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Lead-induced oxidative stress and role of antioxidants in its management

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INTRODUCTION

Lead induced oxidative stress:

Lead is a persistent and common environmental contaminant. lead damages cellular material and alters cellular genetics. The mechanism all of these toxic metals have in common involves oxidative damage. Toxic metals increase production of free radicals and decrease availability of antioxidant reserves to respond to the resultant damage. Low-level exposures to lead may cause cognitive dysfunction, neurobehavioral disorders, neurological damage, hypertension, and renal impairment. The pathogenesis of lead toxicity is multifactorial, as lead directly interrupts enzyme activation, competitively inhibits trace mineral absorption, binds to sulfhydryl proteins (interrupting structural protein synthesis), alters calcium homeostasis, and lowers the level of available sulfhydryl antioxidant reserves in the body (Ercal *et al.,* 2001).

Mechanisms of lead toxicity: The effect of lead on oxidant/ antioxidant balance :

Lead toxicity leads to free radical damage via two separate, although related, pathways :

- The generation of reactive oxygen species (ROS), including hydroperoxides, singlet oxygen, and hydrogen peroxide and
- The direct depletion of antioxidant reserves (Ercal *et al.,* 2001).

In any biological system where ROS production increases, antioxidant reserves are depleted. In this situation, the negative effects on the human system's ability to deal with increased oxidant stress occur via independent pathways.

Effect of lead toxicity :

Lead binds to glutathione and sulfhydryl-containing enzymes:

One of the effects of lead exposure is on glutathione metabolism. Glutathione is a cysteine-based molecule produced in the interior compartment of the lymphocyte. More than 90 per cent of non-tissue sulphur in the human body is found in the tripeptide glutathione. 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 *et al.,* 1983).

The sulfhydryl complex of glutathione also directly binds to toxic metals that have a high affinity for sulfhydryl groups. 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 (Ahamed *et al.,* 2005).

Lead also binds to enzymes that have functional sulfhydryl groups, rendering them non-functional and further contributing to impairment in oxidative balance. Levels of two specific sulfhydrylcontaining 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 (Gurer-Orhan *et al.,* 2004).

In a study of pediatric lead exposure in Lucknow, India, children with blood lead levels of 11.39 µg/dL had significantly depressed levels of ALAD compared to children with levels of 7.11µg/dL or lower (Ahamed *et al.*, 2005). Depressed levels of ALAD in these children correlated with depressed levels of glutathione. ALAD is a crucial enzyme in lead toxicity because the inhibition of ALAD lowers heme production and increases levels of the substrate delta-aminolevulinic acid (ALA). Elevated levels of ALA, found both in the blood and urine of subjects with lead exposure, are known to stimulate ROS production (Bechara *et al.*, 1996).

Lead generates reactive oxygen species (ROS) :

Erythrocytes have a high affinity for lead, binding 99 per cent of the lead in the bloodstream. Lead has a destabilizing effect on cellular membranes, and in red blood cells (RBC) the effect decreases cell membrane fluidity and increases the rate of erythrocyte hemolysis. Hemolysis appears to be the end result of ROS-generated lipid peroxidation in the RBC membrane (Lawton and Donaldson, 1991). Lead can also bind directly to phosphatidylcholine in the RBC membrane, leading to a decrease in phospholipid levels (Shafiq-ur-Rehman *et al.*, 1993). Lipid peroxidation of cellular membranes has also been identified in tissue from various regions of the brain of lead-exposed rats (Flora and Seth, 2000). Hypochromic or normochromic anemia is a hallmark of lead exposure; it results from ROS generation and subsequent erythrocyte hemolysis (Gurer and Ercal, 2000). Lead is considered, along with silver, mercury, and copper, to be a strong hemolytic agent, able to cause erythrocyte destruction through the formation of lipid peroxides in cell membranes (Ribarov and Benov, 1981). In addition to membrane peroxidation, lead exposure causes hemoglobin oxidation, which can also cause RBC hemolysis. The mechanism responsible for this reaction is lead-induced inhibition of ALAD. ALAD is the enzyme most sensitive to lead's toxic effects – depressed heme formation. Lead has also been shown to both elevate and suppress blood levels of the antioxidant enzymes superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx). Elevations of these enzymes have been seen in lower levels of exposure, while suppression can occur at higher exposure levels over longer periods of time. In one study of 137 lead-exposed workers, those with high blood lead levels (over 40 µg/dL) had significant reductions in blood GPx that correlated with elevated erythrocyte MDA levels (Kasperczyk *et al.*, 2004). Those with lower exposures (25-40 µg/dL) had elevated levels of GPx, a suggested compensatory reaction for increased lipid peroxidation.

The role of antioxidants in addressing lead-induced oxidative stress :

Antioxidants are an inhibitor of the process of oxidation, even at relatively small concentration and thus have diverse physiological role in the body. Antioxidant constituents of the plant material act as radical scavengers, and helps in converting the radicals to less reactive species. A variety of free radical scavenging antioxidants is found in dietary sources like fruits, vegetables and tea, etc. According to literature, these are "substance that when present in low concentration compared to those of the oxidisable substrates significantly delay or inhibit the oxidation of that substance.

Antioxidants defence both enzymatic and non enzymatic reactions protect the body against oxidative damage. Non enzymatic antioxidants are frequently added to the food to prevent lipid oxidation. Several lipid antioxidants can exert pro-oxidant effect towards other molecule under certain circumstances thus the antioxidants for food and therapeutic use must be characterized carefully.

Antioxidants that effective in lead induced oxidative stress :

Vitamin C, E, beta carotene, α -Lipoic acid, NAC, taurine, selenium, methionine.

Vitamin C :

Vitamin C (ascorbic acid) is a very important, and powerful, antioxidant that works in aqueous environments of the body. Vitamin C cooperates with vitamin E to regenerate α-tocopherol (Young and Woodside, 2001) from α-tocopherol radicals in membranes and lipoproteins. Ascorbic acid, behaves as a vinylogous carboxylic acid, wherein the double bond ("vinyl") transmits electron pairs between the hydroxyl and the carbonyl. Ascorbate acts as an antioxidant by being available for energetically favorable oxidation. Reactive oxygen species oxidize (take electrons from) ascorbate first to monodehydroascorbate and then dehydroascorbate. The reactive oxygen species are reduced to water, while the oxidized forms of ascorbate are relatively stable and unreactive, and do not cause cellular damage. Vitamin C scavenges the aqueous reactive oxygen species (ROS) by very rapid electron transfer that inhibits lipid peroxidation. (Jones *et al.*, 1995). Vitamin C has been consistently shown to protect the concentration of molecules such as ALAD that are associated with red blood cell manufacture. Vitamin C improves iron absorption if it can mix with food in the stomach (food or liquid being preferable forms), as well as increasing iron's capacity to displace lead during food absorption. (Roberts, 2010). Lead toxicity can be prevented by the supplementation of vitamin C which reduced ROS generation. The beneficial effect of vitamin C was possibly due to a reduction in lipid per oxidation potential (Tohamy and Nattat, 2010).

Vitamin E:

α-tocopherol is the most active form of vitamin E in humans and is a powerful biological antioxidant which is considered to be the major membrane bound antioxidant

employed by the cell. Its main antioxidant function is protection against lipid peroxidation. During the antioxidant reaction, α-tocopherol is converted to a α-tocopherol radical by the donation of labile hydrogen to a lipid or lipid peroxyl radical. The α-tocopherol radical can thus be reduced to the original α-tocopherol form by ascorbic acid (Kojo, 2004). Vitamin E perform a unique function by interrupting free radical chain reactions via capturing the free radical. The free hydroxyl group on the aromatic ring is responsible for the antioxidant properties. The hydrogen from this group is donated to the free radical, resulting in a relatively stable free radical form of the vitamin. The antioxidant function of this micronutrient enhances immunity by maintaining the functional and structural integrity of important immune cells (Arita *et al.*, 1995). Vitamin E has the ability to prevent cell injury by maintaining the sulfhydryl groups of membrane proteins and by quenching free radicals (Basu and Dickerson, 1996). Intramuscular administration of vitamin E prevented inhibition of blood ALAD activity, elevation of urinary ALA excretion and was effective in reducing the lead induced altered biogenic amines levels in brain during the concomitant exposure lead. (Dhawan *et al.,* 1989). Vitamin E supplementation during concomitant lead exposure also prevented lead deposition in liver and blood.

Carotenoids :

Carotenoids are pigments that are found in plants and micro-organisms. Various studies have indicated that carotenoids may prevent or inhibit certain types of cancer, arthrosclerosis, age-related muscular degeneration and other diseases. The antioxidant activity of carotenoids arises primarily as a consequence of the ability of the conjugated double-bonded structure to delocalize unpaired electrons (Mortensen *et al.,* 2001). This is primarily responsible for the excellent ability of α-carotene to physically quench singlet oxygen without degradation, and for the chemical reactivity of α-carotene with free radicals such as the peroxyl (ROO•), hydroxyl (•OH) and superoxide radicals (O2 •-).

α-Lipoic acid (LA) :

α-Lipoic Acid (1,2-dithione-3-pentanoic acid) is a sulfur-containing antioxidant with metal-chelating and antiglycation capabilities. Lipoic acid is active in both lipid and aqueous phases (Kagan *et al.,* 1992). LA is readily absorbed from diet and is rapidly converted to dihydrolipoic acid (DHLA) by NADH or NADPH in most tissues.

DHLA possess metal chelating properties which help the body to get rid of accumulated ingested toxins (Fig. 1). DHLA may act as a strong chain-breaking antioxidant and may enhance the antioxidant potency of other antioxidants like vitamin C in both the aqueous and in hydrophobic membrane phase. The possible mechanisms for the protecting

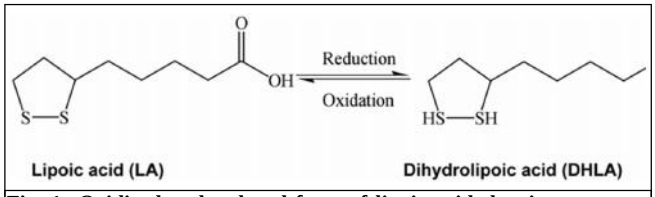

Fig. 1: Oxidized and reduced form of lipoic acid showing presence of thiol groups as the possible metal chelating sites

effects of LA against oxidative stress may be as follows:

- LA can promote the antioxidant defense by inducing phase two enzymes, such as glutathione synthetase to elevate antioxidant GSH (Ames *et al.,* 2003).
- LA satisfies two criteria to be a chelating agent *i.e.*, absorption into the intracellular environment and complexing metals previously bound to other sulfhydryl proteins. Both LA and DHLA can chelate heavy metals, but the R-form is more effective for chelation.LA is most effective in chelating Cu_2+, Zn_2+ and Pb_2+ (Ou *et al.,* 1995).

N-acetylcysteine (NAC) :

N-acetyl-L-cysteine (NAC), is a thiolcontaining anti-oxidant that has been used to mitigate various conditions of oxidative stress. Its antioxidant action is believed to originate from its ability to stimulate GSH synthesis, therefore maintaining intracellular GSH levels NAC is known to have metal-chelating properties and has been used in several clinical conditions (Banner *et al.,* 1986). Thiol groups present in NAC act to reduce free radical and provide chelating site for metals. Thus, NAC has a strong ability to restore the impaired prooxidant/ antioxidant balance in metal poisoning. NAC can cross the cell membrane, therefore, provide intracellular effects.

Taurine :

Taurine (2-aminoethanesulfonic acid) is a nonessential sulfur-containing amino acid that functions with glycine and gamma-amino butyric acid as a neuro inhibitory transmitter. Taurine can act as a direct antioxidant by scavenging reactive oxygen species or as an indirect antioxidant by preventing changes in membrane permeability due to oxidant injury. As a direct antioxidant, taurine is able to quench and detoxify some reactive intermediates such as hypochlorous acid generated by myeloperoxidase nitric oxide and H_2O_2 (Cozzi *et al.,* 1995). On the other hand, as an indirect antioxidant, taurine protect cells via intercalating into the membrane and stabilizing it (Gordon Heller, 1992).

Selenium :

Selenium is a required mineral for the metalloenzyme glutathione peroxidase (GPx). GPx plays a key role in recycling

glutathione and is effective in reducing free radical damage in specific disease states. Lead can bind to selenium and form highly bonded selenium-lead complexes, which have been proposed as a mechanism for selenium's protective effect in lead toxicity (Flora *et al.,* 1982).

Methionine :

Methionine is the preferred substrate for glutathione production by hepatocytes and acts as a precursor for glutathione production in the liver. Lead-exposed rats treated with 100 mg/kg body weight of methionine demonstrated a significant decline in lipid peroxides in the liver. Methionine has been shown to react with ROS to form methionine sulfoxide and to increase ROS-scavenging by improving hepatic glutathione levels (Flora *et al.*, 2003). Methionine supplementation also led to increases in thiol molecule groups, sulfur-based protein, and non-protein molecules that act as antioxidants to prevent peroxidation in the liver and kidneys of animals exposed to lead or alcohol (Jurczuk *et al.*, 2006).

Conclusion :

Generation of highly reactive oxygen species aftermath of lead 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, including disrupted pro-oxidant/antioxidant balance. The dietary supplementation of antioxidants are useful in lead-exposed humans or animals. Lead affects mammalian systems by directly lowering antioxidant reserves and generating ROS, specifically hydroperoxides and lipoperoxides. These ROS alter cellular membranes and tissue, resulting in vascular, neurological, and genetic damage. Antioxidants, specifically vitamins C, E, taurine, methionine, selenium, alpha-lipoic acid, and Nacetylcysteine have been shown to lower ROS-generated cellular damage.

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