

ORIGINAL ARTICLE

Protective Role of Sodium Selenite on Mercuric Chloride Induced Oxidative and Renal Stress in Rats

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Background: Reactive oxygen species are known to play a major role in mercuric chloride induced oxidative and renal stress. Sodium selenite as an exogenous source of selenium is used for endogenous selenoprotein synthesis to scavenge the free radicals. The study was designed to investigate the possible protective role of sodium selenite in mercuric chloride induced renal stress, by using biochemical approaches. Adult male *Albinos Wistar* rats were randomly divided into four groups. The first group was served as the control, the second group was given sodium selenite (0.25 mg/kg b.w), while the third group was given mercuric chloride (0.25 mg/kg), finally, the fourth group was given combined treatment of sodium selenite and mercuric chloride for 3 weeks.

Results: The effects of sodium selenite on mercuric chloride induced oxidative and renal stress were evaluated by serum creatinine, urea, uric acid, bilirubin levels and LDH activity, kidney tissue lipid peroxidation, GSH levels, GSH-Px, GST and catalase activities and hematological parameters. Administration of mercuric chloride induced significant increase in serum: creatinine, urea, uric acid and bilirubin concentration showing renal stress. Mercuric chloride also induced oxidative stress, as indicated by decreased kidney tissue of GSH level, GSH-Px, GST, and catalase activities along with increase the level of lipid peroxidation. Furthermore, treatment with mercuric chloride caused a marked elevation of kidney weight and decreased body weight and erythrocytes, hemoglobin, hematocrit levels. Sodium selenite treatment markedly reduced elevated serum: creatinine, urea, uric acid and bilirubin levels, and LDH activity and counteracted the deleterious effects of mercuric chloride on oxidative stress markers and hematological parameters and attenuated histopathological changes caused by HgCl₂ in kidney.

Conclusion: Our results indicate that sodium selenite could have a beneficial role against mercuric chloride induced nephrotoxicity and oxidative stress in rat.

Key words: antioxidant enzymes, lipid peroxidation, mercury, renal stress, sodium selenite

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Conclusion: Our results indicate that sodium selenite could have a beneficial role against mercuric chloride induced nephrotoxicity and oxidative stress in rat.

Key words: antioxidant enzymes, lipid peroxidation, mercury, renal stress, sodium selenite

Mercury is a well-known human and animal inducer of extensive kidney damage and nephrotoxicant. Acute oral or parenteral exposure induces extensive kidney damage (Fowler and Woods, 1977; Goyer and Rhyne, 1975; Magos *et al.*, 1987; Woods, 1989). Studies in vivo and in vitro have demonstrated that mercury induced lipid peroxidation, suggesting the involvement of oxidative stress in its cytotoxicity (Lund *et al.*, 1991; Stacey and Kappus, 1982; Yonaha and Sagai, 1983). Lund *et al.* (1993) reported that mercury enhances renal mitochondrial hydrogen peroxide formation in vivo and in vitro. However, causative correlation between mercury induced lipid peroxidation and cellular toxicity remains controversial. Some authors reported that lipid peroxidation plays a critical role in cell injury induced by mercury (Lund *et al.*, 1991) in renal cells, whereas other investigators showed that lipid peroxidation is not directly responsible for mercury induced cell injury in hepatocytes and renal cells (Paller, 1985; Strubelt *et al.*, 1996). It is believed that antioxidants should be one of the important components of effective treatment for mercury poisoning. Indeed, HgCl₂ induced injury can be ameliorated by superoxide dismutase (Girardi and Elias, 1995) and non-enzymatic antioxidants like vitamin C, Vitamin E, cysteine and selenium (Karin and Elias Armer, 2003) have proven helpful to overcome oxidative damage.

Selenium (Se) appears in various forms such as selenite, selenate, selenomethionine, and selenocysteine and it is considered as an essential trace element for living organism, including humans, because it forms part of several enzymes such as glutathione peroxidase (GSH-Px), iodotyrosine 5'-deiodinase (Cabanero *et al.*, 2004), and thioredoxin reductase (Rotruck *et al.*, 1973; Xia *et al.*, 2003; Perottoni *et al.*, 2004a). Se plays a very important

part in human body despite its slight content of about 14-20 mg. The need for Se in human and animal nutrition is well recognized. Organoselenium compounds such as selenoamino acids and derived compounds are one of the chemical forms of the selenium in foods (Block *et al.*, 2001; Perottoni *et al.*, 2004b). Se has been found to have detoxification effects on various heavy metals (Diplock *et al.*, 1986). The interaction between Hg and Se in the body of mammals has been known for more than three decades, and it may be involved in a variety of toxicological and biochemical processes. Previous studies reported the co-accumulation of Se and Hg in different tissues of various biotas (Chem *et al.*, 2006). Since Parizek and Ostadova (1967) found that the toxicity of inorganic mercury was decreased by simultaneous injection of selenite, many studies have been carried out to examine the role of Se in the detoxification of Hg, which have led to many hypotheses about the mechanism of this interaction (reviewed by Curin-Aralar and Furness, 1991; Juresa *et al.*, 2005). The purpose of this study was to evaluate the protective role of selenium on mercury chloride induced oxidative and renal stress in rats.

MATERIALS AND METHODS

All chemicals used in this work were purchased from Sigma Chemical Company. Laboratory animals, *Albino Wistar* male rats, were brought from the Algiers Pasteur Institute at the age of 8 weeks, with an average live weight of 200g. They were located in a room with an ambient temperature of 21±1°C and up to 12h of light daily. The rats were divided into four experimental groups; each consists of eight rats. The first group was served as the control. The second group was given sodium selenite at a dose of 0.25 mg/kg body weight, while the third group (HgCl₂) was intraperitoneally given mercuric

chloride at a dose of 0.25 mg/kg body weight. Finally, the fourth group was given combined treatment with sodium selenite and mercuric chloride. The treatment of all groups was lasted for 3 consecutive weeks.

Twenty four hours after the last administration, blood was collected by retro-orbital sinus puncture into two vials, from each anesthetized rat. Blood samples were collected into non-heparinized tubes. After centrifugation at 3000 rpm for 10 min, the serum was separated immediately and stored at 20°C until determination of urea, creatinine, uric acid and bilirubin levels and LDH activity. And into EDTA tubes, for determination of hematological parameters. Subsequently, rats were decapitated and kidneys were removed.

Tissue preparation

About 500 mg of kidney was homogenized in 4 ml of buffer solution of phosphate buffered saline (w/v: 500 mg tissue with 4 ml PBS, pH 7.4) homogenates were centrifuged at 10,000xg for 15 min at 4°C. And the resultant supernatant was used for determination of: reduced glutathione (GSH), Thiobarbituric acid-reactive substance (TBARS) level, and glutathione peroxidase (GSH-Px), glutathione-S-transferase (GST) and catalase activities.

Determination of Biochemical parameters

Serum urea, creatinine, uric acid and bilirubin levels and LDH activity were determined spectrophotometrically using an automated analyzer.

Determination of hematological parameters

Hematological parameters were determined spectrophotometrically using an automated analyzer.

Determination of lipid peroxidation (LPO)

Lipid peroxidation level in the liver was

measured by the method of Buege and Aust (1978). 125 µl of supernatant were homogenized by sonication with 50 µl of PBS, 125 µl of 20% TCA + BHT 1% (TCA-BHT) in order to precipitate proteins, and centrifuged (1000xg, 10 min, 4°C), afterwards, 200 µl of supernatant were mixed with 40 µl of HCl (0.6M) and 160 µl of TBA dissolved in Tris (120 mM), and then the mixture was heated at 80°C for 10 min, the absorbance of the resultant supernatant was obtained at 530 nm. The amount of TBARS was calculated using a molar extinction coefficient of 1.56×10^5 M/cm.

Determination of reduced glutathione (GSH)

GSH content in liver was measured spectrophotometrically by using Ellman's reagent (DTNB) as a coloring reagent, following the method described by Weeckbeker et Cory (1988).

Determination of glutathione-S-transferase (GST) (EC2.5.1.18)

The cytosolic glutathione-S-transferase activity was determined spectrophotometrically at 37°C by method of Habig *et al* (1974). The reaction mixture (1 ml) contained 0.334 ml of 100 mM phosphate buffer (pH 6.5), 0.033 ml of 30 mM CDNB and 0.33 ml of reduced glutathione. After pre-incubating the reaction mixture for 2 min the reaction was started by adding 0.01 ml of diluted cytosol and the absorbance was followed for 3 min at 340 nm. The specific activity of GST is expressed as µmole of GSH-CDNB conjugate formed/ min /mg protein using extinction coefficient of $9.6 \text{ M}^{-1} \text{ cm}^{-1}$

Determination of GSH-Px (E.C.1.11.1.9)

Glutathione peroxidase (EC 1.11.1.9) activity was modified from the method of Flohe and Gunzler (1984). For the enzyme reaction, 0.2 ml of the supernatant was placed into a tube and mixed with 0.4 ml GSH (reduced glutathione, sigma

product, analytical grade), and the mixture was put into an ice bath for 30min. Then the mixture was centrifuged for 10min at 3000rpm, 0.48ml of the supernatant was placed into a cuvette, and 2.2ml of 0.32M Na₂HPO₄ and 0.32ml of 1m mol/l 5,5'-dithio-bis(2-nitrobenzoic acid) (DTNB, sigma) were added for color development. The absorbance at wavelength 412nm was measured with a UV spectrophotometer after 5min. The enzyme activity was calculated as a decrease in GSH within the reaction time as compared to that in the non-enzyme reaction.

Determination of catalase (CAT) (EC 1.11.1.6)

It was estimated in the liver homogenate in a UV-VIS spectrophotometer as describe by Aebi (1984). The reaction mixture (1ml, vol) contained 0.02ml of suitably diluted cytosol in phosphate buffer. The specific activity of catalase has been expressed as μmol of H₂O₂ consumed/min/ mg protein. The difference in absorbance at 240nm per unit time is a measure of catalase activity.

Histopathological examination

Kidney from autopsied animals were excised out and fixed in formalin (10%). Five micron thick section were prepared by using microtome and these section were stained with hematoxyline and eosin. For histological alterations these slides were observed under light microscope.

Protein quantification

Protein was measured by the method of Bradford (1976) using bovine serum albumin as the standard.

Statistical analysis

The data were subjected to student *t* test for comparison between groups. The values are expressed as mean \pm SEM. Significance level was set at $P < 0.05$, $P < 0.01$, $P < 0.001$.

RESULTS

Effects of treatments on body, absolute and relative kidney weights

Table 1 shows the effect of mercuric chloride, sodium selenite and combined treatment with mercuric chloride and sodium selenite. The marked decreased in rats body weight was observed in mercuric chloride treated rats and mercuric chloride + sodium selenite group, but the result was not significant as compared to control. Along sodium selenite showed increased body weight but result was not significant. The kidneys of rats treated with mercuric chloride were enlarged. Mercuric chloride treated rats showed a highly significant increased kidney weight and relative kidney weight ($P \leq 0.001$) as compared to control. Combined treatment with sodium selenite showed significant increased relative kidney weight, while alone sodium selenite treatment had showed no significant effect.

Effects of treatment on serum biochemical parameters

A highly significant ($P \leq 0.001$) elevation in serum urea, creatinine, uric acid, total bilirubin and direct bilirubin levels was observed in mercuric chloride intoxicated rats. Only sodium selenite treatment did not show any significant alteration. However, the combined treatment of sodium selenite with mercuric chloride show a highly significant decline in serum urea, creatinine, uric acid, total and direct bilirubin was noticed respect to mercuric chloride treated animals (table 2). A significant ($P \leq 0.05$) elevation in serum lactate dehydrogenase activity was observed in mercuric chloride intoxicated rats. Only sodium selenite treatment did not show any significant alteration. However, the combined treatment of sodium selenite with mercuric chloride results a decline in serum lactate dehydrogenase

activity was noticed respect to mercuric chloride treated animals (table 2).

Effects of treatments on hematological parameters

Mercuric chloride exposure induced a highly significant depleted in red blood cells (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), platelet (PLT) contents and a significant increase in white blood cells (WBC), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), lymphocyte (LYM) levels in mercury intoxicated rats was noticed. Sodium selenite alone treatment did not show any significant decline. In combined treatment of mercuric chloride with sodium selenite, a significant increase in RBC, HGB, HCT, MCV, PLT contents and no significant depletion in WBC, MCH, MCHC, LYM levels was recorded with respect to mercury intoxicated rats (table 3).

Effects of treatments on renal oxidative stress parameters

Mercuric chloride exposure a significant depleted in reduced glutathione level, GSH-Px, GST and catalase activities. And highly significant

increase in kidney lipid peroxidation level in mercury intoxicated rats was noticed. Sodium selenite alone treatment did not show any significant decline. In combined treatment of mercuric chloride with sodium selenite highly significant increase in reduced glutathione level, GSH-Px, GST and catalase activities. And significant depletion in lipid peroxidation level was recorded with respect to mercury intoxicated rats (Fig.1 and 2).

Histological studies

The histological change in kidney are presented in Fig. 3. Mercuric chloride induced various pathological alterations in kidney of rats. This alteration were characterized by renal tubular damage, indicating by degeneration of tubular cells (Fig 3.C). In combination group were sodium selenite was administration with mercuric chloride showed reparative changes. Kidney showed prominent recovery in the form of normal renal tubular (Fig 3D). Kidney of the control group had a regular histological structure (Fig. 3A). Furthermore, no histological alteration were observed in the kidney of sodium selenite treated group (Fig.3B).

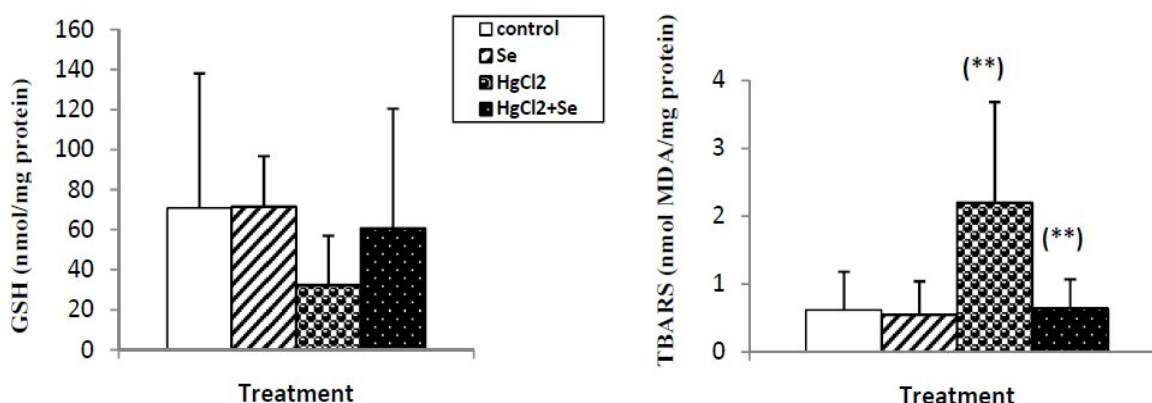


Figure 1: Reduced glutathione (nmol/ mg protein) and TBARS (nmol MDA /mg protein) levels in kidney of control and rats treated with selenium, mercuric chloride, and combined treatment of mercuric chloride with selenium after 3weeks of treatment. Values are given as mean \pm SEM for group of 8animals each significant difference: * compared to controls (*P,0.05; **P,0.01; ***P,0.001).

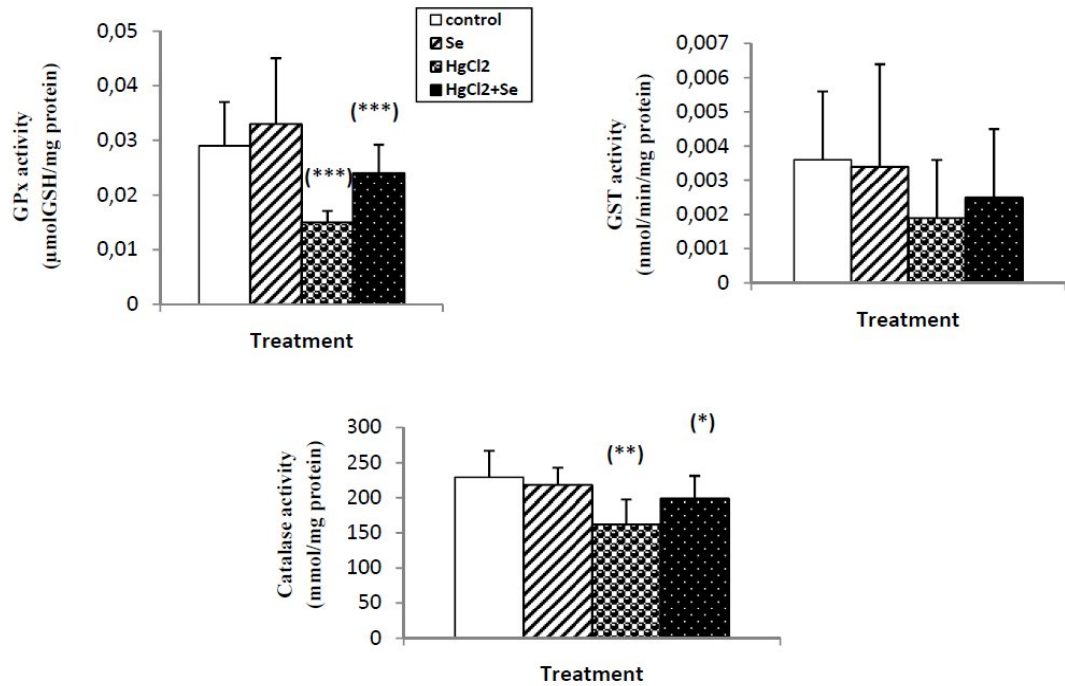


Figure 2: Enzyme activities of GPx (4mol GSH/ mg protein), GST (nmol /min/mg protein) and Catalase (mmol/mg protein) in kidney of control and rats treated with selenium, mercuric chloride, and combined treatment of mercuric chloride with selenium after 3weeks of treatment. Values are given as mean \pm SEM for group of 8 animals each significant difference: * compared to controls (*P,0.05; **P,0.01; ***P,0.001).

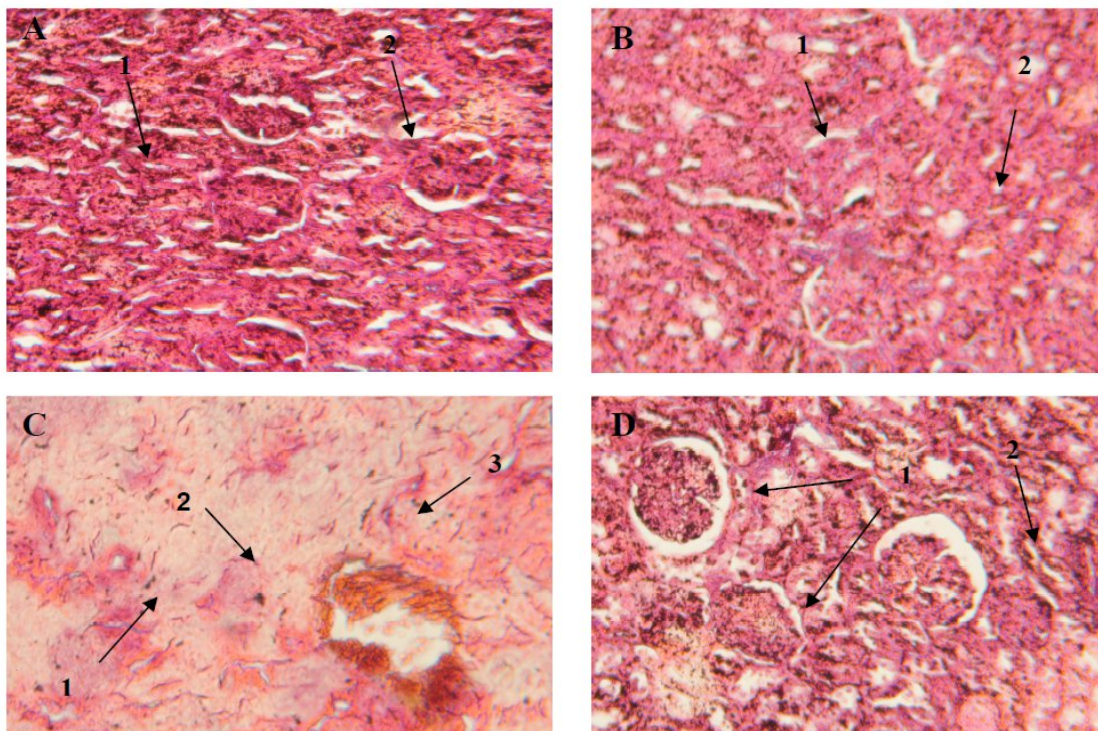


Figure 3: T.S. of kidney of male rat treated with mercuric chloride (Hg) alone, and in combination with sodium selenite . (A) control (H&E100X): showing well develop glomerulus (1), with normal tubular cells; (B) sodium selenite alone treatment (H&E 100X): showing normal glomerulus (1), and normal tubular cells; (C) mercury treatment (H&E100X): showing degeneration of tubular cells (1), loss of nucleus (2), degeneration of glomerulus (3); (D) combined treatment of mercuric chloride with sodium selenite (H&E100X): showing normal glomerulus (1), normal tubular cells (2).

Table 1: Changes in body and absolute and relative kidney weights of control and rats treated with selenium (Se), mercuric chloride, and combined treatment of mercuric chloride with selenium after 3 weeks of treatment.

Parameters	Treatment groups			
	Control	Se	HgCl ₂	HgCl ₂ +Se
Initial body weight (g)	240.13±37.1	241.3±36.1	240.87±25.3	240.81±21.5
Final body weight (g)	244.03±32.2	247.16±30.2	229.48±14.8	231.61±18.4
Absolute kidney weight (g)	1.81±0.18	1.71±0.23	2.2±0.19***	1.86±0.26**
Relative kidney weight (g/100g b.w)	0.75±0.15	0.69±0.12	0.95±0.11***	0.8±0.1**

Values are given as mean ± SEM for group of 8 animals each. *P≤0.05 compared to controls. **P≤0.01 compared to controls. ***P≤0.001 compared to controls.

Table 2: Changes in biochemical parameters of control and rats treated with selenium (Se), mercuric chloride, and combined treatment of mercuric chloride with selenium after 3 weeks of treatment.

Parameters	Treatment groups			
	Control	Se	HgCl ₂	HgCl ₂ +Se
Urea (g/l)	0.47±0.062	0.47±0.062	0.89±0.039***	0.61±0.046***
Creatinine (mg/l)	2.68±1.02	2.38±0.72	7.13±2.5 ***	4.87±1.54*
Uric acid (mg/l)	21.67±4.10	23.93±4.63	45.7±2.22***	33.10±3.03***
LDH (U/l)	409.25±208	399.64±175	606.53±204*	540±160
Total Billirubin (mg/l)	1.84±0.15	1.73±0.35	3.59±0.35***	2.56±0.19***
Direct Billirubin (mg/l)	0.35±0.11	0.28±0.09	0.73±0.03***	0.53±0.10***

Values are given as mean ± SEM for group of 8 animals each. *P≤0.05 compared to controls. **P≤0.01 compared to controls. ***P≤0.001 compared to controls.

Table 3: Changes in Hematological parameters of control and rats treated with selenium, mercuric chloride, and combined treatment of mercuric chloride with selenium after 3 weeks of treatment.

Parameters	Treatment groups			
	Control	Se	HgCl ₂	HgCl ₂ +Se
WBC (10 ³ /μl)	8.35±1.94	7.39±2.69	13.66±3.88**	11.22±2.69
RBC (10 ⁶ /μl)	10.08±0.61	9.8±0.92	9.18±0.59**	8.61±0.34*
HGB (g/dl)	17.26±0.38	16.38±1.67	15.26±0.6***	15.36±0.64
HCT (%)	56.05±1.37	53.6±5.32	47.66±3.06**	48.28±3.06
MCH (Pg)	17.16±1.05	17.38±0.84	18.38±0.45*	17.83±0.81
MCV(fl)	55.59±2.04	54.79±2.81	51.18±3.06	51.46±3.81
MCHC (g/dl)	30.71±0.97	30.74±1.15	33.39±9.76	31.82±0.95
PLT (10 ³ /μl)	839.62±155	819.75±792	648.62±266*	766±131
LYM (%)	45.46±3.70	44.21±2.78	67.6±12.3 ***	61.68±5.83*

Values are given as mean ± SEM for group of 8 animals each. *P≤0.05 compared to controls. **P≤0.01 compared to controls. ***P≤0.001 compared to controls.

DISCUSSION

In the present study, oxidative stress induced by HgCl₂ was evidenced in kidney of rats by increase in

lipid peroxidation level and the stimulation of GSH-Px, GST and catalase activities. Accordingly, oxidative stress induced by HgCl₂ has been previously reported (Lund *et al.*, 1993; Sener *et al.*,

2007). As a consequence of lipid peroxidation biological membranes are affected causing cellular damage, release of LDH to extracellular media. And increased activity of this enzyme in the blood (Kaplan and Pesce, 1996). Renal damage observed in rats exposed to HgCl_2 was also evidenced by increase in the plasmatic levels of urea, creatinine and uric acid, which are renal markers of damage. It has been reported that mercury can cause hematological alteration, such as hemolysis of red blood cells (Zolla *et al.*, 1997). In this study, toxicity induced by HgCl_2 was marked by hematological alterations in rats, demonstrated by the reduction in erythrocyte, hemoglobin and hematocrit counts, indicating anemia. To support the hypothesis of hemolytic anemia, bilirubin content was evaluated. Rats treated with HgCl_2 presented an increase in bilirubin content, one of the most sensitive parameters that reflect the prognosis of acute hepatic disease (Batra and Acharya, 2003). In the present study, the hyperbilirubinemia observed is mostly of the indirect (unconjugated) category. This could be attributable to hemolysis. Which demonstrate no variance on size of erythrocytes, and MCV, MCH and MCHC values, excluding evidence of iron deficient anemia (Brugnara, 2000). A reduction in other hematological parameters platelet and increase in leukocyte, lymphocyte counts were demonstrated in HgCl_2 exposed rats. It is known that mercury can induce abnormal responses in the immune system, including leukocyte count, a marker of cellular defense (Friberg and Enestrom, 1991; WHO, 1991). In the present study, serum urea, creatinine, uric acid levels were significantly increased after 3 weeks mercuric chloride (0.25mg/kg), showing insufficiency of renal function. Studies in animals have established that tubular injury plays a central

role in the reduction of glomerular filtration rate in acute tubular necrosis. Two major tubular abnormalities could be involved in the decrease in glomerular function in mercuric chloride treated rats: obstruction and backleak of glomerular filtrate (Girardi and Elias, 1995). The alterations in glomerular function in mercuric chloride treated rats may also be secondary to ROS (reactive oxygen species), which induce mesangial cells contraction, altering the filtration surface area and modifying the ultrafiltration coefficient factors that decrease the glomerular filtration rate (Stohs and Bagchi, 1995; Zalups, 2000). No significant change in renal and hematological parameters after treatment of sodium selenite in mercuric chloride treated rats showed the evidence for correction of toxicity developed by mercuric chloride treatment. The activity of GSH-Px, GST and catalase that can clear to protect the cells from being injured represents the competence of clearing free radicals from the organism. MDA content manifests the level of lipid peroxidation, and then indirectly represents the level of damage of the cell of renal mitochondria. Evaluating from GSH, MDA levels and GSH-Px, GST, catalase activities in kidney of rats. Hg alone significantly decreased GSH level, GSH-Px, GST, catalase activities and increased MDA content along with histological damage in kidney.

Co-administration of Hg and Se significantly increased GSH level, and activities of GSH-Px, GST, catalase and decreased MDA content. The effect of Hg and Se interaction depended on the molar ratio of these elements administered to animals. The maximal effect of Se on Hg induced nephrotoxicity was observed when Se was given the same mol as Hg. Hg can give rise to free radicals that induce lipid, protein, and DNA oxidation. Hg has a great affinity for SH groups of proteins and enzymes that

are crucial in cell metabolism. Woods *et al.* (1990a, b) have reported that in vitro Hg^{+2} both hinders the antioxidant potential of GSH and yields reactive species via thiol complexation. Lipid oxidation yields hydroperoxides and aldehydes, such as MDA (Perottoni *et al.*, 2004a). Endogenous antioxidant enzymes such as GSH-Px, GST, and catalase are involved in the protection against oxidative stress and lipid peroxidation in kidney (Pokorny, 1987). Induction of these antioxidant enzymes indicates an adaptive onset of the redox defence system, whereas inhibition is thought to contribute to oxidative stress in mouse brain following mercury intoxication (Yee and Choi, 1994; Hussain *et al.*, 1997). Se can enhance antioxidant ability by enhancing activities of antioxidant enzymes and by increasing contents of the antioxidants. Rotruck *et al.* (1973) and Xia *et al.* (2003) reported that Se is crucial in several enzymes with physiological antioxidant properties, including GSH-Px and thioredoxin. Besides, the ability of Se to reduce Hg toxicity has been extensively investigated (Cuvin-Aralar and Furness, 1991; Sasakura and Suzuki, 1998; Perottoni *et al.*, 2004a). It has been demonstrated that HgCl_2 lower the activity of the selenoenzyme GSH-Px in the renal mitochondria after prolonged treatment. Their direct inhibitory action, presumably via covalent reaction with the selenol group of the selenocysteine residue (Chandienne and Tappel, 1984) is one mechanism whereby they impair the activity of GSH-Px and possible other selenoenzymes, following prolonged exposure. Selenite treatment prevented HgCl_2 induced decline in GSH-Px activity in the renal mitochondria of rats (Santos *et al.*, 1997). The protective effect of Se against Hg induced nephrotoxicity may be related to the formation of a Se-Hg complex. This conclusion is based on previous

studies demonstrating that pre-treatment with sodium selenite increased whole retention of Hg, conceivably due to the formation of inert Se-Hg complexes (Perottoni *et al.*, 2004b). And the complexes reduced the availability of Hg (Sasakura and Suzuki, 1998; Gailer *et al.*, 2000). Yoneda and Suzuki (1997) also demonstrated that Se forms an equimolar complex with Hg in the plasma which subsequently binds to selenoprotein P. Simultaneous administration equimolar doses of sodium selenite prevented not only methyl mercury induced increase of oxidized glutathione, inhibition of GSH-Px in kidney (Hoffman and Heinz, 1998), but also histological and functional damage in kidney as well (Magos *et al.*, 1987; Perottoni *et al.*, 2004a,b). Although the exact mechanism of mercuric chloride induced nephrotoxicity is not well understood, several studies suggested the involvement of free radicals. Oxidative stress develops when the disturbances between reactive oxygen forms are produced in excess and the factors preventing their harmful effect occur. It has been shown in various studies that mercuric chloride administrations are associated with increased formation of free radicals, and with heavy oxidative stress. This will lead to oxidative damage cell components e.g. proteins, lipids and nucleic acids (Boya *et al.*, 1999). HgCl_2 inhibits activities of antioxidant enzymes (GSH-Px, GST, and catalase) and there is depletion of cellular thiols (Song *et al.*, 1998) in rat kidney and testes suggesting that HgCl_2 toxicity results from generation of reactive oxygen species. Selenite metabolite are similar to thiols, and therefore compounds that react with thiols are expected to react also with selenols (Sheen and Ajith, 2003) may be the one mechanism to restore the activity of antioxidant. Mercuric chloride induced nephrotoxicity is associated with increased

level of MDA. MDA and 4-HNE (4-hydroxy-2-nonenal) are the end products produced by the decomposition of W_3 and W_6 polyunsaturated fatty acids (Seppanen *et al.*, 2004; Valko *et al.*, 2005) due to $HgCl_2$ administration, platinum sulphhydryl group complexes formed are taken up by renal cells and stabilized by intracellular GSH for several hours, in case of intracellular GSH depletion the complexes undergo the rapid transformation to receive metabolites, this depletion seems to be the prime factor that permits lipid peroxidation and impair antioxidant enzymes (Stohs and Bagchi, 1995). Nephroprotectant by the exogenous selenite might be directly related to its antioxidant activity.

Selenite, an important exogenous source for endogenous selenium compounds, is known to be extensively biotransformed (Duque, 1991). It undergoes glutathione dependent reduction to form, consecutively, GS-Se-SG, GS-she, and hydrogen selenide (HSeH). The last is methylated sequentially, resulting in production of methylselenol (CH_3SeH), then the volatile and expirale dimethyl selenide (CH_3SeCH_3), and finally trimethylselenonium ion ($(CH_3)_3Se$), which is excreted in urine. Selenide is also the precursor for selenocysteine and thus is needed for synthesis of selenoproteins. Additionally, selenide is also a toxic metabolite of selenite, whereas methylselenol is thought to be involved in both toxicity and anticarcinogenic activity (Tsen and Tappel, 1958; Spallholz, 1994) of selenite.

Taking into account the results of this study, it is concluded that $HgCl_2$ administration produces severe nephrotoxicity in rats, increase in the serum: urea, creatinine, uric acid and bilirubin levels, and activity of antioxidant enzymes and GSH level were decreased in kidney along with increase the lipid peroxidation level. Co-administration with sodium

selenite, show significant modification in the activity of antioxidant enzymes. We suggest that the use of sodium selenite may offer a beneficial strategy against $HgCl_2$ toxicity.

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