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PROTECTIVE ROLE OF TAURINE AGAINST MERCURIC CHLORIDE INTOXICATED RATS

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Abstract

The present study has been designed to investigate the influence of taurine on mercury intoxicated kidney tissue of rats (*Rattus norvegicus*). At sub-lethal dose of mercuric chloride (2mg/kg body weight) treatment, creatinine, and blood urea nitrogen (BUN) and lipid peroxidation (LPO) contents were significantly increased in serum and kidney tissues respectively. And simultaneously, reduced glutathione (GSH) content, glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD) activities were significantly decreased due to rupture of kidney tissue caused by mercury poison. During the recovery period, mercury chloride intoxicated rats were again treated with taurine (50mg/kg body weight) for another 15 days. It shows the remarkable recovery of the animal from the adverse effect of mercury toxicity. An enhanced level of LPO content and altered level of antioxidant system were restored to near normal level in mercury intoxicated animals. The result suggested that taurine play a vital role to reduce the toxic effect of mercury in the kidney tissue of rats.

Key Words: Mercury; Taurine; Rat; Antioxidants; LPO; BUN; Creatinine.

Introduction

Mercury is potent toxic agents that are released into the environment mainly through anthropogenic action [1]. The symptoms of nephrotoxicity caused by mercury in man and experimental animals reflect reabsorptive and secretary defects largely concentrated in peroximal tubules. The system caused by mercury included phosphaturia, glucosuria, ketonuria, protenuria, and wasting of various cations, has been found in nephrotoxicity induced by heavy metals [2,3]. Heavy metals are known to induce cell injury in the kidney and may be significant contribution to nephrotoxicity [4,5]. The protein which are blocked by heavy metal action on the protein of plasma membrane tissue to form metal-binding complexes in the kidney [6]. Once the complex is formed it may cause cellular damage in the respective tissue. Mercury poisoning leads to renal disturbances in various animals by the way of forming these types of complexes [7]. Mercury has been recognized as a hazardous environmental pollutant. The toxicity of mercury compounds is thought to be due to their high affinity for cysteine thiol functions [8]. Exposure of animals to mercuric compounds induces an oxidative stress, which was monitored by the accumulation of lipid peroxidation products [9], production of active oxygen species [10] and decreases in antioxidant enzymesw [11]. Mercury is environmental pollutants with significant health effects in humans, including nephrotoxicity [12].

Taurine (2 – amino ethane sulphonic acid) is the major free intra cellular amino acid which is found in millimolar concentration in many animal tissues [13]. It is essential sulfonated beta amino acid derived from methionine and cysteine metabolism [14]. Metabolic actions of taurine include bile acid conjugation, detoxification, membrane stabilization, osmoregulation, and modulation of cellular calcium level [15,16]. Clinically, taurine, which achieves good uptake via oral supplementation, has been used with varying degrees of success in the treatment of the following conditions

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cardiovascular disease, hypercholestrolemia, epilepsy disease, Alzheimer's disease, hepatic disorder, alcoholism, and cystic fibrosis [15,17]. It plays various important physiological role including osmoregulation, bile acid conjugation, modulation of the central nervous system, cell proliferation, viability and prevention of oxidant – induced injury in many tissues [16,18,19]. The beneficial effect of taurine as an antioxidant in biological system have been attributed to its ability to stabilize biomembranes [13] and also scavenging reactive oxygen species [20,21] in animals. Within this point of view, the present work has been designed to study the efficacy of taurine on mercury intoxicated kidney tissue for the incidence of antioxidant system.

2. Materials and Methods

Chemicals

Mercuric chloride ($HgCl_2$), Taurine and all other necessary reagents of analytical grade were bought from HiMedia laboratories Ltd. Mumbai, India.

Animals

The Wister strain rats (45 days old) of the Wister strain weighing ranging from 200±5g were used in this experiments. They were divided at random into four 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) of RMMCH, 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 15 days single dose)-treated group (Hg); Group-III Mercuric chloride (2 mg/kg orally single dose) + Taurine (50 mg/kg daily orally. for 10 days) treated group (Hg +taurine), Group-IV taurine (50 mg/kg daily for 10 days)-treated control group.

Experimental protocol was approved by the Institutional Animals Ethics Committee (IAEC) of RMMCH, 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 kidney tissue was isolated immediately in the cold room. The isolated whole kidney tissue was used for the following estimations.

Assay of blood urea nitrogen (BUN) in serum

Blood urea nitrogen in serum was estimated by the method of Skeggs [22]. 0.5 ml of serum was taken in the 60 ml glass bottle stoppers are placed 2 ml of protein free filtrate solution from unknown and blank bottles. To each bottle is added 8.5 ml of distilled water and the solution is well mixed. With constant rotating of the bottle 8.5 ml of diacetyl monoxime solution is added. The contents are thoroughly mixed. Again with constant rotating of the bottles, 8.5 ml of arsenic sulfuric acid solution is added and thoroughly mixed. The stoppered bottles are placed in a constant temperature bath of 100°C for exactly 20 minutes. The bottles are then allowed to gradually cool in ambient air for at least 15 minutes and then cooled in a 25°C water bath for at least another 15 minutes. These bottles are kept away from direct light during the heating and cooling periods. The yellow colour developed was read at 475 nm in spectrophotometer against reagent blank. A series of standards containing 10 to 60 mg/100ml of urea nitrogen processed similarly

Estimation of creatinine in serum

Serum creatinine was estimated by the method of Bonses and Taussly, [23]. Diluted 1.0 ml of serum with 1 ml of distilled water and precipitated the protein by adding 1.0 ml of 10% sodium tungstate and 1.0 ml of 2 N sulphuric acid. The contents were mixed well and centrifuged. To 3.0 ml of tungstate filtrate, 2.0ml of picric acid solution and 2.0 ml of 0.75 N sodium hydroxide were added. The yellow colour developed was read at 540nm in a spectrophotometer after 30 minutes along with a series of standards containing 10-50 μg of creatinine. Blank contained 3.0 ml of water and was processed similarly.

Estimation of lipid peroxidation

The level of lipid per oxidation in kidney tissue was estimated with the method of Nichens and Samuelson[24]. Whole kidney 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 kidney tissue was determined according to the method of Beutler and Kelley [25]. The kidney 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.

Estimation of glutathione peroxidase

The activity of glutathione peroxidases was assayed using the method of Rotruck *et al*. [26]. The liver tissue was homogenized in PBS buffer and centrifuged at 2500 rpm for 5 minutes. 0.2 ml of the enzyme preparation (supernatant) was taken in a clean test tube, and then was added the following enzyme mixture: The enzyme assay mixture contained 0.2 ml of phosphate buffer, 0.2 ml of EDTA, 0.1 ml of sodium azide. In the reaction, the mixture was mixed well and kept at 37°C for two minutes in an incubator. Then 0.2 ml of reduced glutathione and 0.1 ml of H2O2 were again added to the above mixture and incubated at 37°C exactly for 10 minutes. The reaction was arrested by the addition of 0.5 ml of 10% TCA. Reduced glutathione content was estimated in the supernatant obtained after centrifugation at 3000 rpm for 10 minutes. A blank was prepared similarly to which 0.2 ml of the enzyme was added after the incubation period. Reduced glutathione used to construct the standard graph.

Estimation of Catalase

Catalase was assayed colorimetrically with adopting the method of Sinha [27]. The whole kidney tissue was homogenized in phosphate buffer solution. 0.1 ml of the homogenate was taken in a test tube and 1.0 ml of phosphate buffer was added. 0.4 ml of hydrogen peroxide was added to the above mixture. After 30 and 60 seconds 2.0 ml of dichromate acetic acid reagent was added. Test tubes were kept in boiling water bath (60°C) for 10 minutes. The mixture was cooled immediately in tap water and the colour was read at 620 nm againist a reagent blank in UV-visible spectrophotometer (Spectronic-20, Bausch and Lamb).20-100μ moles of H_2O_2 is used as standard

Estimation of superoxide dismutase

The activity of superoixde dismutase was assayed with the method of Kakkar *et al*, [28]. The kidney tissue was homogenized with 3 ml of 0.25 M sucrose solution and centrifuged at 10,000 rpm in cold condition for 30 minutes. The supernatant was dialysed against Tris HCL buffer (0.0025M, pH 7.4). The supernatant, thus, obtained was used as an enzyme source. The assay mixture (2.0 ml) contained 1.2 ml of sodium pyrophosphate buffer, 0.1 ml of PMS, 0.3 ml of NBT, 0.1 ml of enzyme preparation (tissue homogenate) and 0.3 ml of water. The reaction was started by the addition of 0.2 ml of NADH solution and then it was incubated at 30°C for 90 seconds. After incubation the reaction was arrested by the addition of 1.0 ml of glacial acetic acid. The reaction reaction mixture was stirred and shaken with 4.0 ml of n-butanol. The mixture was allowed to stand for 10 minutes and then centrifuged for 15 minutes at 3000 rpm. After centrifugation, the butanol layer was separated. The colour intensity of the chromogen was measured at 560 mm in UV visible spectrophotometer (Spectronic-20, Bausch and Lamb). Water was used as blank.

Statistical analysis

Statistical significance was evaluated using ANOVA followed by Duncan Multiple Range Test (DMRT) [29].

Results

Level of Blood urea nitrogen (BUN)

In the normal untreated control rat, *Rattus norvegicus,* the level of BUN in serum was 4.62±0.15 (mg/dl). At sub-lethal dose of mercuric chloride fed animal shows the increased level of BUN (7.28±0.22, $P<0.05$) as compared to normal rats. But during the recovery period, (Mercuric chloride followed by taurine),

the increased level of BUN was attained to reach near normal level (P<0.05) as compared to mercury intoxicated rats. Taurine alone treatment shows the normal level of BUN in serum (Table-1).

Table 1. Level of BUN, Creatinine in the serum of rats treated with mercuric chloride followed by taurine

Parameters	Control	$HgCl_2$	$HgCl_2$ + Taurine	Taurine
Creatnine mg/dl	42.54±0.27	69.19±0.02*	45.73±0.72**	40.18±0.05
BUN mg/dl	4.62±0.15	7.28±0.12*	4.49±0.31**	4.82±0.21

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

Level of creatinine

In the normal untreated control rat, *Rattus norvegicus*, the level of creatinine in serum was 42.54±0.27 (mg/dl). At sub-lethal dose of mercuric chloride fed animal shows an increased level of creatinine (69.19± 0.02, p<0.05) as compared to normal rats. But during the recovery period, the increased level of creatinine was decreased to reach near normal level (P<0.05) as compared to mercury treated rats. Taurine alone treatment also shows the similar type of trend (Table-1).

Level of lipid peroxidation (LPO)

In the normal untreated control rats, *Rattus norvegicus*, the level of LPO content in the kidney tissue was 1.634±0.08 (nmole/mg tissue). At sub- lethal dose of mercuric chloride treated animal shows an increased level of LPO content (3.294±0.36, nmole/mg tissue) P<.0.05) as compared to control rats. But during the recovery period, the increased level of LPO was decreased attained to reach near normal level (P<0.05). Taurine alone treatment shows the normal level of LPO in the kidney tissue (Table-2).

Table 2. Level of lipid peroxidation and antioxidants in the liver tissue of rats treated with mercuric chloride followed by taurine

Parameters	Control	$HgCl_2$	$HgCl_2$ + Taurine	Taurine
Lipid peroxidation (nmoles/g. wet wt.of tissue)	1.634±0.08	3.294±0.31*	1.644±0.04**	1.707±0.08
Reduced glutathione (μmoles/g. wet wt.of tissue)	27.690±0.37	16.538±0.52*	27.870±0.48**	30.075±0.43
Glutathione peroxidase (μmoles/mg. protein/min)	0.136±0.01	0.105±0.01*	0.151±0.17**	0.161±0.01
Catalase (μmoles/mg. protein/min)	31.712±0.86	16.908±0.15*	31.902±0.19**	32.122±0.42
Super oxide dismutase (Units/mg. protein)	12.209±0.12	5.423±0.44*	11.180±0.40**	11.373±0.37

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

In the normal untreated control rats, *Rattus norvogicus,* the level of reduced glutathione content in the kidney tissue was 27.690± 0.37 μg/mg protein). At sub-lethal dose of mercuric chloride treatment decreased level of glutathione content (16.538±0.092; P< 0.05) was noticed in the kidney tissue of mercury intoxicated animal. During the recovery period, the decreased level of GSH content was slowly increased to reach normal level. Taurine alone treatment also shows the normal level of GSH content in the kidney tissue (Table-2).

Level of glutathione peroxidase (GPx)

In the normal untreated control rat, *Rattas norvegicus*, the level of GPX activity in the kidney tissue was 0.136±0.01 μg/mg protein). At sub-lethal dose of mercuric chloride treatment for animal shows the decreased level of GPX (0.105±, P<0.05) when compared to normal rat. during the recovery period, the decreased level of GPX activity was significantly enhanced to reach near normal level. Taurine alone treatment shows the maintained the level of GPX activity in the kidney tissue (Table-2).

Level of catalase (CAT)

The level of catalase in the normal untreated rat kidney tissue was 31.712±0.64 μmoles/ mg protein/min). At sub-lethal dose of mercuric chloride intoxicated animal kidneys tissue shows the significantly decreased level of catalase activity (16.908 ± 0.47, P<0.05). But during the recovery period, the decreased level of catalase activity was increased to reach to near normal level (P<0.05) as compared to mercury treated rats. Taurine alone treatment also shows the same trend in the level of catalase in the kidney tissue (Table-2).

Level of superoxide dismutase (SOD)

The level of SOD activity in the normal untreated rat kidney tissue was 12.209± 0.87 units /mg protein. At sub-lethal dose of mercuric chloride treatment, the intoxicated kidney tissue shows the significantly decreased level of SOD activity (5.423±0.46, P<0.05). during the recovery period, the deceased level of SOD activity was significantly elevated to reach near normal level. Taurine alone treatment also shows the normal level of SOD activity in the kidney tissue (Table 2).

Discussion

Kidney is one of the vital organs to eliminate the waste substance from the body. It also acts as a target organ in hypertension but it is caused by kidney disease. Acute ingestion of mercuric chloride induced kidney

damage ultimately leading to death. These effects include renal dysfunction, manifestation of oliguria or anuria due to acute tubular necrosis [30]. Chronic renal effects also induced proteinuria with hypoproteinuria and edema which occurs due to exposure of inorganic mercury [31]. Nephrotoxicity of mercury depends on the chemical structure of the compound, i.e., Mercuric chloride is highly nephrotoxic and often used in many animal model of acute tubular necrosis [7,32].

Blood urea nitrogen (BUN) and creatinine are the main indicators for the function of kidney [33,34]. Heavy metal mainly alter the level of this contents due to their accumulation in the kidney tissue [34,35]. Table 1 shows an enhanced level of and creatinine and BUN contents in Hg intoxicated rat serum. In the clinical plasma examination renal LPO content was also increased. These finding confirmed that renal dysfunction was mainly produced by mercury poisoning. The results might be due to the level of mercury accumulation in the kidney was significantly increased with chronic exposure of mercury. The accumulated amount of mercury is the net consequence of uptake, bio transformation and elimination process within kidney tissues. Mercury is taken up by renal cortical epithelial cells mainly via passive diffusion and also active transport. There is an increased risk of renal injury developing more severe form of the nephropathy induced by mercuric chloride. This could be, in part, to a decreased capacity to reabsorb filtered mercury, which could be an additional mechanism responsible for the decreased renal function. The same results were observed by Zalups [7]. Endo et al., [36] in the mercury treated rats. They are reported that the inorganic mercury is predominantly accumulated in the kidney, mainly in the proximal tubules and caused functional disorder. The renal accumulation of mercury involves glomerular filtration, followed by reabsorbed at the distal part of the proximal tubules [37].

Lipid peroxidation is a chemical mechanism capable of disrupting the structure and function of the biological membranes. Intracellular generation of peroxides mainly promotes hydrogen peroxides (H_2O_2), could be involved in the mercury toxicity [38]. Moreover, lipid peroxidation has been shown to contribute to nephrotoxicity [39]. The oxidative damage was caused by the increased in the level of LPO content kidney tissue. Ribarov and Binov [40] have also observed that an increased in the level of LPO content in kidney tissue of rats when treated with heavy metal. In the present study, the levels of GSH and antioxidant system were reduced. The reduced GSH stores can account for the inhibition of GPx activity. The free radicals scavenger enzyme like GPx, CAT, SOD and reduced glutathione were significantly decreased in kidney due to mercury toxicity. The inhibition of SOD by mercury may be due to interaction directly with super oxide molecules. SOD is a metabolic enzyme which depending on its sub cellular origin. Catalase is found mainly in the peroxisome and removes H_2O_2 produced during oxidation. Chandravathy and Reddy, [41] have also observed a significant decrease in catalase activity in kidney tissue of rats when treated with cadmium. Catalase is an enzyme catalyses decomposition of H_2O_2 to water and O_2 and efficient inhibitor of LPO when hydrogen peroxide accumulates in a cell containing free ferrous ions. In the present study the decreased level of catalase activity in Kidney tissue following mercury exposure may there fore be an important role in enhancing oxidative stress of cellular system. GPx is another antiperoxidative enzyme, which is present, both in cytosol and mitochondrial matrix and is found to decrease during exposure to mercury. The mercury toxicant may inhibit the GPx directly by impairing the functional groups, or indirected by rendering the supply of reduced glutathione and NADPH. During the recovery period, the level of LPO and GSH contents and GPx, CAT and SOD activities were altered by taurine. Taurine has been demonstrated to function as a direct antioxidant that scavenges oxygen free radicals, thus inhibiting lipid peroxidation, and as an indirect antioxidant that prevents the increase in membrane permeability resulting from oxidative injury in kidney [42,43]. As an indirect of antioxidant, taurine has been proposed as a membrane stabilizer that can maintain the membrane organization, prevent ion leakage and water influx and subsequently avoid cell swelling [43,44,45,46]. The accumulated amount of mercury in the kidney was effectively reduced by taurine [35] (Taurine is a special amino acid, which possesses an amino group and a sulphonate group. These functional groups might bind with heavy metal and stimulated the excretion of such compounds. In this study, it was also found that the amount of mercury in the feces of rat fed with supplement of taurine was slight increased. There is some evidence that taurine directly reduces the production of free radicals [42]. Therefore, it is reasonable to assume that taurine may act as a good

scavanger in reducing the production of lipid peroxidation induced by heavy metal [45,47,48,49]. At the same time the taurine maintain both GPx activity and detoxification at an optimum level (Table 2). From these study, we conclude that the imbalance between production of oxygen free radicals and the endogenous antioxidant system, defense system and taurine reduces the oxidative stress through inhibition of lipid peroxidation and also through the increased level of a GPx, CAT and SOD activities which replenish GSH stores and allow for the correct cell defense against ROS in mercury intoxicated animal. Hence, the supplementation of taurine may play a vital role to reduce the toxic effect of mercury in the kidney of rats.

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