

Review

Lead toxicity, oxidative damage and health implications. A review

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The toxicity of Lead was recognized centuries ago, and it continued to pose serious threat to the health of children as well as adults. This review presents an overview of the current knowledge of toxic effects of Lead induced oxidative damage and also suggests some possible measures which could reduce the toxic effects of the metal. This paper examines the effects of Lead in blood, soft tissues, haematopoietic system and the antioxidant defense system. On the other hand, data also indicated that lead is an essential element at low dietary intakes. Its deficiency was shown to depress growth, disturb iron metabolism, alter activities of some enzymes and disturb the metabolism of cholesterol, phospholipids and bile acids. It was found that lead toxicity is significant but a preventable health problem. Furthermore, work is needed to find the effective and safe intervention for lowering the lead exposure at the general population level.

Key words: Lead toxicity, oxidative damage, haematological, antioxidant.

INTRODUCTION

Lead is ubiquitous, and the most common environmental pollutant naturally present in the earth's crust in small concentrations, for centuries it has been mined and disseminated throughout the environment from where it has gradually become incorporated into the structural tissue of plants, animals and humans (Pracheta et al., 2009). However, both occupational and environmental exposure has made lead a serious problem in many developing and industrializing countries (Yucebiligic et al., 2003). It has many undesired effects, including neurological (Senapati et al., 2001; Soltaninejad et al., 2003; Bellinger, 2008; Sharma et al., 2011), behavioural

(Moreira et al., 2001; De Marca, 2005; Adeniyi et al., 2008), immunological (Razani-Boroujerdi et al., 1999; Bunn et al., 2001; Rosenberg et al., 2007), renal (Lockitch, 1993; Vargas et al., 2003; Rastogi, 2008; Sharma et al., 2011c), hepatic (Lockitch, 1993; Patra et al., 2001; Sharma et al., 2011b), cardiovascular system and haematological dysfunctions (Mousa et al., 2002; Adeniyi et al., 2008). Lead pollution can also cause irreversible encephalopathy, seizure, coma and even death. Fatigue, memory loss, high blood pressure, nephropathy, gastrointestinal disturbances, weight loss and immuno-suppression are other common toxic effects of lead exposure in animals. Prenatal exposure to metal may also cause birth defects, miscarriage and underdeveloped babies (Ehle and Mckee, 1990; Pracheta et al., 2009).

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Abbreviations: **ACP**, Acid phosphatase; **ALA**, aminolevulinic acid; **ALAD**, δ-aminolevulinic acid dehydratase; **ALP**, alkaline phosphatase; **ALT**, alanine transaminase; **AST**, aspartate transaminase; **CAT**, catalase; **GPX**, glutathione peroxidase; **GSH**, reduced glutathione; **GST**, glutathione-S-transferase; **HDL**, high density lipoprotein; **LDL**, low density lipoprotein; **LPO**, lipid peroxidation; **ROS**, reactive oxygen species; **SOD**, superoxide dismutase.

EFFECTS OF LEAD AND ITS POTENTIAL HEALTH EFFECTS

Lead is a poison that affects virtually every system in the body. Children are more vulnerable to lead exposure than adults because of the frequency of pica, hand-to-mouth activity, and a higher rate of intestinal absorption and

retention. The most deleterious effects of lead are on erythropoiesis, soft tissues, kidney function, and the central nervous system (ATSDR, 1993).

Effect of Lead in soft tissue

Levels of lead in soft tissue appear to be relatively constant during life, despite a fairly high turnover rate (Barry, 1975). Lead is stored in almost all soft tissues (Doyle and Younger, 1984); autopsy studies show that liver is the largest repository of soft tissue lead (33%), followed by kidney cortex and medulla, pancreas, ovary, spleen, prostate, adrenal gland, brain, fat, testis, heart, and skeletal muscle (Senapati et al., 2001; Adeniyi et al., 2008; Sharma et al., 2011b, c; Sharma et al., 2011). Dose related accumulation of most lead in heart and kidney in new born rat pups was reported by Singh et al. (1976). It is observed that chronic oral administration of low doses of lead results in accumulation particularly in bone, kidney and skeletal muscle in most animal species (NRC, 1972). Lead of 1700 µg/dl after 35 days of exposure resulted in a testicular Pb concentration of 0.8 µg/dl in Sprague- Dawley rats. Thoreux- Manlay et al. (1995), reached testicular lead concentrations of 2.0, 1.6, 2.6, and 4.3 µg/dl with Pb B of 56, 91, 196, and 332 µg/dl respectively after 30 days of exposure. The liver contains numerous proteins to which Pb may bind. One of these proteins is metallothionein (Hamer, 1986), which has a high affinity for lead in vitro (Waalkes et al., 1984), although lead can induce metallothionein production in liver (Waalkes and Klaasen, 1985; Ikebuchi et al., 1986). Apart from this other proteins were also known to bind Pb in vivo (Shelton and Egle, 1982; Goering, 1993). The higher concentrations of lead in tissues following occupational or experimental exposure were associated with oxidative damage of DNA, protein and lipid which suggests that lead-induced oxidative stress play a role in lead –induced toxic effects (Monteiro et al. 1986; Patra et al., 2001).

Effects of Lead on respiratory and gastrointestinal system

Lead poisoning occurs as a result of ingestion or inhalation of inorganic lead particles or through transdermal absorption of organic alkyl lead. The respiratory tract provides the most effective route of absorption as it only depends on the size of lead particles and on the metabolic activity of the body. Airborne lead particles that are less than 0.5 to 1 microns in diameters are generally completely absorbed by the alveoli. Gastrointestinal absorption of lead is less effective and depends on a number of factors, for example, the presence of food in the stomach, the concentration of lead ingestion, the nutritional status and the age. The rate of lead absorption increases with iron, zinc and calcium

deficiencies.

Effects of lead on haematopoietic system

Lead may be rapidly absorbed and reached considerable amount in the blood (Haque et al., 2006). Once absorbed, 99% of blood lead is transported to the erythrocytes as lead diphosphate (Freeman, 1970). Increment of blood lead level -following lead acetate and lead nitrate administration was demonstrated in the experimental animals (Ferguson et al., 1998; Sharma et al., 2011d). Some reports suggested that this element is strongly bound to macromolecules in the intracellular compartment because lead binding proteins have been isolated from kidney, liver, blood and brain (Moussa et al., 2001). The half- life of lead differs for each of the compartment, ranging from 25 to 40 days in erythrocytes, 40 days in soft tissues and as many as 28 years in bone. We have also reported the protective effects of *Withania somnifera* root extract supplementation on blood profiles and serological parameters in male mice subjected to lead nitrate (Sharma et al., 2011d). We have also found the therapeutic potential of hydromethanolic root extract of *W. somnifera* on neurological parameters in Swiss albino mice subjected to lead nitrate (Sharma et al., 2011). On the basis of experiments performed in our laboratory we elucidated the protective potential of the hydromethanolic extract of *W. somnifera* in the regulation of lead nitrate induced nephrotoxicity and hepatotoxicity in Swiss albino mice (Sharma et al., 2011b, c).

Lead exposure and generation of oxidative stress

Oxidative stress occurs when generation of free radicals (i.e. substances with one or more unpaired electrons) exceed the capacity of antioxidant defense mechanisms (that is, pathways that provide protection against harmful effect of free radicals). Lead induced oxidative stress has been identified as the primary contributory agent in the pathogenesis of lead poisoning (Xu et al., 2008). Reactive oxygen species (ROS) generated as a result of lead exposure has been identified in liver, kidney, brain, lung, endothelial tissue, testes and sperm.

Lead causes oxidative stress by inducing the generation of ROS, reducing the antioxidant defense system of cells via depleting glutathione, interfering with some essential metal, inhibiting sulfhydryl dependent enzymes or antioxidant enzymes activities or increasing susceptibility of cells to oxidative attack by altering membrane integrity and fatty acid composition (Sharma et al., 2011b, c; Sharma et al., 2011).

Effect of lead on the antioxidant defense system

Although, the mechanism by which lead induce oxidative

stress is not fully understood, a large number of evidences indicate that multiple mechanism balance between reactive oxygen metabolites and antioxidant defense results in "oxidative stress" (Gibananada and Hussain, 2002). Participation of iron in fenton reaction *in vivo*, leading to production of more reactive hydroxyl radicals from superoxide radicals and H_2O_2 (Halliwell, 1994a) results in increased lipidperoxidation. This might be one of the reasons for significant alteration in lipidperoxidation (LPO) and significant changes in the activity of antioxidant enzymes. Usually the deleterious effects of oxidative stress are counteracted by endogenous antioxidant enzymes, mainly superoxide dismutase (SOD), Catalase (CAT) and glutathione (GSH) (Winterbourn, 1993). The binding activity of lead compounds with oxidative stress factors and the gene erythropoiesis ration of reactive oxygen species, such as hydrogen peroxide and its interaction with different metals and also toxic activity of delta-aminolevulinic acid (ALA) are reported earlier (Ariza et al., 1998; Ding et al., 2000).

SOD and catalase are considered primary enzymes since they are involved in direct elimination of ROS. SOD plays an important role in protecting the cells against the toxic effects of O_2^- by catalyzing its dismutation reactions. The enzyme 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 (Halliwell and Gutteridge, 1989). SOD keeps the concentration of superoxide radicals at low levels and therefore plays an important role in the defense against oxidative stress (Fridovich, 1997). Various findings demonstrated that lead has inhibitory effects on superoxide dismutase and catalase also found to inhibit antioxidant enzymes involved in the prevention of lipid peroxidation such as superoxide dismutase and catalase (Soltanienejad et al., 2003; Vaziri et al., 2003). The biological role of SOD is to dismutase superoxide ion, hydrogen peroxide (H_2O_2), produced in this reaction is eliminated by catalase, one of the most active enzymes in the human organism.

Catalase is a heme protein, which catalyzes the reduction of hydrogen peroxides (converts H_2O_2 to oxygen and water) and protects tissues from highly reactive hydroxyl radicals. Various reports regarding influence of lead on SOD and CAT activities have given divergent results. Some studies showed decreased activities of SOD and CAT (Ramstoeck et al., 1980; Chaurasia and Kar, 1997a; Chaurasia and Kar, 1997b) and others showed increased activities (Adler et al., 1993; Ahamed et al., 2006). Superoxide anions (O_2^-) itself directly affects the activity of catalase and peroxidase by affecting intracellular enzymes (Ghosh and Myers, 1998), creatine phosphokinase (Lee et al., 1998). SOD was found to be decreased in the treated animal's tissues particularly in liver, kidney and testis (Sharma et

al., 2011b, c). A decrease in SOD was explained by direct blocking action of the metal on -SH group of the enzyme (Kasperczyk et al., 2004). Decreased catalase activity observed in lead-exposed animals were attributed to the interference of lead by both processes (Sandhir et al., 1994 and 1995).

The lower activities of CAT and SOD may partly be explained by the interaction between lead and essential metals such as copper, zinc, and iron. Copper and Zinc are essential cofactors for SOD, whereas CAT also contains haem as the prosthetic group, the biosynthesis of which is inhibited by lead (Patil et al., 2006). Several studies reported alterations in antioxidant enzyme activities such as SOD, catalase and glutathione peroxidase (GPX) and changes in the concentrations of some non-enzymatic antioxidant molecules, such as glutathione (GSH) in lead exposed animals (McGowan et al., 1986) and workers (Sugawara et al., 1991; Solliway et al., 1996; Gayathri et al., 2007; Mohammad et al., 2008). These findings suggest a possible involvement of oxidative stress in the pathophysiology of lead toxicity.

One of the effects of lead exposure is on glutathione metabolism. GSH is one of the most important compounds, which helps in the detoxification and excretion of heavy metals. Glutathione is a cysteine-based molecule produced in the interior compartment of the lymphocyte. More than 90 percent of non-tissue sulphur in the human body is found in the tripeptide glutathione (Meister and Anderson, 1983). In addition to acting as an important antioxidant for quenching free radicals, glutathione is a substrate responsible for the metabolism of specific drugs and toxins through glutathione conjugation in the liver (Meister and Anderson, 1983). The sulfhydryl complex of glutathione also directly binds to toxic metals that have a high affinity for sulfhydryl groups. It binds with heavy metals. Patra and Swarup (2000) observed effect of lead on erythrocyte antioxidant defense, lipid peroxide level and thiol groups in calves. Sugawara et al. (1991) have reported a significant decrease in GSH content of erythrocytes from workers exposed to lead. Indirect depletion of GSH may occur when lead inhibits the enzyme and aminolevulinic acid dehydratase (ALAD) before it catalyzes the condensation of two molecules of d-aminolevulinic acid (δ -ALA) to porphobilinogen (Haeger-Aronsen et al., 1971). When the activity of ALAD is inhibited an effect of lead exposure which has been confirmed experimentally by several authors, the amount of δ -ALA increased (Ribarov and Bochev, 1982; Gibbs et al., 1991). Since δ -ALA itself is known to be a potent inducer of lipid peroxidation (LPO) and ROI formation both *in vivo* and *in vitro*, its accumulation may facilitate the depletion of GSH from lead-burdened cells (Monteiro et al., 1986, 1989; Hermes-Lima et al., 1991; Oteiza and Bechara, 1993). The involvement of ROS in Pb poisoning has been addressed by Schwartz et al. (2000) who found a decrease in GSH and an increase in oxidized glutathione

(GSSH) concentration in lead acetate treated rats. In addition, they also found that the effect was reduced by treatment with N- acetyl cystein, a precursor of GSH. This provided a possibility of antioxidant therapy for individuals who were exposed to lead. GSH/GSSH ratio is an important component of antioxidant defense system in mammalian cells, which was considered a sensitive indicator of oxidative stress (Wilson et al., 2000).

Mercury, arsenic, and lead effectively inactivate the glutathione molecule so it is unavailable as an antioxidant or as a substrate in liver metabolism (Christie and Costa 1984). Concentrations of glutathione in the blood have been shown to be significantly lower than control levels both in animal studies of lead exposure and in lead-exposed children and adults (Hsu, 1981; Ahamed et al., 2005). Levels of two specific sulfhydryl containing enzymes that are inhibited by lead – deltaaminolevulinic acid dehydrogenase (ALAD) and glutathione reductase (GR) – have been demonstrated to be depressed in both animal and human lead-exposure studies (Farant et al., 1982; Gurer-Orhan et al., 2004; Ahmad et al., 2005).

Lipid peroxidation, a basic cellular deteriorative change, is one of the primary effects induced by oxidative stress and occurs readily in the tissues due to presence of membrane rich in polyunsaturated highly oxidizable fatty acids (Cini et al., 1994). Lead, being a heavy metal and potent environmental pollutant in elicits variety of toxic manifestations in the living systems (Perlstein and Attala, 1966; Choice and Richter, 1972; Quinlan et al., 1988; Acharya et al., 1994). The toxic effects of lead in various tissues/ organs have hardly been believed due to some peroxidative activities, except in few tissues (Quinlan et al., 1988; Acharya et al., 1994).

On the contrary, the generation of elevated quantities of thiobarbituric acid reactive substances from the brain in lead treated mice is possibly due to the presence of high level of poly-unsaturated fatty acids and free iron. Yiin and Lin (1995) demonstrated a significant enhancement of malondialdehyde (MDA) when lead was incubated with linoic, linolenic and arachidonic acid. These initial studies for the first time and subsequent studies on lead exposed animals showed increased lipid peroxidation or decrease in antioxidant defense mechanism (Adegbesan and Adenuga, 2007; Bokara et al., 2008). A number of researchers have also shown enhanced rate of lipid peroxidation in brain of lead exposed rats (Yiin and Lin, 1995; Adegbesan and Adenuga, 2007; Bokara et al., 2008). They also showed that the level of lipid peroxidation was directly proportional to lead concentrations in brain regions (Shafiq-ur-Rehman et al., 1995; Adonaylo and Oteiza, 1999; Saxena and Flora, 2006). Similar effects were shown by Sandhir and Gill (1995) and Sharma et al. (2011b) in liver of lead exposed rats.

Lead binds to plasmic protein, where it causes alterations in high number of enzymes. Georing (1993) found that lead can also perturb protein synthesis in

hepatocytes. The decrease in protein content of mice treated with Pb may be due to decreased hepatic DNA and RNA (Shalan et al., 2005). Hassanin (1994) and El-Zayat et al. (1996) reported decrease in hepatic total protein content in response to lead intoxication. They attributed that to a decreased utilization of free amino acids for protein synthesis. B-2-microglobulinuria and enzymuria were reported in lead toxicity in children (Gourrier et al., 1991). According to Pachathundikandi and Varghese (2006), lead toxicity results in protein loss. Hassanin (1994) and El- Zafat et al. (1996) observed decrease in hepatic total protein content in response to lead intoxication. This may be because Pb^{2+} disturbs intracellular Ca^{2+} homeostasis (Simons, 1993) and damages the endoplasmic reticulum which in turn results in reduction of protein synthesis. In addition, lead has been shown to enter in cells through voltage dependent Ca^{2+} channels at a higher rate than Ca^{2+} as an intracellular secondary messenger. Interaction between lead and two second messenger mediators of Ca^{2+} signals (Calmodulin and protein kinase C) have been studied extensively (Goldstein, 1993). Calmodulin exhibits a higher affinity for lead than it does for Ca^{2+} , leading to an up regulation of the enzymes (Habermann et al., 1983).

Treatments for lead toxicity

Therapies to remove heavy metals from the body include chelation and supportive measures. Chelation is a chemical process that has applications in many areas, including medical treatment, environmental site rehabilitation, water purification and so forth. Several chelating compounds have been used to manage lead toxicity in the event of manage lead toxicity in the event of exposure but none are suitable in reducing lead burden in chronic lead exposure. Moreover, these chelators in turn are potentially toxic (Gilman et al., 1991) and often fail to remove Pb burden from all body tissues.

Although, lead poisoning has been studied for years, some of the toxic effects still cannot be explained (Aykir-Burns et al., 2003). The use of chelating agents and few antioxidants such as vitamin C and E (Mehta et al., 2001) can enhance lead excretion in lead poisoning but these cannot be routinely recommended as these posses many side effects (Flora and Tandon, 1990). In order to address this problem, natural therapies to promote chelation, detoxification and protection are gaining popularity because of minimal side effects. Medicinal properties of plants have also been investigated in the light of recent scientific developments throughout the world, due to their potent pharmacological activities, low toxicity and economic viability (Janmeda et al., 2011). Thus, there has been increased interest in the therapeutic potential of plant products or medicinal plants having beneficial role in reducing lead poisoning.

CONCLUSION

It was found that lead toxicity is significant but a preventable health problem. Identification of various lead sources that surround us can help towards prevention of lead toxicity. However, lead is also toxic to humans, with the most deleterious effects on the hemopoietic, nervous, hepatic and renal systems. It has now become clear that high to moderate doses of lead exposure induces generation of free radicals resulting in oxidative damage to critical biomolecules, lipids, proteins and DNA. 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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