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Antioxidant enzyme activity and lipid peroxidation in liver of female rats co-exposed to lead and cadmium: Effects of vitamin E and Mn^{2+}

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Abstract
The oxidative status of liver of female rats exposed to lead acetate and cadmium acetate either alone or in combination at a dose of 0.05 mg/kg body wt intraperitoneally for 15 days was studied. After the administration of lead alone, the activity of superoxide dismutase (SOD) decreased in liver, whereas no changes were observed in catalase (CAT) activity, and glutathione (GSH) and thiobarbituric acid (TBARS) levels. Cadmium exposure and combined exposure to lead and cadmium led to decrease in GSH content and increased TBARS levels. Moreover, animals exposed to either cadmium alone or in combination with lead showed a decrease in SOD activity and an increase in CAT activity. The *in vitro* experiments showed that vitamin E failed to restore the antioxidant enzyme activities in metal treated postmitochondrial supernatant fraction of liver. But Mn^{2+} ions protected the mitochondria from lipid peroxidation and could completely restore Mn-superoxide dismutase (Mn-SOD) activity following metal intoxication. The results of this study indicate that despite the ability of lead and cadmium to induce oxidative stress the effect in liver is not intensified by combined exposure to both lead and cadmium. The observed changes in various oxidative stress parameters in the liver of rats co-exposed to lead and cadmium may result from an independent effect of lead and /cadmium and also from their interaction such as changes in metal accumulation and content of essential elements like Cu, Zn and Fe. These results suggest that when lead and cadmium are present together in similar concentrations, cadmium mediates major effects due to its more reactive nature.

Keywords: *Lead, cadmium, vitamin E, Mn^{2+}, antioxidant enzymes,* in vitro *mechanism*

Introduction

Both lead and cadmium are toxic heavy metals of great environmental and occupational concern with deleterious effects such as neurotoxicity, hepatotoxicity and nephrotoxicity. Though specific differences in the toxicities of these metals may be related to differences in solubilities, absorbability, transport, chemical activity and the complexes that are formed within the body, evidence suggests that one of the basic mechanisms involved in metal induced toxicity might be via reactive oxygen species (ROS) [1–3]. Since both lead and cadmium can result in formation of covalent attachments with sulfhydryl groups of proteins [4], depletion of a cell's major sulfhydryl reserves seems to be an important indirect mechanism for oxidative stress induced by these metals. Lead induced oxidative stress may result from its effects on cell membranes [5,6], interaction with hemoglobin [7,8], δ-amino-levulininic acid (δ-ALA)-induced generation of ROS [9,10], and/or its effect on antioxidant defense system of cells [11]. Cadmium exposure results in elevated lipid peroxidation [12,13] and alterations in cellular defense systems and thiol status [14,15]

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though this metal does not appear to generate free radicals [16]. The toxic effects by these divalent metal ions can be prevented to some extent either by chelating with molecules such as metallothionein or enhancing the antioxidant defense mechanism. Vitamin E is a liposoluble antioxidant, which plays an important role in stabilizing the cell membranes by scavenging the oxidative free radicals [17,18].

Most of the animal studies performed to understand biochemical toxicity were carried out with very high concentration of metals and little attention was given to the effect of simultaneous exposure to more than one metal. On the other hand, populations in real life always have multiple exposures, indicating the need for experimental work with combinations of substances. However, until now there is little information regarding the oxidative stress occurring during simultaneous intoxication with these two metals. This prompted us to examine the involvement of lead and cadmium in the progress of oxidative stress and health effects of their action at co-exposure. Also we have investigated a possible protective role of vitamin E on hepatic antioxidative defense systems after intraperitoneal (i.p.) injection of lead and cadmium.

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Materials and methods

Animals and treatments

Adult virgin female rats weighing 180–220 g were maintained under controlled conditions of light and temperature and having free access to diet and tap water. Ovarian cycle was checked daily by vaginal cytology. Animals displaying at least three 4-day cycles were selected for the experiment. There were four groups of 5–8 animals each in the study. Group 1 animals were given sodium acetate as control, group 2 lead acetate, group 3 cadmium acetate and group 4 received lead acetate and cadmium acetate in combination. The animals were treated intraperitoneally with 0.05 mg/kg body weight dose per day for 15 days. The combined exposure consisted of 0.025 of lead acetate +0.025 mg/kg cadmium acetate. The dose was selected on the basis of our previous studies on the effect of simultaneous exposure of lead and cadmium on hepatic estradiol metabolism [19]. The animals were sacrificed by decapitation and the livers were quickly excised, rinsed in ice-cold saline to clear them of blood, weighed, finely minced in the same solution and homogenized (10% w/v) in a Potter Elvehjem homogenizer with a Teflon pestle. Liver homogenate was used for the determination of reduced glutathione and thiobarbituric acid reactive substances (TBARS); mitochondria and postmitochondrial supernatant from both control and metal treated rats, obtained by differential centrifugation [20] were used for enzyme assays.

In vitro *experiments*

Liver mitochondrial and postmitochondrial fraction obtained as indicated above were incubated at 37°C for 20 min with 0.25 μM lead acetate and/or 1.5 μM cadmium acetate in a mixture containing 0.175 M KCl, 25 mM Tris-HCl at pH 7.4 in a total volume of 1 ml. Vitamin E (200 μM dissolved in 25 μl dimethyl sulfoxide) and $MnSO_4$ (30 μM), when used, were added 30 s before the addition of metal [21]. The reaction was stopped on ice. Aliquots of the suspension were used to determine lipid peroxidation and enzyme activities.

Biochemical analyses

Lipid peroxidation was determined as TBARS in the homogenate according to Braughler et al. [22] Reduced glutathione (GSH) content was measured in the homogenate following the method by Beutler and Gelbart [23]. Superoxide dismutase (SOD) was determined by the modified method of NADH-phenazinemethosulphate-nitroblue tetrazolium formazan inhibition reaction spectrophotometrically [24]. Catalase activity was assayed by following the decrease of H_2O_2 at 240 nm [25].

Metal analysis

Lead and cadmium concentrations were determined in liver samples. The samples were digested in reagent grade nitric acid-perchloric acid (2:1) mixture. The digestion was continued until samples became colorless. Then the acid mixture was evaporated and the precipitate thus obtained was dissolved in a few drops of concentrated HCl. The sample was diluted to 1 ml with distilled water and the readings were taken in GBC 902 double beam atomic absorption spectrophotometer. Sensitivities of the assays were 0.06 and 0.009 mg/ml for lead and cadmium, respectively.

Statistical analyses

Comparison of values was done by analysis of variance (ANOVA) followed by Student's *t*-test. $P \leq 0.05$ was considered as statistically significant. All values represent the mean ± S.E.M.

Results

Rats administered lead acetate showed no change in hepatic GSH content and lipid peroxidation levels (Table I) as compared to control. On cadmium exposure GSH content was decreased with increase in lipid peroxidation. The changes observed in cadmium intoxicated rats were more as compared to lead and combined treatment groups.

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Table I. Effect of lead and cadmium alone and in combination on hepatic GSH, TBARS levels and antioxidant enzyme activities of female rats (0.05 mg/kg body weight per day for 15 days).

	GSH (nmols/g tissue)	TBARS (nmols/mg protein)	Catalase (units/mg protein)	Superoxide Dismutase (units/mg protein)
Control	1.34 ± 0.08	24.04 ± 1.4	204.8 ± 12.9	0.38 ± 0.03
Pb	1.2 ± 0.04	28.9 ± 1.93	223.86 ± 5.47	0.26 ± 0.01*
Cd	0.57 ± 0.03$^{*\ **}$	34.74 ± 2.8*	396.2 ± 21.16$^{*\ **}$	0.19 ± 0.01$^{*\ **}$
Pb + Cd	0.89 ± 0.03$^{*\ **\ ***}$	32 ± 0.89*	282.67 ± 5.95$^{*\ **\ ***}$	0.25 ± 0.02$^{*\ ***}$

$^{*}P \leq 0.001$ vs. control.$^{**}P \leq 0.001$ vs. lead group.$^{***}P \leq 0.01$ vs. cadmium group.
Values are expressed as Mean ± SEM ($n = 5$ in each group).

Significant decrease in the activity of hepatic superoxide dismutase was found in lead exposed animals whereas catalase activity was not changed by lead treatment (Table I). Cadmium exposure resulted in marked changes in the antioxidant defense system. In cadmium and combined metal exposed groups the activity of superoxide dismutase was significantly decreased and catalase activity was increased, where the combined metal exposed groups showed intermediate effects. These alterations have demonstrated the cadmium-induced increase in lipid peroxidation indicative of oxidative stress consistent with the accumulation of cadmium in liver compared to other treatment groups (Table II). The concentration of cadmium in cadmium and combined metal exposed groups was higher than in control and lead exposed groups. Similarly in the case of lead and combined metal exposed groups the lead concentration was significantly higher than that in control and cadmium exposed groups (Table II).

The effect of vitamin E on lipid peroxidation in hepatic post-mitochondrial supernatant following metal incubation is shown in Figure 1. The TBARS level found in fractions following incubation with metals in the presence of vitamin E is equal to that of control. The activities of CuZnSOD (Figure 2) and catalase (Figure 3) were reduced when hepatic postmitochondrial supernatant was incubated with lead, cadmium and lead + cadmium. But vitamin E could not protect the antioxidant enzymes from metal intoxication. The effect of Mn^{2+} ions on rat liver mitochondria lipid peroxidation following metal incubation is shown in Figure 4. The data indicate that Mn^{2+} ions protect the mitochondria from lipid peroxidation, as the TBARS levels found in mitochondrial fractions following incubation with metal in the presence of Mn^{2+} is equal to that of control. In contrast to vitamin E, Mn^{2+} could completely restore MnSOD activity following metal intoxication (Figure 5).

Table II. Lead and cadmium levels in the liver of female rats exposed to lead and cadmium alone and in combination for 15 days (0.05 mg/kg body weight per day).

	Lead (μg/g)	Cadmium (μg/g)
Control	1.1 ± 0.1	0.296 ± 0.027
Pb	1.63 ± 0.14*	0.28 ± 0.017
Cd	1.13 ± 0.06**	2.0 ± 0.09$^{*\ **}$
Pb + Cd	1.46 ± 0.06$^{*\ ***}$	1.9 ± 0.16$^{*\ **}$

$^{*}P \leq 0.001$ vs. control.$^{**}P \leq 0.001$ vs. lead group.$^{***}P \leq 0.01$ vs. cadmium group.
Values are expressed as Mean ± SEM ($n = 5$ in each group).

Discussion

Both lead and cadmium are sulfhydryl reactive metals. Recent studies indicate that these transition metals act as catalysts in the oxidative reactions of biological macromolecules; therefore the toxicity associated with these metals might be due to oxidative tissue damage [26,27]. Generation of highly ROS such as hydrogen peroxide, superoxide radicals, hydroxyl radicals and lipid peroxides on heavy metal exposure are known to damage various cellular components including membrane lipids, protein and DNA and thereby contribute to cellular dysfunction. The products of lipid peroxidation react with amino acid residues such as cysteine and lysine and disturb protein function [28,29]. Both *in vivo* and *in vitro* studies have suggested generation of ROS and alteration of antioxidant system in animals as one of the mechanisms for the toxic effects by lead and cadmium [30,31,15]. Our results show that after 15 days of metal exposure hepatic GSH content is decreased in cadmium and combined metal treated groups. GSH constitutes the first line of defense against

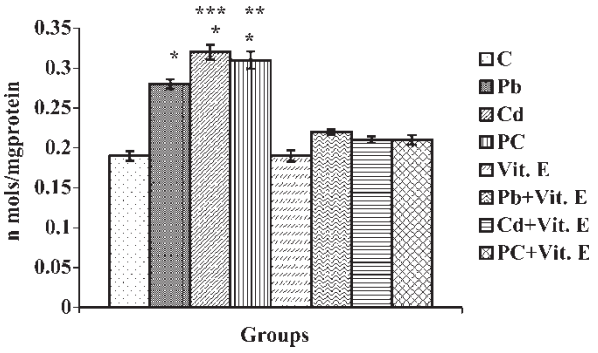

Figure 1. TBARS levels in hepatic post-mitochondria fraction after treatment with lead and cadmium alone and in combination *in vitro*: The role of Vitamin E. $^{*}P < 0.001$ vs. control; $^{**}P < 0.01$, $^{***}P < 0.001$ vs. lead group ($n = 5$).

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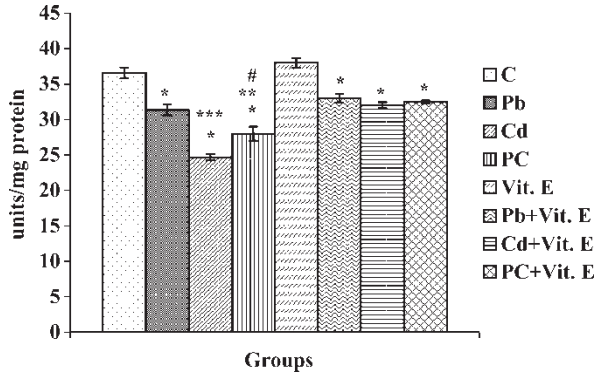

Figure 2. Cu, Zn-SOD activity in hepatic post-mitochondria fraction after treatment with lead and cadmium alone and in combination *in vitro*: The role of Vitamin E. $^{*}P < 0.001$ vs. control; $^{**}P < 0.01$, $^{***}P < 0.001$ vs. lead and $^{\#}P < 0.01$ vs. cadmium group ($n = 5$)

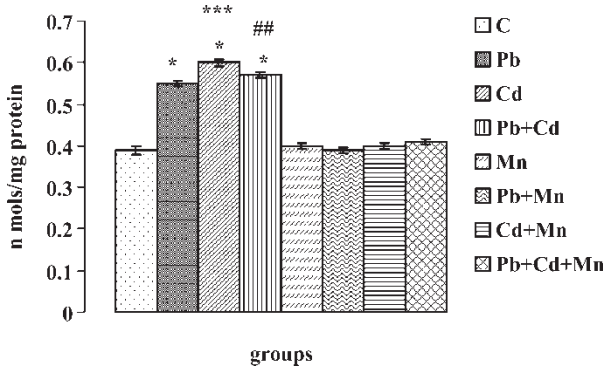

Figure 4. TBARS levels in hepatic mitochondria fraction after treatment with lead and cadmium alone and in combination *in vitro*: The role of Mn^{2+}. $^{*}P < 0.001$ vs. control; $^{***}P < 0.001$ vs. lead; $^{\#}P < 0.001$ vs. cadmium group. ($n = 5$).

free radical induced damage. It accounts for about 90% of the intracellular non-protein thiol content. One of the mechanisms for the observed decrease in GSH content in the present study could be the binding of these divalent metals with -SH groups [32–35]. It has been reported earlier that thiol group inactivation causes oxidative stress, permeability transition, and hepatic dysfunction [36]. In fact there is a direct correlation between GSH depletion and enhanced lipid peroxidation. The increase in TBARS in the present study indicates failure of antioxidant defense mechanism, which prevents the formation of excess free radicals.

The observed changes in the activities of various hepatic antioxidant enzymes after treatment with lead and cadmium for 15 days indicate that these enzymes depend on various transition metals for proper molecular structure and activity. Both lead and cadmium can readily displace zinc and copper, which are cofactors for superoxide dismutase, causing a decrease in the enzyme activity [12,37]. Copper ions appear to have a functional role in the reaction by undergoing alternate oxidation whereas zinc ions seem to stabilize the enzyme. The decrease in the liver activity of this enzyme in rats exposed to lead and cadmium either alone or in combination may be connected with a decreased availability of these bioelements as a result of their immobilization in the form bound to metallothionein. Bauer et al. [38] reported that ^{111}Cd was able to occupy the site of Zn in the Cu, Zn-SOD molecule creating an inactive form of the enzyme ($Cu^{111}Cd$-SOD). After 15 days of metal exposure we have observed a significant increase in catalase activity in cadmium and combined treatment groups. This could be due to the early displacement of the transition metals present in the active site of superoxide dismutase by the heavy metals with no significant inhibition in the catalase activity. Casalino et al. [21] reported in their *in vitro* experiments on hepatic postmitochondrial supernatant that the order of cadmium's inhibitory effect on antioxidant enzyme activities is Mn-SOD > Cu, Zn-SOD > catalase. To counter the deleterious action of ROS, antioxidant enzymes are also synthesized in

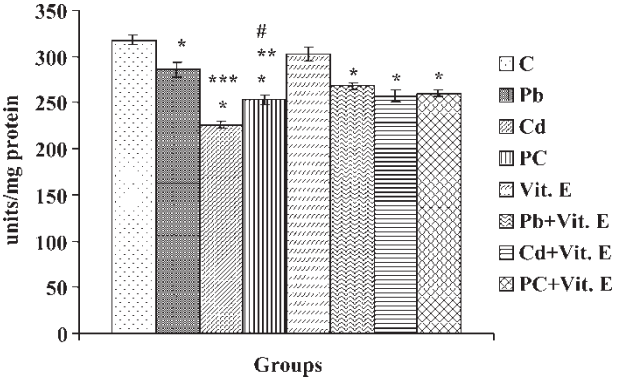

Figure 3. Catalase activity in hepatic post-mitochondria fraction after treatment with lead and cadmium alone and in combination *in vitro*: The role of Vitamin E. $^{*}P < 0.001$ vs. control; $^{**}P < 0.01$,$^{***}P < 0.001$ vs. lead and $\#P < 0.001$ vs. cadmium group ($n = 5$).

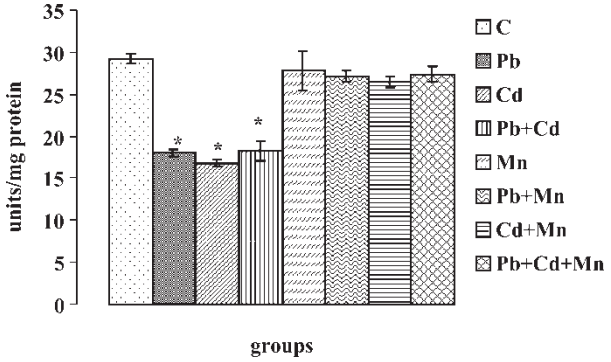

Figure 5. Mn-SOD activity in hepatic mitochondria fraction after treatment with lead and cadmium alone and in combination *in vitro*: The role of Mn^{2+}. $^{*}P < 0.001$ vs. control group ($n = 5$).

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response to the higher production of ROS. Thus the increased level of catalase activity observed after metal exposure for 15 days is probably in response of higher production of ROS.

In vitro experiments were carried out with the concentration of lead and cadmium reaching the tissues after *in vivo* exposure for 15 days. The results on liver post mitochondrial supernatant, which are in contrast to the *in vivo* results, indicate that different kinds of mechanism exist for *in vivo* and *in vitro* metal-enzyme interaction.

To have further understanding of metal interaction, Cu, Zn-SOD, Mn-SOD, CAT and TBARS were estimated in post mitochondrial and mitochondrial fraction of liver and effects of vitamin E and Mn^{2+} ions were also studied. The results clearly demonstrate increases in TBARS in both mitochondrial and postmitochondrial fractions of metal treated groups, which is partially or completely restored to control value by vitamin E and Mn^{2+}. Cu, Zn-SOD activity was decreased in both single and combined metal treated groups as compared to control. The alterations in the enzyme activity could be due to the replacement of Zn/Cu ions by the metals. There are various reports that vitamin E can reverse the inhibitory effect of metals on antioxidant enzymes [39–41]. However, in the present study the enzyme activities in metal treated groups are not restored to control values in postmitochondrial supernatant when pre-exposed to vitamin E. Our findings agree with the previous reports indicating that a decrease in lipid peroxidation by α-lipoic acid [42] or vitamin E [21] does not restore cadmium inhibited antioxidant enzyme activities. Mitochondrial respiration, the major source of ROS is promoted by lipid peroxidation and therefore increases oxidative stress by cadmium exposure [34]. Mitochondrial SOD, Mn-SOD protects mitochondria against oxidative stress. Mn-SOD activity like Cu, Zn-SOD activity was significantly decreased in both single and combined metal treated groups. This could be due to a nonspecific interaction between the metals and MnSOD since the enzyme activity was completely restored when mitochondria were incubated with lead, cadmium or lead and cadmium along with Mn^{2+}. The antioxidant activity of Mn^{2+} has been observed in isolated hepatocytes, in which cadmium induced cell injury was much reduced in the presence of manganese [43]. A recent study has shown that the transport system for Mn is used for cadmium uptake in mammalian cells [44], indicating a competition between the two metals if they are present together.

It is interesting to note that the changes in the various indicators of oxidative stress such as MDA, CAT and SOD observed in the liver of the rats co-exposed to lead and cadmium might result from an independent effect of lead and/or cadmium and also from their interaction. The interactive effect may involve changes in metal accumulation and concentration of various essential elements such as Zn, Cu and Fe in the serum and liver. In the present investigation, combined exposure to lead and cadmium showed intermediate results in various parameters studied. In most of the studies reporting on combined exposure to metals, researchers have used the same concentrations of the metal in both individual and combined treatment [45,46]. The results obtained from such studies showed either additive effects in the combined exposure group as the concentration of the metals are increased, or antagonistic effects depending on the nature of the metals used, whereas in the present study, the total concentration of metals in the combined exposure group is the same as that in the individual-metal treatment group. This pattern avoids multiple stress in the combined-treatment group. It is interesting to note that the changes following combined treatment with lead and cadmium in the present study more often paralleled the effects of cadmium alone than the changes seen with lead alone. This suggests that when lead and cadmium are present together in similar concentrations, cadmium mediates major effects due to its more reactive nature.

In summary, our results show that both lead and cadmium either alone or in combination disrupt the hepatic antioxidant defense mechanisms where the effects produced by the combined treatment of metals are not additive. Also the administration of antioxidant agent can reduce the metal induced oxidative stress and can provide some beneficial effects against heavy metal toxicity.

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