IJAS Iranian Journal of Applied Animal Science

Metal-Induced Oxidative Stress and Cellular Signaling Alteration in Animals

Review Article

C. Losacco[1*] and A. Perillo[1]

[1] Department of Veterinary Medicine, University of Bari 'Aldo Moro', S.P. Casamassima km 3, Valenzano 70010, Bari, Italy

Received on: 28 May 2018
Revised on: 2 Jul 2018
Accepted on: 15 Jul 2018
Online Published on: Sep 2018

*Correspondence E-mail: c.losacco@yahoo.it

Online version is available on: www.ijas.ir

ABSTRACT

Contamination by heavy metals has attracted increasing attention considering the ability of these elements in producing serious consequence to ecosystem, and especially on animals health. Due to their widespread use in human activities such as industry, agriculture and even as medicine (e.g. arsenic, selenium and platinum), numerous health risks may be associated with exposure to these substances. All heavy metals, in spite some of them are essential micronutrients, have their toxic effects because of their bioaccumulation on living organisms, and so generally exhibit chronic toxicity via metabolic interference and mutagenesis. They are also classified as carcinogens (known or probable) according to the U.S. Environmental Protection Agency, and the International Agency for Research on Cancer (IARC). In the present paper, the lead, cadmium and chromium disease processes (induced toxicity) were summarized with particular emphasis on the generation and the role of reactive oxygen species (ROS), the unifying factor in determining toxicity for all these metals.

KEY WORDS health, heavy metals, oxidative stress, toxicity.

INTRODUCTION

Metals pollution is a health and environmental problem of great concern. According to the data reported by the Agency for Toxic Substances and Diseases Registry (ATSDR), five of the 20 most harmful substances on the planet are heavy metals: Arsenic, Lead, Mercury, Cadmium, Chromium (ATSDR, 2006). Exposure to these elements, particularly at chronic low dose levels, is still a major public health concern. Epidemiological and experimental studies showing an association between exposure and cancer incidence in humans and animals and according to the United States Environmental Protection Agency (US EPA), and the International Agency for Research on Cancer (IARC), these metals are also classified as either "known" or "probable" human carcinogens.

Metals are natural constituents of all ecosystems, moving between atmosphere, hydrosphere, lithosphere, and biosphere (Bargagli, 2000). Potential sources of heavy metals exposure include natural sources (e.g., groundwater, metal ores), industrial processes, commercial products, folk remedies, and contaminated food and herbal products. During last decades, the concentration of heavy metals in air, water and soil is progressively increased, both in urban and extra-urban areas, due to their exponential use in industrial processes.

Further, metal pollution represent a big hazard for the ecosystem and for human and animal health (Nagajyoti *et al*. 2010; Jaishankar *et al*. 2013). The known ability of these elements to bioaccumulate and reach the animal food chain is of concern. Metals can enter the bodies via food, drinking water and air. Entering our bodies they produce toxicity by

forming complexes with cellular compounds containing sulfur, oxygen, or nitrogen.

Several studies have shown the ability of heavy metals to accumulate in plants and animals tissues (Medeiros *et al*. 1988; Olson *et al*. 2000; Liu, 2003; Li *et al*. 2005; Maia *et al*. 2006). So, bioaccumulation of toxic metals can occur both in the body and in the food chain. Different reports have shown the presence of one or more toxic metals in fodder and feed used for livestock food ration (Caggiano *et al*. 2005; Maia *et al*. 2006). Moreover eco-toxicological studies have shown the direct correlation between presence of heavy metals in the food ration and accumulation in the tissues of sheep and cattle that had taken it (Sedki *et al*. 2003). These elements are accumulated in living organisms when they are taken up, and stored faster than they are broken down (metabolized) or excreted (Pandey and Madhuri, 2014).

The main target of storage of these substances are represented by the liver and, in particular, by the kidneys. Thus, metals through bio-accumulation can enter in the food chain and animals products may represent a direct source of such contaminants to humans.

Therefore, the aim of this mini-review is to illustrate the implications of heavy metals (mainly Lead, Chromium, and Cadmium) in inducing disease processes by oxidative stress and their toxicity management in animals.

Heavy metals and their mechanism of toxicity

The mechanisms of metal-induced toxicity continue to be of interest and has been extensively studied and reported by various workers. In spite some of them are essential micronutrients playing pivotal role in mediating (balancing) biological functioning of cells in plants, humans and animals, metals may have their toxic effects via metabolic interference on biochemical and physiological functions of living organisms (Pandey and Madhuri, 2014; Sharma *et al*. 2014).

They produce toxicity by forming complexes with several cellular compounds and organelles such as cell membrane, mitochondrial, lysosome, endoplasmic reticulum, nuclei, and some enzymes involved in metabolism, detoxification, and damage repair (Granchi *et al*. 1998; Wang and Shi, 2001; Pulido and Parrish, 2003; Tchounwou *et al*. 2012; Ghasemi *et al*. 2014). Moreover various studies confirmed that prolonged exposure to metals could activate cellular signaling that result in dysregulation of cellular pathways and subsequent toxicity (Fitsanakis and Aschne, 2005; Florea and Busselberg, 2006).

One of the mechanisms associated with heavy metal toxicity is mediated primarily via the generation of free radical species in various tissues and activation of mainly redox-sensitive transcription factors (Faix *et al*. 2005; Gasemi *et al*. 2014), which are in turn toxicant and implicated in the pathophysiology of many diseases (Mittler, 2002).

The oxidative stress mediated toxicity of heavy metals involves damage primarily to liver (hepatotoxicity), central nervous system (neurotoxicity), DNA (genotoxicity), and kidney (nephrotoxicity) in animals and humans (Florea and Busselberg, 2006; Ghasemi *et al*. 2014). It is also known that some heavy metals play a carcinogenic, mutagenic and teratogenic action (Jaishankar *et al*. 2014).

Among the heavy metals lead, cadmium, and chromium may are found in all environmental compartments, and have a variety of applications in human and animal activities. In fact these elements are ubiquitous in air and water and are pollutants that continue to threaten the quality of public health around the world. Their exposure cause a broad range of adverse health effects in humans and animals and they are known to induce multiple organ damage in intestinal tract as well as skeletal, central nervous, and reproductive systems (Martin and Griswold, 2009). Their toxic effects are produced by metabolic interference and oxidative damage and consequent beginning of disease processes (Leonard *et al*. 2004; Flora *et al*. 2008).

Lead is considered to be one of the oldest and major environmental toxin studied and has been incriminated as a cause of accidental poisoning in both human and domestic animals more than any other substance (Casas and Sordo 2006; Florea and Busselberg, 2006; Flora *et al*. 2012; Gidlow, 2015).

Moreover, Lead exposure has been found to increase risk of numerous conditions that may lead to adverse effects on nervous system function, including hypertension, impaired renal and thyroid function, vitamin D deficiency, and preterm birth (Markowitz, 2000; CDC, 2005; Florea and Busselberg, 2006; ATSDR, 2007; Mason *et al*. 2014). Younger are especially at greater risk because they have higher intestinal Pb absorption and more vulnerable nervous systems which are still under development (Ziegler *et al*. 1978; Lidsky and Schneider, 2003; Ahamed and Siddiqui, 2007). Neurons in general have a high metabolic rate, which makes them more susceptible to different heavy metals producing changes in neuronal function and may lead to secondary alterations in neuronal anatomy (Nava-Ruiz and Mendez-Armeda; 2013).

The neurotoxicity of lead has been well established through numerous studies but the cellular processes of lead neurotoxicity remain unknown, thus, oxidative stress plays a primary role in lead-induced neurotoxicity (Reddy *et al*. 2002; Lidsky and Schneider, 2003; Marchetti, 2003; Florea and Busselberg, 2006; Ahamed and Siddiqui, 2007; Mason *et al*. 2014).

Cadmium may enter into the animal production process accompanied with some feed ingredients. According to

current knowledge, cadmiun is not added as feed additives for animal growth, but is often present in mineral supplements such as phosphates, zinc sulfate and zinc-oxide as an impurity. In veterinary medicine cadmium salts are used in the formulation of anthelmintics, acaricides and antiseptics.

The Cadmium toxicity is associated with pulmonary (Lauwerys *et al*. 1974), renal (Hong *et al*. 2004), hepatic (Koyu *et al*. 2006), skeletal (Murata *et al*. 1970), reproductive (Rehm and Waalkes, 1988) and cardiovascular dysfunctions (Tellez-Plaza *et al*. 2008). This non-essential metal is also classified as a group I human carcinogen by the International Agency for Research on Cancer (IARC, 1993).

Studies on cadmium bound to metallothionein are also of interest because cadmium-metallothionein complexes may have different toxic profiles and are found in relatively high levels in organ meats (e.g., liver and kidney) (ATSDR, 2012).

Although a number of different routes by which lead and cadmium induced toxicity have been reported, the basic mechanisms can be synthesized as the interactions between cadmium/lead and essential metals (Ahamed and Siddiqui, 2007; Vesey, 2010), such as zinc and selenium, and the oxidative stress consequent to Lead/Cadmium exposure (Farmand *et al*. 2005; Liu *et al*. 2009; Zhai *et al*. 2015). Lead and Cadmium are able to bind and to interact with many of the same enzymes as these metals but does not properly function as a cofactor, thus interfering with the enzyme's ability to catalyze its normal reaction(s) (Sharma *et al*. 2014). To some extent these two mechanisms are still interrelated because lead/cadmium are now known to induce metabolic disorder and production of ROS and reactive nitrogen species (RNS) and hence these heavy metal exhibits ability to generate adverse effects in the oxidative and antioxidative systems (Oteiza *et al*. 1995; Brenneisen *et al*. 2005).

Chromium is considered an essential metals with potential for toxicity (Goyer, 2001). This metal exists in a series of oxidation states with a valence from +2 to +6 (Jacobs and Testa, 2005; Tchounwou *et al*. 2012); the most important stable states are 0 (elemental metal), +3 (trivalent), and +6 (hexavalent) (Patlolla *et al*. 2009a). Trivalent (Cr[III]) and hexavalent (Cr[VI]) compounds are the most commonly occurring forms and are thought to be the most biologically significant (Zhitkovich, 2005), both being toxic to animals, humans and plants (Mohanty and Kumar Patra; 2013). Chromium (III) is an essential dietary mineral in low doses.

Chromium is used as a growth promoter in various animal species (turkeys, ruminants) and is also used for the improvement of the reproductive efficiency. The trivalent form of chromium is considered essential (micronutrient) for the normal glucose and lipid metabolism (Codd *et al*. 2001). It is thought to be a cofactor for insulin action as a component of the "glucose tolerance factor" (Goyer, 2001).

The contribution of organic chromium in nutrition is well known, for example in bovine farms, where the diet supplementation improved the efficiency of insulin effects and increasing the animals performances. Also, chromium (III) bound to DNA *in vitro*, thus enhancing RNA synthesis.

Chromium supplementation in diets of "travel-stressed cattle" significantly decreased serum cortisol and increased serum immunoglobulin (Goyer, 2001).

The Food and Nutrition Board of the United States Academy of Sciences has established a safe and adequate daily intake for chromium in adults of 50-200 micrograms per day (ATSDR, 2012).

The toxicity of chromium compounds is largely dependent on oxidation state and on the ligand (Bagchi *et al*. 2002; Valko *et al*. 2005; Tchounwou *et al*. 2012). After entering the body Cr(III) binds directly to transferrin, an iron-transporting protein in the plasma. In contrast, after absorption chromium(VI) is rapidly taken up by erythrocytes, crosses cell membranes, and is reduced to chromium(III) inside the cell. Furthermore the absorption of Cr VI is 3-5 times higher than that of chromium(III) in rats and humans (Goyer, 2001).

Regardless of the source, chromium(III) is widely distributed in the body and accounts for most of the chromium in plasma or tissues. The greatest uptake of chromium(III) as a protein complex is via bone marrow, lungs, lymph nodes, spleen, kidney, and liver, the highest being in the lungs (Bagchi *et al*. 2002).

Studies have implicated the toxicity of chromium in renal impairment, skin blisters, anemia, haemolysis, tissue edema, liver dysfunction, neuronal cell injury, depletion of antioxidant enzymes (superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione (GSH)) and DNA damage. Because of its mutagenic properties, chromium(VI) is categorized as a group 1 human carcinogen by the International Agency for the Research on Cancer (Dayan and Paine, 2001).

Oxidative stress

Heavy metal toxicity is mediated primarily by interference with metabolic intracellular activity and with generation of injurious free radical species in various tissues. Imbalance in the production and removal of reactive oxygen species (ROS) is the main mechanism of metals induced oxidative stress (Mathew *et al*. 2011; Patra *et al*. 2011; Nita and Grzybowski, 2016; Batool *et al*. 2017). Oxidative stress is a situation when ROS concentration is transiently or chronically enhanced, disturbing cellular metabolism and its regulation and damaging cellular constituents. Moreover, the

metals disrupt cellular and antioxidant defense, and free radicals may be involved in particular pathways due to the specificity of especially designed sensor molecules and signal transducers (Winterbourn, 2008).

The enhanced ROS concentration produce an unstable cellular environment (oxidative stress) causing massive cellular injury and extensive damage to the lipids, proteins, and biological macromolecules.

Generation of oxidative stress has been considered as a major pathway of lead, cadmium and chromium(III) induced toxicity, resulting in tissue damage, DNA damage, lipid peroxidation, oxidation of sulfhydryl groups of proteins, depletion of protein, altered gene expression and apoptosis and a broad spectrum of degenerative disease including neurodegeneration.

For example, the neurotoxicity associated with lead poisoning is linked to production of ROS which caused increase or decrease in the levels of lipid peroxidation or antioxidant defense mechanisms in the brain of experimental animals, and the effects were concentration dependent (Yiin and Lin, 1995; Adegbesan and Adenuga, 2007; Sanders *et al*. 2009; Sharma *et al*. 2014).

The mechanisms of lead-induced oxidative stress primarily include damage to cell membrane and DNA as well as the enzymatic (catalase, SOD, GPx, and glucose-6-phosphate dehydrogenase (G6PD)) and pool of non-enzymatic antioxidant molecules such as thiols including GSH of animals and human systems (Valko *et al*. 2005; Flora *et al*. 2008).

Oxidative stress has therefore been proposed as a major mechanism behind cadmium toxicity (Ghasemi *et al*. 2014). Cadmium-induced injuries including DNA damage, lipid peroxidation, enzyme inhibition, cytotoxicity and mutagenesis (Jaishankar *et al*. 2014). ROS increasing has been implicated in chronic cadmium nephrotoxicity (Shaikh *et al*. 1999; Liu *et al*. 2009), immunotoxicity (Zhang *et al*. 2000) and carcinogenesis (Waalkes, 2003).

Tandon *et al*. (2003) reported a higher level of malondialdehyde (MDA), an important marker of lipid peroxidation, in blood, liver and brain in cadmium intoxicated rats. In another study, Xiao *et al*. (2002) shown that in the kidneys of rats this process causes increased lipid peroxidation and tissue damage.

At last the studies have shown that also the chromium toxicity is mainly associated with generation of highly reactive oxydant species and with cross linking mechanism which leads to multiform DNA damages, e.g., strand breakage, DNA–protein cross-links, DNA–DNA cross-links, Cr–DNA adducts and base modifications in cells (Bagchi *et al*. 2002; Arakawa *et al*. 2012; Ghasemi *et al*. 2014). Thus, chromium is a ROS promoting agent, resulting in DNA damage that leads to apoptosis and carcinogenicity. To clarify how ROS induce cellular response and signal transduction is quite important for understanding of the mechanisms of metal-induced carcinogenesis. Certainly, many researchers have implicated the involvement of ROS signaling in metal-induced carcinogenesis and cell death over the last decade (Ghasemi *et al*. 2014).

Generation of highly reactive oxygen species aftermath or during exposure to lead, cadmium and chromium may result in systematic mobilization and depletion of the cell intrinsic antioxidant defenses and formation of reactive oxygen intermediates (Patra *et al*. 2011). The oxidative injuries induced by metals can be counteracted by use of antioxidants such as chelators, vitamin E and C, herbal medicine, and through increasing the antioxidants level.

Recent strategies of treatment, consisting in dietary supplementation with antioxidants, suggest that these substances may play an important role in reducing some hazards of heavy metals toxicity (Ercal *et al*. 2001; Bashandi 2012). Evidences suggested that supplementation of antioxidant may play significant protective effects through rebalancing the impaired prooxidant/antioxidant ratio and so reducing metals toxicity.

Concluding remarks

Heavy metal toxicity has proven to be a problem of great concern and there are several health risks associated with it. Reported sources of heavy metals in the environment include geogenic, industrial, agricultural, pharmaceutical, domestic effluents, and atmospheric sources (He *et al*. 2005; Tchounwou *et al*. 2012). While some metals are essential, others are highly toxic, even in very small amounts. Intake of metals occurs by ingestion of food and water and by inhaling contaminated air. Some metals get accumulated in the body and in the food chain, exhibiting a chronic toxicity. They may act as a pseudo element of the body while at certain concentration they may interfere with cellular signaling and metabolic processes. The toxicity could be more pronounced in specific tissues and at the cellular level, different organelles and (membrane) proteins are targeted and several pathways could be involved, depending on the metal component.

Transition metals are known to influence the oxidative status of biological macromolecules. So these elements act their toxicities inducing intracellular dysfunction and tissue damage through generation of an imbalance between the prooxidant elements and the antioxidants (reducing elements) in the body (Faix *et al*. 2005; Valko *et al*. 2005; Jomova and Valko, 2011; Belyaeva *et al*. 2012; Bahavar *et al*. 2013; Sharma *et al*. 2014; Gasemi *et al*. 2014). Moreover, many researchers have demonstrated that reactive oxygen species production and oxidative stress play a key role in the toxicity and carcinogenicity of metals such as

lead (Tchounwou *et al*. 2004; Yedjou and Tchounwou, 2008), cadmium (Tchounwou *et al*. 2001), and chromium (Patlolla *et al*. 2009a; Patlolla *et al*. 2009b). Because of their high degree of toxicity, these elements rank among the priority metals that are of great public health significance.

Normally living organisms are well equipped with antioxidants that directly or indirectly protect cells against the adverse effects of xenobiotics, carcinogens and toxic radicals. Data suggest that antioxidant supplementation may play an important role in abating the oxidative damage and the pathotoxicity of metals (Patrick, 2003; Ranjbar *et al*. 2008; Ghasemi *et al*. 2014). Currently, chelation treatment is considered the best known therapy against metals toxicity, and include the use of chelating agents, metallothionein, and antioxidant therapy with melatonin, vitamin E, vitamin C, N-acetylcystein and herbal medicine (Valko *et al*. 2006; Kostova and Balkansky, 2013; Tavakol *et al*. 2015).

CONCLUSION

However, the effectiveness of antioxidant treatments is related to the type of heavy metal and its chemical form, as well as on the understanding of the underlying mechanisms of their toxicity. In this regard, elucidating the cellular and molecular mechanism by which metals causes oxidative injuries is needed for health risks assessment of human and animal exposure to toxic metals.

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