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Invited critical review

Low level lead exposure and oxidative stress: Current opinions

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Abstract

Lead continues to pose a serious threat to the health of many children as well as adults. Concern about lead exposure as a significant public health problem has increased as evidence has mounted regarding adverse health effects at successively lower levels. This issue is complicated by the fact that there is no demonstrated biological function of lead in human. Lead potentially induces oxidative stress and evidence is accumulating to support the role of oxidative stress in the pathophysiology of lead toxicity. Lead is capable of inducing oxidative damage to brain, heart, kidneys, and reproductive organs. The mechanisms for lead-induced oxidative stress include the effects of lead on membranes, DNA, and antioxidant defense systems of cells. Recent epidemiological and toxicological studies have reported that lead exposure causes several diseases including hypertension, kidney disease, neurodegenerative disease and cognitive impairment. Although all these diseases include components of oxidative stress, the relevance of oxidative stress to lead-related diseases with low lead exposure has been criticized because most of the mechanistic studies have been conducted at moderate to higher dose levels. The association between low level lead exposure and oxidative stress has not been explored systematically. The present review focuses on mechanisms for lead-induced oxidative stress and relevance of oxidative stress to lead-related human disease with low lead exposure.

Keywords: Low level lead exposure; Reactive oxygen species; Human diseases; Oxidative stress; Antioxidants

Contents

1. Introduction

The detection and prevention of lead toxicity have been a major international public health priority. Although the population exposure to lead has fallen over the last three decades with the introduction of low lead paint, unleaded petrol, and banning of lead solders in food cans, sub-clinically

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significant lead exposure from these sources remains [1]. Additionally, newer sources of exposure are emerging such as contamination of traditional medicines used in many countries including the United Kingdom, United States of America, Europe, and Asia [2–4].

In the 1960s, a blood lead level (BLL) of 60 μg/dL was considered safe. Due to increased understanding of lead toxicology, the acceptable BLL was reduced to 25 μg/dL in 1985 and 10 μg/dL in 1991 [5]. Despite these changes, sub-clinical effects of lead exposure have been reported at BLL < 10 μg/dL [6,7]. This issue is complicated by the fact that there is no demonstrated biological function of lead in human. As such, it is arguable that a 'safe' BLL cannot be defined.

Lead is related to a broad range of physiologic, biochemical, and behavioral dysfunctions [8]. Lead potentially induces oxidative stress and evidence is accumulating to support the role of oxidative stress in the pathophysiology of lead toxicity [9,10]. Until now, evidence on lead-induced oxidative stress has been based mostly on *in vitro* experiments [11,12] or studies conducted in animals [13,14]. Several epidemiological studies among workers with high occupational exposure to lead have reported associations between lead exposure and oxidative stress markers [15–17].

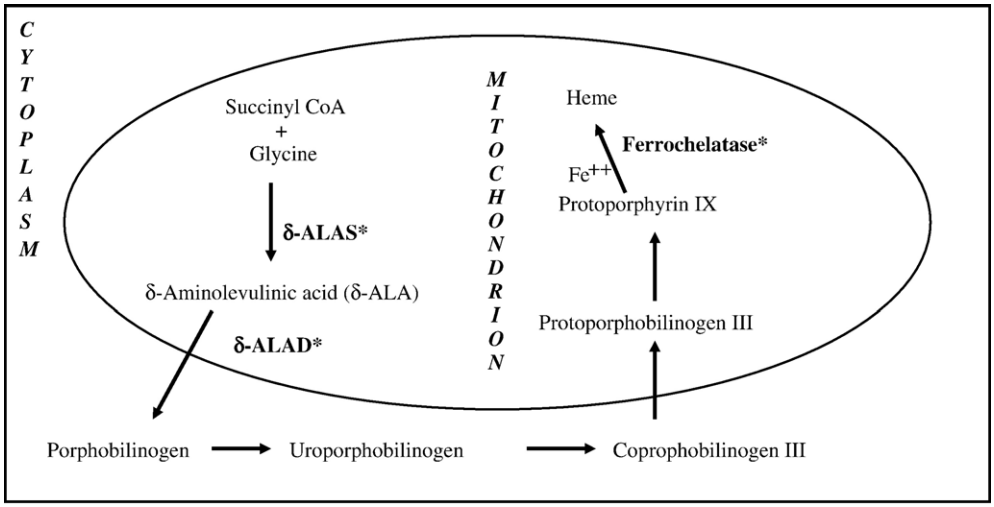
Recent epidemiological studies have reported that low level lead exposure has a graded association with several disease outcomes such as hypertension, peripheral artery disease, kidney disease, neurodegenerative disease, and cognitive impairment [18–23]. Although all these diseases include components of oxidative stress, the relevance of oxidative stress to lead-related disease with low level exposure has been criticized because mechanistic studies have been conducted at levels not typically observed in general population.

The association between low level lead exposure and oxidative stress has not been explored systematically. The present review focuses on (i) the interaction of lead in the heme biosynthetic pathway, (ii) potential mechanisms for lead-induced oxidative stress and its effect on antioxidant defense systems, and (iii) studies indicating relevance of oxidative stress to lead-related human diseases with low lead exposure.

2. Lead interactions in heme biosynthetic pathway

The hematopoietic system is one of the target organs in lead toxicity. The enzymes in the biosynthetic pathway of heme in which the effects of lead are of the clinical interest are δ-aminolevulinic acid synthetase (δ-ALAS), δ-aminolevulinic acid dehydratase (δ-ALAD), and ferrochelatase [24] (Fig. 1). The series of reactions leading to heme biosynthesis begins with succinyl coenzyme A (CoA) and glycine and ends with the insertion of an iron (Fe^{++}) into a molecule of protoporphyrin to form heme. In the first step, the enzyme δ-ALAS catalyzes the formation of δ-ALA from glycine and succinyl CoA, whereas in the second step, δ-ALAD catalyzes the formation of porphobilinogen (PBG) from two molecule of δ-ALA. Due to its affinity for –SH group, lead is known to inhibit δ-ALAD activity that has been used as a laboratory tool for the detection of lead intoxication [25]. Over 99% of the lead present in the blood accumulates in erythrocytes. Of this, over 80% is bound to δ-ALAD [26]. Austrin et al. [27] found 50% inhibition of δ-ALAD activity at a BLL of 15 μg/dL. In an earlier study, we found that BLLs 7.1 μg/dL inhibit the activity of δ-ALAD [28]. Recently, Sakai and Morita [29] found that threshold value of blood lead for δ-ALAD inhibition was extremely low (approximately 5 μg/dL). Inhibition of δ-ALAD by lead accounts for the accumulation of δ-ALA in blood and urine; urinary δ-ALA has also been used as a biomarker for lead exposure or a marker of early biologic effect of lead [30].

In the last step, ferrochelatase incorporates iron (Fe^{++}) into the protoporphyrin molecule to form heme. Lead inhibits ferrochelatase activity and therefore, prevents incorporation of



* Activity of enzymes inhibited by lead

δ-ALAS: Delta-aminolevulinic acid synthetase, δ-ALAD: Delta-aminolevulinic acid dehydratase, Co A: Coenzyme A

Fig. 1. Lead interactions in heme biosynthetic pathway.

iron into protoporphyrin. This reaction leads to binding of zinc, producing zinc protoporphyrin (ZPP) [31]. The presence of ZPP has been proposed as an indicator of recent lead intoxication and thus can be used as a biomarker of exposure. However, because of the abundance of hemoglobin (Hb), even in serious cases of lead intoxication, increased ZPP is relatively harmless because it may constitute less than 1% of the total Hb produced [32].

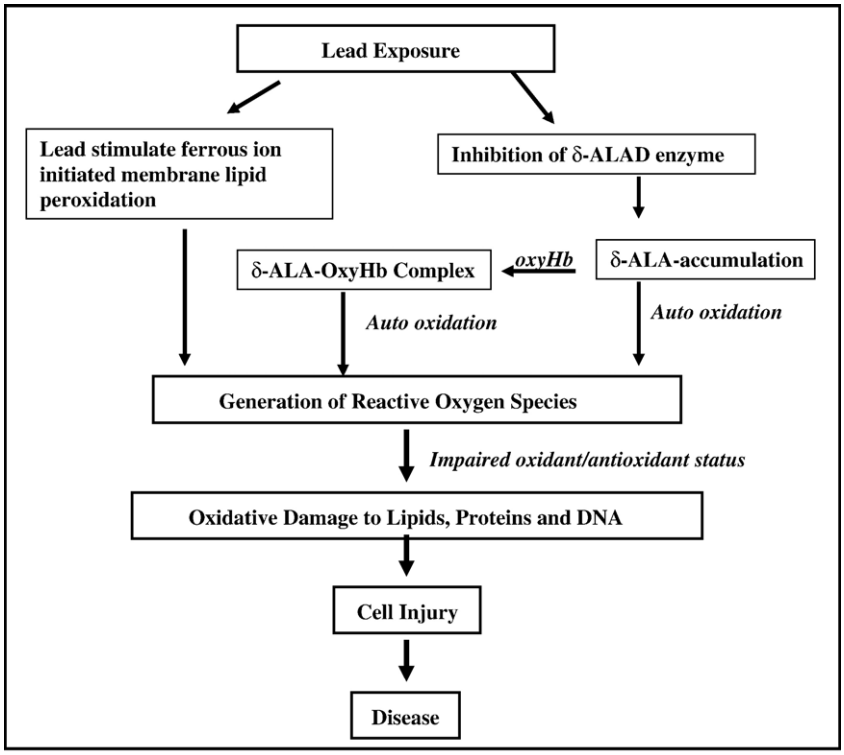
3. Mechanisms for lead-induced free radicals generation

Oxidative stress appears to be a possible mode of the molecular mechanism of lead toxicity [33,34]. Oxidative stress occurs when generation of free radicals (*i.e.* substances with one or more unpaired electrons) exceed the capacity of antioxidant defense mechanisms (*i.e.* pathways that provide protection against harmful effect of free radicals). The depletion of glutathione and protein bound sulfhydryl groups and the changes in the activity of various antioxidant enzymes indicative of lipid peroxidation have been implicated in lead-induced oxidative tissue damage [9,35]. Lead seems to be quite capable of causing oxidative damage to heart, liver, kidney, reproductive organs, brain, and erythrocytes [28,36–39].

The participation of free radicals in lead toxicity may occur at different levels: (i) inhibition of δ-ALAD by lead accounts for the accumulation of its substrate δ-ALA, that can be rapidly oxidized to generate free radicals as superoxide ion ($O_2^{\cdot -}$), hydroxyl radical ($OH^{\cdot}$), and hydrogen peroxide (H_2O_2) [16], and (ii) lead *per se* has the capacity to stimulate ferrous ion initiated membrane lipid peroxidation [33,34] (Fig. 2).

3.1. Pro-oxidative effect delta-aminolevulinic acid (δ-ALA)

Several studies have reported how accumulated δ-ALA induces ROS generation [40,41]. The δ-ALA undergoes enolization and auto-oxidation at pH 7.0–8.0. The conversion of the δ-ALA keto form into the δ-ALA enol form is shown to be necessary for auto-oxidation reactions because levulinic acid, without the amino group ($-NH_2$) that is thought to facilitate the enolization, has not been found to be active in oxidation reactions [40]. The enolized δ-ALA then autoxidizes and generates $O_2^{\cdot -}$, as evidenced by the parallel reduction of ferricytochrome *c*, and also by electron spin resonance spin trapping experiments [42]. Monteiro et al. [43] reported that δ-ALA/oxyHb coupled oxidation also results in ROS generation. The steps of the reactions were reported as follows: (i) δ-ALA enol form is generated following tautomerization, (ii) δ-ALA enol acts as an electron donor to molecular oxygen, together with an electron transfer from oxyHb to oxygen resulting in metHb, δ-ALA radical, and H_2O_2 generation. The $O_2^{\cdot -}$ and H_2O_2, and which are now present as a result of both δ-ALA and δ-ALA/oxyHb coupled auto-oxidation, can interact and generate $HO^{\cdot}$ radicals, which have the highest reactivity among ROS. Inhibition of δ-ALA/oxyHb coupled oxidation by SOD, CAT, and mannitol suggests the involvement of $O_2^{\cdot -}$, H_2O_2, and HO. respectively, in the process. Besides oxyHb, metHb and other ferric and ferrous



δ-ALAD: Delta-aminolevulinic acid dehydratase, δ-ALA: Delta-aminolevulinic acid, OgyHb: Oxy-hemoglobin

Fig. 2. Possible mechanisms for lead-induced oxidative damage to cells.

complexes were also shown to trigger δ-ALA oxidation [42]. This is evidenced by induction of oxygen uptake by δ-ALA in the presence of Fe-ATP and Fe-EDTA complexes as well as oxyHb and metHb. Furthermore, many authors tentatively attribute the neurological symptoms of lead toxicity to the ability of δ-ALA to inhibit either the K^+-stimulated release of γ-aminobutyric acid (GABA) from preloaded rat brain synaptosomes or the binding of GABA to synaptic membranes [15,32,40,44]. Therefore, it may be concluded that δ-ALA accumulated in lead-intoxication can be suggested as a source of ROS, which is now accepted as being associated with the pathophysiology of lead toxicity.

The δ-ALA also has the potential of genotoxicity. Douki et al. [45] demonstrated that the final oxidation product of δ-ALA, 4, 5-dioxovaleric acid, is an effective alkylating agent of the guanine moieties within both nucleoside and isolated DNA. The same group reported increased levels of 8-oxo-7, 8-dihydro-2-deoxyguanosine and 5-hydroxy-2-deoxycytidine in organ DNA of rats chronically treated with δ-ALA, and involvement of $HO^{\bullet}$ in δ-ALA-induced DNA damage [46]. The δ-ALA induces single-strand breaks in plasmid pBR222 DNA [47]. Hiraku and Kawanishi [48] reported that free radicals generated by copper-catalyzed oxidation of δ-ALA could cause oxidative damage to DNA fragments obtained from c-Ha-ras proto-oncogene. Taken together, these findings imply a genotoxic potential of δ-ALA. This possible consequence of δ-ALA accumulation deserves further studies of lead toxicity.

3.2. Lead-induced membrane lipid peroxidation

Lead is known to have toxic effects on membrane structure and functions [49]. The effects on erythrocyte membranes in particular, have been intensely analyzed because erythrocytes have a high affinity for lead and contain a majority of lead found in the blood stream, and are more vulnerable to oxidative damage than many other cells [50].

On cell membrane, the presence of double bonds in the fatty acid 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 are the polyunsaturated fatty acids with more than two double bonds [51]. After incubation of linoic, linolenic, and arachidonic acid with lead, the concentration of a final product of oxidative stress, malondialdehyde (MDA) was increased with the number of double bonds of fatty acid [52]. Another mechanism for lead-induced membrane oxidative damage is the effect on changes in the fatty acid composition of membrane [53]. Because fatty acid chain length and unsaturation are associated with membrane susceptibility to peroxidation, lead-induced arachidonic acid elongation might be responsible for the enhanced lipid peroxidation in the membrane [54]. By causing lateral phase separation and/or by increasing lipid peroxidation rates, lead could affect membrane-related processes such as the activity of membrane enzymes, endo- and exocytosis, the transport of solutes across the bilayer, and signal transduction processes [33].

Taken together, these data suggest that altered lipid composition of membranes due to lead exposure may result in altered membrane integrity, permeability, and function. These would increase the susceptibility to lipid peroxidation.

4. Effects of lead on antioxidant defense systems of cells

Several antioxidant molecules such as glutathione (GSH) and glutathione disulfide (GSSG) levels and antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR) activities are the most commonly used parameters to evaluate lead-induced oxidative damage [16,17,35–38].

GSH is a tripeptide containing cysteine that has a reactive –SH group with reductive potency. Accordingly, GSH plays a vital role in the protection of cells against oxidative stress. It can act as a non-enzymatic antioxidant by direct interaction of the –SH group with ROS, or it can be involved in the enzymatic detoxification reactions for ROS, as a cofactor or a coenzyme [35]. It possesses carboxylic acid groups, an amino group, a –SH group, and two peptide linkages as sites for reactions of metals. Lead binds exclusively to the –SH group, which decreases the GSH levels and can interfere with the antioxidant activity of GSH [34]. Another component of antioxidant defense system, GR, reduces GSSG back to GSH and thereby supports the antioxidant defense system indirectly. GR possesses a disulfide at its active site that was suggested as target for lead, resulting in the inhibition of the enzyme [55]. This inhibition leads to decreased GSH/GSSG ratios that will render cells more susceptible to oxidative damage.

GPx, CAT, and SOD are metalloproteins and accomplish their antioxidant functions by enzymatically detoxifying the peroxides (–OOH), H_2O_2, and $O_2^{\bullet -}$ respectively. CAT decomposes H_2O_2 into H_2O and O_2. GPx needs GSH to decompose H_2O_2 or other peroxides with the simultaneous oxidation of GSH into GSSG. CAT has been suggested to provide important pathway for H_2O_2 decomposition at higher steady state H_2O_2 concentration, whereas GPx is believed to play a more important role in H_2O_2 decomposition under lower steady state levels of H_2O_2 [56]. Since these antioxidant enzymes depend on various essential trace elements and prosthetic groups for proper molecular structure and enzymatic activity, they are potential targets for lead toxicity. As shown by Othman and El-Missiry [57], administration of selenium prior to injection of lead into male rats, produced noticeable prophylactic action against lead by means of increased activities of SOD and GR, and GSH content. Although the protective effect was attributed to the formation of inactive selenium–lead complex [58], it was mentioned that such interactions could not be the sole mechanism for the beneficial effects of selenium. SOD dismutates the $O_2^{\bullet -}$ in to H_2O_2 and requires copper and zinc for its activity. Copper ions appear to have a functional role in the reaction by undergoing alternate oxidation and reduction, where zinc ions seem to stabilize the enzyme instead of having a role in the catalytic cycle [59]. Another type, MnSOD, contains manganese at its active site and is not detected in mammalian erythrocytes, but is present in human liver to some extent. Mylroie et al. [59] observed: (i) high correlation between decreased SOD and decreased copper concentrations in the blood of animals, (ii) no effect on SOD with increased BLLs in

the presence of normal copper concentration, and (iii) that dietary copper supplementation prevented the lead-induced decrease in SOD activity. Therefore, they have suggested an indirect inhibitory effect on SOD *in vivo* due to the lead-induced copper deficiency. Inhibition of SOD activity by lead was also shown in an *in vitro* study where the authors indicated that this effect of lead can lead to decreased scavenging of ROS and result in oxidative damage [60]. However, Ariza et al. [61] demonstrated rapid induction of cellular H_2O_2 following treatment of AS52 cells with 1M lead, which they suggested to be increased by the stimulatory effect of lead on the activities of CuZn–SOD and xanthine oxidase that produce H_2O_2.

Lead inherence facilitates conversion of Hb into metHb. This reaction is possible not only in pure Hb solution, but also in lysates, wherein antioxidant defense systems are present. It seems that during Hb oxidation in the presence of lead, H_2O_2 is generated, which may induce lipid peroxidation in erythrocyte cell membranes [62]. Ribarov et al. [63] found that lead significantly enhances the auto-oxidation of Hb in an *in vitro* liposome model. The inhibition of this effect by SOD and CAT suggested that $O_2^{\cdot-}$ and H_2O_2 are somehow involved in the process. As a result, they speculated that lead might induce generation of ROS by interacting with oxyHb, leading to peroxidative damage of erythrocyte membranes.

5. Oxidative stress to lead-related diseases with low exposure

Investigators have extensively studied that higher levels lead exposure causes oxidative damage to brain, heart, kidneys, and reproductive organs. However, only few studies demonstrated that low levels lead exposure also induces oxidative stress. We have discussed some studies indicating relevance of oxidative stress to lead-related human diseases with low exposure (Table 1).

Lead may induce oxidative damage to reproductive organs. Sperm ROS generation was significantly higher in lead-exposed rats with BLLs of 33.6 μg/dL which was associated with the decrease of sperm motility, motile sperm counts, and sperm–oocyte penetration rate [64]. Furthermore, lead-induced ROS generation was associated with early onset of sperm capacitation and premature acrosome reaction, and reduced zona-intact oocyte penetrating capability [36]. Batra et al. [65] observed a significant decrease in δ-ALAD and SOD activity in rat testis with relatively lower BLL (18.6 μg/dL). Our previous study suggested that moderate BLL 23.4 μg/dL might be a risk factor the development of prostate cancer in human through generating the ROS [66]. However, low levels lead exposure and oxidative damage to reproductive organs could be the area of worthy investigation.

Table 1
Recent studies indicating relevance of oxidative stress to lead-related diseases with low exposure

Subjects	Exposure/dose	Mean BLL	Target sites	Outcomes	References
Adults	Environmental exposure	2.8 μg/dL	Serum	BLLs showed graded associations; positive with serum GGT and inverse with serum vitamin C and E, and carotenoids	[22]
Adult Parkinson's disease patients	Environmental exposure	3.5 μg/dL	Brain	BLLs was significantly associated with homocysteine, a risk factor for heart disease	[76]
Children	Environmental exposure	7.4 μg/dL	Blood	Significant correlation of BLLs and δ-ALAD activity with oxidative stress parameters	[28]
Children	Environmental exposure	7.32 μg/dL	Blood	Blood levels of MDA, SOD, GPx and GR were significantly influenced by BLLs	[78]
Adolescents	Environmental exposure	9.9 μg/dL	Blood	Significant correlation of BLLs and δ-ALAD activity with oxidative stress parameters	[75]
Adults prostate cancer patients	Environmental exposure	23.4 μg/dL	Prostate gland	Results suggest that lead may be risk factor for PCA and/or BPH possibly through generation of ROS	[66]
Rabbits	Exposed to lead oxide (PbO) at 30 $\mu g/m^3$ for four days	1.2–2.0 μg/dL	Lung	PbO-related ROS generation disrupted pulmonary macrophage-mediated functions	[70]
SD rats	Received 100 ppm of lead in drinking water for 3 months	3.2 μg/dL	Vessel	Lead-induced hypertension may be caused by ROS generation	[77]
SD rats	Received 100 ppm of lead in drinking water chow for 12 weeks	12.4 μg/dL	Vessel	Lead-induced hypertension may be caused by hydroxy radical and peroxynitrite generation	[37]
Portan rats	Orally received 50 mg/kg of lead daily for three months	18.6 μg/dL	Testis	Lead decreases the activity of δ-ALAD and SOD in the testis	[65]
Buffalo rats	Intragastrically received 35 mg/kg of lead once a week or 70 mg/kg of lead twice a week for 7 weeks	16.8 μg/dL	Blood	Inhibition of lipoprotein lipase in the context of arteriosclerosis	[71]
SD rats	Received 100 ppm of lead in drinking water for 12 weeks	Not determined	Kidney	Lead-induced hypertension through dysregulation of activities of SOD, CAT, GPx, and guanylate cyclase in renal cortex, medulla, and thoracic aorta	[10]

Exposure to low levels of lead causes hypertension in humans and animals [10,37,67–69]. In a study published in 2006, Menke and colleagues [23] found an increased risk of death from all causes as well as from cardiovascular disease and stroke in association with BLL as low as 2 μg/dL. The study analyzed data from more than 13,946 adult participants in the third National Health and Nutrition Examination Survey (NHANES III) mortality study. So, how does lead actually cause cardiovascular effects? Animal studies show that lead can promote the growth of vascular smooth cells, which play a role in the formation of atherosclerotic plaques. Lead's promotion of oxidative stress is thought to play a role in its cardiovascular effects. In rabbit, after inhalational exposure to lead oxide (PbO) particles between 0.5 and 3.0 μg at 30 μg/m^3 for 4 days (BLL 1.2–2.0 μg/dL), enhanced H_2O_2, and $O_2^{\cdot-}$ production was noted, and pulmonary macrophage-mediated functions were disrupted [70]. Ding et al. [67] found that lead-induced hypertension was associated with an increase in ROS, which enhanced vascular reactivity with rather low BLLs (3.2 μg/dL) in SD rats. They also showed that lead-induced hypertension might be caused by hydroxyl radical and peroxynitrite generation at average BLL of 12.4 μg/dL in lead-treated rats [37]. Lead was shown to promote hydroxyl radical generation and lipid peroxidation in cultured aortic endothelial cells [69]. Similar changes were observed in rats given moderate doses of lead (average BLL of 16.8 μg/dL) that caused the increase of serum lipid peroxidation in a dose-response manner [71]. On the basis of these studies, it can be speculated that ROS might be involved in the genesis of lead-related hypertension, through either direct vaso-constrictive effect [72] or by inactivation of endothelium-derived relaxing factor [73].

Recent epidemiological studies of the general population suggest kidney function may be altered at the lowest levels of blood lead studied to date in relation to renal effects. In a review Ekong and colleagues [21] wrote that lead contributed to kidney damage at concentration below 5 μg/dL. Muntner et al. [18] examined the association between low BLLs with chronic kidney diseases among adults of U.S. participating in NHANES III (n=15,211). BLL 4.2 μg/dL was strongly associated with chronic kidney disease. In addition, lead's effects on kidney damage are thought to play a major role in its effect on blood pressure. This is because the kidney helps to regulate the blood volume and vascular tone, which are the principle determinants of blood pressure. The kidney is the organ through which we get rid of the excess salt and fluids. Consequently, impairment of ability of kidney to efficiently excrete salts and fluids can result in the rise in blood volume and, hence blood pressure. Also kidney produces hormones that regulate the tone of blood vessels. Thus, alterations of kidney function or structure can cause the blood vessels to constrict throughout the body, thereby raising blood pressure. Lead-induced kidney damage also includes the components of ROS. Farmand et al. [10] have shown that rats exposed to lead in drinking water (100 ppm lead acetate) for 12 weeks induce hypertension through the dysregulation of activities of SOD, CAT, GPx, and guanylate cyclase in renal cortex, medulla, and thoracic aorta.

Several studies reported that levels of MDA, GSH/GSSG ratio, and activity of antioxidant enzymes were strongly correlated with higher BLL (approximately 30 μg/dL to >100 μg/dL) [16,17,39,41]. Dursun et al. [74] had similar results in a group with a relatively low exposure to lead (BLL 15 μg/dL). A study from our group also found that BLL 9.9 μg/dL significantly associated with δ-ALAD, MDA and CAT among urban adolescents from general population of Lucknow, India [75]. Lee et al. [22] examined the association of BLL with the oxidative stress markers of γ-glutamyltransferase (GGT), vitamin C, carotenoids, and vitamin E among 10,098 adult participants in the NHNES III. After adjusting for known confounding effects, BLL (2.8 μg/dL) showed graded associations, positive with serum GGT and inverse with serum vitamin C, carotenoids, and vitamin E. Authors suggest that strong association of BLL with oxidative stress markers in this population suggests that oxidative stress should be considered in the pathogenesis of lead-related diseases among population with low exposure to lead. Schafer et al. [76] found a significant positive association between BLL (3.5 μg/dL) and homocysteine in an older, community-dwelling, adult, population-based sample in a major US urban area. Elevated homocysteine level increases the risk of heart diseases, strokes, peripheral vascular diseases and cognitive functions. Authors suggest that the mechanisms of this impairment might involve the components of oxidative stress. In pregnant women with low levels of blood lead from 2.7–12.6 μg/dL, an inverse relationship was observed between BLL and serum levels of α-tocopherol and ascorbic acid [77]. Our group also examined the association of low levels lead exposure with markers of oxidative stress among children of general population. BLL 7.1 μg/dL was significantly associated with δ-ALAD, GSH, MDA, and CAT [28]. Diouf et al. [78] investigated the effects of low levels lead exposure on heme synthesis and some markers of oxidative stress among Senegalese children. They found that BLL 7.3 μg/dL was significantly associated with urinary δ-ALA levels, erythrocyte GPx and GR activities, and blood selenium levels. Therefore, low levels lead exposure seems to be capable to induce oxidative stress among human of general population wherein many diseases are thought to be associated with lead-induced generation of free radicals.

6. Conclusion

It has now become clear that high to moderate doses of lead exposure induce generation of free radicals resulting in oxidative damage to critical biomolecules, lipids, proteins and DNA. There may be two independent sources of lead-induced oxidative damage; the first is the pro-oxidative effect of δ-ALA, and the second is connected with the direct effect of lead on membrane lipids. Although, recent studies suggest that oxidative stress due to low levels lead exposure might be involved in many human diseases, the detailed mechanistic studies indicating relevance of oxidative stress markers to lead-related human diseases with low exposure still warrant further investigations. Furthermore, work is needed to find the effective and safe intervention for lowering the lead exposure at the general population level.

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