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Review Article

Arsenic-induced oxidative stress and its reversibility

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ABSTRACT

This review summarizes the literature describing the molecular mechanisms of arsenic-induced oxidative stress, its relevant biomarkers, and its relation to various diseases, including preventive and therapeutic strategies. Arsenic alters multiple cellular pathways including expression of growth factors, suppression of cell cycle checkpoint proteins, promotion of and resistance to apoptosis, inhibition of DNA repair, alterations in DNA methylation, decreased immunosurveillance, and increased oxidative stress, by disturbing the pro/antioxidant balance. These alterations play prominent roles in disease manifestation, such as carcinogenicity, genotoxicity, diabetes, cardiovascular and nervous systems disorders. The exact molecular and cellular mechanisms involved in arsenic toxicity are rather unrevealed. Arsenic alters cellular glutathione levels either by utilizing this electron donor for the conversion of pentavalent to trivalent arsenicals or directly binding with it or by oxidizing glutathione via arsenic-induced free radical generation. Arsenic forms oxygen-based radicals ($OH^{\bullet}$, $O_2^{\bullet-}$) under physiological conditions by directly binding with critical thiols. As a carcinogen, it acts through epigenetic mechanisms rather than as a classical mutagen. The carcinogenic potential of arsenic may be attributed to activation of redox-sensitive transcription factors and other signaling pathways involving nuclear factor κB, activator protein-1, and p53. Modulation of cellular thiols for protection against reactive oxygen species has been used as a therapeutic strategy against arsenic. *N*-acetylcysteine, α-lipoic acid, vitamin E, quercetin, and a few herbal extracts show prophylactic activity against the majority of arsenic-mediated injuries in both in vitro and in vivo models. This review also updates the reader on recent advances in chelation therapy and newer therapeutic strategies suggested to treat arsenic-induced oxidative damage.

Contents

Abbreviations: GSH, glutathione; GSSG, glutathione disulfide; NAC, *N*-acetylcysteine; ROS, reactive oxygen species; RNS, reactive nitrogen species; $O_2^{\bullet-}$, superoxide anion; $^{\bullet}OH$, hydroxyl radical; $^1O_2$, singlet oxygen; MMA^V, monomethyl arsonate; MMA^{III}, monomethyl arsonous; ODD, oxidative DNA damage; PDH, pyruvate dehydrogenase; XO, xanthine oxidase; ESR, electron spin resonance; 8-OHdG, 8-hydroxy-2-deoxyguanosine; ALAD, δ-aminolevulinic acid dehydratase; GST, glutathione *S*-transferase; TNFα, tumor necrosis factor α; DMSA, *meso*-2,3-dimercaptosuccinic acid; MiADMSA, monoisoamyl-DMSA; MMP, mitochondria membrane potential; SOD, superoxide dismutase; GPx, glutathione peroxidase; GR, glutathione reductase; AST, aspartate aminotransaminase; CAT, catalase; CK-2, casein kinase 2; RTK, receptor tyrosine kinase; NTK, nonreceptor tyrosine kinase; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; JNK, c-jun N-terminal kinase; PKC, protein kinase C; CDK, cyclin-dependent kinase; AP-1, activator protein 1; NF-κB, nuclear factor κB; GADD45, growth arrest and DNA damage 45; LDL, low-density lipoprotein; Nrf2, transcription factor NF-E2-related factor 2.

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Introduction

In today's world, environmental and occupational surroundings can generate a variety of modes for exposure to various forms of metals. Common sources of metal exposure include groundwater contamination, leather tanning, and mining [1]. Even though heavy metals such as iron and copper in trace amounts are vital for normal biological functioning of cells, extensive exposure to certain heavy metals could be linked to cellular damage, inflammation, and cancer [1,2]. Arsenic (As) is one of the most widely studied elements in the field of metal intoxication after lead (Pb). Arsenic is a metalloid found in water, soil, and air from natural and anthropogenic sources and exists in inorganic as well as organic forms [3]. The major inorganic forms of arsenic (As_i) include trivalent meta-arsenite (As^{3+}) and pentavalent arsenate (As^{5+}). Whereas As in surface water mainly exists as As^{5+}, As^{3+} is more prevalent in deep anoxic wells. Trivalent arsenic is known to be more toxic than the pentavalent form [4]. Humans can be exposed to arsenic via air and food; the major exposure route of As_i is through contaminated drinking water, especially in India, Bangladesh, China, and some Central and South American countries [5]. Arsenic concentrations in drinking water in Argentina (200 ppb) [6,7], Mexico (400 ppb) [8,9], Taiwan (50–1980 ppb) [10], and the Indo-Bangladesh region (800 ppb) have been reported to be well above the WHO guidelines' maximum permissible value (10 ppb) [11]. Chronic arsenicosis due to drinking arsenic-contaminated water is reported to affect more than 200 million people worldwide, with approximately 38 million residing in the Indo-Bangladesh region [5,12,13]. Various reported epidemiological studies have linked arsenic intoxication with internal cancers [14–18], blackfoot disease [19], vascular diseases [20,21], and diabetes [22–24].

The mode of action of arsenicals is quite complicated, and to understand it, multifactorial determinants need to be addressed. These determinants range from physicochemical properties, such as the valence state (trivalent/ pentavalent), degree of methylation, charge at physiological pH, and electrostatic attraction and repulsion to active sites on important macromolecules, to pharmacokinetic factors (absorption, distribution, metabolism, protein binding, and excretion). Oxidative stress is currently the most widely accepted and studied mechanism of arsenic toxicity [25].

Thus, one of the major areas of current research interest has been to understand the mechanism of arsenic-induced oxidative stress with the aim of finding a suitable, safe, and specific treatment using chelation therapy, alone or in combination with an antioxidant. In this review article, I attempt to highlight the various pathways that mediate arsenic-induced oxidative stress and the potential prophylactic and therapeutic measures employing strategies such as using antioxidants, chelation, or their combination.

Arsenic-induced reactive oxygen species generation

Arsenic may induce oxidative stress by cycling between oxidation states of metals such as As, Fe, etc., or by interacting with antioxidants and increasing inflammation, resulting in the accumulation of free radicals in cells [26]. Major arsenic-induced ROS include superoxide anion ($O_2^{\bullet-}$), hydroxyl radical ($^{\bullet}OH$), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), and peroxyl radicals.

Oxygen-derived radicals form a most important class of radical species generated in living systems because molecular oxygen that has a unique electronic configuration forms $O_2^{\bullet-}$ by addition of one electron [27]. Superoxide anions, arising through metabolic processes or after oxygen “activation” by physical irradiation, are considered “primary” ROS. They can further interact directly, through enzyme- or metal-catalyzed processes, with other molecules to generate “secondary” ROS [2]. For instance, $^{\bullet}OH$ generated through superoxide-mediated process involving hydrogen peroxide plays an important role in mediating the genotoxic effects of arsenic [28]. Yamanaka and colleagues were the first to demonstrate arsenic-induced free radical formation [29,30]. Molecular oxygen reacts with dimethylarsine (a trivalent arsenic form and a minor in vivo metabolite of dimethylarsinic acid) to form dimethylarsinic radical and superoxide anion. Further, the addition of another molecule of molecular oxygen results in a dimethylarsinic peroxyl radical and these arsenic radicals are known to be detrimental to cells [30]. Liu et al. also demonstrated arsenic-induced free radical formation in mouse livers [28].

Experimental results have shown the generation of $O_2^{\bullet-}$ and H_2O_2 after arsenic exposure in some cell lines such as human vascular smooth muscle cells [31], human–hamster hybrid cells [28], and vascular endothelial cells [32], whereas other cell lines such as HEL30 [33], NB4 [34], and CHOK1 [35] have shown induction of H_2O_2. Furthermore, arsenic-induced $^{\bullet}OH$ generation too has been reported in the striatum of rats [36]. Apart from the direct evidence of arsenic-induced ROS, indirect evidence too has been reported. For instance,