

Review Article

Oxidative Stress in Lead and Cadmium Toxicity and Its Amelioration

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Received 12 January 2011; Accepted 21 January 2011

Academic Editor: Cristina Castillo Rodríguez

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Oxidative stress has been implicated to play a role, at least in part, in pathogenesis of many disease conditions and toxicities in animals. Overproduction of reactive oxygen species and free radicals beyond the cells intrinsic capacity to neutralize following xenobiotics exposure leads to a state of oxidative stress and resultant damages of lipids, protein, and DNA. Lead and cadmium are the common environmental heavy metal pollutants and have widespread distribution. Both natural and anthropogenic sources including mining, smelting, and other industrial processes are responsible for human and animal exposure. These pollutants, many a times, are copollutants leading to concurrent exposure to living beings and resultant synergistic deleterious health effects. Several mechanisms have been explained for the damaging effects on the body system. Of late, oxidative stress has been implicated in the pathogenesis of the lead- and cadmium-induced pathotoxicity. Several ameliorative measures to counteract the oxidative damage to the body system aftermath or during exposure to these toxicants have been assessed with the use of antioxidants. The present review focuses on mechanism of lead- and cadmium-induced oxidate damages and the ameliorative measures to counteract the oxidative damage and pathotoxicity with the use of supplemented antioxidants for their beneficial effects.

1. Introduction

The diverse deleterious health effect upon exposure to toxic heavy metals in the environment is a matter of serious concern and a global issue. Much emphasis has been given to elucidate the mechanism of toxicity due to common environmental toxicants and to develop a safer chemotherapeutic approach to mitigate the toxic effects. Lead and cadmium are the two most abundant toxic metals in the environment. The coexposure to these two toxic metals has synergistic cytotoxicity that may, at times, turn to antagonistic effects, because exposure to higher mixture concentrations may enhance cellular defense mechanisms [1, 2], including induction of metallothioneins synthesis upon exposure to cadmium. The concurrent higher levels of lead and cadmium have been recorded in several field situations. The common sources of lead and cadmium are diverse in nature including natural and anthropogenic processes such

as combustion of coal and mineral oil, smelters, mining and alloy processing units, paint industries, and so forth. [2–5]. The quantity of lead used in the present decade far exceeds the total amount consumed in all previous eras [2]. The anthropogenic activities and vehicular emissions contribute to the entry of toxic metals to humans and other animals food chains [6].

Cadmium is an important environmental pollutant present in soil, water, air and food. Anthropogenic sources add 3–10 times more cadmium to the atmosphere than natural sources [7]. Major occupational exposure occurs from nonferrous smelters during production and processing of cadmium, its alloys, and compounds, and the exposure is increasingly common during recycling of electronic waste.

Lead and cadmium do not have any detectable beneficial biological roles. On the contrary, their detrimental effects on physiological, biochemical, and behavioral dysfunctions have been documented in animals and humans by several

investigators [8, 9]. The higher levels affect the central and peripheral nervous systems [10], haemopoietic system [11], cardiovascular system [12], kidneys [13], liver [14], and reproductive systems [15, 16]. Cadmium is more toxic than lead and causes renal and hepatic damage in exposed animals [13, 14].

Of late, lead- and cadmium-induced tissue damages have been attributed, at least in part, to toxicant-induced oxidative stress [17, 18]. Cadmium stimulates the formation of metallothioneins and reactive oxygen species (ROS), thus causing oxidative damage to erythrocytes and various tissues resulting in loss of membrane functions [19]. Long-term exposure to Cd increases lipid peroxidation and causes inhibition of SOD activity indicating oxidative damage in liver, kidney and testes [20]. The various toxic effects induced by Cd in biological systems have been linked to increased lipid peroxidation, an as early and sensitive consequence of Cd exposure. The increase in lipid peroxidation due to Cd toxicity have been attributed to alterations in the antioxidant defense system which includes enzymes such as glutathione peroxidase (GPx), glutathione-S-transferase, superoxide dismutase (SOD), and catalase (CAT), and nonenzymatic molecule like glutathione, which normally protect against free radical toxicity.

2. Lead-Induced Oxidative Stress

The mechanism of lead-induced oxidative stress involves an imbalance between generation and removal of ROS (reactive oxygen species) in tissues and cellular components causing damage to membranes, DNA and proteins. The presence of double bonds in the fatty acid on cell membrane weakens the C-H bonds on the carbon atom adjacent to the double bonds and makes H removal easier. Therefore, fatty acids containing zero to two double bonds are more resistant to oxidative stress than polyunsaturated fatty acids with more than two double bonds [21]. The above fact was substantiated after incubation of linoleic, linolenic, and arachidonic acid with lead in which the concentration of a final product of oxidative stress, malondialdehyde (MDA) was increased with the number of double bonds of fatty acid [22].

The intrinsic mechanism underlying lead-induced oxidative damage to membranes is associated with changes in its fatty acid composition [23]. The fatty acid chain length and unsaturation are the determinant for membrane susceptibility to peroxidation, and lead induced arachidonic acid elongation might be responsible for the enhanced lipid peroxidation of the membrane [24]. Thus, lead affects membrane-related processes such as the activity of membrane enzymes, endo- and exocytosis, transport of solutes across the bilayer, and signal transduction processes by causing lateral phase separation [25].

Lead accumulation in tissues causes oxidative DNA damages including strand break, although the evidence of lead-induced oxidative damage to DNA is less conclusive [18]. The δ -aminolevulinic acid dehydrase (ALAD) is highly sensitive to the toxic effects of lead [26]. The accumulation of δ -aminolevulinic acid (ALA) upon exposure to lead

induces generation of ROS [27, 28] and resultant oxidative stress [29]. The final oxidation product of ALA, 4,5-dioxovaleric acid is an effective alkylating agent of the quinine moieties within both nucleoside and isolated DNA [30]. Increased level of 8-oxo-7, 8-dihydro-2-deoxyguanosine and 5-hydroxyl-2-deoxycytidine following chronic treatment with ALA in rats has been attributed for ALA-induced DNA damage [31]. There are recent data suggesting lead-induced alteration in gene expression [32] and it appears to interact with zinc-binding sites on an important DNA-associated protein, human protamine [33].

The effect on the antioxidant defense systems of cells is the second mechanism for lead-induced oxidative stress. Lead and other metals such as Hg and Cd have a high affinity for sulfhydryl (SH) groups. Mercaptides are formed with the SH group of cysteine, that are less stable complexes [34]. Lead is shown to alter antioxidant activities by inhibiting functional SH groups in several enzymes such as ALAD, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glucose-6-phosphate dehydrogenase (G6PD) [35–38]. G6PD contains many SH group and supplies cells with most of the extramitochondrial NADPH through the oxidation of glucose-6-phosphate to 6-phosphogluconate. G6PD is inhibited by lead [39]. However, there are more complex effects of lead on G6PD, as evidenced by *in vivo* studies. G6PD activity increases in RBCs of lead-treated rats [40] and lead-exposed workers [41]. The most important regulation of the pentose phosphate pathway is the NADP-/NADPH ratio, which is known to change in favor of the oxidized form under oxidative stress conditions. Therefore, lead exposure results in an increase or decrease in G6PD activity depending on the concentration and duration of lead exposure, and magnitude of oxidative stress inside the cell [42].

GPx, CAT, and SOD are potential targets for lead toxicity because these antioxidant enzymes depend on various essential trace elements for proper molecular structure and activity [43]. Since lead-associated reduction in selenium uptake may increase the susceptibility of the cell to oxidative stress, an antagonistic effect between selenium and lead was found to affect GPx activity that requires selenium as a cofactor [44]. On the other hand, administration of selenium before lead exposure produces significant prophylactic action against lead-induced oxidative stress by means of increasing SOD, glutathione reductase (GR) activity, and glutathione (GSH) content in male rats [45]. In summary, impaired antioxidant defenses can be a result of the inhibitory effects of lead on various enzymes, which in turn causes the cells to be more susceptible to oxidative insult.

3. Cadmium and Oxidative Stress

Cadmium is a well-recognized environmental pollutant with numerous adverse health effects. It principally affects lung, liver, kidney, and testes following acute intoxication, and nephrotoxicity, immunotoxicity, osteotoxicity and tumors on prolong exposures. Reactive oxygen species (ROS) are often implicated in Cd-induced deleterious health effects. There are direct evidence of the generation of free radicals

in animals following acute Cd overload, and indirect evidence of involvement of ROS in chronic Cd toxicity and carcinogenesis. Cd-generated superoxide anion, hydrogen peroxide, and hydroxyl radicals *in vivo* have been detected by the electron spin resonance spectra, which are often accompanied by activation of redox sensitive transcription factors (e.g., NF- κ B, AP-1 and Nrf2) and alteration of ROS-related gene expression. It is generally agreed upon that oxidative stress plays important roles in acute Cd poisoning.

However, direct evidence for oxidative stress is often obscure following long-term and environmentally-relevant low levels of Cd exposure. Alterations in ROS-related gene expression during chronic exposures are also less significant compared to acute Cd poisoning. This is probably due to induced adaptation mechanisms such as overexpression of metallothionein and glutathione following chronic Cd exposures, which in turn diminish Cd-induced oxidative stress. In chronic Cd-transformed cells, less ROS signals are detected with fluorescence probes. Acquired apoptotic tolerance renders damaged cells to proliferate with inherent oxidative DNA lesions, potentially leading to tumorigenesis. Thus, ROS are generated following acute Cd overload that play an important roles in tissue damage. Adaptation to chronic Cd exposure reduces ROS production, but acquired Cd tolerance with aberrant gene expression plays important roles in chronic Cd toxicity and carcinogenesis.

The basic mechanisms involved in cadmium carcinogenesis are gene regulation of proto-oncogenes [46], oxidative stress [47–51], disruption of cadherins, inhibition of DNA repair and interference with apoptosis [52]. Cadmium is a potent cell poison, and known to cause oxidative stress by increasing lipid peroxidation and/or by changing intracellular glutathione levels. It affects the ubiquitin/ATP-dependent proteolytic pathway. However, the cellular mechanisms involved in cadmium toxicity are still not well understood, especially in neuronal cells. The treatment of neuronal cells culture with different concentrations of the metal ion to examine the relationship between cadmium-induced oxidative stress and the ubiquitin/ATP-dependent pathway revealed decreased glutathione levels, and marked increases in protein-mixed disulfides (Pr-SSGs) [53]. The increases in intracellular levels of Pr-SSGs were concurrent with increases in the levels of ubiquitinated proteins (Ub proteins) when the HT4 cells were subjected to lower (25 μ m or less) concentrations of cadmium. However, higher concentrations of cadmium (50 μ m) led to increases in Pr-SSGs but inhibited ubiquitination, probably reflecting inhibition of ubiquitinating enzymes.

The cadmium-induced changes in Pr-SSGs and Ub proteins are not affected when more than 85% of intracellular glutathione is removed from the cells by the glutathione synthetase inhibitor L-buthionine-(S, R)-sulfoximine. However, the reducing agent dithiothreitol, that prevents build-up of Pr-SSGs in the cell also blocks the accumulation of Ub proteins induced by cadmium. In addition, dithiothreitol blocks the effects of higher (50 μ m) concentrations of cadmium on cytotoxicity and on glutathione, Pr-SSGs, and Ub proteins. Together, these results strongly suggest that changes in the levels of intracellular Pr-SSGs and ubiquitin-protein

conjugates in neuronal cells are the responses closely associated with the disruption of intracellular sulfhydryl homeostasis caused by cadmium-mediated oxidative stress.

The testis is the important target organ of Cd toxicity. Many studies indicate that Cd induces testicular damage in many species of animals including mice, hamsters, rabbits, guinea pigs and dogs [54, 55]. Cadmium has profound effect on sex organ weight, a primary indicator of possible alteration in androgen status [56, 57]. Several mechanisms of Cd-induced testicular toxicity have been proposed. Lafuente et al. [58] reported increased Cd accumulation in the hypothalamus, pituitary, and testis and decreased plasma levels of follicle stimulating hormone in rats, suggesting a possible effect of Cd on the hypothalamic-pituitary-testicular axis.

Several studies also suggest participation of reactive oxygen species (ROS) in Cd-induced testicular damage [59]. Both acute and chronic Cd exposure is associated with elevated lipid peroxidation in the lung, brain, kidney, liver, erythrocytes, and testis [60–64]. The reactive oxygen species (ROS) play both beneficial and harmful roles in living organisms [65]. ROS can be generated by both exogenous and endogenous sources. Cadmium is one of the exogenous sources shown to indirectly produce ROS in various cell lines [66–68]. The production and accumulation of ROS inhibit the electron transfer chain in mitochondria [69]. In general, the accumulated ROS consists of various amounts of hydrogen peroxide, hydroxyl ions, singlet oxygen, superoxide anions, lipid hydroperoxides, phospholipid hydroperoxides, and so forth. Excessive production of ROS disturbs the balance between the ROS and antioxidant agents (enzymes and antioxidant substances) in the cells. Hydrogen peroxide is the common substrate for catalase and GPx enzymes in the cells. While catalase decomposes H₂O₂ into water and oxygen, GPx oxidizes GSH to GSSG by utilizing H₂O₂. Glutathione reductase (GR) is another enzyme required for the antioxidant defense mechanism in cells. It reduces GSSG into GSH. Both GPx and GR work in tandem in the cells in order to maintain the GSH/GSSG ratio at a steady state level. When the cells are under oxidative stress, catalase, GR and GPx respond by altering their activities.

4. Amelioration of Lead- and Cadmium-Induced Oxidative Stress

Abatement of lead and cadmium toxicity with rebalancing the impaired prooxidant/antioxidant ratio through supplementation of antioxidant nutrients are still not completely clear. However, evidences suggest significant protective effects of antioxidant nutrients such as vitamin-C, carotenoids, selenium, vitamin-E, and so forth.

Vitamin C is a major antioxidant that scavenges the aqueous ROS by very rapid electron transfer that inhibits lipid peroxidation [21]. Administration of vitamin C significantly inhibits the lipid peroxidation levels of liver and brain, and increased the CAT levels of kidney in lead-exposed rats [17]. Lead-induced ROS production as examined by rat sperm chemiluminescence generation reduced by 40% with supplementation of 500 mg vitamin C/l drinking water

[70]. Vitamin C supplementation in lead-exposed animals significantly reduces blood, liver, and renal lead levels, and associated biochemical changes indicating a significant protective action of vitamin C against toxic effects of lead on heme synthesis and drug metabolism [71]. The combination of vitamin C and thiamine have been proved effective in reducing lead levels in blood, liver, and kidney along with reduction in lead-induced inhibition in the activity of blood δ -ALAD and blood zinc protoporphyrin [72].

There has been considerable debate concerning the relationship between vitamin C nutritional status and lead-induced toxic effects. Early reports suggest vitamin C as a possible chelator of lead, with similar potency to that of EDTA [8]. Vitamin and/mineral supplementation in African American women was found to reduce blood lead level (BLL) from 5.1 to 1.1 mg/dl, which was negatively correlated with serum levels of vitamin E and C [73]. Ascorbic acid increases urinary elimination of lead and reduces the hepatic and renal lead burden in rats [74].

A cross-sectional study analyzed 4213 young and 15365 adult Americans with mean BLL of 2.5–3.5 mg/dl, respectively. The BLL had inverse relationship with serum vitamin C [75]. Vitamin C supplementation resulted in small reductions in lead retention in 85 human volunteers who consumed a lead-containing drink [76]. However, workers occupationally exposed to lead, and with BLL ranged from 28.9 to 76.4 mg/dl, supplementation of vitamin C and zinc did not significantly reduce BLL [77]. The vitamin C supplementation did not alter the blood and sperm lead levels in lead-treated rats with BLL of 36 mg/dl [70]. A recent report stated that rats treated with ascorbic acid did not reduce lead burden in the liver, kidney, brain, and blood [17]. Although it is biologically plausible that vitamin C may affect lead absorption and excretion, the effect is more obvious in low-exposed subjects with higher vitamin C supplementation. In humans and animals exposed to high levels of lead, the reduction of BLL by vitamin C is less significant.

Vitamin E is the generic term used to describe at least eight natural-occurring compounds that possess the biological activity of α -tocopherol. The group is comprised of α -, β -, γ - and δ -tocopherol and α -, β -, γ - and δ -tocotrienol. RRR- α -tocopherol has the highest biological activity [78], the other tocopherols and tocotrienols are less biologically active but they are at least as abundant as α -tocopherol in certain foods [79]. Vitamin E is nature's major lipid soluble chain-breaking antioxidant that is known to protect biological membranes and lipoproteins from oxidative stress [80]. The main biological function of vitamin E is its direct influence on cellular responses to oxidative stress through modulation of signal transduction pathways [81]. One of the protective roles of vitamin E on lead-induced damage is prevention of lipid peroxidation and inhibition of SOD and CAT activities in liver [82]. In lead-exposed rats, supplementation of vitamin E and/or C reduced sperm ROS generation, prevented loss of sperm motility and oocyte penetration capacity [70]. The interaction between vitamin E and other antioxidants might have a more efficient protective action against lead toxicity. Vitamin E and C jointly protect

lipid structures against peroxidation [83]. Although vitamin E is located in membranes and vitamin C in aqueous phases, vitamin C is able to recycle oxidized vitamin E [84]. Vitamin C repairs the tocopherol radical, thus recovering the chain-breaking antioxidant capacity of vitamin E [83]. Vitamin E alone or in combination with conventional chelator, CaNa_2EDTA has been reported to decrease the lead-induced lipid peroxide levels in liver and brain in rats [17].

Carotenoids play a significant role in reduction of lead-induced stress in all species. The reaction of carotenoids with radicals is partly due to its roles in photosynthesis, thus electron transfer from β -carotene to P680, with the β -carotene being oxidized to its radical cation CAR [85]. Dietary β -carotene mediates prevention of lipid peroxidation, and reduces the incidence of many diseases including cancer, atherosclerosis, age-related macular degeneration, and multiple sclerosis [86, 87]. However, the generally accepted beneficial roles of carotenoids as antioxidants have been seriously challenged by the results from clinical trials that suggest deleterious effects of administered β -carotene in heavy smokers [88]. There have been considerable recent investigations in the interaction of β -carotene and other antioxidants [89].

The antioxidant effects of *Spirulina fusiformis*, bluegreen algae rich in β -carotene and SOD, against lead toxicity have been examined in the testes of Swiss mice. The antioxidant nutrients scavenged the free radicals after lead administration and ROS generation in mice testes [90]. Supplementation with multiple antioxidants including vitamin C, vitamin E, β -carotene, selenium, and zinc resulted in significant increase of SOD and GPx in 36 workers exposed to lead [91]. The interaction of carotenoids and carotenoid radicals with other antioxidants is of importance with respect to anti- and, possibly, pro-oxidative reactions of carotenoids. The nature of the reaction between the tocopherol (TOH) and various carotenoids shows a marked variation depending on the specific tocopherol homologue, of which α -TOH is the most active. β -carotene radical interacts with vitamin C in the aqueous phase, and carotenoid radical are efficiently reconverted to the parent carotenoid by vitamin C [89, 92].

Interactions between zinc and lead have been investigated at absorptive and enzymatic sites [93]. Zinc and lead compete for similar binding sites on the metallothionein-like transport protein in the gastrointestinal tract [94]. The competition between zinc and lead might decrease the absorption of lead, thus reducing lead toxicity. Dietary supplementation with zinc and in combination with ascorbic acid [95] and thiamine [96] reduces lead toxicity in humans. Zinc has an important role in spermatogenesis in the male reproductive system, and the most probable site of action is the primary spermatocyte. Zinc supplementation competes for and effectively reduces the availability of binding sites for lead uptake. In another study, zinc was administrated to lead-exposed rats along with chelating agents CaNa_2EDTA , succimer, and D-penicillamine. Zinc enhanced the efficacy of lead chelation by reducing the blood, hepatic and renal lead level, and overturning the inhibited activity on blood ALAD [97]. A recent study has shown prevention of δ -ALAD inhibition and increased cellular SOD in the testis of

lead-exposed rats following zinc supplementation [98]. The protective effects of zinc against testicular damage caused by lead might be due to competition between lead and zinc. There is still no strong and direct evidence to conclude that the beneficial effects of zinc are mediated by antioxidation.

Zinc is a trace element essential for living organisms. More than 300 enzymes require Zn for their activity. It plays an important role in the DNA replication, transcription, and protein synthesis, influencing cell division and differentiation [99]. Zn has a relationship with many enzymes in the body and can prevent cell damage through activation of the antioxidant system [100–102]. It is an essential component of the oxidant defense system and functions at many levels [103]. Zn deficiency increases lipid peroxidation in various rat tissues, whereas Zn supplementation corrects the impairment [102]. Cotreatment with Cd and Zn prevents damage to the testes from Cd exposure [104]. This suggests Cd interference in Zn-related metabolic functions. The competitive mechanism of interaction and Zn-induced metallothionein induction are the plausible mechanism behind protective effects of Zn against Cd toxicity. This is substantiated by the findings that Cd treatment decreases the testicular Zn concentration and elevates the levels of hepatic and renal metallothioneins [105]. Zn pretreatment can prevent of cadmium-induced testicular tumors which may be attributed to the ability of Zn to reduce the cytotoxicity of Cd in interstitial cells by enhancing efflux of Cd and decreasing accumulation of Cd in the nuclei of this target cell population in the rat testis [106]. So, Cd altered testicular function mediated through induction of oxidative stress could be reversed by administration of Zn.

Selenium is a cofactor of GPx, a cyto-antioxidant enzyme. Selenium enhances the availability of GSH, which is one of the most abundant intrinsic antioxidants that helps in preventing lipid peroxidation and resultant cell damage. Lead exposure decreases the activity of GPx due to the interaction of lead with the essential selenocysteine moiety of the enzyme [107]. Protection against liver and kidney damage by selenium is attributed to enhanced antioxidant capacity of cells, as evidenced by increased SOD and GR activities and elevated GSH content following selenium supplementation [45]. The combination of selenium and other antioxidants has been shown to reduce oxidative stress in animals. DNA damage in the liver and spleen induced by fumonisin B1 was protected by the mixture of antioxidants coenzyme Q10, L-carnitine, vitamin E and selenium in rats [108]. Combined administration of antioxidants containing selenium, vitamin C, vitamin E, β -carotene, and N-acetyl cysteine has been reported to prevent both the diabetes- and galactosemia-induced elevation of oxidative stress in rats [109]. Despite the above findings, the beneficial role of selenium alone on lead-induced oxidative stress is still unclear in human studies.

5. Conclusion

Generation of highly reactive oxygen species aftermath of lead and cadmium exposure may result in systematic mobilization and depletion of the cell intrinsic antioxidant defenses. Formation of reactive oxygen intermediates

beyond the scavenging capacity of these antioxidant defense mechanisms results in accumulation of harmful free radicals and likelihood of oxidative damage to critical biomolecules, such as enzymes, proteins, DNA, and membrane lipids. Several mechanisms have been proposed to mediate the oxidative stress caused by lead and cadmium, including disrupted pro-oxidant/antioxidant balance. Although many investigators have shown lead-induced oxidative damage, and some antioxidants were found to reduce lead toxicity, the mechanisms of dietary supplementation of antioxidants remain to be further clarified in lead-exposed humans or animals.

Evidences suggest that in presence of varying concentrations of cadmium, the mitochondrial enzymes are more effective in reducing various ROS than their cytoplasmic counterparts. This observation reveals that most oxidation-reduction reactions take place in the mitochondria, leading to the formation of several ROS. As less ROS are produced in the cytoplasm, the activities of antioxidant enzymes in the cytoplasm are not as high as the mitochondrial enzymes with cadmium treatments. Thus, more oxidative stress is observed in the mitochondria than in the cytoplasm. Each antioxidant enzyme shows its own pattern of activation or inhibition upon exposure of cells to different concentrations of lead and cadmium.

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