Chapter

Introductory Chapter: Free Radical Biology in Metal Toxicities—Role of Antioxidants

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1. Introduction

Industrial revolution imparts a high level of metal contamination in this world [1–3]. Although technology advances to control pollution, it fails to check environmental heavy metal pollution. As metals used not always leads to biodegradation, hence, these heavy metals circulate in human life chains and accumulate in living organisms [4]. Some metals like zinc and iron are physiologically essential, but they may also alter the function of organisms when the exposure dose exceeds a critical threshold, which is species specific, and can depend on multiple factors including age, sex, and functional norms of physiological system [5]. Rodents are as sensitive and near similar to human monitoring system against metal toxicity studies [6].

In the last few decades there has been a tremendous interest on oxygen-free radicals, more generally known as "reactive oxygen species," (ROS) and of "reactive nitrogen species" (RNS) in experimental and clinical studies on various environmental pollutants [6]. ROS and RNS are found to be generated during irradiation or metal catalyzed reaction or its presence in atmosphere as pollutants or simply generates due to inflammation in the physiological system. Some examples of free radicals are hydrogen peroxide, singlet oxygen, hypochlorous acid, superoxide radical, hydroxyl radical, and nitric oxide [7].

It has generated interest that oxygen metabolism induces over production of free radicals due to altered pathophysiology in the system. Another hypothesis is that inadequate antioxidants in the body also impairs body defense system and ability to fight against pollutants especially heavy metal pollutants. Antioxidants can prevent cellular damage by interacting with free radicals and terminating chain reaction process [8, 9].

2. Metal toxicities

Metals play an important role by conjugating at the active sites of enzymes and participate directly in catalysis, stabilize macromolecular structures of proteins and nucleic acids, thereby affecting structural and functional integration.

The molecular mechanisms including enzymatic functions of metal induced bio-toxicities have been established. Possible recognition of essential biological

roles of metals, of course, in no way obviates the primary objective of ecological and toxicological investigation, i.e., to eliminate the hazards created by metals. In this regard, Bertrand's early enunciation of the necessity to consider physiological and toxicological effects of metals as a biological continuum is important [10]. Bertrand further emphasized that, metals induce a double humped, biphasic dose response curve, which allows a gross division into two general regions.

i. Potentially, every element has a biological function which can be assessed properly only against a background of deficiency state.

ii. Potentially, every element is toxic when presented to an organism in high enough concentration.

The toxicity of a metal or its compounds in a biological system is influenced by a number of factors like:

i. The intrinsic toxicity of metal

ii. The dose of metal

iii. The combining capacity of metal

iv. The capacity of biological system to absorb and transport the metal to the target organ most susceptible to the metal intoxication

v. The capacity of the metal to transform to a less toxic or a more toxic form at the target organ or during transfer

vi. The ability of the metal to bind to essential macromolecules

vii. The homeostatic mechanism of the organism to either excrete or sequester the metal

Excess doses of some non-toxic metal compounds may interfere with normal cellular or physiological process by non-specific activity such as changing the osmotic pressure and pH or physically changing the microenvironment of the GI tract. The defensive homeostatic mechanism of cells and tissues combat metal intoxication either by sequestering the metal in a harmless way or by enhanced excretion of the toxic metal [11]. Cellular injury from toxic metals may occur by a number of diverse molecular mechanisms and at many levels of biological organization within a given target organ or cell population. It has become increasingly evident that the toxic potential of metals such as nickel, cadmium, mercury, lead is highly dependent on their intracellular bioavailability. Apart from these, there are several interactive factors that are capable of influencing the toxic effects of these heavy metals. Nutritional status, the presence or absence of other essential metals, contribution of proper antioxidants may greatly alter the distribution of metals within intracellular compartments. Normally it has been found that occupational metal exposed toxicities in developed countries are in decreasing trend but in third world countries the toxicities from metal exposure is still serious issues which make an impact on the health of the occupationally exposed people with impairments of neurological, reproductive, immunological and cardiovascular functions [12]. The European Commission initiated an action program concerning the environmental protection from heavy metals exposure [13].

3. Free radicals biology and metals

Oxidation occurs when free radicals attack biological molecules, removing an electron. Under certain conditions, unsaturated fatty acids can undergo oxidation, known as lipid peroxidation which sets off a chain reaction that generates large number of free radicals, which are both cytotoxic and genotoxic capable of altering DNA functions. The mechanism of heavy metal toxicity through electron transfer most often involves the cross linking of the sulfhydryl groups of proteins. Free radicals can also be generated directly from molecular oxygen in a two-step process to produce superoxide anion. In the continued presence of heavy metals, the superoxide anions formed can then combine with protons in the dismutation reaction, generating hydrogen peroxide (H_2O_2) in the process. Superoxide anions can also produce highly toxic hydroxyl radicals. Suitable mechanisms have evolved so that the steady-state concentrations of potentially toxic oxygen-derived free radicals are kept in check under normal physiological conditions by the body's intrinsic antioxidant defense system. Nevertheless, the enhanced generation of these ROS can overwhelm the intrinsic defenses of the cell, resulting in a condition known as oxidative stress [14]. Heavy metal can produce oxidative stress; therefore, it was conceivable that reactive oxygen species (ROS) may trigger signaling pathways resulting in the activation of the hypoxia-inducible factor (HIF)-1 transcription factor and up-regulation of hypoxia-related genes. The activity of the HIF-1 transcription factor as assessed in transient transfection assays was stimulated by heavy metals but this activation was not diminished when oxidative stress was attenuated nor was HIF-dependent transcription enhanced by hydrogen peroxide. It was reported that ROS are produced during the exposure of cells to metals that mimic hypoxia, but the formation of ROS was not involved in the activation of HIF-1-dependent genes [15]. One explanation of the heavy metal-induced activation of the HIF-1 transcription factor is based on the assumption that it replaces iron in the oxygen carrier, Fe(II)-hybrid hemoglobin. Substitution of iron by other heavy metals switch signal to permanent hypoxia, which in turn activates the HIF-1 factor [16]. The pretreatment of human blood lymphocytes with either CAT (a H_2O_2 scavenger), or SOD (a scavenger of O_2^- radical) significantly reduced markers of heavy metal- induced genetic and cellular damage. Glutathione depletion, a marker of oxidative stress, was found in human alveolar epithelial Type II-like cell line after treatment with heavy metal containing ultra-fine metal dust [17]. After controlling for confounders, plasma lipid peroxidation levels were significantly increased and erythrocyte antioxidants were significantly decreased in metal exposed experimental animals as compared with controls [18].

4. Role of antioxidant on metal toxicity

Free radicals are reactive chemical species that contain one or more unpaired electrons e.g. hydrogen peroxide, singlet oxygen, hypochlorous acid, superoxide radical, hydroxyl radical, and nitric oxide. As heavy metals generate free radicals hence it must be quenched by an antioxidant otherwise these free radicals will react with membrane lipid, protein, carbohydrate and nucleic acid molecules and change their functional moiety in cellular system. It has been found that human nuclear DNA receives approximately 10,000 oxidative 'hits' every day. It clearly reflects that each of the cells is under firing from ROS and the situation becomes worst if the cell is targeted by heavy metals. The antioxidant defense system against metal toxicities are fundamentally superoxide dismutase, glutathione, peroxidases, and catalase besides Fe and Cu binding proteins like albumin, transferrin, lactoferrin,

haptoglobin, uric acid, bilirubin and carotenoids. Further antioxidant vitamins like vitamin C, vitamin E, Vitamin B12 are also considered as protective agents against metal toxicities. Some endogenous and exogenous polyphenolic compounds like flavonoids and ligands are also found to be protective against metal toxicities as antioxidants. Finally, there are specific nuclear repair enzymes, proteases, and other enzymes that constantly target oxidized molecules for catabolism [19]. Antioxidants are intimately capable of protecting cellular damage by interfering with ROS and stop the free radical due to metal induced chain reactions.

The success of an antioxidant against metal induced oxidative stress depends on its capability to (i) quenching free radicals (ii) chelating redox metals (iii) regenerate some more antioxidants within "antioxidant network", (iv) successfully induce cell signaling to express adaptive genes, (v) readily absorption capability, (vi) must have adequate concentration in tissue and biofluid and (vii) capability to act on both membrane and aqueous areas.

Regarding antioxidant supplementation against metal induced oxidative stress one must remember that higher doses of supplementary antioxidants do not always offer protection against free radicals. It is widely accepted that in a healthy organism there exists a balance between oxidants and various antioxidants. High levels of antioxidants may also disturb oxidant and antioxidant balance with unpredictable and unexpected consequences.

5. Conclusion

The steps of metal toxicity are as following: liberation of toxic metal > reaction with target molecules > cellular dysfunction > respond to reaction (repair) or (dis-repair) > developmental toxicity. Mode of action typically starts with the reaction of metals with target molecules and ends with toxic manifestations and entire these process oxidative stress and oxidant and antioxidant imbalances play a key role.

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