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Review Article

ARSENIC AND ITS MITOCHONDRIAL TOXICITY: A REVIEW

A. Arunachalam[1]*, N. Nanthini[2], S. Malathi[2] and A. Ragapriya[2]

[1]Head, [2]M. Phil. Scholar, PG and Research Department of Zoology,
Vivekanandha College of Arts and Sciences for Women, Elayampalayam,Tiruchengode, India

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ABSTRACT

The present review article deals with environmental origin of arsenic (As) and its oxidative stress mediated mitochondrial toxicity of arsenic. It is a metalloid compound occurs naturally, being the 20th most abundant element in the earth's crust, and is a component of more than 245 minerals. The presence of As in the environment may be due to both natural and anthropogenic sources. The symptoms of As toxicity either through consumption of contaminated ground water or food crops. The toxicity of As compounds depends on a number of factors. Mostly inorganic trivalent form of Asarsenite (As^{III}) is more toxic than arsenate (As^{V}). Reactive oxygen species (ROS)-mediated oxidative damage is a common denominator in As pathogenesis. In addition, arsenic induces morphological and molecular changes in the integrity of mitochondria through ROS mediated oxidative stress. Further the mechanisms of free radical formation derived from the superoxide radical, combined with glutathione-depleting agents, increase the sensitivity of cells to arsenic toxicity because of its sulfhydryl groups (SH). Finally this review article included origin of 'As' and oxidative stress mediated mitochondrial toxicity to address the 'As' induced mechanism of mitochondrial dysfunction.

Keywords: Arsenic, Toxicity, Ground water, Mitochondria, Oxidative stress.

INTRODUCTION

Environmental pollution is any discharge of material or energy into the water, land or air that causes or may cause acute (short-term) or chronic (long-term) ruinous to the Earth's ecological balance or that lowers the quality of life. Pollutants may cause primary damage, with direct identifiable impact on the environment, or secondary damage in the form of minor perturbations in the delicate balance of the biological food web that are detectable only over long time periods. People may be exposed to potentially harmful chemical, physical and biological agents in air, food, water and soil. Heavy metals are the major pollutant found in the environment.

Heavy metals have been used in many different areas for thousands of years. Heavy metals are thus commonly defined as those having a specific density of more than 5 g/cm^3. "Heavy metals" are chemical elements with a specific gravity at least 5 times that of water. The specific gravity of water is 1 at 4°C (39°F). Specific gravity is a measure of density of a given amount of a solid substance when it is compared to an equal amount of water. Some well-known toxic metals with a specific gravity 5 or more times that of water is arsenic (5.7 As), cadmium (8.65 Cd), iron (7.9 Fe), lead (11.34 pb), and mercury (13.546 Hg) (Lide, 1992). The main threats to human health from heavy metals are associated with exposure to lead, cadmium, mercury and arsenic. Emissions of heavy metals to the environment occur *via* a wide range of processes and pathways, including to the air (*e.g.* during combustion, extraction and processing), to surface waters (*via* runoff

*Corresponding Author: Dr. A. Arunachalam, Head, Department of Zoology, Vivekanandha College of Arts and Sciences for Women, Elayampalayam, Tiruchengode, India, Email: arunachalam5452@gmail.com

and releases from storage and transport) and to the soil and hence into ground waters and crops (Jarup, 2003).

Since the middle of the 19th century, production of heavy metals increased steeply for more than 100 years, with concomitant emissions to the environment (Jarup, 2003). Heavy metal contamination of soil results from anthropogenic as well as natural activities. Anthropogenic activities such as mining, smelting operation and agriculture have locally increased the levels of heavy metals such as cobalt (Co), chromium (Cr), Cd, Pb, As and Ni in soil up to dangerous levels (Sharma and Agrawal, 2005).

Arsenic

Arsenic (As) is ubiquitous in nature and its abundance ranks twentieth in the Earth's crust, fourteenth in seawater and twelfth in the human body. It is an element in the environment that can be found naturally in rocks, soil, water, air, plants and animals. Arsenic appears in three allotropic forms: yellow, black and grey; the stable form is a silver-gray, brittle crystalline solid. It tarnishes rapidly in air, and at high temperatures burns forming a white cloud of arsenic trioxide. Arsenic is a member of group VA of the periodic table, which combines readily with many elements. The metallic form is brittle, tarnishes and when heated it rapidly oxidizes to arsenic trioxide, which has a garlic odour. The non metallic form is less reactive but will dissolve when heated with strong oxidizing acids and alkalis. The table 1 shows the chemical properties of Arsenic (As).

Table 1. Chemical properties of arsenic.

Parameters	**Properties**
Atomic number	33
Atomic mass	74.9216 g.mol $^{-1}$
Electronegativity according to Pauling	2.0
Density	5.7 g.cm^{-3} at 14°C
Melting point	814 °C (36 atm)
Boiling point	615 °C (sublimation)
Vanderwaals radius	0.139 nm
Ionic radius	0.222 nm (-2) 0,047 nm (+5) 0,058 (+3)
Isotopes	8
Electronic shell	[Ar] 3d^{10} 4s^{2} 4p^{3}
Energy of first ionization	947 kJ.mol $^{-1}$
Energy of second ionization	1798 kJ.mol $^{-1}$
Energy of third ionization	2736 kJ.mol $^{-1}$
Standard potential	- 0.3 V (As^{3+}/ As)
Discovered by	The ancients

Sources of Arsenic

Arsenicals are used commercially and industrially as alloying agents in the manufacture of transistors, lasers and semi-conductors, as well as in the processing of glass, pigments, textiles, paper, metal adhesives, ceramics, wood preservatives, ammunition, and explosives. They are also used in the hide tanning process and to a limited extent, as pesticides, feed additives, and pharmaceuticals, including veterinary drugs (Hughes *et al.*, 2011).

The principal sources of arsenic in ambient air are the burning of fossil fuels (especially coal), metal production, agricultural use, and waste incineration. Arsenic is introduced into water through the erosion and weathering of soil, minerals, and ores, from industrial effluents, and via atmospheric deposition (Hindmarsh and McCurdy, 1986; Hutton and Symon, 1986) (Figure 2).

Figure 1 Sources of arsenic

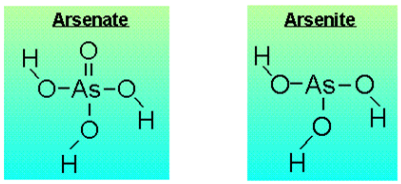

Figure 2. Structure of arsenate and arsenite.

General Aspects of As Toxicity

Among the As species found in the soil environment, compounds of $As^{V}$and As^{III} (Figure 1) are the most important inorganic As species in the soil, because their compounds are highly soluble in water (Vaughan, 1993) and may change valency states depending on the pH (Masscheleyn *et al.*, 1991) and redox conditions (Marin *et al.*, 1993). Moreover organic As compound sexist in both the trivalent and pentavalent states in soils (Vaughan, 1993).

Arsenic contamination in the environment is becoming a serious public health problem in several regions. It is known that arsenite (As^{III}) is more toxic than arsenate (As^{V}), with inorganic As being more toxic than organic As (Petrick *et al.*, 2000). However, different organic As species have different toxicity. For example, as final As metabolites, monomethyl arsonic acid (MMA^{V}) and dimethylarsinic acid (DMA^{V})are less toxic than inorganic arsenic, whereas the toxicity of intermediate metabolites such as monomethylarsonous acid (MMA^{III}) and dimethylarsinous acid (DMA^{III}) are much more toxic than inorganic arsenic (Petrick*et al.*, 2000). The toxicity of various arsenic species increasesin the order of As^{V}< MMA^{V}< DMA^{V}<As^{III}< MMA^{III}≈ DMA^{III}.

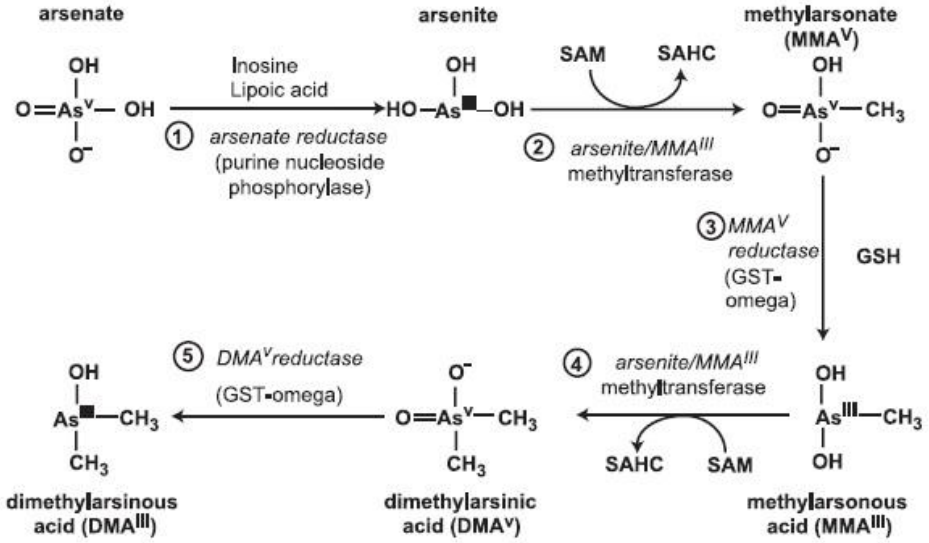

Figure 3 Metabolism of arsenic.

Arsenic induced reactive oxygen species (ROS)

Many mechanistic studies of As toxicity have suggested that reactive oxygen species and reactive nitrogen species aregenerated during inorganic As metabolism in living cells (Shi *et al.*, 2004).

Arsenic induces morphologic changes in mitochondrial integrity and a rapid decline of mitochondrial membrane potential. Mitochondrial alterations are considered to be primary sites where an uncontrolled random formation of superoxide anion radical occurs. Several studies proposed that the mechanisms of free radical formation derived from the mitochiondria through As toxicity (Cohen *et al.*, 2006; Valko*et al*., 2005).Experimental results based on both *in vivo* and *in vitro* studies of As-exposed humans and animals suggest the possible involvement of increased formation of peroxyl radicals ($ROO^{\bullet}$), superoxide anion radical ($O_2^{\bullet-}$), singlet oxygen ($^1O_2$), hydroxylradical ($^{\bullet}OH$), hydrogen peroxide (H_2O_2), dimethylarsenic radical[$(CH_3)_2As^{\bullet}$], blood nonproteinsulfydryls and/or oxidant-induced DNA damage (Flora *et al.*, 2007). The exact mechanism responsible for the generation of all these reactive species has yet to be fully elucidated, but some studies have proposed the formation of intermediary arsine species.

In addition to reactive oxygen species, arsenic exposure caninitiate the generation of reactive nitrogen species (RNS).Several contradictory results describing arsenic-induced production of NO have been reported, one of which concluded that there was no arsenic-induced increase in NO generation in hepatocytes and human liver cells, which inhibited inducible NO synthase gene expression in cytokine-stimulated humanliver cells and hepatocytes (Hughes, 2002; Flora *et al.*, 2008; Germolec *et al*., 1996). However, in another study, arsenite was said to inhibit inducible NO synthase gene expression in ratpulmonary artery smooth muscle cells (Kodavanti *et al*., 1998). A third study with low levels of arsenite (<5 μM) similarly recorded no change in intracellular concentration of Ca (II), nor any NO generation, according to results from EPR spectroscopy (Barchowsky*et al*., 1999).

As Toxicity in Mitochondria

Mitochondria are the largest source of ATP production and are very sensitive to the oxidative state of the cell. Under normal conditions a proton gradient is built from the transfer of electrons from various electron donors, with molecular oxygen being the final electron acceptor. The established proton gradient is coupled to the production of ATP from ADP. While this provides the cell with a large portion of its ATP pool, there are many points in this process where reactive by-products can be produced (Brand *et al.*, 2004). Electron transfer to oxygen must be tightly controlled or electron "leaking" can result in superoxide production, a highly reactive oxygen species (Han *et al*., 2001). Excessive cellular damage will initiate apoptosis or give rise to a variety of pathological conditions (Ozben, 2007; Li *et al*., 2013). Mitochondrial diseases may be inherited or induced and result in a variety of pathologies, including diabetes mellitus, various neuropathies and myopathies (Maassen *et al*., 2002; Finsterer, 2005). Arsenic is known to alter mitochondrial membrane potential and disrupt electron transport, particularly by altered activity of

complex I (Han *et al.*, 2008). Altered activity of complex I and III of the electron transport in particular is associated with an increase in mitochondrial ROS (Chen *et al.*, 2003; Hirst *et al.*, 2008).

Mitochondria are suggested to be one of the important sites of ROS production (Figure 3). The mitochondrial respiratory chain produces O_2 from the reaction of molecular oxygen with semi ubiquinone (Flora, 2011).

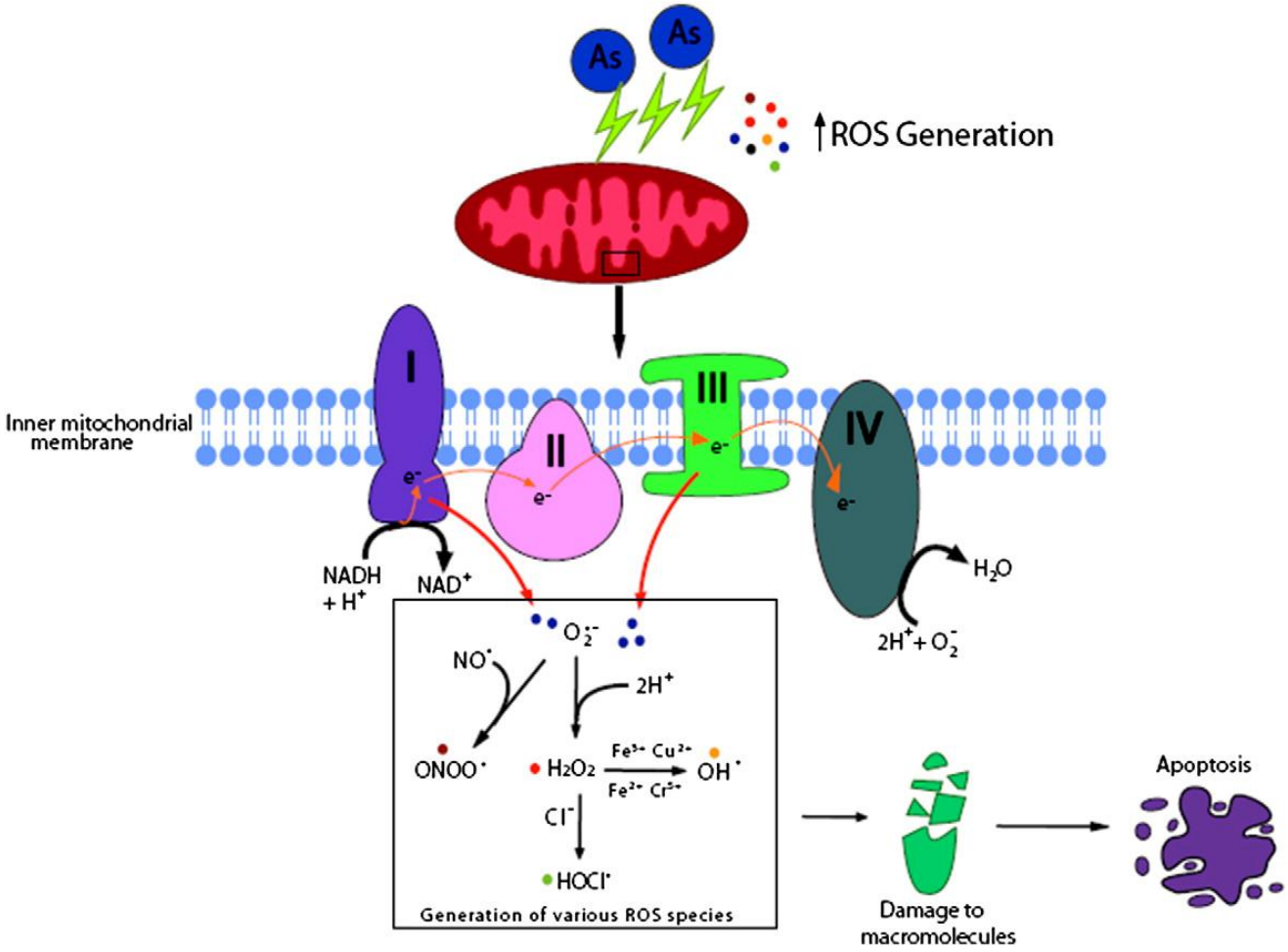

Figure 4 Arsenic-induced mitochondrial generation of various reactive oxygen species and their effects. Arsenic induces significant ROS generation mainly through complex I and complex II of the electron transport chain (ETC).

In addition to mitochondria, three other sources of ROS have been proposed: (i) Generation of intermediary arsine species may produce significant amounts of free radicals (Yamanaka *et al.*, 1997; Yamanaka *et al.*, 2001; Yamanaka and Okada, 1994). (ii) Methylated arsenic species can release redox-active iron from ferritin. Free iron plays acentral role in generating harmful oxygen species by promoting the conversion of O_2 and H_2O_2 into the highly reactive OH radical throughthe Haber–Weiss reaction (Ahmad *et al.*, 2000). (iii) ROS can be generated during oxidation of arsenite to arsenate (Del Razo *et al.*, 2001; Rossman, 2003).

CONCLUSION

The above discussion points to the fact that reactive oxygen species play the most crucial role in exerting the toxic effects of arsenic on various tissues. Although the mechanism of arsenic-induced toxicity still remains poorly understood, the mitochondria are presumed to be one of the major targets for the generation of reactive species, which trigger a cascade of events leading to cell death. Arsenic triggers various signaling pathways that control important functions such as proliferation, differentiation, and apoptosis. Arsenic detection in biological samples is the most common indication of exposure; analysis of various

macromolecules and ROS levels can also provide indications of arsenic-inflicted toxicity.

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