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EFFECT OF TAURINE AND GLUTATHIONE ON MERCURY TOXICITY IN LIVER TISSUE OF RATS

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Abstract
The present investigation examined the ability of taurine and glutathione as an antioxidant to protect against mercury induced oxidative stress and hepatotoxicity. Mercury hepatotoxicity was induced by oral administration of mercury at a dose of 2 mg/kg body weight daily for 30 days. Hepatotoxicity was assessed by reduced serum total protein level and increased serum levels alanine aminotransferase (ALT), and aspartate aminotransaminase (AST) and alkaline phosphatase (ALP) and total protein. Mercury treatment increased lipid peroxidation (LPO) measured as thiobarbituric acid reactive substances (TBARS) concentration and decreased reduced glutathione (GSH) content in the rat liver. Again taurine and glutathione is administrated for 15 days. During this period, taurine improved liver functions, as indicated by decline of serum transaminases and ALP levels and elevation of serum total protein. Moreover, taurine significantly reduced AST, ALT, ALP and hepatic TBARS and increased GSH content and total protein in the hepatic tissue. These results indicate that taurine has a protective action against mercury induced hepatic damage in rats than glutathione.

Key Words: Mercuric chloride; Biochemical study; Glutathione; Taurine; Rats.

Introduction

Human activities are mainly responsible for promoting the pollution in the environment by the way of introducing unwanted toxic compounds. There is an accumulating contamination of water sources and food chain with these compounds. Four principle categories of pollutants, which jeopardize the environments, are radionucleotides, petroleum hydrocarbons, pesticides and heavy metals. Among these, heavy metals are the most dangerous ones because of their stability in the biological system [1]. Hence, industrial pollution of the environment with metal compounds is becoming a significant problem [2]. Continuous exposure to this toxic heavy metal is usually the result of environmental contamination from human activities such as mining, smelting, fossil fuel combustion and industrial use [3]. Metallic contamination constitutes a danger to public health if such contaminated area water is used for drinking and other domestic purposes. Heavy metal can be toxic if it is accumulated in an organism in large amount [4,5]. Therefore, a continuous intake of low amounts of heavy metal over long period could build up metal accumulation in various organs and lead to organ damage [4,6]. Mercury in its various chemical forms is a ubiquitous environmental contaminant to which the general population is exposed primarily through the diet (organic mercury). The toxic potential of acute exposure to high levels of mercury compounds has been well appreciated for many years [7].

Mercury is a widespread contaminant in the environment and chronic exposure to low level of Hg is quite common as a result of the contamination of food and drinking water. Mercury is highly toxic and moderate level of exposure can cause immune system alternation ranging from immune suppression to immune stimulation such as increasing susceptibility to a variety of virus, autoantibody formation and autoimmune disease [7,8]. Taurine (2-aminoethanesulfonic acid) is the major intracellular free amino acid, which is normally present in most mammalian tissues [9]. Although taurine is not a constituent of any structural mammalian protein, it plays various important physiological roles including osmoregulation, bile acid conjugation, modulation of the

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functioning of the central nervous system, cell proliferation, viability, and prevention of oxidant-induced injury in many tissues (9,10,11). The beneficial effects of taurine as an antioxidant in biological systems have been attributed to its ability to stabilize biomembranes [12], scavenge reactive oxygen species [13], and reduce the production of lipid peroxidation end products [14]. Taurine may have a protective effect on the deteriorated hepatic function that results from oxygen free radicals in the mercury -induced hepatotoxicity. GSH is a low molecular weight sulfhydryl-containing compound in mammalian cells [15]. GSH is an essential tripeptide made up of the amino acid such as glutamate, cysteine, and glycine [14]. The glutathione (GSH) is a cellular thiol, which is present in all mammalian tissues [16]. It provides a reducing milieu for the maintenance of protein thiols and antioxidant, reduction of ribonucleotides and protection against oxidative and free radicals-mediated damage and other types of toxic injury [4,6,17,18].

The redox status of mitochondrial GSH particularly plays a vital role in cell injury since mitochondrial GSH exerts a major role in the homeostatis of $Ca2^{+}$ [19] and thiols [20] to regulate the permeability of the inner membrane. This is the most abundant endogenous non-protein thiol [21], which carries out various physiological functions such as detoxification of free radical and peroxides, regulation of cell growth and protein function and maintenance of immune [21]. The present investigation examined the ability of taurine and glutathione to protect against mercury -induced oxidative stress and hepatotoxicity.

Materials and methods

Animals

Normal adult male rats of the wistar strain weighing between 220±20 g were used in this experiment. All the animals were fed on a standard rat chow and water *ad libitum* and kept in a temperature controlled environment (20–22 ◦C) with an alternating cycle of 12 hr light and dark. Experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) at Annamalai University.

Experimental protocol and groups

The wister strain rats (45 days old) weighing between 200±5g were used in this experiments. They were divided at random into six groups (each of six rats). All the animals were fed on a standard rat feed and water *ad libitum*. Experimental protocol was approved by the Institutional Animals Ethics Committee (IAEC) at Annamalai University. Wistar albino rats were divided into four groups each consisting of six animals: Group-I saline (0.9% NaCl)-treated control group ; Group-II Mercuric chloride (2 mg/kg orally.,for 30 days single dose)-treated group (Hg); Group-III Mercuric chloride (2 mg/kg orally single dose) + Taurine (50 mg/kg daily orally. for 15 days) treated group (Hg +taurine), Group-IV Mercuric chloride (2 mg/kg orally single dose) + Glutathione (50 mg/kg daily orally. for 15 days) treated group (Hg +Glutathione), Group-IV taurine (50 mg/kg daily for 15 days)-treated control group, Group-VI glutathione (50 mg/kg daily for 15 days)-treated control group Experimental protocol was approved by the Institutional Animals Ethics Committee (IAEC) at Annamalai University. The animals were sacrificed under light ether anesthesia and hearts were collected and after decapitation, trunk blood was collected; the serum was separated and measured the blood urea nitrogen, creatinine. The animals were sacrificed by cervical dislocation and then the whole liver tissue was isolated immediately in the cold room. The isolated whole liver tissue was used for the following estimations.

Estimation of serum aspartate amino transferase (AST) and alanine amino transferase (ALT)

The activity of AST and ALT was determined by adopting the method of King [22]. 1 ml of substrate (AST-1.33g of L-aspartic acid and 15 mg of α- Ketoglutaric acid were dissolved in 20.5 ml of phosphate buffer and 1N sodium hydroxide to adjust pH 7.5 and made upto 50 ml with phosphate buffer; ALT – 1.78g of DL-alanine and 30mg of α-ketoglutaric acid were dissolved in 20 ml of buffer. The pH was adjusted to 7.5 with 1N sodium hydroxide and made upto 100 ml with buffer. A few drops of chloroform was added) was taken in a clean test tube and it was incubated for 5 minutes at 37°C. Then 0.2 ml of serum was added in the test tube and incubation was maintained for an hour in the case of AST and 30 minutes for ALT. The reaction was arrested by adding1.0 ml of DNPH reagent and then the tubes were kept at room temperature for 20 minutes. Then 10 ml of 0.4N sodium hydroxide solution was added and the colour developed was read at 520 nm against a reagent blank in UV spectrophotometer. Pyruvic acid was also treated in similar manner for the standard. The activities of serum AST and ALT are expressed as U/L of serum.

Assay of alkaline phosphatase (ALP) in serum

Serum ALP was assayed by the method of King [22]. 1.0ml of buffer substrate was added to 0.2 mL of serum and incubated at 37°C for one hour. The tubes were removed and 1.0 mL of 10% TCA was added, mixed and centrifuged to 10 minutes 1.0 mL of supernatant was

treated with 1.0 mL ammonium molybdate and 0.4 mL of ANSA. A system devoid of enzyme served as control. A series of potassium dihydrogen phosphate standards in the concentration of 2-8 μg were also processed similarly. The absorbance was measured in spectrophotometer at 620 nm.

Estimation of total protein in serum

The total protein content in serum and tissues was estimated by adopting the method of Lowry *et al* [23]. The tissues was isolated from the experimental animals and then homogenized in cold 10% TCA solution. The homogenized tissues were centrifuged for 15 minutes at 3000rpm. The supernatant was discarded and the precipitate was taken and then dissolved in 1.0 ml of 0.1 N NaOH. From this 0.5 ml of supernatant (0.5 ml of serum-in case of serum separated from blood) was mixed with 4.0 ml of alkaline copper reagent. This was allowed to stand at room temperature for 10 minutes. Then 0.5 ml of folin-ciocalteu reagent was added and mixed well. The absorption of blue colour developed was read in an UV spectrophotometer at 620 nm. Standards in the concentration range of 20-100 μg were treated in a similar manner along with blank containing 1.0 ml of distilled water. The protein content was expressed as g/dl in serum and mg/g wet wt. of tissue.

Estimation of lipid peroxidation

The level of lipid per oxidation in liver tissue was estimated with the method of Nichens and Samuelson [24]. The tissue homogenate was prepared in tris – HCL buffer (pH 7.5). 1 ml of the tissue homogenate was taken in a clean test tube and 2.0 ml of TBA-TCA-HCL reagent was added and then mixed thoroughly. The mixture was kept in a boiling water bath (60°C) for 15 minutes. After cooling, the mixture was centrifuged at 1000 rpm for 10 minutes and the supernatant was taken to read the absorbance of the chromophore at 535 nm againist the reagent blank in a UV visible spectrophotometer (Spectronic –20, Bausch and Lamb). 1, 1', 3, 3' tetra methoxy propane was used to construct the standard graph.

Estimation of reduced glutathione

The glutathione (reduced) in whole liver tissue was determined according to the method of Beutler and Kelley [25]. The tissue was homogenized in PBS buffer solution and centrifuged at 2500 rpm for 5 minutes. 0.2 ml of the sample (supernatant) was taken n a clean test tube and 1.8 ml of EDTA solution was added. To this 3.0 ml of precipitating reagent was added and mixed thoroughly and kept for 5 minutes before centrifugation at 3000 rpm for 10 minutes. In each test tube, 2.0 ml of the filtrate was taken and to this 4.0 ml of 0.3M disodium hydrogen phosphate solution and 1.0 ml of DTNB reagent were added. The appearance of yellow colour was read at 412 nm in UV-visible spectrophotometer (Spectronic-20, Bausch and Lamb). A set of standard solution containing 20-100 μg of reduced glutathione was treated similarly.

Statistical analysis

Data were subjected to analysis of variance (ANOVA) followed by Duncan's Multiple Range Test (DMRT) [26]. All statistical tests were considered significant at 5% level ($P < 0.05$).

Results

Level of aspartate transaminase (AST) in serum

In the normal untreated control rat, *Rattus norvegicus,* the level of AST in serum was 17.08±1.09 (mg/dl). At sub-lethal dose of mercuric chloride fed animal shows the increased level of AST (50.12±1.53, $P<0.05$) as compared to normal rats. But during the recovery period, (Mercuric chloride followed by taurine mercuric chloride followed by glutathione), the increased level of AST was attained to reach near normal level ($P<0.05$) as compared to mercury intoxicated rats. Taurine and glutathione alone treatment shows the normal level of AST in serum (Table 1).

Level of alanine transaminase (ALT) in serum

In the normal untreated control rat, *Rattus norvegicus*, the level of ALT in serum was 41.13±1.52 (mg/dl). At sub-lethal dose of mercuric chloride fed animal shows an increased level of ALT (122.45±1.94, $P<0.05$) as compared to normal rats. But during the recovery period, the increased level of ALT was decreased to reach near normal level ($P<0.05$) as compared to mercury treated rats. Taurine and glutathione alone treatment also shows the similar type of trend (Table 1).

Level of alkaline phosphatase (ALP) in serum

In the normal untreated control rats, *Rattus norvegicus*, the level of ALP activity was 111.76±0.38 (mg/dl). At sub- lethal dose of mercuric chloride treated animal shows an increased level of ALP content (290.64±0.27mg/dl) $P<0.05$) as compared to control rats. But during the recovery period, the increased level of ALP was decreased attained to reach near normal level ($P<0.05$). Taurine and glutathione alone treatment also shows the similar type of trend (Table 1).

Level of total protein in serum

In the normal untreated control rats, *Rattus norvogicus,* the level of total protein in the serum of rats 7.09±1.45 (g/dl). At sub-lethal dose of mercuric chloride treatment decreased level of total protein content (6.05±0.99; *P*< 0.05) was noticed in the serum of mercury intoxicated animal. During the recovery period, the decreased level of total protein content was slowly increased to reach normal level. Taurine and glutathione alone treatment also shows the similar type of trend (Table 1).

Table 1. Effect of taurine and glutathione in the serum of mercury intoxicated rats

Parameters	Control	$HgCl_2$	$HgCl_2$ + Taurine	$HgCl_2$ + Glutathione	Taurine	Glutathione
AST(U/l)	17.08±1.09	50.12±1.53	29.81±1.23*	30.16±1.04	17.16±1.03	17.85±1.62
ALT(U/l)	41.13±1.52	122.45±1.94	65.46±1.46*	67.21±1.53	38.86±1.63	38.98±1.56
ALP U/L	111.76±0.38	290.64±0.27*	121.64±0.37**	128.51±1.07	110.91±0.39	111.06±1.47
Protein(g/dl)	7.09±1.45	6.05±0.99*	7.01±1.56**	7.24±1.47	6.71±0.98	6.94±1.07

Mean ± S.D of six individual observations Significance *(P<0.05) Group II compared with group I Significance **(P<0.05) group III compared with group II

Table 2. Level of lipid peroxidation (nmoles/g wet tissue) and glutathione (μmoles/g wet tissue) in the liver tissue of rats treated with mercuric chloride followed by taurine and glutathione

Parameters	Control	HgCl2	HgCl2 + Taurine	HgCl2 + Glutathione	Taurine	Glutathione
LPO	1.81±0.10	3.50±0.52*	1.73±0.06**	1.63±0.84**	1.70±0.09	1.61±0.87
GSH	30.58±0.93	20.55±0.29*	30.85±0.74**	29.46±0.64**	34.46±0.11	33.43±0.56

Mean ± S.D of six individual observations Significance *(P<0.05) Group II compared with group I Significance **(P<0.05) group III compared with group II

Level of lipid peroxidation (LPO) in liver tissue

In the normal untreated control rat, *Rattus norvegicus,* the level of LPO in liver tissue was 17.08±1.09 (μmole/g wet wt.of tissue). At sub-lethal dose of mercuric chloride fed animal shows the increased level of LPO (50.12±1.53, *P*<0.05) as compared to normal rats. But during the recovery period (Mercuric chloride followed by taurine; Mercuric chloride followed by glutathione) the increased level of LPO was attained to reach near normal level (*P*<0.05) as compared to mercury intoxicated rats. Taurine and glutathione alone treatment also shows the similar type of trend (Table 2).

Level of reduced glutathione (GSH) in liver tissue

In the normal untreated control rats, *Rattus norvogicus,* the level of GSH in the liver of rats 7.09±1.45 (μnmole/g wet wt.of tissue). At sub-lethal dose of mercuric chloride treatment decreased level of GSH content (6.05±0.99; *P*<0.05) was noticed in the liver tissue of mercury intoxicated animal. During the recovery period, the decreased level of GSH content was increased to reach normal level. Taurine and glutathione alone treatment also shows the similar type of trend (Table 2).

Discussion

Mercury is a transition metal and it promotes the formation of reactive oxygen species (ROS) such as hydrogen peroxides. These ROS enhances the peroxides and reactive hydroxyl radicals [27]. These lipid peroxides and hydroxyl radical may cause cell membrane damage and thus destroy the cell. Mercury also inhibits the activities of free radical quenching enzymes catalase, superoxide dismutase and glutathine peroxidase [28]. It is generally accepted that the consumption of contaminated fish is the primary route of exposure to mercury for humans. However, in some countries or areas, rice consumption is also an important pathway of mercury exposure, especially for inland people or people who live in undeveloped areas. In most of the area, limited by family income, fish is rarely presented in people's daily diets, and rice becomes the most important energy source than any other single food or vegetable. In the present work, AST, ALT and ALP in serum were significantly increased (Table 1) and enhancement of LPO content and simultaneously decreased level of GSH, CAT, GPx and SOD were observed in mercury intoxicated animals (Table 2). These results suggested that the mercury induced hepatotoxicity and oxidative stress in animals. AST, and ALT, also serve as biomarkers for liver function.

Mercury intoxication showed a significant increase in AST, ALT and ALP activities. These results may be due to hepato cellular necrosis which causes increase in the permeability of cell membrane resulting in the release of these enzymes in the blood stream [29,30,31] have also observed similar type of results in rat serum when treated with cadmium. They are also observed that the liver

damage is mainly responsible for elevating the AST ALT, and ALP level in Cd intoxicated animals serum [32,33]. However, the levels of TBARS and GSH in the liver are additional indicators of liver injury. TBARS is an end product of lipid peroxidation. The level of TBARS of the plasma and liver was increased with the increasing dose of cadmium and the level of TBARS of the plasma was also increased with exposure time. Other paper also indicated that cadmium might increase the level of TBARS in the tissues of experimental animal [34,35].

The level of TBARS in the plasma and liver of rat was significantly reduced when the rats were fed diet with the supplement of taurine. The level of GSH in the liver of rats was reduced by contaminated cadmium, which was similar to that of other report [34, 36]. In the present study, the high correlation of mercury and taurine in rat liver indicated that taurine most likely playing an important role in the metabolism and toxic effects of mercury. Further biochemical studies showed that dietary exposure gave rise to different changes of antioxidants. These biochemical responses may represent a presence of oxidative stress through providing protective effects Rana et al [30]. However, the alteration of SOD was different from GSH-Px and GSH. The most likely explanation was that selenium playing a crucial role. Selenium presents in the active site of GSH-Px, and is essential for its catalytic activity, therefore, it acts as a cofactor of this key antioxidant enzyme in which it contributes both catalytic activity and spatial conformation [37]. Moreover, mercury treatment produced a significant elevation in hepatic TBARS and a decline in GSH, GSH-Px, and catalase concentration suggesting a role of oxidative stress in mercury hepatotoxicity. The relationship between oxidative stress and hepatotoxicity is patent in the present investigation, where an increase in indices of oxidative stress is positively correlated with biochemical parameters characteristic of hepatotoxicity (Table 2).

Lipid peroxidation is a chemical mechanism capable of disrupting the structure and the function of the biological membranes that occurs as a result of free radical attack on lipids. The ability of mercury to produce ROS was indicated in our study by the increased amount of hepatic lipid peroxides measured as TBARS. Other studies have demonstrated that intracellular generation of peroxides, mainly hydrogen peroxide (H2O2), could be involved in the initiation of mercury hepatotoxicity in vitro [38,39] and in vivo [40,41]. When ROS begin to accumulate, hepatic cells exhibit a defensive mechanism by using various antioxidant enzymes. The main detoxifying systems for peroxides are catalase and GSH [18]. In the current study, depletion of GSH stores can account for the inhibition of GSH-Px activity. In addition, high levels of peroxides may explain catalase activity inhibition [18]. Taurine supplementation in our study significantly differed. This was clearly manifested by the improvement in all the biochemical variables determining mercury (Table 1). In addition, taurine inhibited lipid peroxidation, diminished the decrease in catalase and GSH-Px activities, and abrogated GSH depletion induced by mercury .Consistent with our finding, taurine has been demonstrated to protect against hepatotoxicity induced by several free radicals generating insults including lipopolysaccharide [42], acetaminophen [43], thioacetamide [44], and ischemia/reperfusion [45]. Moreover, the antioxidant effect of taurine was shown in other organs including the lung [46], kidney [47], and heart [48].

Taurine has been demonstrated to function as a direct antioxidant that scavenges or quenches oxygen free radicals, thus inhibiting lipid peroxidation, and as an indirect antioxidant that prevents the increase in membrane permeability resulting from oxidant injury in many tissues including liver [45]. Taurine might stimulate s-nitrosylation of GSH producing s-nitrosoglutathione, which is approximately 100times more potent than the classical GSH. In addition, s-nitrosylation of cysteine residues by nitrosoglutathione can inactivate caspase-3, thus preventing hepatic cell apoptosis. As an indirect antioxidant, taurine has been proposed as a membrane stabilizer that can maintain membrane organization, prevent ion leakage and water influx, and subsequently, avoid cell swelling [45,48]. The stabilizing effect of taurine on cellular membrane has been suggested to be associated with the interaction between taurine and polyunsaturated fatty acids in the membrane, which results in an increase in the affinity of taurine for its carrier transport and the interaction between taurine and the sites related to anion transport and water influx. This property of taurine may also partly account for its protection against mercury-induced hepatocyte necrosis. On the other hand, taurine can also function as a regulator of intracellular calcium homeostasis [10].

Taurine has been shown to protect against endothelial cell death by modulating intracellular calcium fluxes [49,50,51]. Finally, taurine may ameliorate mercury-induced hepatic injury by enhancing the activities of endogenous antioxidants. Support for this concept comes from our results, which show that taurine produced a remarkable significant increase in hepatic GSH level and GSH-Px and catalase activities. This could be attributed to the role of taurine in maintaining a normal IGF-I level [52] and its antioxidant action against lipid peroxidation, thus conserving the internal antioxidants system. The stimulatory effect of taurine on endogenous antioxidants was reported by others [47,53].

Together, the results of the present study demonstrate that administration of taurine has a therapeutic role in preventing cyclosporine-induced hepatotoxicity, possibly through its unique cytoprotective properties such as antioxidant activity.

In conclusion, we suggest that: (a) the imbalance between production of oxygen free radicals and the endogenous antioxidant defense system, as a result of the effect of mercury, is the main mechanism responsible for peroxide accumulation and hepatotoxicity; and (b) taurine reduces the oxidative stress through the inhibition of lipid peroxidation (a widely known mechanism) but also through the increase of the activity of catalase and GSH-Px which replenish GSH stores and allow for the correct cell defense against ROS. The present study concludes that taurine protects the mercury induced toxicity in rats than glutathione.

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