Protective Effects of Taurine Against Inflammation and Apoptosis in Cadmium-Induced Hepatotoxicity

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Abstract

Cadmium (Cd), a heavy metal contaminant, which seriously threatens human and animal health. Taurine (Tau) has been used to 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 on Cd-induced liver toxicity in mice. 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 restored 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 important hepatic protective function against the inflammation and apoptosis induced by Cd.

1. 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 (Joseph 2009). China is the largest producer of Cd worldwide, with an annual Cd production of approximately 8200 tons, accounting for 1/3 of the total global production. 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 (Liu et al. 2016). As the primary organ for detoxification and metabolism, hence liver is extremely susceptible to Cd exposure (Shao et al. 2014, Zhang et al. 2020). Environmental Cd exposure was associated with liver dysfunction, hepatic necroinflammation, non-alcoholic fatty liver disease, and liver fibrosis (Alshammari et al. 2021, Baba et al. 2013, He et al. 2019, Hyder et al. 2013). In addition, growing evidence reported potential relationships between Cd exposure and inflammation, oxidative stress and apoptosis (Arab-Nozari et al. 2020, Cao et al. 2017, Li et al. 2021). It is thus crucial to find the supplements or drugs to protect hepatotoxicity resulted from Cd.

Taurine, a semi-essential amino acid, is present in free form in mammalian muscles, liver, brain, retina, adrenal gland and other tissues, and involves in several essential biological events, including formation of bile salts, detoxification, biological membrane stabilization, osmoregulation, and regulation of intracellular Ca^{2+} concentration (Huxtable 1992, Ishikura et al. 2011, Marcinkiewicz & Kontny 2014, Ripps & Shen 2012, Sun et al. 2016, Wen et al. 2019). Recent studies showed that Tau has functions against oxidative stress and inflammatory reactions, thus preventing apoptosis and necrotic cell death. Oral administration of Tau prevented Cd induced decreases in antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), glutathione S-transferase (GST) and glutathione reductase (GR) (Sinha et al. 2009). In addition, Tau significantly decreased inflammatory cytokines including tumor necrosis factor- α and interleukin-6 in lipopolysaccharide-induced liver injury (Liu et al. 2017). 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 (Jeong et al. 2009).

Recently, Tau has been reported to ameliorate hepatotoxicity induced by various toxicants in liver (Abdel-Daim et al. 2019, Abdel-Moneim et al. 2015). However, the exact mechanism of Tau on Cd induced liver disease has not been elucidated. These made us to hypothesize that whether Tau has the protective effects in Cd induced hepatotoxicity.

2. Materials And Methods

2.1 Materials

Cadmium chloride was purchased from Sigma-Aldrich (St. Louis, MO, USA). Assay kit including total protein (TP), lactate dehydrogenase (LDH), alanine transaminase (ALT), 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 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-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 Shengggong Bioengineering Ltd. Company (Shanghai, China).

2.2 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 ± 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.

2.3 Experimental design

The animals were divided into 4 groups, consisting of six mice in each group: control group (received normal saline), Tau group (received Tau intraperitoneally at a dose of 500 mg/kg body weight for 14 days, once daily), Cd group (animals received Cd intraperitoneally at a dose of 2 mg/kg body weight for 14 days, once daily); Cd + Tau group (received Tau one hour prior to Cd injection for 14 days, once daily).

2.4 Collection of samples

After 14 days treatment, each mouse was weighed and sacrificed. Serum was separated by centrifugation (3000 rpm for 10 min) for liver function assessment. 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 – 80°C.

2.5 Evaluation of body and liver weights

The body weights of the mice were weighed from the beginning of the experiment and then every two days until day 14. After the experiment, the mice were anesthetized and dissected, and the liver tissues were quickly isolated and weighed.

2.6 Histopathological analysis

Fresh liver samples were fixed in 4% paraformaldehyde solution at 4°C overnight, and embedded in paraffin after gradient dehydration and xylene transparency. Sections were cut into 5 µm thickness and stained with hematoxylin and eosin (H&E). The sections were analyzed by Olympus light microscope.

2.7 Electron microscopic investigations

The fresh liver tissues were cut into 1 mm³ sections and fixed with 2.5% glutaraldehyde at 4°C overnight. After fixed with osmium tetroxide, the samples were washed with 0.1M PBS and fixed in 1% osmic acid for 2 hours. Then the tissue samples were dehydrated by ethanol gradient and embedded in the resin to prepare ultrathin sections. After stained in uranyl acetate and lead citrate, sections were observed under a transmission electron microscope (TEM) (H7800, Hitachi, Japan).

2.8 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.

2.9 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.

2.10 Quantitative real-time PCR analysis

Total RNA from livers was isolated using TRIzol reagent (Vazyme Biotech, Nanjing, China). Then, the cDNA 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 is, forward: 5'-GGTTGTCTCCTGCGACTTCA-3', reverse: 5'-GGGTGGTCCAGGGTTTCTTA - 3'. The primer sequence of TNF-α is, forward: 5'-ACTGAACTTCGGGGTGATCG-3', reverse: 5'-TGATCTGAGTGTGAGGGTCTGG-3'. The primer sequence of IL-1β is, forward: 5'-ATGAAAGACGGCACACCCAC-3', reverse: 5'-GCTTGTGCTCTGCTTGTGAG-3'. The primer sequence of IL-6 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.

2.11 Western blot analysis

Western blot was performed as described previously (Zheng et al. 2020). 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 proteins bands were detected by enhanced chemiluminescence reagents (Vazyme Biotech, Nanjing, China).

2.12 Statistical analyses

Data were evaluated by one-way analysis of variance (ANOVA) using SPSS V22.0 Software (Armonk, NY, USA). Data were expressed as mean $\pm$ SD from at least three independent experiments. $P < 0.05$ was regarded as statistically significant.

3. Results

3.1 Tau alleviates body weight loss induced by Cd

The mice weight was monitored every other day during the experiment. 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).

3.2 Tau alleviates Cd-Induced histological and ultrastructural changes

To identify the protective effects of Tau on Cd induced liver injury, histological examination was analyzed by H&E staining. It was observed that the Cd treatment resulted in the loss of cellular architecture, such as intracellular vacuolization, widespread nucleus dissolved and even disappeared, and inflammatory cell infiltration (Fig. 2). But in the Cd + Tau treated mice, the number of vacuoles and necrosis was much reduced, and the basic morphology of hepatocytes was maintained, 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 Cd group. In the Cd + Tau group, the nuclear pycnosis was mild, the mitochondrial matrix density was higher, and the broken mitochondria cristas were dramatically reduced compared with the Cd group (Fig. 3). These results demonstrate that Tau protects the liver from Cd-induced damage.

3.3 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, Cd significantly increased serum levels of ALT and AST compared with control ($p < 0.01$) (Fig. 4A, B). However, Tau supplement significantly inhibited the increase of ALT and AST induced by Cd ($p < 0.05$). In addition, there was no significant different in LDH and TP levels among the treatment groups (Fig. 4C, D).

3.4 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, compared to the control group, the contents of GSH in the liver tissues were significantly increased in Cd group, 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.

3.5 Tau reduced Cd-induced inflammation

Based on the fact that the excessive release of inflammatory cytokines plays a key role in Cd-induced liver injury, the mRNA expressions of TNF- α , IL-1 β and IL-6 in liver were detected by qRT-PCR. The result showed that TNF- α , IL-1 β and IL-6 relative mRNA expressions significantly elevated in the Cd treated group compared with the control group ($p < 0.01$). Tau supplement significantly decreased TNF- α and IL-1 β expressions compared to Cd group ($P < 0.05$ or $P < 0.01$) (Fig. 6A, B). However, Tau failed to restore IL-6 levels in our study (Fig. 6C).

3.6 Tau alleviates Cd-induced apoptosis

To explore apoptotic effect of Tau on liver damage induced by Cd, the expressions of Bax, Bcl-2 and cleaved caspase-3 in liver tissues were detected by western blot. The results showed that Cd significantly increased the Bax/ Bcl-2 ratio (Fig. 7B), and levels of active caspase-3 (Fig. 7C), but all of which were reversed by Tau supplementation. These results suggest Tau has function to inhibit the apoptosis induced by Cd.

4. Discussion

Previous studies have shown that Tau supplementation provides beneficial effects against various hepatotoxic substances such as arsenic (Li et al. 2017), lead (Flora et al. 2004) and mercury (Jagadeesan & Sankarsami Pillai 2007). In this study, Tau has been observed to reverse Cd induced weight loss, and ameliorate the pathological lesions in hepatocyte. In addition, Tau reduced the levels of ALT and AST in serum and the mRNA expressions of TNF- α and IL-1 β in liver tissue. Moreover, we revealed that Tau

attenuated Cd-induced hepatocyte apoptosis. Our results suggest that Tau could prevent Cd induced hepatotoxicity by inhibiting inflammation and apoptosis.

Body and organ weights are important indexes to reflect animal health status and organ toxicity (Abdel-Wahab 2014, Crissman et al. 2004, Yuet Ping et al. 2013). Studies have shown that Cd exposure can significantly decrease the weight of mice (Yang et al. 2019). In this research, we observed that Tau reversed the inhibitory effect of Cd on weight gain. In addition, we showed that Cd caused significant damage to the histological features of liver. That is in line with (Cao et al. 2017) and (Gong et al. 2019), which reported that Cd exposure resulted in swelling, coagulative necrosis and ballooning degeneration of hepatocytes. However, Tau treatment reversed these 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 (Uzunhisarcikli & Aslanturk 2019).

Hepatic injury is directly reflected by the elevated serum hepatic enzymes, such as AST, ALT, and LDH (Gong et al. 2019, Hwang & Wang 2001). In the present study, the serum ALT and AST were significantly increased after Cd administration, which were markedly ameliorated by Tau, indicating Tau has the protective effect on Cd-induced liver injury. 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 (Hwang & Wang 2001).

Studies have demonstrated Cd can induce oxidative damage in different tissues by enhancing membrane lipid peroxidation and changing cellular antioxidant system (Amamou et al. 2015, Dai et al. 2020, Ren et al. 2019). In this study, the activities of GSH were significantly increased in the liver of Cd-treated mice. However, The hepatic SOD and MDA content was not affected by Cd treatment. These results are in line with previous studies (Liu et al. 2015), 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 (Eşrefoglu et al. 2007). These different results may be attributed to the difference of dosage, time and method of Cd treatment. More importantly, Tau administration failed to restore the increase in GSH, which indicated, to a certain extent, that the endogenous antioxidant capacity of liver was in a compensatory state.

TNF- α , produced by activated macrophages, is a mediator of local and systemic inflammation (Olszowski et al. 2012, Tracey 2002). IL-1 β and IL-6 plays an important role in transmitting information, activating and regulating immune cells, mediating the activation, proliferation and differentiation of T and B cells, and in inflammatory response (Låg et al. 2010, Olszowski et al. 2012). Cd causes up-regulation of different inflammatory markers such as TNF- α and IL-6, -8, -1 β , which are involved in Cd induced inflammation, apoptosis and cancer development (Lee & Lim 2011).

It was also observed in our study that these cytokine levels were significantly increased in the Cd administered. Similar results also demonstrated by (Liu et al. 2015), who found that the mRNA expression level of TNF- α , IL-6 and IL-1 β in the liver were elevated after Cd exposure. Tau has been shown

to inhibit TNF- α , IL-6, and TGF- β 1 secretion in CCl₄ induced rat liver damage (Abdel-Moneim et al. 2015). Liu et al (Liu et al. 2017) also reported that Tau protects rat liver by relieving the inflammatory response and oxidative stress induced by lipopolysaccharide. In our study, Tau significantly decreased the transcription level TNF- α and IL-1 β .

The anti-apoptotic protein Bcl-2 and the pro-apoptotic protein Bax belong to the Bcl-2 protein family, which regulate mitochondrial outer membrane permeability and are the main target molecules in the study of apoptosis mechanism (Shimizu et al. 2000, Vyssokikh et al. 2002). Tau has been shown to downregulate Bax and caspase 3 expression and upregulate Bcl-2 expression in ethanol induced hepatocytes (Wu et al. 2018). In the presented work, we showed that Cd up-regulated the expression of Bax and cleaved caspase-3 while down-regulated the expression of anti-apoptotic Bcl-2. This result is in agreement with (Baiomy & Mansour 2016, Elmallah et al. 2017, Zhou et al. 2013). Tau treatment could, however, effectively reduce the level of apoptosis. That is in line with that Tau treatment protects mouse liver against arsenic-induced apoptosis (Li et al. 2017).

In conclusion, the present study demonstrated that Tau has protective function against Cd induced liver injury. The underlying mechanisms are mainly through anti-inflammatory and anti-apoptotic effects. However, further experiments are needed to investigate the exact mechanism of Tau protection against Cd hepatotoxicity and to elucidate its pharmacological functions in liver diseases.

Declarations

Conflict of Interests

The authors declare that there are no conflicts of interest.

Ethical Approval

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

Consent to Participate and Publish

All the authors listed have approved the manuscript for publication.

Authors Contributions

Sheng Cui contributed to the conception of the study; Jiaming Zheng and Guobin Qiu performed the experiment; Yewen Zhou contributed significantly to analysis and manuscript preparation; Kezhe Ma helped perform the analysis with constructive discussions.

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Availability of data and materials

All the necessary data are provided in this manuscript.

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Figures

Figure 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

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

Figure 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.

Figure 3

Electron micrographs of hepatocytes. Scale bar in nucleus= 2 um; scale bar in mitochondria= 0.5 um.

Figure 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 <0.05, ** p <0.01 compared with control group, # p <0.05 compared with Cd group.

Figure 5

Effects of Tau on the contents of GSH and MDA and the activities of SOD. Data were presented as the means $\pm$ SD. * p <0.05, ** p <0.01 compared with control group, ## p <0.01 compared with Cd group.

Figure 6

Effects of Tau on Cd-induced inflammatory cytokines. The levels of TNF- α , IL-1 β and IL-6 in liver tissue were measured. 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.

Figure 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.