructions. The protein concentrations were determined using the BCA protein assay reagent.

Quantitative Real-Time PCR Analysis

Total RNA from livers was isolated using TRIzol reagent (Vazyme Biotech, Nanjing, China). Then, the cDNA was synthesized by a commercial reverse transcriptase kit (Vazyme Biotech, Nanjing, China) according to the manufacturer's instructions. Real-time PCR was performed using the SYBR Green master mix (Vazyme Biotech, Nanjing, China). The primer sequence of GAPDH (XM_036165840.1) is, forward: 5'-GGTTGTCTCTCGCGACTTCA-3', reverse: 5'-GGGTGGTCCAGGGTTTCTTA-3'. The primer sequence of TNF- α (NM_013693.3) is, forward: 5'-ACTGAACTTCGGGGTGATCG-3', reverse: 5'-TGATCTGAGTGTGAGGGTCTGG-3'. The primer sequence of IL-1 β (XM_006498795.5) is, forward: 5'-ATGAAAGACGGCACACCCAC-3', reverse: 5'-GCTTGTGCTCTGCTTGTGAG-3'. The primer sequence of IL-6 (NM_001314054.1) is, forward: 5'-TGCAAGAGACTTCCATCCAGT-3', reverse: 5'-GTGAAGTAGGGAAGGCCG-3'. The PCR protocol was as following: denaturation for 30 s at 95 °C, followed by 40 cycles of 10 s at 95 °C and 30 s at 60 °C. The mRNA relative expression was calculated by the $2^{-\Delta\Delta C_t}$ method and normalized to the mean of the values for GAPDH.

Western Blot Analysis

Western blot was performed as described previously [34]. Protein concentrations were quantified with a BCA protein assay kit. Equal amounts of protein were separated by 12%

SDS-polyacrylamide gels and transferred onto PVDF membranes. Membranes were blocked with 5% (w/v) skim milk at room temperature for 1 h, followed by incubation with primary antibodies at 4 °C overnight. After incubated in horseradish peroxidase labeled-secondary antibodies for 1 h at room temperature, the protein bands were detected by enhanced chemiluminescence reagents (Vazyme Biotech, Nanjing, China).

Statistical Analyses

The data were analyzed using SPSS V22.0 Software (Armonk, NY, USA). Experimental groups were evaluated using one-way analysis of variance (ANOVA) and the group means were compared by Duncan's multiple range test (DMRT). Data were expressed as mean \pm SD from at least three independent experiments. $P < 0.05$ was regarded as statistically significant.

Results

Tau Alleviates Body Weight Loss Induced by Cd

The results showed that Cd treatment significantly reduced the body weight ($P < 0.01$). However, there were no significant differences in body weight increase between control groups, Tau-treated groups, and Cd + Tau -treated groups (Fig. 1A, B). In addition, Cd treatment significantly increased the liver weight ($P < 0.01$), but which was not restored by Tau supplement (Fig. 1C).

Tau Alleviates Cd-Induced Histological and Ultrastructural Changes

It was observed that the Cd treatment resulted in notable lesions including irregular hepatic cord arrangement, intracellular vacuolization, nuclear condensation, and inflammatory cell infiltration (Fig. 2). However, the Cd + Tau group demonstrated a great degree of alleviation in destruction of hepatocytes compared with Cd, although the inflammatory cells were still visible.

Furthermore, TEM results showed that the hepatocytes appeared the apoptosis characteristics, such as nuclear condense, disintegration, and even necrosis, and the mitochondria were swollen and appeared with obvious cristolysis in the Cd group. Tau treatment partially reduced the damage in hepatocytes; the nuclear morphology and mitochondria cristae were preserved (Fig. 3). These results demonstrate that Tau protects the liver from Cd-induced damage.

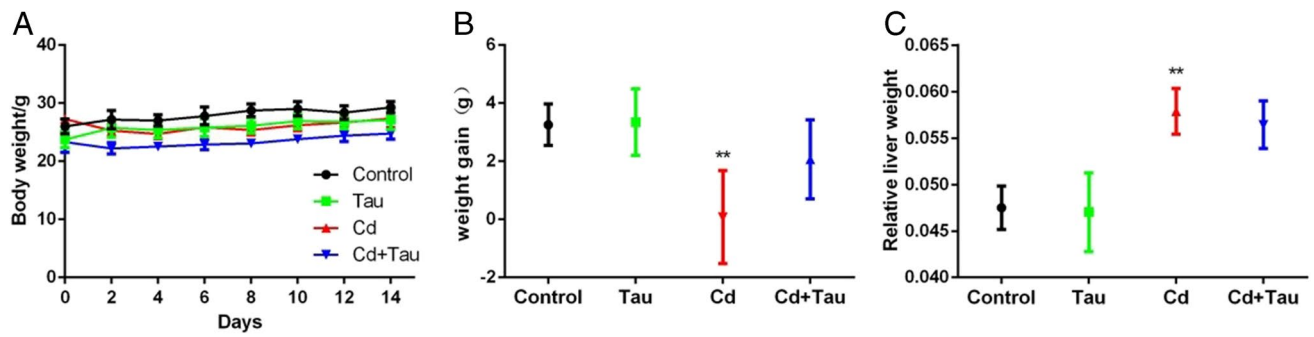
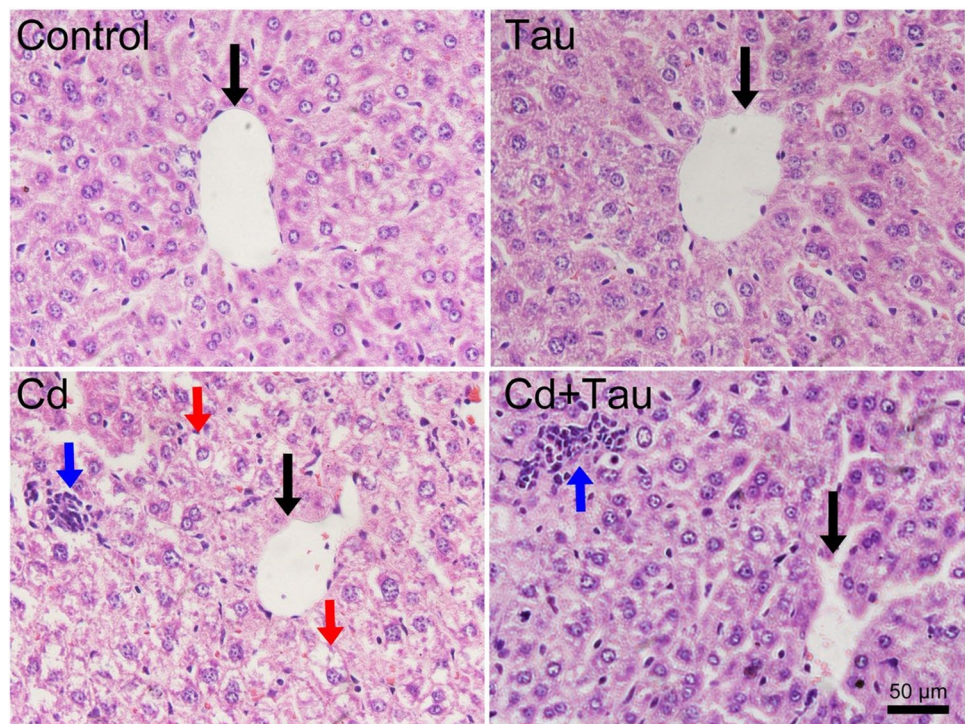


Fig. 1 Tau prevented body weight reduction induced by Cd. **A.** Body weight were conducted every other day during treatment. **B.** Comparison of weight gain between the groups. **C.** Comparison of relative

liver weight between the groups. Data were presented as means \pm SD. ** $p < 0.01$ compared with control groups

Fig. 2 Tau treatment prevented liver damage induced by Cd (H&E staining $\times 640$). After treatment, mice were sacrificed and the livers from each experimental group were processed for histological evaluation. Representative histological changes of liver tissues obtained from mice in different groups. Black arrows refer to central vein, blue arrow refers to area of inflammatory cell infiltration, and red arrow refers to intracellular vacuolization



Tau Attenuates Liver Dysfunction Induced by Cd

We next determined serum ALT, AST, LDH, and TP levels, the indicators of liver function. As shown in Fig. 4, compared to control group, the levels of serum ALT and AST in Cd treatment group were significantly elevated by 160.7% and 109.3% respectively ($P < 0.01$) (Fig. 4A, B). However, treatment with Tau reduced the levels of ALT and AST by 44.8% and 25.1%, respectively, compared to the Cd exposed group ($P < 0.05$). In addition, there was

no significant difference in LDH and TP levels among the treatment groups (Fig. 4C, D).

Tau Has No Significant Effect on Oxidative Markers

Numerous studies have shown that oxidative stress plays a critical role in Cd induced hepatotoxicity. As shown in Fig. 5, Cd increased GSH contents by 41.4% compared with control, but Tau failed to restore the increase of GSH ($P < 0.01$). Furthermore, SOD activities and MDA contents were not significantly different between the control and Cd groups.

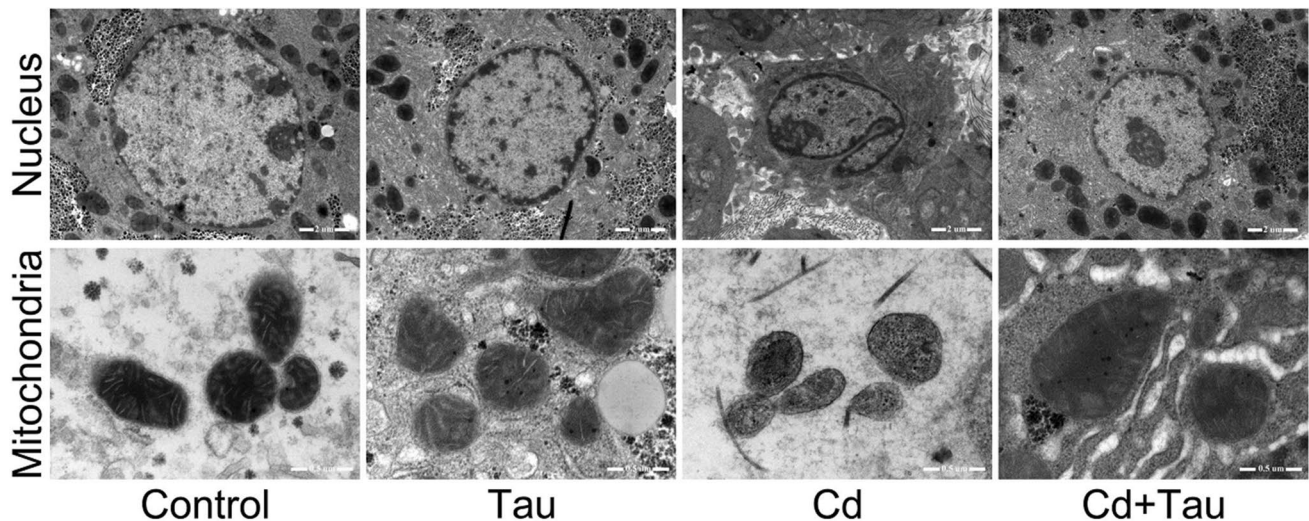


Fig. 3 Electron micrographs of hepatocytes. Scale bar in nucleus = 2 μ m; scale bar in mitochondria = 0.5 μ m

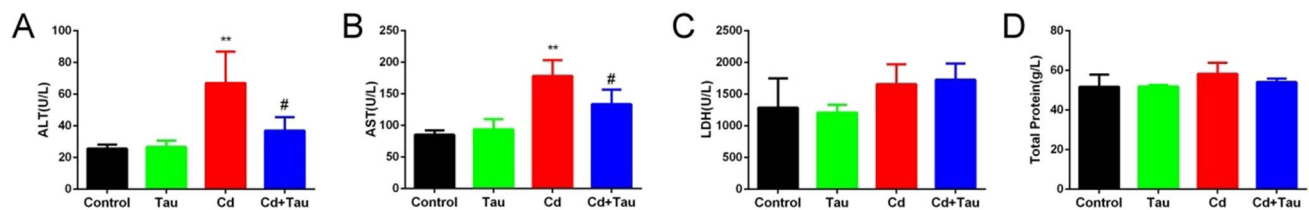


Fig. 4 Effects of Tau on serum levels of ALT, AST, LDH, and TP. Serum levels of ALT (**A**), AST (**B**), LDH (**C**), and TP (**D**) were measured. Data were presented as the means \pm SD. ** $P < 0.01$ compared with control group, # $P < 0.05$ compared with Cd group

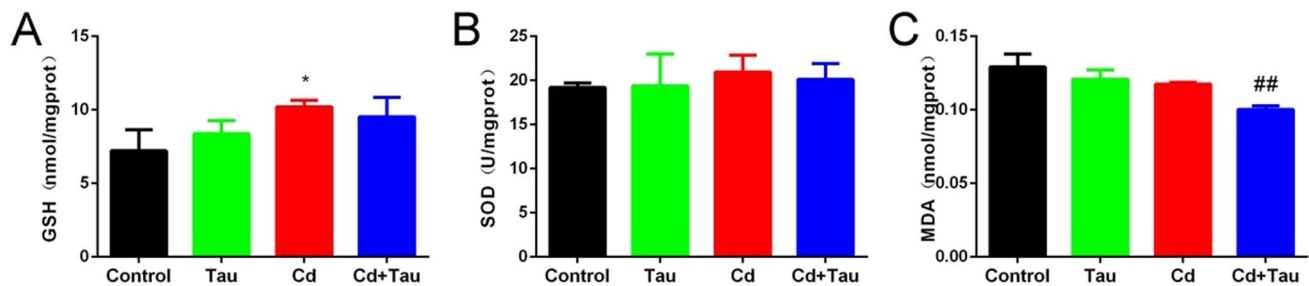


Fig. 5 Effects of Tau on the contents of GSH (**A**) and the activities of SOD (**B**) and MDA (**C**). Data were presented as the means \pm SD. * $P < 0.05$ compared with control group, ## $P < 0.01$ compared with Cd group

Tau Reduced Cd-Induced Inflammation

The mRNA expressions of pro-inflammatory cytokines in the liver were detected. As shown in Fig. 6, Cd caused a significant increase of TNF- α , IL-1 β , and IL-6 levels by 260.2%, 239.0%, and 139.2%, respectively, compared with control group ($P < 0.01$). Tau supplement significantly reduced TNF- α and IL-1 β expressions by 38.8% and 57.1%, respectively, compared to the Cd group ($P < 0.05$ or $P < 0.01$) (Fig. 6A, B), and partly restore IL-6 levels in our study (Fig. 6C).

Tau Alleviates Cd-Induced Apoptosis

Western blotting showed that Cd significantly increased the Bax/Bcl-2 ratio (Fig. 7B), and levels of active caspase-3 by 887.0% and 43.9%, respectively, compared with control (Fig. 7C), but all of which were decreased by Tau supplementation by 50.3% and 33.0%, respectively, compared to the Cd group. These results suggest Tau has the function to inhibit the apoptosis induced by Cd.

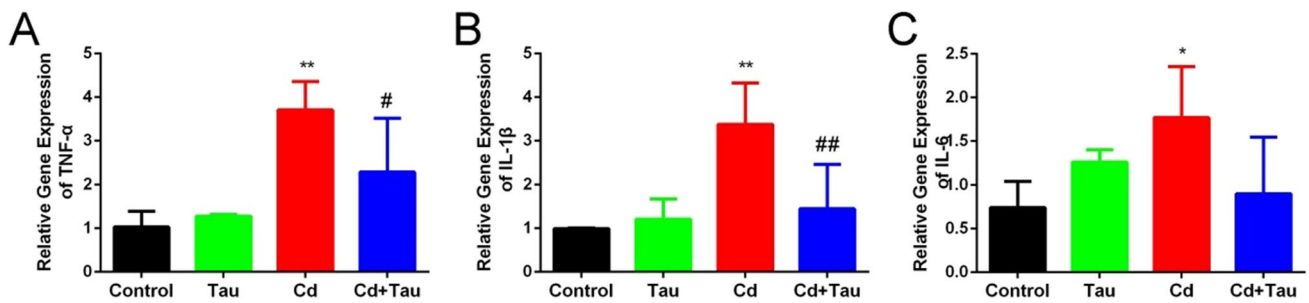
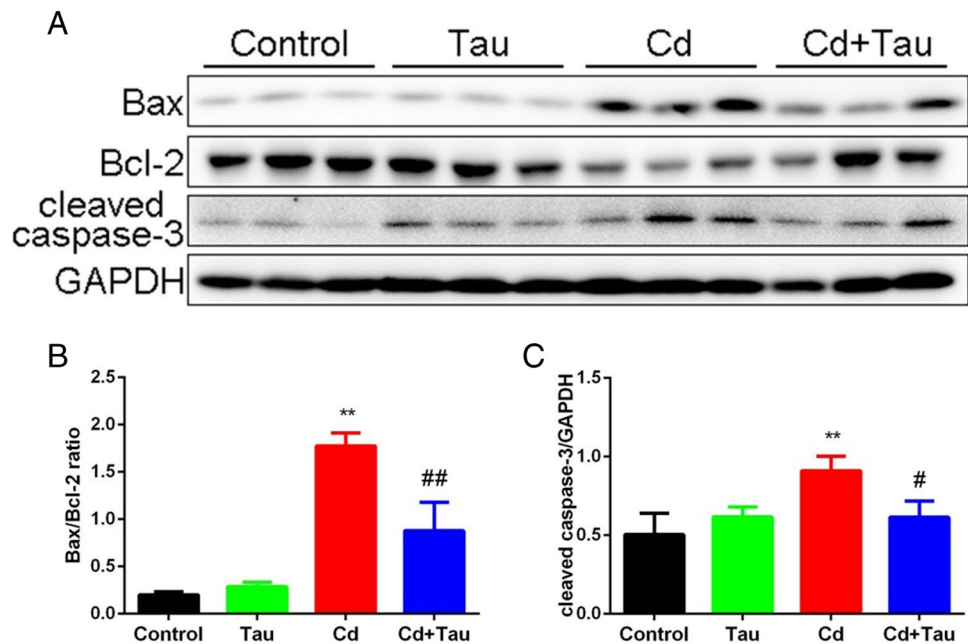


Fig. 6 Effects of Tau on Cd-induced inflammatory cytokines. The levels of TNF- α (A), IL-1 β (B), and IL-6 (C) in liver tissue were measured. Data were presented as the means \pm SD. * P < 0.05, ** P < 0.01 compared with control group, # P < 0.05, ## P < 0.01 compared with Cd group

Fig. 7 Effects of Tau on Cd-induced the protein expression levels of Bax, Bcl-2 and cleaved caspase-3. GAPDH served as the loading control. Data were presented as the means \pm SD. ** P < 0.01 compared with control group, # P < 0.05, ## P < 0.01 compared with Cd group. (A) Representative immunoblot analysis. (B) The ratio of Bax and Bcl-2. (C) The expressions of cleaved caspase-3



Discussion

Previous studies have shown that Tau supplementation provides beneficial effects against various hepatotoxic substances such as arsenic [35], lead [36], and mercury [37]. In this study, Tau has been observed to reverse the alterations of Cd induced hepatic damages. Moreover, Tau attenuated Cd-induced hepatocyte inflammation and apoptosis, supporting the beneficial role of Tau against Cd-induced hepatotoxicity. A graphical abstract of the protective effect of Tau against Cd-induced hepatic damage is shown in Fig. S1.

Body and organ weights are important indexes to reflect animal health status and organ toxicity [38–40]. Studies have shown that Cd exposure can significantly decrease the weight of mice [41, 42]. In this research, we observed that Tau reversed the inhibitory effect of Cd on weight gain. In addition, Tau treatment reversed the cellular abnormalities and kept the liver histologically almost

normal. These findings are also supported by studies that Tau supplementation reduced bisphenol A-induced liver injury [43]. Hepatic injury is directly reflected by the elevated serum hepatic enzymes, such as AST, ALT, and LDH [44, 45]. In the present study, the serum ALT and AST were remarkably ameliorated by Tau, further supporting the histopathologic analysis. This result is also reported by other papers that Tau significantly reduced the levels of AST and ALT in serum of rats induced by Cd [44] and fipronil [26].

Studies have demonstrated Cd can induce oxidative damage in different tissues by enhancing membrane lipid peroxidation and changing the cellular antioxidant system [46–48]. Tau can affect a series of enzymes involved in oxidative insult in Cd exposed tissues [49]. Moreover, Tau administration can increase GSH levels by inducing cysteine to synthesize GSH as cysteine is a precursor of Tau and GSH [50]. In this study, the activities of GSH were significantly increased, but the contents of SOD and MDA were

not affected by Cd treatment. These results are in line with previous studies [51], which reported that the hepatic GSH contents increased significantly and the MDA content was not affected after Cd exposure. On the contrary, other studies have shown that Cd-induced liver injury was accompanied by a significant increase in MDA levels, while GSH levels and SOD activities were significantly decreased [52]. These different results may be attributed to the difference of dosage, time, and method of Cd treatment. In addition, the toxic effect of Cd varies with sex in experimental animals, which might be a factor that affected the results [53]. More importantly, Tau administration failed to restore the increase in GSH, which indicated, to a certain extent, that the endogenous antioxidant capacity of the liver was in a compensatory state.

Cd induces different inflammatory markers such as TNF- α and IL-6, -8, and -1 β , which are involved in Cd induced inflammation, apoptosis, and cancer development [54]. It was also observed in our study that these cytokine levels were significantly increased after Cd administered. Similar results were also demonstrated by [51]. Nuclear factor- κ B (NF- κ B) is a key regulator of inflammatory genes. Tau could react with hypochlorous acid to generate taurine chloramines, which could inhibit the activation of NF- κ B by stabilizing the I- κ B and prevents inflammatory reactions [23, 55]. Tau has been shown to inhibit TNF- α , IL-6, and TGF- β 1 secretion in CCl₄ induced rat liver damage [32]. In addition, Liu et al. [29] also reported that Tau protects rat liver by relieving the inflammatory response and oxidative stress induced by lipopolysaccharide. In our study, Tau significantly restored the transcription level of TNF- α , IL-1 β , and IL-6, which partially contributing to reduction of hepatic inflammation.

Tau serves as a sulfur-containing β -amino acid synthesized in the liver from cysteine. It may enhance the elimination of Cd through the chelation of its two functional groups ($-\text{NH}_2$ and $-\text{SO}_3\text{H}$) [28]. The cytoprotective action of Tau is also evidenced by its potential to regulate mitochondrial protein synthesis, enhance electron transport chain activity, and prevent mitochondrial oxidant production [56]. Previous studies suggested that Tau alleviates the liver damage induced by γ -irradiation in rats through anti-inflammatory and anti-apoptotic pathways [57]. Furthermore, Tau has been shown to downregulate Bax and caspase 3 expression and upregulate Bcl-2 expression in ethanol induced hepatocytes [58]. In this study, Tau treatment could effectively inhibit Bax/Bcl-2 ratio and prevent cleaved caspase-3 activation induced by Cd. These results suggested that Tau could exert a positive role in maintaining mitochondrial homeostasis, and thereby significantly inhibited the activation of caspase-3, which is in line with previous studies that oral administration of Tau protects mouse liver against arsenic-induced apoptosis [35] and Cd-induced oxidative stress [28].

In conclusion, the present study demonstrated that Tau has a protective function against Cd-induced liver injury. The underlying mechanisms are mainly through anti-inflammatory and anti-apoptotic effects. However, the findings of this study have to be seen in light of some limitations. The precise signaling pathway of Tau hepatoprotective toxicity and the appropriate therapeutic dose of Tau on long-term Cd poisoning under environmental conditions still require further in-depth studies.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12011-022-03252-0>.

Author Contribution Sheng Cui contributed to the conception of the study. Jiaming Zheng and Guobin Qiu performed experiment, collected and analyzed data, and wrote the paper. Yewen Zhou and Kezhe Ma contributed significantly to analysis and manuscript preparation. All authors read and approved the final manuscript.

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Data Availability All data used to support the findings of this study are included within the article.

Declarations

Ethics Approval All procedures were approved by the Animal Care and Use Committee at Yangzhou University (approval ID: SYXK (Su) 2017-0044).

Consent to Participate Not applicable.

Consent for Publication The authors confirm that the work described has not been published before.

Competing Interests The authors declare no competing interests.

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