Lead exposure and neurodegenerative diseases

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ABSTRACT

Lead (Pb) pollution has been considered as a major threat for human health. Lead may be able to induce inflammatory cascades in various tissues. Allergic asthma and neurodegenerative diseases inflammatory diseases that the association between lead exposure and occurrence of these problems has been proven. The aim of present review is to summarize literature on the effects of lead exposure and occurrence of neurodegenerative problems. This study indicates lead may causes neurodegenerative diseases via direct and indirect induction of inflammatory cascades.

Keywords: inflammation, neurodegenerative diseases, lead exposure

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INTRODUCTION

Lead (Pb) is one of the most environmental pollutants, and several studies have demonstrated that lead is a trigger for respiratory problems. Lead is a natural components of the earth's crust with unique properties such as softness, high malleability, ductility, low melting point that poses a major threat to human health in several aspects [1]. Lead is a persistent metal in all parts of the environment in air, water, soil and primarily deriving from a variety of manufactured products like leaded gasoline, paints, ceramics, solders, water pipes, hair dye, cosmetics, airplanes, farm equipment, shielding for x-ray machines, and etc. [2]. Lead is considered as a potent environmental toxin with non-biodegradable nature and its toxic effects are well studied [3]. It was indicated that blood lead levels were significantly increased with age, smoking status, and alcohol consumption.

Human exposure to lead occurs mainly via digestive and respiratory tracts. Lead is widely distributed in the body, and interferes with several biochemical processes by binding to sulfhydryl and other nucleophilic functional groups and contributing to oxidative stress [4]. Lead may disturb physiological functions and induce numerous adverse effects in respiratory system such as COPD like changes in the lung [5], asthma [6] and lung cancer [7] and nervous system problems [8].

Lead has been found to induce oxidative stress by over production of free radicals, and cause cell membrane damage, via lipid peroxidation, which mediated the activation of inflammatory signaling cascades [9]. Oxidative stress and inflammation process has an essential role in the adverse health effects [10-48]. This study was designed to provide an overview of studies about association between lead exposure and inflammatory responses in nervous systems as an underlying mechanism contributing to lead toxic effects.

Toxicology of lead
Respiratory and gastrointestinal (GI) tracts are the main rout of exposure to lead [49]. Tetraethyl lead (leaded gasoline) passes through the skin. Almost 35–40% of inhaled lead particles is deposited in the lungs, 37% of all lead particles ≤1 μm are deposited in alveolar region and 50% of the lead deposited in the respiratory tract is absorbed and enters the systemic circulation (49). 5 to 15% of ingested inorganic lead is absorbed through the gastrointestinal

mucosa; however, this percentage depends to age, pregnancy and nutritional factor such as calcium, zinc, iron magnesium and phosphate status [50].

It has been indicated that lead absorption in children is faster adults. Calcium, zinc, iron, magnesium and phosphate deficiency increased gastrointestinal absorption of lead [50]. Tetra ethylor alkyl-lead (leaded gasoline) among inorganic lead can only absorbed through the skin [51].

About 99 % of circulating lead is bound to erythrocytes and is diffused into the brain, liver, renal cortex, aorta, lungs, spleen, teeth, and bones for 4-6 weeks [52]. About 80-95% of lead is deposited in the bone in adults, while in children about 70 % is deposited in bone 22. Lead is deposited in bone up to 30 years and increased with age. Inorganic lead is not metabolized and excreted unchanged in the urine [53]. The fecal excretion of absorbed lead may occur through secretion into the bile, gastric fluid, and saliva [54]. Two studies indicated that lead can also be excreted through the nails and sweat [55]. Blood levels $\geq$10 µg/dL is unsafe for infants, children, and women of childbearing age and blood levels $\geq$30 µg/dL is unsafe for workers in occupational exposure [56].

The lead toxicity mainly related to the ability of lead metal ions to replace other bivalent cations like Ca^{2+}, Mg^{2+}, Fe^{2+} and monovalent cations like Na^+, which finally disturbs the cell hemostasis and changes in various biological processes including cell adhesion, cellular signaling, protein folding, maturation, apoptosis, ionic transportation, enzyme regulation, oxidant-antioxidant balance and inflammatory responses [57].

Tissue inflammation in experimental models exposed to lead has been reported. These data suggest that lead may directly or indirectly induces the inflammatory responses and tissue dysfunction associated with these pathophysiologic conditions such as asthma [58].

MATERIALS AND METHODS

Online literature resources were checked using different search engines such as Medline, Pubmed, Iran medex, Scopus, and Google Scholar from 1970 to 2015 to identify articles, editorials, and reviews about the contribution of inflammation in the occurrence of neurodegenerative diseases after lead exposure.

Neurodegenerative diseases
The central nervous system comprise of two major types of cells, neurons and glial cells. According to the strong evidences, astrocytes are the type of brain cells that are responsible for sequestration of lead in brain tissue [59]. As a result, activation of astroglia is one of the modes of action underlying lead neurotoxicity, which may cause loss of the buffering function of astroglia. This leads to the death of neuronal cells by initiating the inflammatory events arising from the production of a wide range of cytokines and chemokines [60].

The mechanisms underlying the neurotoxic effects of lead have been linked to excitotoxicity, alteration of neurotransmitter storage and release, induction of brain cell apoptosis, inflammation and oxidative stress [61]. Particularly, lead-associated increase in inflammatory mediators has been reported in human population studies as well as experimental animal models and cell culture systems [62].

For instance, Ghareeb et al. have reported that lead exposure in rats caused increase in inflammatory markers, NO and TNFα, coupled with a significant decrease of glutathione (GSH) levels and impairment of antioxidant activities of superoxide dismutase (SOD) and catalase (CAT) [63].

Cyclooxygenase-2 (COX-2) is a source of inflammatory mediators and a multifunctional neuronal modulator. COX-2 catalyzes the conversion of free arachidonic acid (AA) to the intermediate prostaglandin H2 (PGH2), which is then transformed by a range of enzymes and non-enzymatic mechanisms into the primary prostanoids, PGE2, PGF2α, PGD2, PGI2, and TXA2 and ROS are generated simultaneously [64].

In peripheral tissues, COX-1 is the constitutively expressed form of cyclooxygenase, and COX-2 presents as an inducible form. In contrast, in normal brain COX-2 is the fundamental form exclusively expressed in neurons [65].

Immunoreactivity of COX-2 has been detected in the forebrain areas, including dentate gyrus granule cells, pyramidal cell neurons in the hippocampus, the piriform cortex, superficial cell layers of neocortex and the amygdala [66]. Whereas, under pathologic conditions, such as hypoxia/ischemia and seizures, as well as in neurodegenerative diseases, including Alzheimer's disease (AD), COX-2 over-expression has been associated with neurotoxicity [67]. Thus, this reflects a role of COX-2 in neuro-inflammation and neural cell death, which is

reinforced by the therapeutic implications of COX-2 inhibitors and arachidonic acid shunting in alleviating brain injuries [68].

Animal models have suggested that chronic lead exposure causes potential proinflammatory effect in CNS in immature rat brain, which might be achieved through activation of glial cells [61]. Activated glial cells generate an inflammatory reaction in the brain by producing cytokines. Developmental lead exposure has been shown to promote changes in inter-region gene expression of pro-inflammatory effectors, such as IL-1β, IL-18, IL-33, caspase 1 and NOS2 [69]. Elevated blood lead levels (BLLs) impair the blood-brain barrier function [70]. The blood-brain barrier consists of many endothelial cells that surrounded by astrocytes [71]. Lead toxicity could disturb the communication between the astrocytes and the endothelial cells and plasma penetrates in to the interstitial spaces of the brain, resulting in edema [72].

This phenomenon causes neuronal cells death and induces inflammatory cascade with a wide range of cytokines and chemokines. Edema increases brain pressure, which can cause irreversible brain damage such as decreased attention, visual-motor reasoning skills and social behavior [73]. Intracerebral implantation of a lead pellet caused neuronal degeneration in the rats that is related to the inflammation and apoptosis induced by leached lead [73]. A number of changes were observed following implantation of the lead ball including of the elevation of the number of neutrophils, macrophages and neuronal apoptosis. It was also observed that the expression of genes encoding N-methyl-d-aspartate receptors, related gene to cognitive function and regulate apoptosis, was suppressed after lead implantation [74]. Astrocytes, the major cell type of the central nervous system, are responsible for sequestration of this metal in brain tissue. Lead caused endoplasmic reticulum (ER) stress responses in the astrocytes [74]. ER stress influences cell immune responses or metabolism by inducing inflammation [74].

In addition, it was observed chronic glial activation accompanied by inflammatory responses as a new mechanism of lead neurotoxicity in immature rat brain. Glial activation was determined by the increased level of glial fibrillary acidic protein and S-100beta proteins in all parts of the brain. These modifications were occurred parallel to the elevation of proinflammatory cytokines such as interleukin (IL)-1beta and tumor necrosis factor-alpha in hippocampus, and IL-6 in forebrain [75]. Several studies indicated that lead exacerbated neurinflmmation due to viral infections [75].

Lead poisoning exacerbated meningoencephalitis due to adenovirus type 12 36-year-old woman with serum lead level 199 µ/dL [61]. It was observed that lead chloride and lead nitrate enhancedencephalitogenic potential of Langatvirus and increased mortality following infection by complex means in mice [63].

CONCLUSION

Lead is an extremely harmful environmental pollutant that affects many major organ systems. It can specially disturb inflammatory system whose protection should be considered as of primary importance. Lead caused increase in inflammatory mediators in human, experimental animal and cell culture systems. One of the main mechanism underlying the toxic effects of lead on nervous is inflammation. However, it will no doubt the complicated immune network and regulatory pathways underlying inflammatory disease. Moreover, the direct effect of lead on inflammatory components affects the immune system.

The toxic effects of lead on immune system is related to various factors such as lead concentration and time of exposure. Lead exposure at low to moderate levels induced immune cells. Lead caused inflammatory cascade induction in central nervous systems via activating of glial cells, impairing the blood-brain barrier function and over expression of inflammatory mediators.

In addition, the role of oxidative stress in the induction of inflammatory responses may be considered. Lead cold disturb the balance of oxidant-antioxidant system in nervous systems. Decreased antioxidant content (GSH, SOD and CAT) and increased MDA and NO in various tissue after lead exposure were observed. In conclusion, inflammation as main mechanism involved in the pathogenesis of neurodegenerative diseases.

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