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Heavy metals induced toxicity in biological systems: A concise review

Ayaz Mahmood Dar [1, *], M. Suliman Dar [2], Muzaffar Hussain Najar[1]

[1] *Department of Chemistry Govt Degree College Kulgam, University of Kashmir, J&K India*

[2] *Centre for Biodiversity and Taxonomy,*

Department of Botany University of Kashmir,Srinagar, J&K India

ABSTRACT

It is well known that heavy metals play a crucial role in inducing the toxic and irritating effects in biological systems. One of the major mechanisms associated with toxicity of heavy metals has been attributed to generation of reactive oxygen species (ROS), which develops oxidative stress or that are responsible for initiating DNA strand scission, etc which leads to apoptosis. The toxicity by the oxidative stress may include hepatotoxicity, neurotoxicity, genotoxicity and nephrotoxicity in biological systems. Their degree of toxicity depends on several factors including the dose, route of exposure and chemical species, age, gender, genetics and nutritional status of exposed individuals. Heavy metals are also reported to impact lipid oxidation, inflammatory responses and associated factors leading to apoptosis. The present review provides an analysis of their environmental occurrence, production and effects, potential for human exposure, oxidative stress and other effects by chromium, arsenic, lead, mercury and cadmium. These metallic elements are considered systemic toxicants that are known to induce multiple organ damage, even at lower levels of exposure.

Keywords*: *Apoptosis, Heavy metals, ROS, Toxicity, oxidation

I INTRODUCTION

Heavy metals being defined on the basis of number of parameters like density, specific gravity, atomic number/atomic weight, chemical properties and toxicity. The category of heavy metals may include light elements and may exclusion of the heaviest metals. In terms of specific gravity, those elements which have five times the specific gravity of water are considered as heavy metals. In terms of toxicity, all those elements which are toxic in sufficient quantities are put in the category of heavy metals. The heavy metals having serious environmental and adverse health implications are bismuth, chromium, arsenic, lead, cadmium and mercury. The accumulation of these elements can cause vomiting, abdominal pain, diarrhoea, cardiovascular disturbances, dermatological problems, chest pain, etc. In spite of being heavily toxic, the heavy metals also play important role in carrying smooth biochemical activities inside the cells [1].

Natural sources, artificial sources (industries, commercial products and contaminated food products) are the primary sources of heavy metals. Because of their accumulation in the environment, all heavy elements like

chromium, lead, mercury, cadmium, bismuth and arsenic are of particular interest. Entering our bodies via food chain, heavy metals produce cytotoxicity by forming complexes with compounds containing sulfur, oxygen or nitrogen. The complexes deactivate enzymes or modify macromolecular structures, leading to cellular disabilities and can cause apoptosis [2].

The heavy metals induce toxicity actually via the production of free radicals which may cause oxidative stress. In fact, oxidative stress is the imbalance between the generation of oxidants and production of antioxidants. The reactive oxygen species (ROS) are having the ability to cause DNA damage, oxidation of sulfhydryl groups of proteins, lipid peroxidation, etc which in turn leads to toxicity in liver, neurons and kidney [3].

Herein this review article reveals an update on source and intake of heavy metals, their induced atrocities in the body, their adverse physiological results and treatment to overcome their toxicity. The elements Cr, As, Pb, Cd and Hg are associated with many adverse health effects generated through oxidative damage and disease processes [4].

II. ARSENIC

2.1. Chemistry

The three chemical existing forms of Arsenic are: organic, inorganic and arsine gas, with organic arsenic having low toxicity while as inorganic arsenic and arsine gas being more toxic. The major inorganic forms of arsenic include the trivalent arsenite and the pentavalent arsenate. The organic forms are the methylated metabolites are monomethyl arsonic acid (MMA), dimethyl arsinic acid (DMA) and trimethyl arsine oxide (TMA). It involves the three common oxidation states (+5, +3 and –3) to form complexes in body. The American drinking water supplies contain lower than 5μg/L of Arsenic. It has been estimated that about 3.5 lac people might drink water containing more than 50μg/L. The exposure to arsenic initially occurs by ingestion, inhalation and absorption via skin. Arsenic occurs naturally in seafood like arsenobetaine, etc. The average dose of inorganic arsenic that has been estimated to be lethal is 0.6 mg/kg [5].

2.2. Intake

The inorganic Arsenic; As (III) or As (V) has been shown to be absorbed from the gastrointestinal (GI) tract. The dissolved arsenic is absorbed more efficiently than its compounds of low solubility such as lead arsenide, gallium arsenide. Skin infections have been reported in persons having extensive contact with solutions of inorganic arsenic. The airborne arsenic is largely As (III) and its absorption from lungs is largely dependent on chemical form and particle size [6]. Biochemically, arsenic acts as a stimulator which may activate other carcinogens responsible to generate tumours in lungs, skin, liver, bladder and kidney [7]. The inorganic arsenic after entering into RBC's, rapidly binds to haemoglobin and gets redistributed quickly to the liver, kidneys, heart and lungs and to a lesser extent to the nervous system, GI tract and spleen. Arsenic undergoes hepatic biomethylation to form methylated metabolites i.e. MMA, DMA and TMA with relatively lower toxicity [8].

2.3. Oxidative stress by Arsenic

Arsenic is known to generate oxidative stress by causing disruption of cell signaling pathways via ROS generation [9]. The arsenic induced ROS ($O_2^{\cdot -}$) was found to be playing a central role in this process. It was later on transformed to the more reactive oxygenated species such as H_2O_2 and $^{\cdot}OH$ by Fenton type reaction. These species while interacting with the biological macromolecules may further lead to DNA damage. Its hypomethylation or hypermethylation may lead to the alterations in regulatory mechanisms of cell proliferation and death. This study indicated that in addition to lipid peroxidation (LPO), arsenic induced oxidative stress resulting alterations in some anti-oxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1), as well as on sulfhydryl group containing peptides and proteins. This stress causes late complications in diabetes mellitus [10].

2.4. Toxicity, symptoms and treatment

The As (III) intoxicates cells either by binding with the sulfhydryl groups of some enzymes or through depletion of lipoate. Lipoate is involved in the Krebs cycle. Hence the depletion of lipoate causes inhibition of the Krebs cycle, leading to ATP depletion. As (IV) on the other hand replaces the stable phosphate ester bond in ATP with the arsenate ester bond, thereby causing arsenolysis, inhibiting phosphorylation and depleting ATP. Clinically arsenic poisoning may lead to nausea, vomiting, abdominal pain and bloody rice water diarrhea. It also results into dermatologic changes (hyper pigmentation and keratosis on the palms and soles); nails may exhibit transverse white bands known as Mees lines. Arsenic poisoning begins either by removal of source or after chelating with dimercaprol or succimer (2, 3-dimercaptosuccinic acid) that is chelation therapy [11].

III LEAD

3.1. Chemistry

The two chemically existing forms of lead are: organic and inorganic lead. Lead exists in two main oxidation states (+2 and +4). The stable oxidation state of lead is Pb^{2+} i.e. lead acetate. Lead having sign convention Pb, derived from a Latin word (Pb: plumbum, At. No: 82) is another very noxious and lethal metal detectable in all phases of the environment and in food chain [12]. Lead is more often used in the battery rods, ammunition and devices to shield X-rays leading to its exposure to the industrial people. Ingestion in the form of contaminated food and more importantly drinking water is the important source of lead in humans. Exposure can also occur via inadvertent ingestion of contaminated soil/dust or lead-based paint. It gets into water from the corrosion of plumbing materials. Lead poisoning (saturnism, plumbism) is a condition caused by increased levels of lead in the blood [13].

3.2. Intake

The Board of Disease Control (BDC) states that a blood lead level (BLL) of 10μg/dL or above is a cause for serious concern [14]. However, lead can effect development of animals even at blood Lead Level below 10μg/dL [15]. After exceeding safe limit, lead can induce a broad range of physiological, biochemical and behavioural malfunctions in humans including peripheral and CNS, cardiovascular system, kidney, liver and

reproductory systems [16]. It has been shown to reduce cognitive capacity in children. This kind of neurotoxicity was later on found to be associated with lead sponsored ROS production which caused change in the levels of lipid peroxidation [17].

Since lead has no known biochemically relevant role in biological system, its toxicity comes due to its ability to mimic other biologically important metals, most notably calcium, iron and zinc which act as cofactors in many enzyme controlled reactions. Lead is able to bind and interact with many of the same enzymes as these metals but due to its differing chemistry, does not properly function as a cofactor, thus interfering with the enzyme's ability to catalyze its normal reaction(s). Moreover, lead is now known to induce ROS and RNS production and hence this heavy metal exhibits ability to generate oxidative stress in the body treated with varying concentrations of lead [18].

3.3. Oxidative stress by Lead

The mechanisms of lead-induced oxidative stress primarily include damage to cell membrane, DNA and enzymes (catalase, SOD, GPx and glucose-6-phosphate dehydrogenase) and group of non-enzymatic antioxidants [4]. It is known that the fatty acids constituting the cellular membrane are highly prone to react with ROS because of unsaturation and get peroxidized in completely different manner which disturbs key functions of membrane [19]. Lead is also shown to induce changes in the composition of proteins and lipids of RBC membrane and to inhibit haemoglobin synthesis [20].

3.4. Toxicity, symptoms and treatment

Lead as a systemic toxicant is a neurotoxin that has been linked to visual deterioration, central and peripheral nervous system disorders, renal dysfunction, decreased fertility, renal failure and hypertensive cardiovascular disease [21]. Lead has two main toxic hematologic effects: reduction of lifespan of erythrocyte and decreased hemoglobin biosynthesis. At lower levels (1-50 mg/dL) lead may cause cognitive changes whereas at moderate levels (50-70 mg/dL) children may display a decrease in day to day activity. The symptoms of its toxicity include anaemia, peripheral motor neuropathy, GI complaints such as anorexia, muscle and joint pain, vomiting and abdominal pain and growth delay. The most effective treatment for lead toxicity is removal of source or by the chelation therapy (dimercaprol or succimer and $CaNa_2EDTA$) [22].

IV CADMIUM

4.1. Chemistry

It was discovered in 1817 by Friedrich Strohmeyer as an impurity in zinc carbonate (calamine). Its atomic number 48 and is chemically similar to the two other metals in group 12, zinc and mercury. It resembles with zinc and mercury in terms of oxidation state (+2) and low melting point, respectively. Cadmium is relatively the most abundant and toxic element. It is used in making batteries, cadmium pigments, coatings and plating, chemical stabilizers, metal coatings, alloys, barrier to control neutrons in nuclear fusion, television phosphors, television picture tubes and semiconductors [23].

4.2. Intake

The main sources of exposure to cadmium are industries working on Cadmium, diet, drinking water and tobacco. The initial route of exposure in industrial settings is inhalation of cadmium-possessing fumes which can result initially in metal fume fever but may progress to chemical pneumonitis, pulmonary edema and death. Cadmium possessing a long half-life (17-30 years) in humans and its accumulation starts in liver and kidney [24]. This long half-life is mainly due to its low excretion and its continued accumulation in the living system. Cadmium is one of six substances banned by the European Union's Restriction on Hazardous Substances directive due to its potential carcinogenic nature and it may cause cancers of lung, prostrate, pancreas and kidney in humans. The International Agency for Research on Cancer (USA) has classified Cadmium into the number 1 category of carcinogens [25].

4.3. Oxidative stress by cadmium

Cd^{2+} being a non-redox-active metal, cannot initiate by itself the Fenton reactions [26]. However, it generates non radical hydrogen peroxide, which becomes a source of free radical via the Fenton reaction. Some of the mechanisms through which Cd induces the formation of ROS include the following: decrease in the intracellular GSH content, combination with thiol groups of enzymes involved in antioxidant mechanisms like SOD, glutathione peroxidase and catalase and inhibits their activities [27], formation of cadmium-selenium complexes in the active centre of glutathione peroxidase and inhibits the enzyme activity and inhibition of complex III of mitochondrial electronic transport chain and increases ROS production which may damage mitochondrial membrane and trigger onset of apoptosis. Possibly Cd induced oxidative stress is involved in causing DNA damage/mutations [28], oxidation of proteins and lipid peroxidation, which may cause alterations in lipid composition of cellular membranes. Taking into account the effect of Cd on the central nervous system (CNS) and endocrine system, it is currently classified as an endocrine/neuroendocrine disruptor [29].

4.4. Toxicity, symptoms and treatment

The EPA standard for maximum concentration of Cd in drinking water is 5μg/L. FDA has allowed Cd in food colouring up to 15 ppb. Cd toxicity involves the organs such as gastrointestinal tract, lungs, kidney and bone as well as pulmonary and neurological systems. Cd causes neurotoxicity and alters brain metabolism by alterations in the synthesis and/or metabolism of biogenic amines and amino acid neurotransmitters in the CNS. The symptoms include headache, sleep disorders, increased salivation, memory deficits, choking, throat dryness, cough, chest pain, restlessness, irritability, nausea, vomiting, kidney dysfunction (glucosuria, proteinuria and aminoaciduria), itai-itai disease and renal and hepatic failures. Lung and prostate are the primary targets for the Cd induced cancer. The most effective treatment for cadmium toxicity is removal of source of Cd or by the chelation therapy through melatonin. Chelation therapy is however inadvisable to use because it exposes the kidney to large quantities of toxic cadmium in nephrons [23].

V MERCURY

5.1. Chemistry

It is a highly reactive and toxic transition element. Its zero oxidation state (Hg^0) exists as vapour or as liquid metal, its cationic mercurous state Hg^+ exists as inorganic salts, and its mercuric state Hg^{2+} may form either inorganic salts or organomercury compounds. These three groups vary in effects. The different forms of mercury include elemental mercury vapour (Hg), inorganic mercurous (Hg II), mercuric (Hg III) and organic mercuric compounds [30]. These forms have toxic effects in number of organs such as brain, kidney and lungs [31]. It has been shown that mercurous and mercuric ions impart their toxicological effects mainly through molecular interactions by binding to the thiol groups present in different molecules such as GSH, cysteine and metallothionene [32].

5.2. Intake

The mercury is poorly absorbed by ingestion and skin contact. It is hazardous due to its potential to release mercury vapour. Survey reveal that < 0.01% of ingested mercury is absorbed through the intact gastrointestinal tract, from where it enters the circulatory system and is distributed throughout the body. Chronic exposures occur by inhalation, even at low concentrations in the range 0.7-42 $\mu g/m^3$. Inorganic mercury, mercury (II) chloride, primarily affects gastrointestinal tract and kidneys. Mercury salts inflict little neurological damage without continuous or heavy exposure. Mercury (II) salts are usually more toxic than their mercury (I) counterparts because of their greater solubility in water and rapid absorption by the gastrointestinal tract [33]. In organic mercuric compounds, the most dangerous mercury compound, dimethyl mercury, is so toxic that even a small drop spilled on the skin, or even a latex glove, can cause death. Methyl mercury is the major source of organic mercury for all individuals [34]. It enters the food chain through bioaccumulation in the environment, reaching high concentrations among populations of some species. Kidneys contain the greatest concentrations of mercury following exposure to the inorganic salts of mercury and mercury vapour, whereas organic mercury has a greater affinity for the brain, the posterior cortex in particular. Mercury vapour also has greater affinity for the central nervous system than inorganic mercury salts.

5.3. Oxidative stress by Mercury

It is well established that various stimuli, including toxic chemicals, enhance the synthesis of a class of proteins known as stress proteins [35]. This large super family of proteins collectively referred to as stress proteins include heat-shock proteins (hsps) and glucose-regulated proteins (grps). This particular stress protein response has evolved as a cellular strategy to protect and repair other essential cellular proteins. The differential expression of four HSPs has been observed in renal cortex and medulla of mercury treated rats. Its toxicity is due to its high affinity to sulfhydryl groups of proteins and enzymes and its ability to disrupt cell cycle progress in various tissues.

5.4. Toxicity, symptoms and treatment

The entry of mercury occurs by way of inhalation of the vapour, ingestion of the liquid or cutaneous exposure. Although, in patients who have normal GI mucosa, toxicity rarely develops after ingestion, patients, who have

abnormal GI mucosa, may absorb enough mercury for toxicity to occur. Occasionally mercury becomes trapped within the appendix, but without signs of mercury toxicity or appendicitis it can be safely monitored and allowed to pass on its own. If vomiting with subsequent aspiration of elemental mercury occurs, the risk for toxicity is increased because mercury is well absorbed within the lungs. Toxicity from elemental mercury occurs from inhalation of the vapour because mercury is well absorbed into the pulmonary circulation allowing distribution to the brain, kidneys, gut and lungs. Initial symptoms commonly include GI upset, constipation, abdominal pain and poor appetite and may mimic a viral illness. Other symptoms include dry mouth, headache and muscle pains. Chronic exposure results in two distinct clinical syndromes, acrodynia and erethism. In acrodynia, symptoms include sweating, hypertension, tachycardia, pruritus, weakness, poor muscle tone, insomnia, anorexia and an erythematous, desquamating rash to the palms and soles. Other symptoms in mouth include reddened, swollen gums. On the other hand, in erethism, patients may exhibit memory loss, drowsiness, withdrawal, lethargy, depression and irritability. Removal of the patient from the source of the toxic exposure is the most important intervention. In spite of several controversies regarding its use, still chelation therapy is considered the mainstay of treatment. Chelators are charged molecules capable of binding the metal ion forming a neutral complex excreted by the kidney. Several agents are available such as succimer, dimercaprol and D-penicillamine. In patients who have developed renal failure, hemodialysis may be required, with or without the inclusion of a chelation agent [35].

VI CHROMIUM

6.1. Chemistry

Chromium (Cr) is a naturally occurring element present in the earth's crust, with oxidation states ranging from Cr(II) to Cr(VI) [36]. Chromium compounds are stable in the trivalent Cr(III) and occur in nature in ores, such as ferrochromite. The hexavalent Cr(VI) form is the second-most stable state [37]. Elemental chromium Cr(0) does not occur naturally. Chromium enters into various environmental matrices (air, water and soil) from a wide variety of natural and anthropogenic sources (Cr(VI)) with the largest release coming from industrial establishments. Hexavalent chromium Cr(VI) is a toxic industrial pollutant that is classified as human carcinogen by several regulatory and non-regulatory agencies [38]. The health hazard associated with exposure to chromium depends on its oxidation state, ranging from the low toxicity of the metal form Cr(0) to the high toxicity of the hexavalent form.

6.2. Intake

The American Occupational Safety and Health Administration (OSHA) recently set a "safe" level of 5µg/m^3, for an 8h time-weighted average, even though this revised level may still pose a carcinogenic risk [39]. Non-occupational exposure occurs via ingestion of chromium containing food and water whereas occupational exposure occurs via inhalation [40]. Chromium concentrations range between 1 to 3000 mg/kg in soil, 5 to 800µg/L in sea water and 26-5.2 mg/L in rivers and lakes [41]. Chromium content in foods varies greatly and depends on the processing and preparation. In general, most fresh foods typically contain chromium levels

ranging from <10 to 1,300 µg/kg. Even though the principal route of human exposure to chromium is through inhalation and the lung is the primary target organ, significant human exposure to chromium has also been reported to take place through the skin [42]. The environmental exposure to Cr(VI)-containing compounds is known to cause multiorgan toxicity such as renal damage, allergy and asthma and cancer of the respiratory tract in humans [43].

6.3. Oxidative stress by Chromium

The stress is related to the ease with which Cr(VI) can pass through cell membranes and its subsequent intracellular reduction to reactive intermediates. Since Cr(III) is poorly absorbed by any route, the toxicity of chromium is mainly attributable to the Cr(VI) form. Cr(VI) enters many types of cells and under physiological conditions and is reduced by hydrogen peroxide (H_2O_2), glutathione (GSH) reductase, ascorbic acid and GSH to produce reactive intermediates, including Cr(V), Cr(IV), thiyl radicals, hydroxyl radicals and ultimately Cr(III). Any of these species could attack DNA, proteins and membrane lipids, thereby disrupting cellular integrity and functions [44]. DNA strand breaks in peripheral lymphocytes and lipid peroxidation products in urine observed in chromium-exposed workers also support the evidence of Cr (VI)-induced toxicity to humans [45]. Oxidative damage is considered to be the underlying cause of these genotoxic effects including chromosomal abnormalities and DNA strand breaks [46].

6.4. Toxicity, symptoms and treatment

The intentional ingestion of extremely high doses of Cr (VI) compounds by humans has resulted in severe respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal and neurological effects as part of the sequelae leading to death or in patients who survived because of medical treatment [47]. Although the evidence of carcinogenicity of chromium in humans and terrestrial mammals seems strong, the mechanism by which it causes cancer is not completely understood [48]. The main symptoms due to ingestion of chromium (VI) compounds are irritation and ulcers in the stomach and small intestine, anaemia, sperm damage and male reproductive system damage, allergic reactions (redness and swelling of the skin) and increase in stomach tumors. Chromium poisoning ends with either by removal of source or by the chelation therapy; after chelating with dimercaprol or succimer (2, 3-dimercaptosuccinic acid).

VII CONCLUSION

The heavy metals thus exhibit the ability to induce oxidative stress by generating ROS. Oxidative stress due to heavy metals is the outcome of a negative shift of the balance between the production of ROS and the ability of the biological systems to readily counteract the ROS mediated damage or repair of it rapidly. The heavy metals toxicity is caused either by their direct binding with thiol groups of the proteins/enzymes thereby causing perturbations in their three-dimensional conformations or by replacing the divalent metal ions from their catalytic pocket which are essentially required by concerned proteins/enzymes as cofactors for their optimal activity. In either of these situations, these biomolecules tend to lose their native characteristics due to unfolding or denaturation and then their functions are greatly compromised, which lead to serious bearings onto their

biological activity and finally the cellular health. All forms of life maintain a reducing environment within their cells. This reducing environment is preserved by enzymes that maintain the reduced state through a constant input of metabolic energy. Disturbances in this normal redox state by heavy metals can cause toxic effects indirectly through the production of peroxides and free radicals that induce oxidative stress, which is responsible for the damage of several key components of the cells, including proteins, lipid and DNA. In conclusion, the present stage of knowledge about the impact of heavy metals in biological systems indicates that enhanced formation of free radicals and ROS or RNS or their intermediates can be regarded as a common factor in determining heavy metal induced toxicity and carcinogenicity.

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