



Prophylactic and therapeutic effects of taurine against aluminum-induced acute hepatotoxicity in mice

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ABSTRACT

Aluminum is a well known neurotoxin and a possible candidate of hepatotoxins to humans. Using natural antioxidants against metal-induced hepatotoxicity is a modern approach. In the present study, Aluminum ($AlCl_3$) intoxication (a single injection of 25 mg Al^{3+} /kg, i.p.) for 24 h in mice resulted in elevations in serum alanine aminotransferase activity and serum tumor necrosis factor and hepatic malondialdehyde levels. Aluminum reduced the activities of glutathione peroxidase, glutathione S-transferase, quinone oxidoreductase, and catalase in liver. In addition, Al caused hepatic hemorrhage, cellular degeneration as well as necrosis of hepatocytes. Ultrastructure examination showed swelling of mitochondria, derangement of rough endoplasmic reticulum cisternae and pleomorphic nuclei with abnormal chromatin distribution. Taurine, a sulfur-containing amino acid was administered to mice daily for 5 days before (at 100 mg/kg, i.p.) or 2 h after (a single dose of 1 g/kg, i.p.) aluminum administration. Treating mice with taurine at either dosing regimens, pre- or post-aluminum administration alleviated aluminum oxidative damaging effects. The rate of recovery was better when taurine was administered prior to Al. Taurine had anaphylactic and therapeutic activity against hepatotoxicity induced by aluminum in mice.

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1. Introduction

Aluminum (Al) is a toxic element to humans and animals. Human exposure to aluminum seems inevitable. In addition to environmental exposure from drinking water and cooking utensils, aluminum is a component of food additives, antacids, and renal dialysate [1]. Aluminum is a known neurotoxin associated with many nervous disorders such as encephalopathy and Alzheimer's disease [2]. The toxicity and oxidative stress caused by aluminum is well investigated in nervous tissues [3]. On the other hand, very little is known about the hepatotoxic effects of aluminum. The mechanism of Al-toxicity is poorly understood but it is suggested that aluminum generates reactive oxygen species (ROS) that cause lipid peroxidation (LPO) and oxidative damage to proteins and DNA [4]. Therefore, chelating agents and natural antioxidants which alleviate the oxidative stress or induce the cellular antioxidant milieu would most probably treat and/or protect against aluminum poisoning. Taurine (2-aminoethanesulphonic acid), is a sulfur-containing β -amino acid present in mammalian tissues [5].

Taurine is known to have antioxidant properties [6], stabilize the cell membranes and reduce LPO [7], and display scavenging activity against free radicals [8]. The chemical similarity of taurine to acetylcysteine is an encouraging factor to use taurine against metal-induced hepatotoxicity. Taurine has reduced the toxic effects of copper, cadmium, and lead in rats [9–11] and chromium in mice [12]. Taurine has also been shown to protect against hepatotoxicity induced by either tamoxifen [13] or acetaminophen [14].

In the present study, we investigated the protective and/or therapeutic effects of taurine against aluminum-induced hepatotoxicity in mice. The mechanism of action of taurine is vague, but induction of cellular antioxidants and inhibition of LPO in mice is a suggested way of action of this natural antioxidant. Therefore, a study was undertaken to evaluate the effects of this amino acid at two dosing regimens on the hepatic antioxidant and chemoprotective enzymes as well as on the histopathology of murine liver challenged with Al-intoxication.

2. Methods and materials

2.1. Animal treatment and biological sample preparation

Adult male CF-1 mice (25–35 g) were obtained from Faculty of Veterinary Medicine, King Faisal University, and were maintained in a humidity- and temperature-controlled environment on a

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Table 1
Effect of AlCl₃ and taurine on alanine aminotransferase (sALT), malondialdehyde (MDA), and tumor necrosis factor-alpha (TNF-α).

Treatment	Dose/kg	sALT activity ^a (mU/ml serum)	MDA ^a (nmol/mg protein)	TNF-α ^a (pmol/ml serum)
Control	–	76.6 ± 12.2	0.31 ± 0.03	30.6 ± 2.3
AlCl ₃	25 mg Al ³⁺ × 1	273.0 ± 18.8*	1.03 ± 0.08*	217.3 ± 16.3*
AlCl ₃ /taurine	25 mg Al ³⁺ × 1/1 g × 1	173.2 ± 32.1 [†]	0.47 ± 0.05*	143.7 ± 10.4*
Taurine	1 g × 1	58.6 ± 9.2	0.33 ± 0.01	28.1 ± 2.5
Taurine/AlCl ₃	100 mg × 5/25 mg Al ³⁺ × 1	145.2 ± 8.8*	0.48 ± 0.04*	174.9 ± 11.6*
Taurine	100 mg × 5	58.3 ± 4.1	0.32 ± 0.03	32.2 ± 3.1

^a Data are expressed as mean ± SEM (n = 5).

* Indicates a significant difference (P < 0.05) from naïve.

[†] Indicates a significant difference (P < 0.05) from AlCl₃-treated animals.

12-h light/dark cycle with continuous free access to food and water. The mice were divided into 6 groups, 5 mice each. The first group (naïve) was injected with isotonic saline. Aluminum chloride was intraperitoneally (i.p.) injected into mice in groups 2 and 3 at a single dose of 25 mg Al³⁺/kg [15]. After 2 h, group 3 was further treated with taurine (i.p.) at a single dose of 1 g/kg [12]. Group 4 was only treated with a single injection of taurine (1 g/kg). Mice in groups 5 and 6 were intraperitoneally treated with taurine 100 mg/kg daily for 5 days [16]. One day later after the last dose of taurine, group 5 was injected with a single dose of 25 mg Al³⁺/kg. All animal procedures were approved by the University of King Faisal Animal Care and Use Committee and were conducted in agreement with NIH guidelines for the humane care of laboratory animals. Animals were sacrificed 24 h after the final dose; blood was immediately collected for serum preparation and frozen at –80 °C. The livers were quickly perfused *in situ* (via the hepatic portal vein) with normal ice cold saline. The gall bladder was then carefully dissected away, and the remaining liver was homogenized in ice cold buffer and subjected to centrifugation (9000 × g for 15 min), and the supernatant was collected and stored at –80 °C until assayed for enzyme activity. Protein content was immediately determined with Folin-Ciocalteu's phenol reagent (Sigma; St. Louis, MO) according to Lowry et al. [17].

2.2. Enzyme activity and biochemical analyses

Serum alanine aminotransferase (sALT) activity was determined from the serum-dependent absorbance change of NADH oxidation at 340 nm in the presence of optimized concentrations of L-alanine, α-ketoglutarate and purified lactic dehydrogenase enzyme [18]. Malondialdehyde (MDA) was measured through estimation of a stable chromophore formed from the reaction of a chromogenic reagent, N-methyl-2-phenylindole, with MDA at 45 °C [19]. Tumor necrosis factor (TNF-α) level in serum was measured by ELISA method using Bender Medsystems (Vienna, Austria) kit as described by the manufacturer. Glutathione peroxidase activity was determined from the azide insensitive rate of oxidation of NADPH in the presence of hydrogen peroxide, glutathione, and glutathione reductase [20]. Glutathione S-transferase activity was determined from the conjugation of glutathione with 1-chloro-2,4-dinitrobenzene [CDNB] detected by the change in absorbance at 340 nm [21]. Through monitoring the inhibition rate of NADH-dependent reduction of 2,6-dichlorophenolindophenol by 3,3'-methylenebis[4-hydroxycoumarin], the activity of quinone oxidoreductase was determined [22]. Catalase activity was measured from the rate of dismutation of hydrogen peroxide (H₂O₂) to water and molecular oxygen in a two-step coupling reaction [23]. Superoxide dismutase activity was measured in a coupling reaction through formation of formazan dye from tetrazolium salt by superoxide radicals generated by xanthine oxidase and hypoxanthine [24]. Glutathione reductase activity was measured from the rate of reduction of oxidized glutathione by NADPH [25]. Glutathione

(GSH) reacts with 5,5'-dithiobis (2-nitrobenzoic acid) producing the disulphide form or oxidized glutathione (GSSG) and 2-nitro-5-thiobenzoic acid (TNB) and under standardized assay conditions, the rate of formation of TNB was monitored and GSH level was determined [26]. Any elevation in the activities of enzymes in the current investigation does not distinguish between an activation of existing enzyme and an increase arising from increased amounts of enzyme protein.

2.3. Histopathological studies

For the histological examination, pieces of the liver were fixed in 10% neutral buffered formalin (pH 7.2), dehydrated in ascending series of ethyl alcohol (70–100%), cleared in xylene, and embedded in paraffin wax. Paraffin sections of 5 μm in thickness were stained with hematoxylin and eosin (H&E).

2.4. Transmission electron microscopy studies

For electron microscopic examinations of liver tissues, primary fixation was performed in 3% glutaraldehyde in sodium phosphate buffer (200 mM, pH 7.2) for 3 h at 4 °C. Liver tissues were washed with the same buffer and postfixed in 1% osmium tetroxide (Agar Sci. Ltd., England) in sodium phosphate buffer, pH 7.2, for 1 h at 4 °C. Tissue samples were washed with the same buffer for 3 h at 4 °C and then embedded in Araldite (Agar Sci. Ltd., England). Thin sections were cut with Leica EM UC6 (Leica Co., Austria) ultramicrotome. Samples were stained with 2% uranyl acetate and lead citrate. The sections were viewed and photographed on Jeol JEM 1011 transmission electron microscope (Jeol Ltd., Japan) at 80 kV.

2.5. Statistical analysis of data

Results are expressed as the mean ± SEM. Treated group size was 5 animals. Statistical analyses were performed using ANOVA, followed by Fisher's protected least significant difference multiple range test. The data were compared against those from the proper control animals. Differences were considered significant at P < 0.05.

3. Results

3.1. Antioxidants and biochemical study

The treatment of mice with AlCl₃ increased serum alanine aminotransferase (sALT) activity compared to naïve animals (Table 1). Administration of taurine before or following AlCl₃ caused significant reductions in sALT activity when compared to AlCl₃-treated mice. Treating mice with either doses of taurine alone (100 mg for 5 days or a single dose of 1 g) caused insignificant decreases in sALT activity when compared with naïve animals (Table 1). The same scenario was repeated for hepatic malondialdehyde (MDA) and serum tumor necrosis factor (TNF-α), where

Table 2
Effect of AlCl₃ and taurine on activities of some hepatic antioxidant and chemoprotective enzymes.

Treatment	Dose/kg	GPx activity ^{a,b} (nmol/mg/min)	GST activity ^{a,b} (nmol/mg/min)	(NQO) activity ^{a,b} (nmol/mg/min)	Catalase activity ^a (mU/mg)
Control	–	1397 ± 17	2722 ± 172	39.2 ± 1.5	722 ± 130
AlCl ₃	25 mg Al ³⁺ × 1	286 ± 24 [*]	1191 ± 128 [*]	18.4 ± 1.8 [*]	375 ± 20 [*]
AlCl ₃ /taurine	25 mg Al ³⁺ × 1/1 g × 1	952 ± 92 ⁺	3113 ± 166 ⁺	41.5 ± 2.2 ⁺	720 ± 31 ⁺
Taurine	1 g × 1	1302 ± 103	3108 ± 232	46.0 ± 1.5	631 ± 60
Taurine/AlCl ₃	100 mg × 5/25 mg Al ³⁺ × 1	1419 ± 134 ⁺	3037 ± 239 ⁺	37.1 ± 1.8 ⁺	685 ± 59 ⁺
Taurine	100 mg × 5	1194 ± 86	2763 ± 169	38.8 ± 3.2	660 ± 80

^a Data are expressed as mean ± SEM (n = 5).

^b Abbreviations: GPx (glutathione peroxidase), GST (glutathione S-transferase), NQO (NAD(P)H-quinone oxidoreductase).

^{*} Indicates a significant difference (P < 0.05) from naïve.

⁺ Indicates a significant difference (P < 0.05) from AlCl₃-treated animals.

Table 3
Effect of AlCl₃ and taurine on activities of glutathione reductase (GR) and superoxide dismutase (SOD) in liver.

Treatment	Dose/kg	GR activity ^a (nmol/mg/min)	SOD activity ^a (mU/mg)
Control	–	1668 ± 37	1.42 ± 0.27
AlCl ₃	25 mg Al ³⁺ × 1	1589 ± 31	1.46 ± 0.16
AlCl ₃ /taurine	25 mg Al ³⁺ × 1/1 g × 1	1826 ± 90	1.05 ± 0.09
Taurine	1 g × 1	2195 ± 209	0.98 ± 0.07
Taurine/AlCl ₃	100 mg × 5/25 mg Al ³⁺ × 1	2279 ± 376	1.10 ± 0.05
Taurine	100 mg × 5	2072 ± 195	1.07 ± 0.04

^a Mean ± SEM, n = 5.

taurine at both dosing regimens had no effect. Aluminum intoxication resulted in significant elevations in both hepatic MDA and serum TNF-α levels compared to naïve animals (Table 1). Taurine significantly reduced MDA and TNF-α levels in intoxicated animals at both dosing regimens used; pre- and post-AlCl₃ treatment (Table 1).

Treating mice with AlCl₃ resulted in significant reductions in the activities of glutathione peroxidase (GPx), glutathione S-transferase (GST), NADPH-quinone oxidoreductase (NQO), and catalase in liver compared to naïve animals (Table 2). Treatment with taurine either following or after treatment with AlCl₃ caused significant elevations in the activities of all enzymes listed above when compared to AlCl₃-intoxicated animals (Table 2). Taurine alone had no significant effect on the activities of previously mentioned enzymes at both dosing regimens studied (Table 2). Neither AlCl₃ nor taurine at any treatment caused a significant change in the activities of glutathione reductase (GR) or superoxide dismutase (SOD) in liver. The elevations seen in GR activity after taurine administration either alone or in conjunction with AlCl₃ did not achieve a statistical significance (Table 3). The reduction in hepatic reduced glutathione (GSH) level caused by AlCl₃ did not achieve a statistical significance either (P ~ 0.07). Taurine at both regimens studied increased GSH levels in AlCl₃-insulted animals compared to either naïve or AlCl₃-treated animals (Table 4). Hepatic GSH content was significantly elevated in animals treated with taurine alone at either dose regimens investigated when compared with naïve animals (Table 4).

Table 4
Effect of AlCl₃ and taurine on hepatic glutathione (GSH) level.

Treatment	Dose/kg	GSH ^a (μmol/mg)
Control	–	4.23 ± 0.09
AlCl ₃	25 mg Al ³⁺ × 1	3.10 ± 0.04
AlCl ₃ /taurine	25 mg Al ³⁺ × 1/1 g × 1	6.48 ± 0.40 ^{*,+}
Taurine	1 g × 1	6.02 ± 0.15 [*]
Taurine/AlCl ₃	100 mg × 5/25 mg Al ³⁺ × 1	7.12 ± 0.28 ^{*,+}
Taurine	100 mg × 5	6.18 ± 0.29 [*]

^a Mean ± SEM, n = 5.

^{*} Indicates a significant difference (P < 0.05) from naïve.

⁺ Indicates a significant difference (P < 0.05) from AlCl₃-treated animals.

3.2. Histopathology

The histological profile of the normal liver sections showed normal hepatic cells with well preserved cytoplasm, prominent nucleus, nucleolus, central vein and compact arrangement of hepatocytes (Fig. 1A). The liver tissues from mice that received AlCl₃ revealed extensive injuries, characterized by a loss of normal architecture of the parenchymatous tissue, congested sinusoids and blood vessels, infiltration of inflammatory cells, cellular degeneration with nuclear pyknosis and presence of necrotic areas (Fig. 1B). Mice post-treated with taurine presented similar histopathological changes compared with Al-treated mice with attenuated severity (Fig. 1C). In mice treated with taurine prior to Al, hemorrhage and inflammation were less in comparison to Al-treated group (Fig. 1D). Cellular degeneration and necrosis were rare. No histopathological alteration was observed in liver of mice from groups treated only with taurine.

3.3. Electron microscopy

Control group had a round nucleus with a regular nuclear envelope and a very distinct nucleolus. Mitochondria and endoplasmic reticulum were abundant in the hepatocytes (Fig. 2A). Examination of liver from Al-treated mice under transmission electron microscope (Fig. 2B) revealed a reduction in the amount of rough endoplasmic reticulum (RER) in the hepatocytes. RER was disorganized into isolated cisternae that were often closely associated with mitochondria surrounding it. Additional smooth endoplasmic reticulum appeared in the cytoplasm of hepatocytes in Al-treated mice. A swollen appearance of the mitochondria was revealed in the liver along with breaking up of the mitochondrial cristae. Nucleus displayed an irregular outline and condensed heterochromatin was located on the margin of the nuclear envelope. In animals post-treated with taurine, deformation was occasionally seen in the shape of nucleus and there were some heterochromatin fields on the margin of the nuclear envelope. RER cisternae were partially dilated and disintegrated and mitochondria were swollen (Fig. 2C). Membranous structures of the hepatocytes were found to be better preserved in animals pre-treated with taurine. Most of the mitochondria were characterized by the same basic architecture

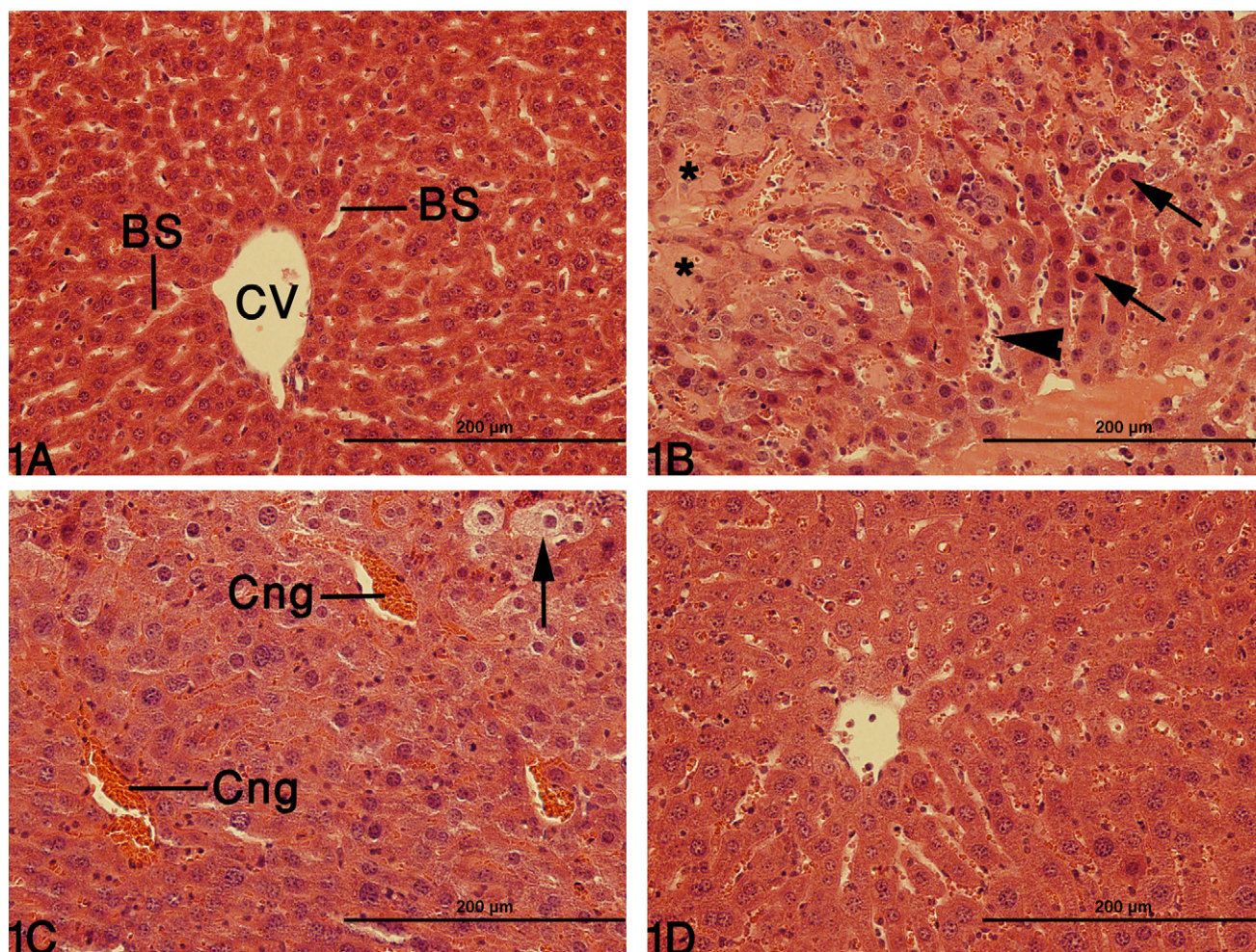


Fig. 1. (A) Liver section of control mice displaying the normal architecture of hepatic cords and their radiation from the central vein (CV), blood sinusoids (BS). (B) Liver section of AlCl_3 (a single dose of $25 \text{ mg Al}^{3+}/\text{kg}$, i.p.)-treated mice for 24 h exhibits marked disturbances of the normal architecture of the hepatic tissues, necrotic areas (*) characterized by the presence of Kupffer cells and other inflammatory cells, cellular degeneration (arrows) and sinusoidal congestion (arrowhead). (C) Liver section of AlCl_3 (a single dose of $25 \text{ mg Al}^{3+}/\text{kg}$, i.p.)+TAU (a single dose of $1 \text{ g}/\text{kg}$, i.p.)-treated mice showing dilation and distinct features of congestion (Cng) and cellular degeneration (arrow). (D) Liver section of TAU ($100 \text{ mg}/\text{kg}$, i.p., 5 days)+ AlCl_3 (a single dose of $25 \text{ mg Al}^{3+}/\text{kg}$, i.p.)-treated mice showing the cellular architecture with nearly normal aspect. H&E stained preparations, scale bars: $200 \mu\text{m}$ (A–D).

of typical liver mitochondria with a folded internal membrane and dense matrix. Integrity of the cristae was kept intact. Endoplasmic reticulum cisternae were in parallel stacks and disintegration was not observed. Nucleus was normally containing little heterochromatin (Fig. 2D). Administration of a 100 mg taurine/kg before aluminum injection was found to be effective in the preservation of cellular integrity.

4. Discussion

Little is known about the hepatotoxic effects of aluminum (Al) in either animals or humans, although humans are daily exposed to Al from drinking water, some foods and drugs. In addition, the mechanism of Al-toxicity is far from clear understanding. In the present study, the hepatotoxic effect of AlCl_3 was demonstrated by ultrastructural observations associated with deleterious changes in the murine hepatocytes. The degeneration of RER might correlate with the reduction of protein synthesis in liver and might also lead to changes in cellular calcium as RER is known to sequester calcium [27]. The high-amplitude swelling of the majority of the mitochondria seen in the liver tissue in the present study is suggestive of a change in the permeability of the mitochondrial membrane [28].

An increase in mitochondrial membrane permeability contributes to changes in the redox status of the mitochondrial thiol groups which in turn may affect the cellular free calcium levels [29]. This significant damage to the hepatic parenchyma cells may explain the 4-times increase in the sALT activity and MDA level and the 7-times elevation in pro-inflammatory cytokine measured; $\text{TNF-}\alpha$ compared to naïve animals (Table 1). This is in accordance with previous reports where Al caused the same effects in liver of rats [30,31] and rabbits [32]. Al was previously reported to elevate the $\text{TNF-}\alpha$ in brain in mice [33]. Al has been reported to cause oxidative stress and LPO [31,34]. The ionic radii of Al^{3+} most closely resemble those of Fe^{3+} , therefore the appearance of Al^{3+} in Fe^{3+} sites is probable. Aluminum is known to be bound by the Fe^{3+} -carrying protein transferrin thus reducing the binding of Fe^{2+} . The increase in free intracellular Fe^{2+} causes the peroxidation of membrane lipids and consequently the damage of the membrane [35].

The similarity of taurine to acetylcysteine [36], an agent used to treat heavy metal-induced toxicity, and the fact that cysteine is a precursor of taurine encouraged the research team in this study to examine the effects of taurine against Al-induced hepatotoxicity in mice. In the present study, taurine alleviated the Al-induced acute liver damage and significantly reduced the elevated sALT activity

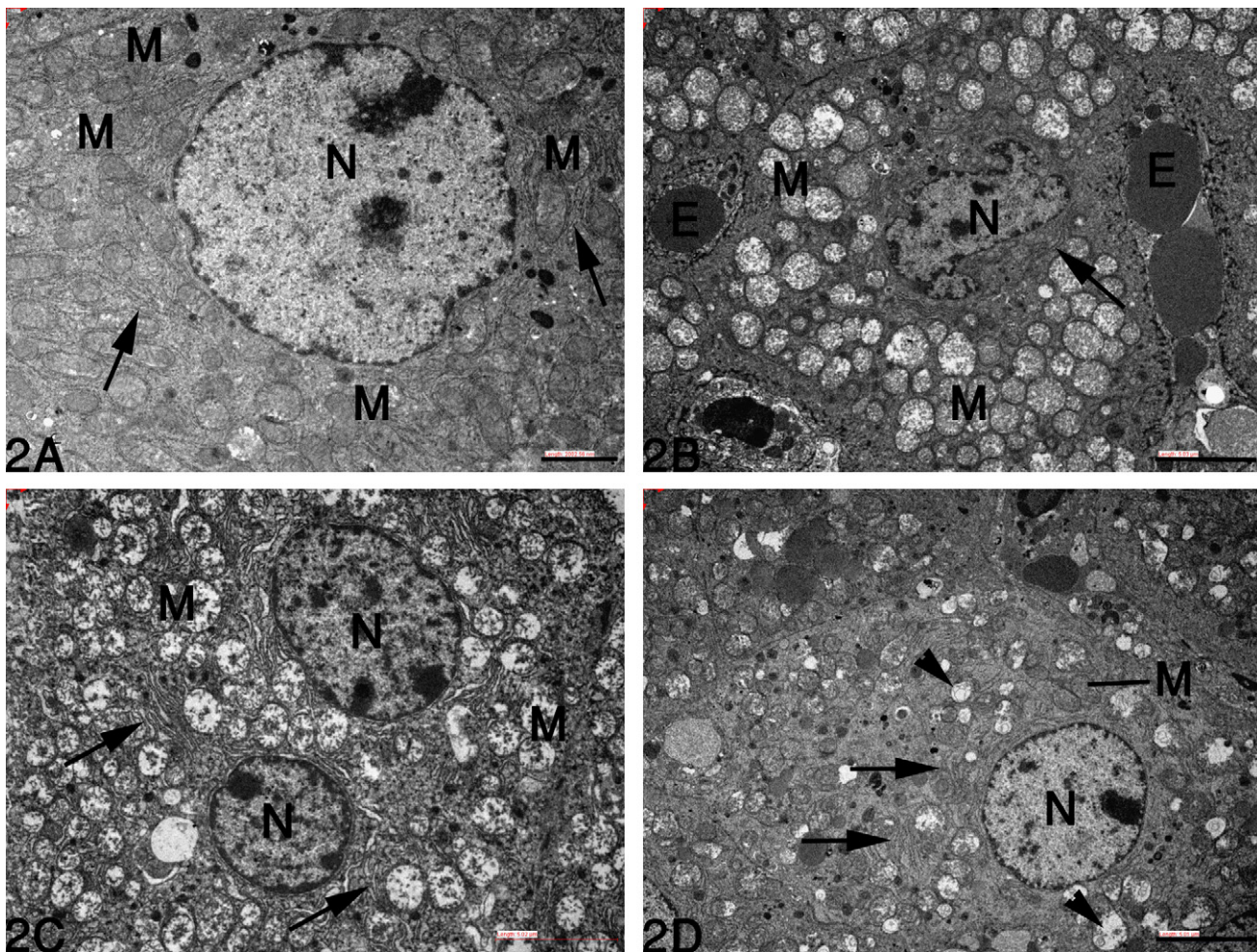


Fig. 2. (A) Electron micrograph of hepatocyte of control mice showing a rounded nucleus (N) having well-discernable nuclear envelope and chromatin particles. Also, parallel cisternae of rough endoplasmic reticulum (arrows) and a lot of mitochondria (M) can be observed. (B) Electron micrograph of hepatocyte of AlCl_3 (a single dose of $25 \text{ mg Al}^{3+}/\text{kg}$, i.p.)-treated mice for 24 h showing damaged hepatocyte with irregular lamellar organization of rough endoplasmic reticulum (arrow) and total destruction of mitochondria (M). The nucleus (N) is shrunken and reveals margination of heterochromatin. Erythrocytes (E) in Disse's space indicate congestion. (C) Electron micrograph of hepatocyte of AlCl_3 (a single dose of $25 \text{ mg Al}^{3+}/\text{kg}$, i.p.) + TAU (a single dose of 1 g/kg , i.p.)-treated mice showing dilatation of rough endoplasmic reticulum (arrow) and swollen mitochondria (M) displaying loss of matrix and cristae. N: nucleus. (D) Electron micrograph of hepatocyte of TAU (100 mg/kg , i.p., 5 days) + AlCl_3 (a single dose of $25 \text{ mg Al}^{3+}/\text{kg}$, i.p.)-treated mice showing the restoration of nuclear shape (N), mitochondrial size (M) and rough endoplasmic reticulum (arrow). Note lysis of cytoplasm (arrowheads). Uranyl acetate and lead citrate stained preparations, scale bars: $2 \mu\text{m}$ (A), $5 \mu\text{m}$ (B–D).

(37%) and MDA (54%) and $\text{TNF-}\alpha$ (34%) levels when given following Al-treatment compared with Al-intoxicated animals (Table 1). The prophylactic treatment of mice with taurine caused ~47, 54, and 20% reductions in sALT activity, MDA, and $\text{TNF-}\alpha$ levels, respectively as compared to Al-treated animals (Table 1). Taurine has been reported to protect against many heavy metals-induced injuries including chromium, cadmium, lead and copper, reducing LPO and sALT [9,10,12,37]. Taurine has been reported to cause a significant reduction in $\text{TNF-}\alpha$ level caused by acetaminophen [38]. The ability of taurine to stabilize cell membrane and inhibit LPO could provide the platform of explanation of counteracting the effects of Al on sALT, MDA, and $\text{TNF-}\alpha$. In addition, taurine was shown to keep cellular calcium homeostasis [39]. Both post- and pre-treatment with taurine resulted in a repair of the ultrastructural alterations induced by Al, however the protective effects were more prominent in the pre-treatment group which showed reappearance of RER and normalization of the mitochondrial size in the hepatocytes proving effective hepatoprotective properties of taurine.

On treating mice with AlCl_3 , significant reductions in the activities of GPx (80%), GST (56%), NQO (53%), and catalase (48%) were shown in liver as compared to naïve animals (Table 2). This was

similar to previous findings [30,32] and in accordance with the degeneration seen in the RER in the current study. Against the mainstream data, Al was reported to elevate the catalase activity in brain not in liver [4]. No previous reports concerning the effect of Al-toxicity on NQO were found. Taurine was equally efficacious when it is given either before or after Al injection and prevented the reductions or restored the normal activities of all the aforementioned enzymes (Table 2). Taurine was shown to prevent the deleterious reductions in the activities of these enzymes in animals challenged with different hepatotoxins [12–14]. The decreased activities of GPx and catalase will result in the accumulation of H_2O_2 and will lead to the formation of superoxide free radicals starting a cascade of reactions leading to the formation of more radicals, oxidative stress, LPO, hepatotoxicity, and finally cell death [40]. Any reduction in the activities of the enzymes caused by Al in the current study does not distinguish between a reduction in the activity of the existing enzyme, or inhibition of transcription or translation processes, therefore, the genotoxic effects of Al on DNA cannot be ruled out. We have observed abundant heterochromatin, disorganization of nuclear content as margination and clumping of chromatin in Al-treated group. Similarly, an increase in

chromatin condensation with discontinuity in nuclear membrane in both the cerebrum and cerebellum of rats orally treated with $AlCl_3$ was revealed [41]. At a molecular level, any effects of Al would be most likely to involve DNA damage. Al does have a genotoxic profile and has been shown to bind to DNA [42]. After treating animals with taurine at either dosing regimens investigated, severely degenerated nuclei were rarely detected. Nuclear content was almost normal in appearance and organization with taurine treatment, which was previously reported to prevent DNA damage [43].

Neither SOD nor GR activity in liver was affected by any treatment (Table 3), although a previous report showed that Al reduced both enzyme activities in liver but after 70 days of treatment [31]. On contrary, it was reported that Al-intoxication resulted in elevations in the activities of SOD and GR in rat but in brain [4]. Similar to our findings, taurine has been shown to exert no effect on SOD [44].

Hepatic GSH level was not significantly affected by Al treatment. Some reports have been shown that Al caused a reduction in the level of GSH [30,32], yet it has been showed that Al-intoxication had no effect on hepatic GSH [45]. On the other hand, treatment of normal or Al-intoxicated animals with taurine resulted in significant elevations in hepatic GSH levels (Table 4) in accordance with a previous report [13]. GSH was the only parameter studied affected by taurine in normal mice. The thiol group of GSH could be used in neutralizing the toxic products produced by Al-intoxication. Taurine was suggested to stimulate the nitrosylation of GSH into nitrosoglutathione [46]. The latter is much potent antioxidant than GSH itself. Increased hepatic GSH level, and GPx and catalase activities were suggested to be attributed to the role of taurine in maintaining normal insulin-like growth factor 1 (IGF-I) level [47].

Taurine (2-aminoethanesulfonic acid) is a unique amino acid that has amino group and sulfonate group. Both groups can bind heavy metals and stimulate excretion of such hazardous metals [10]. Is taurine alleviating Al-induced hepatotoxicity through reducing the bioavailability of Al? This question needs further investigation. Taurine not only can act as a direct antioxidant by scavenging free radicals and inhibiting LPO but, it can also stimulate the activity of glutathione-metabolizing and other cytoprotective enzymes when the cell is exposed to stressful conditions. The toxic effects of Al may be mitigated by taurine through improving the cellular antioxidant defense system, stabilization of cell membrane, and prevention of LPO. Taurine also seems to have direct beneficial effects on liver parenchymal cells, therefore taurine supplementation may be helpful in abrogation of Al-hepatotoxicity.

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