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Invited Review

Insight into the oxidative stress induced by lead and/or cadmium in blood, liver and kidneys

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ABSTRACT

Besides being important occupational hazards, lead and cadmium are nowadays metals of great environmental concern. Both metals, without any physiological functions, can induce serious adverse health effects in various organs and tissues.

Although Pb and Cd are non-redox metals, one of the important mechanisms underlying their toxicity is oxidative stress induction as a result of the generation of reactive species and/or depletion of the antioxidant defense system. Considering that the co-exposure to both metals is a much more realistic scenario, the effects of these metals on oxidative status when simultaneously present in the organism have become one of the contemporary issues in toxicology.

This paper reviews short and long term studies conducted on Pb or Cd-induced oxidative stress in blood, liver and kidneys as the most prominent target organs of the toxicity of these metals and proposes the possible molecular mechanisms of the observed effects. The review is also focused on the results obtained for the effects of the combined treatment with Pb and Cd on oxidative status in target organs and on the mechanisms of their possible interactions.

1. Introduction

Lead (Pb) and cadmium (Cd) are toxic metals of great occupational importance, but are nowadays even more significant as environmental pollutants. Both Pb and Cd can seriously affect organs and various systems of an organism and can cause severe acute and especially chronic intoxications. Current European Cd intake is close to the tolerable weekly intake with recent epidemiological evidence showing that environmental exposure to Cd increases total mortality (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2011; Nawrot et al., 2010), while the quantity of Pb used in the 20th century, even though the use of Pb has been restricted in many different fields of its applications, exceeds by far the total consumption in all previous years (Hsu and Guo, 2002).

Lead poisoning has been known since ancient times and the problem of intoxication with Pb became an important issue in the 18th century, during the industrial revolution when this metal was one of the most widely used industrial metals due to its qualities. Many prevention measures against Pb exposure have been accepted all over the world ever since: lead gasoline was banned as well as lead paints and lead pigments, resulting in diminished lead concentrations in the blood of the general population in Europe and other countries. However, the main anthropogenic sources of Pb remain, such as mining, smelting, lead batteries, crystal and ceramic industry, which undoubtedly contribute to the Pb-induced adverse effects in humans and the environment. Lead toxicity deserves special attention in the light of the fact that children are extremely vulnerable to this toxic metal. On the other hand, Cd was discovered in 1817 and was recognized in the 20th century as a toxic metal that can induce severe intoxications, not only in persons occupationally exposed (smelting, electroplating, production of nickel-cadmium batteries, fertilizers), but also in the general population through food and cigarette smoking. A well-known example of Cd-induced intoxications with dramatic outcomes was documented in Japan as Itai-itai disease (Nordberg, 2009).

Lead is known to induce a broad range of physiological, biochemical and behavioral dysfunctions in laboratory animals and humans, including affecting the central and peripheral nervous system, hematopoietic system, cardiovascular system, kidneys, liver

Abbreviations: Pb, lead; Cd, cadmium; —SH, sulfhydryl groups; ROS, reactive oxygen species; $O_2^{\cdot-}$, superoxide anion; H_2O_2, hydrogen peroxide; $OH^{\cdot}$, hydroxyl radicals; RNS, reactive nitrogen species; NO, nitric oxide; ALAD, δ-aminolevulinic acid dehydratase; ALA, δ-aminolevulinic acid; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; G6PD, glucose-6-phosphate dehydrogenase; Zn, zinc; Mg, magnesium; Se, selenium; GSH, glutathione; GR, glutathione reductase; GST, glutathione-S-transferase; MT, metallothioneins; MDA, malondialdehyde; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; *i.p.*, intraperitoneal; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; MAPKs, mitogen-activated protein kinases; TBARS, thiobarbituric acid reactive substances; iNOS, inducible NO synthase.

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and reproductive system (Agency for Toxic Substances and Disease Registry (ATSDR), 2007). On the other hand, the target organ of Cd chronic toxicity is the kidney, in which Cd has an estimated half-life of 30 years. Studies of populations chronically exposed to low doses of Cd have reported a range of other adverse health outcomes including hypertension, type 2 diabetes mellitus, and cancer (Colacino et al., 2014). Animal studies confirmed Cd adverse effects on liver, kidneys, lungs, pancreas, bones, reproductive organs, hematopoietic, nervous and cardiovascular system as reviewed by Matović et al. (2011). Possible endocrine disruption caused by Cd because of its estrogenic activity (Silva et al., 2012) and effects on thyroid function (Buha et al., 2013) has been shown. Spleen, as a target organ of Cd toxicity and immunomodulatory effects of Cd, has been recently shown by Demenesku et al. (2014). Cd and Cd compounds are carcinogenic to humans (IARC, 1993, 2012).

Cd and Pb toxicity have been comprehensively explored in many *in vitro* and *in vivo* studies and various molecular, cellular and intracellular mechanisms were proposed to explain toxicological profiles of these two toxic metals. Although the pathogenesis of deleterious health effects from Pb and Cd exposure is multifactorial, the mechanisms underlying their toxicity are not completely understood. Among the confirmed mechanisms for both Pb and Cd toxicity is their binding to sulfhydryl (—SH) groups thus affecting many enzymes and other —SH containing molecules. The other is their interaction with bioelements in the organism thus affecting directly and indirectly many physiological and biochemical processes. Recent investigations indicate their influence on necrosis and apoptosis, on gene expression, damaged DNA repair, etc. Complete understanding of these mechanisms is still far from being achieved and this topic remains controversial and incomplete, but up to date investigations indicate oxidative stress as an important molecular mechanism for Pb and Cd toxicity.

Many findings on the oxidative damage to various biological macromolecules caused by exposure to Pb or Cd suggest that even though these metals are non-redox, they can cause disturbances in oxidative status that can significantly contribute to many adverse effects of these two toxic metals. Lipid peroxidation in red blood cell membranes as a consequence of Pb-induced oxidative stress leads to hemolysis and contributes to Pb-induced anemia (Flora et al., 2012). Studies conducted on three different animal species with different dose levels of Cd and via different routes of exposure provide a substantial body of evidence that confirms oxidative stress as one of the important mechanisms of Cd toxicity, with liver as a critical target organ of acute exposure and kidneys as critical target organ of prolonged exposure to Cd (Matović et al., 2013).

Free radical-induced damage caused by Pb and Cd are accomplished by two independent but related mechanisms (Jomova and Valko, 2011). The first mechanism involves generation of reactive oxygen species (ROS), i.e. superoxide anion ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), hydroxyl radicals ($OH^{\cdot}$) and reactive nitrogen species (RNS), i.e. nitric oxide (NO), while the second mechanism is achieved via depletion of the cellular antioxidant pool. Undoubtedly, these two mechanisms are simultaneous and interrelated, since increase in ROS and RNS leads to depletion of the antioxidant pool while at the same time depletion of this pool leads to the increase of reactive species. Although non-transition metals, Pb and Cd were shown to be able to induce ROS production. One of the mechanisms involved in the early stage of Pb-induced oxidative stress is the inhibition of δ-aminolevulinic acid dehydratase (ALAD), an important enzyme in heme biosynthesis, which leads to the accumulation of δ-aminolevulinic acid (ALA) that induces generation of ROS (Bechara, 1996). Concerning Cd, it has been confirmed that this toxic metal can replace Fe in various cytoplasmic and membrane proteins, such as ferritin and apoferritin, hence increasing the amount of freely available Fe ions that participate in Fenton reactions and generate ROS (Wätjen and Beyersmann, 2004). It is also known that Cd accelerates free radical formation by increasing intracellular calcium levels (Thévenod, 2009). Another mechanism for Pb- and Cd-induced oxidative stress is their effect on the antioxidative defense system of cells. Pb and Cd have high affinity for —SH groups in enzymes of the antioxidative defense system, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glucose-6-phosphate dehydrogenase (G6PD), and subsequently inhibit their activity (Jomova and Valko, 2011; Kasperczyk et al., 2012; Nair et al., 2013). Apart from targeting —SH groups, Pb and Cd, as divalent cations, can also replace divalent bioelements that serve as important co-factors of antioxidant enzymes such as GPx, SOD and CAT, resulting in their inactivation. This is in agreement with the generally proven antagonism between Pb and Cd on one side and bioelements, i.e. zinc (Zn), magnesium (Mg), selenium (Se), etc., on the other (Bulat et al., 2008, 2009; Djukić-Ćosić et al., 2006; Gałażyn-Sidorczuk et al., 2012; Matović et al., 2012; Othman and El Missiry, 1998; Soldatović et al., 2002). It has been also confirmed that both metals affect levels of glutathione (GSH), a tripeptide that contains more than 90% of the non-tissue sulfur in the human body and represents one of the most important components of antioxidant non-enzymatic protection. Generally speaking, both metals strongly bind to —SH groups and initially deplete GSH stores. Moreover, these toxic metals also inhibit enzymes glutathione reductase (GR), GPx and glutathione-S-transferase (GST) that are important for maintenance of GSH levels (Ahamed and Siddiqui, 2007; Badisa et al., 2007; Cuypers et al., 2010; Flora et al., 2012). Toxicity of Pb and especially Cd is dependent on metallothioneins (MT), —SH rich proteins of low molecular weights with the capacity to bind metals and protect organisms against metal toxicity. Metallothioneins are mildly inducible by Pb, and to a much greater extent by Cd (Gonick, 2011). The Cd–MT complex is mainly formed in the liver then slowly released into the circulation and later delivered to the kidneys; the retention of Cd in both organs is MT-dependent. These proteins detoxify Cd by sequestering it into inert Cd–MT complex thus preventing Cd reactions with target molecules (Klaassen et al., 2009). The processes that are thought to produce oxidative stress triggered by Pb and Cd are summarized in Fig. 1.

Over the last decades, numerous investigations dealt with various aspects of Pb and Cd toxicity. However it is rather difficult to explain how these two metals with rather similar chemical properties and with proposed rather similar mechanisms of oxidative stress induction, produce quite different and specific effects in the organism.

With regard to the fact that thousands of compounds are present in the environment, from natural or anthropogenic sources, human exposure to toxic agents cannot be characterized as exposure to a single agent, but more correctly as an exposure to the mixtures of these toxic agents (CDC, 2009). Due to their non-biodegradability, Pb and Cd accumulate in ecosystems and have been identified as leading constituents at various waste sites (Fay and Mumtaz, 1996). In addition to environmental exposure, individuals can be simultaneously exposed to these metals in the workplace. Even though exposure to high doses of these metals seldom happens, chronic low co-exposure can still be regarded as a major health concern and global issue (Wang and Fowler, 2008). Concurrent exposure to these metals may produce additive effects or synergistic/antagonistic interactions or even produce completely new effects which are not seen with exposure to only one of the metals. Evaluation of these interactions, especially at the level of several common mechanisms underlying their toxicity, such as oxidative stress induction, is essential for risk assessment of their co-exposure and subsequent mitigation of assessed health risk.

Hence, this review will summarize studies conducted on Pb and Cd-induced oxidative stress in blood, liver and kidneys as the most prominent target organs of their toxicity and also will be focused on the effects of their co-exposure on oxidative status in these organs.