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The promising future of nano-antioxidant therapy against environmental pollutants induced-toxicities

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ABSTRACT

Developmental toxicity caused by exposure to a mixture of environmental pollutants has become a major health concern. Human-made chemicals, including xenoestrogens, pesticides, heavy metals, polycyclic aromatic hydrocarbons (PAHs) are major factors that increase formation of Reactive Oxygen Species (ROS) and adversely influence endogen antioxidant defense. Humans have evolved complex antioxidants systems that protect cells from prooxidant conditions. Deficiency of any these components can cause destruction in the overall antioxidant status of an individual. Antioxidants agents can be endogenous or obtained exogenously, as a part of a diet or through dietary supplements. Although oxidative damage contributes to many pathologies the use of naturally occurring, small-molecule exogenous antioxidants as therapies for these disorders has not been successful. An ideal exogenous antioxidant should be readily absorbed, enough delivered to intracellular location required to decrease pathological oxidative damage, positively affecting gene expression. To develop effective antioxidant therapies the best strategy may be to create new nanoscale drug delivery systems. This review highlights the role of environmental induced oxidative stress factors and novel nanoparticle design techniques of antioxidants.

1. Introduction

Increased formation of reactive oxygen species (ROS) or decreased cellular antioxidant reservoir called oxidative stress results in cellular damage by oxidizing the macromolecules such as proteins, lipids and DNA [1]. Various cell functions including signal transduction pathways, host defense against invasive pathogens, autophagy, cellular proliferation and apoptosis are mediated by the physiological amounts of the ROS [2]. Besides, ROS can be produced in the response to different cytokines and growth factors as a secondary messenger [3]. However, the imbalance between oxidant/antioxidant particles increases ROS levels, resulting in undesirable effects. Excess ROS formation is involved in the pathogenesis of many disorders via its links to the several intracellular signaling pathways. Increasing our knowledge concerning the role of free radicals in various diseases is opening new research areas for the use of antioxidants to prevent or treat different health problems.

Nanoscale and supramolecular drug delivery systems have emerged as prominent methods to improve the pharmacological and therapeutic effects of many natural and synthetic drugs [4]. Antioxidants due to their poor bioavailability and biocompatibility can be encapsulated with nano-materials to form nano-antioxidants to obtain the ideal solubility and permeability profile and also to preserve the antioxidant from the probable enzymatic degradation. Furthermore, the modification of pharmacokinetics and tissue distribution properties as well as improving intracellular penetration and distribution of the targeted compound are among the advantages of nano-formulated antioxidants [5]. In this work, we provide an overview of the oxidative stress process

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and the toxicity mechanisms of different environmental pollutants. Additionally, we discuss the impact of nano-antioxidants and obstacles that therapeutic agents must overcome to reduce oxidative stress. Also, different methods that nano-antioxidants comprises a promising tool to targeting environmental-related oxidative damages will be discussed in this review.

2. Oxidative stress

Oxygen is the substantial element of energy production in aerobic organisms, while on the contrary, it produces chronic toxic effects in cells. Thereby, protective mechanisms should be present to remove these toxic oxygen by-products. Both prokaryotic and eukaryotic organisms gain diverse and vital adaptation systems to combat the oxidative environment, which are known as endogenous antioxidants. Oxidative stress occurs when the endogenous antioxidant defenses are unable to eliminate the excess production of ROS.

The most prominent defense mechanisms are conventional catalytic antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidases (GSH-Px). CATs are heme-containing enzymes mostly found in peroxisomes, that exchange hydrogen peroxide (H_2O_2) to water and O_2. In the next step, H_2O_2 is removed by GSH-Px through coupling its reduction with the oxidation of glutathione (GSH). The ultimate product is H_2O_2 peroxide which is produced via the dismutation activity of the metal-compromised proteins, SODs [6,7]. Additionally, myeloperoxidases utilizes H_2O_2 to form hypochlorous acid and other detrimental oxidant products of chlorine. Furthermore, in Fenton type reactions, H_2O_2 could be reduced to $OH^{-\cdot}$ in the presence of Cu^{2+} or Fe^{2+} as reducing agents.

Insufficiency of endogenous ROS neutralization network in different conditions such as exposure to environmental factors, lifestyle, certain pharmaceutical agents, various pathological disorders alongside with natural aging has drawn attention to the exogenous therapeutic administration of antioxidants [8–11].

The environment has a tight contribution to human health and safety. Individuals who are exposed to substances such as chemicals and pollutants, are more prone to most diseases of major common health implications for instance chronic lung disorders, cancer, diabetes and neural dysfunctions.

Thus, it is now obvious that understanding environmental risk factors, their noxious impact on human everyday life and counteracting related health problems are the fundamental agenda to be underscored. Although cells can adopt to environmental signs such as toxins or stresses through various signaling pathways, deploy of environmental toxic effects are becoming more evident every day [12].

Environmental stresses are putative means of oxidative stress induction and alterations in the cellular redox systems. Mitochondria are the main sources of intracellular ROS production [13,14]. Juxtaposition of mitochondrial DNA to the electron transport chain and also the lack of protective histone proteins lead to rise to the oxidative stress induced mitochondrial DNA damage which is concomitant with mitochondrial genomic instability, disruption of electron transport chain, mitochondrial membrane collapse, inadequate energy generation and ultimately cell death [15]. ROS can also directly inhibit respiratory chain complexes in the mitochondria leading to the additional ROS overload. Finally, the impairment of mitochondrial metabolism as a result of mitochondrial membrane lipid peroxidation and induction of mitochondrial permeability transition pore (MPTP) and cytochrome C release from the inner membrane results in programmed cell death (apoptosis) [16].

The produced ROS in response of various stresses in the cell can attack polyunsaturated fatty acids, which are the major constituents of plasma and organelle membranes with the subsequent formation of lipid peroxyl radicals. Lipid hydroperoxide products such as malondialdehyde, 4-hydroperoxy-2-nonenal, 4-oxo-2-nonenal and 4-hydroxy-2-nonenal are then generated during the abstraction of hydrogen atoms from polyunsaturated lipids which in turn can react with the nucleophilic amino acids and nucleotides to induce numerous signaling impacts [17].

Oxidative endoplasmic reticulum stress and DNA damage are other signaling pathways activated through environmental stresses and/or toxicants [18]. Oxidative stress results in DNA damage via the activation of DNA glycosylases that selectively excise different lesions from DNA [19]. It is well documented that oxidative hazards directly cause DNA adduct and apoptosis would occur in case of insufficient compensatory mechanisms [20]. In addition, redox imbalance and ROS production are the most common cause of endoplasmic reticulum-induced apoptosis. In this context, different environmental toxicants can cause various cellular damages contributed to redox state in the cell. So, designation of novel antioxidant formulations to combat environmental toxicities gain more importance and will be discussed through this review.

3. Environmental induced oxidative stress

3.1. Metals

Metal-induced cytotoxicity has largely been associated with oxidative stress. Oxidative DNA damage, lipid peroxidation and alteration of calcium and sulfidryl homeostasis have been addressed with different metal induced toxicities [21,22].

Antimony (Sb) induces ROS production and mitochondrial dysfunction in the context of mitochondrial membrane potential collapse [21]. Also, it stimulates oxidative stress cascade through activation of c-jun kinase (JKN) pathway [23]. As exposure commences cell death, which is demonstrated with cellular glutathione reservoirs depletion and oxidative hazard, as GSH or NAC (N-acetyl-cysteine) administration prevents the latter toxic effects [24–26]. Interestingly, due to extracellular interactions of ascorbic acid (vitamin C) and vitamin E with transition metals, these antioxidants trigger arsenic-induced oxidative stress and apoptosis [27,28].

However, co-administration of vitamin E and C protects against cell death and oxidative injury in As exposed rats in vivo [29,30]. Cadmium (Cd)-induced toxicity is connected with occupational and environmental pollution mainly from mining and metallurgy industries, manufacturing nickel and cadmium batteries, plastics and pigments. Human beings are exposed to Cd intoxication via the air, food and water as well as cigarette smoke. Cd interferes with ROS generation through replacing Cu and Fe in several cellular proteins such as apoferritin and ferritin which results in the accumulation of unbound free Fe and Cu whose participation in Fenton type reactions produces several reactive species such as H_2O_2, $O_2^{-\cdot}$ and $OH^{-\cdot}$ (Fig. 1). Moreover, Cd has inhibitory effects on antioxidant enzymes CAT and GR. Antioxidants have exerted protection against Cd-associated oxidative stress and cell death [31,32].

In addition to the formation of $OH^{-\cdot}$ through Fenton reaction, Co exposure is able to stimulate hypoxia-inducible factor-1, MAPKs, accretion of p53 and induction of ROS in different cell lines [33,34].

The reduction of *Cu* (II) to *Cu* (I) occurs in the presence of GSH and ascorbic acid, which induces the decomposition of H_2O_2 through Fenton reaction and $OH^{-\cdot}$ generation leading ultimately to peroxidation of membrane lipids [22]. Formation of DNA strand breaks and oxidation of bases and induction of apoptosis in oxidative pathway is also related to the toxic effects of Cu ions [35]. Hg is an abundant environmental pollutant with a high affinity for reduced sulfur groups of thiol-containing residues such as cysteine, glutathione, homocysteine, albumin and NAC. So, Hg mediates its toxic effects through depletion of GSH reservoirs that causes oxidative stress [36,37]. Pb induces ROS formation with direct depletion of antioxidant molecules mainly GSH which has been shown to activate apoptosis cascade [38,39].

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