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Full Length Research Paper

Mechanisms of arsenic toxicity and carcinogenesis

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Industrialization has excessively modified the discharge and distribution of arsenic in the environment through natural and anthropogenic activities. Gastrointestinal tract, Lung and Dermal absorptions account for various adverse effects associated with arsenic toxicity. The knowledge of arsenic biotransformation holds the trivalent species (DMA^{3+} and MMA^{3+}) accountable for most arsenic toxicity with mechanisms of action such as the inhibition of DNA replicating or repair enzymes, interference with tissue respiration and oxidative stress. There is information of transplacental arsenic carcinogenesis and arsenic disruption of endocrine activity but most of these mechanisms remain poorly understood. More importantly, the exact dose at which arsenic induces tumours in vivo is still a major research question and therefore necessitates more scientific investigation/ research.

Key words: Arsenic, toxicity, carcinogenesis.

INTRODUCTION

Advances in industrial activities have resulted in the discharge of arsenic into the environment. There is a wide distribution of arsenic in the environment due to both natural and anthropogenic activities and it is often found in food, soil and air borne particles. The presence of arsenic in plant and human tissues (Dickerson (1980) gives an idea of possible accumulation due to exposure in these tissues. Over the years, several epidemiological and scientific studies have been able to link exposure to arsenic to various adverse effects observed in plants, animal/humans and the environment as a whole (Wang et al., 2002; Dahal et al., 2008; Tseng, 1977). Proposed mechanisms of action in exerting these effects include mitochondrial damage (Liu et al., 2005), altered DNA repair, altered DNA methylation, oxidative stress, cell proliferation, co-carcinogenesis and tumour promotion (Hughes, 2002). The biotransformation of inorganic arsenic in humans is considered a detoxification mechanism considering its methylation to less reactive forms; Monomethylarsonous acid and Dimethylarsinic acid (Vahter, 2002). This paper discusses these various mechanisms of arsenic and its role in carcinogenicity

EXPOSURE PATHWAYS AND TOXICOKINETICS

Regardless of the limited understanding of its molecular mechanism and the related dose at which it causes tumours, exposure to arsenic is regarded as a major public health concern due to its clear carcinogenic potential is (Tchounwou et al., 2004). The primary exposure pathway ingestion (water and food). Inhalation is regarded as a minor pathway and dermal absorption is negligible. The main sources of exposure happen to be drinking water and food. Many foods contain arsenic but at relatively low levels with examples such as vegetables and meat. Furthermore, wine consumption could also constitute a potential source of exposure to arsenic due to the use of pesticides on grapes (Wexler, 1998). Due to several industrial processes involved in production (smelting, manufacturing of pesticides containing arsenic), humans are continuously exposed to risks of developing toxic effects associated with arsenic accumulation.

Arsenic is readily absorbed from the gastrointestinal tract and lungs and is widely distributed in most tissues of the organisms. Great concentrations are deposited in the liver, kidney, lungs and skin. Besides these, small concentrations could be found in the bone and muscles while accumulation in hair and nails is observed as a result of chronic exposure. According to Wexler (1998), organic arsenic compounds are eliminated faster than inorganic although both forms have short half-lives ranging in hours with less than 10% of organic arsenic excreted in faeces and up to 80% excreted in urine in approximately 3 days.

Agricultural activities, mining and coal burning have increased natural deposits in soil thereby modifying human exposure to arsenic. Following exposure, toxicity occurs through various modes classified under carcinogenic and non-carcinogenic (Paradosh and Anupama, 2002). Information on the biotransformation of arsenic reveals the rapid reduction of arsenate (As^{5+}) to arsenite by by the enzyme arsenate reductase which is presumed to be purine nucleoside phosphorylase, sequential methylation

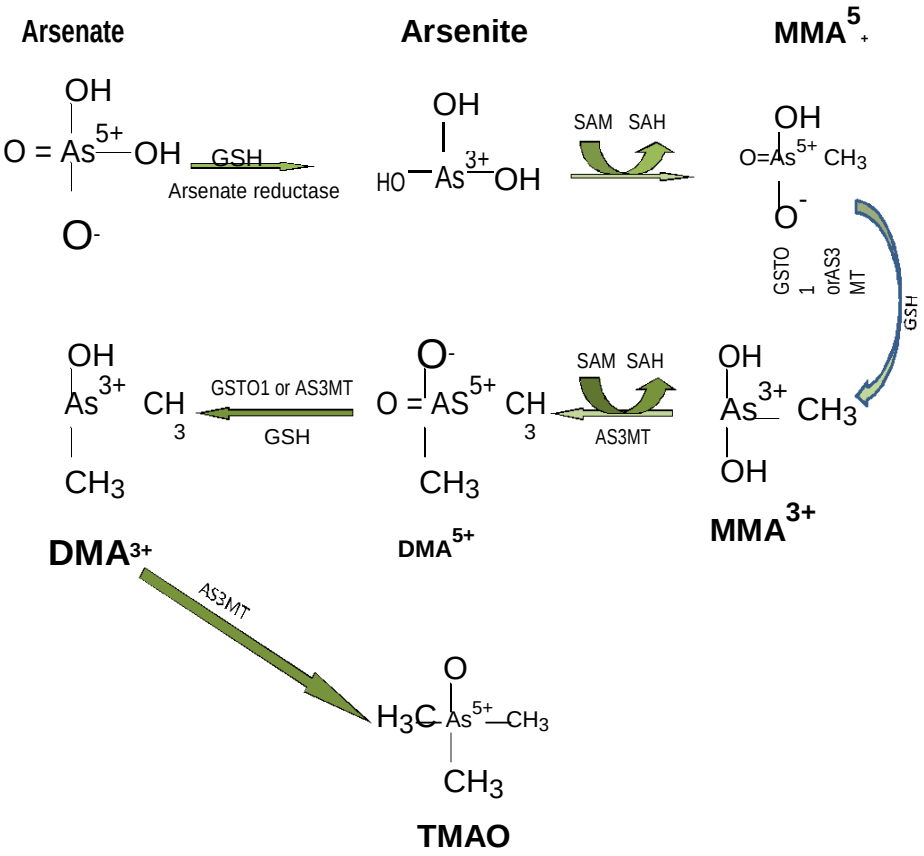

Figure 1. Arsenic metabolism showing arsenate reduction to arsenite and methylation to pentavalent (MMA^{5+}, DMA^{5+}) and trivalent (MMA^{3+}, DMA^{3+}) forms.
GSH, reduced glutathione; GSTO1, glutathione S-transferase omega-1; SAM, S-adenosylmethione; SAH, S-adenosylhomocysteine; AS3MT, arsenic methyltransferase (Cyt 19); MMA5+, mono methylarsonous acid; MMA3+, mono methylarsonous acid; DMA5+, dimethyl arsenic acid; DMA3+, dimethyl arsonous acid; TMAO, trimethyl arsenic oxide. Adapted from Klaassen (2008).

of arsenite by arsenic methyl transferase (AS3MT or Cyt 19) or arsenite methyl using S-adenosylmethionine (SA M) as a methyl group donor to form methylarsonate (MMA^{5+}) and dimethylarsinic acid (DMA^{5+}). Figure 1, illustrates this process showing the intermediate metabolites which are generated (MMA^{3+} and DMA^{3+}) during this process. These trivalent forms of arsenic are now thought to be more toxic than the inorganic species (Klaassen, 2008).

MECHANISM OF TOXICITY

Although the toxicity of arsenic varies according to its valence (that is, trivalent arsenics are more toxic than pentavalent arsenics) and the most toxic being soluble arsenic compounds, the metabolism of arsenic plays a vital role in the manifestation of its toxic effects. The mechanism of arsenic in genotoxicity has not yet been fully understood. However, it is suspected to be a result of arsenic's ability to inhibit DNA replicating or repair enzymes and arsenate's action as a phosphate analog (Li and Rossman, 1989).

The attack of mitochondrial enzymes by arsenic compounds which results in impaired tissue respiration can be related to arsenic cellular toxicity. Equally, its reaction with thiol groups (- SH) especially the enzymes or cofactors which possess two thiols (example, dihydrolipoic acid), resulting in the alteration of various enzymes including those related to tissue respiration is yet another mechanism of its toxicity.

Reactions in the conversion of pyruvate to acetyl CoA during tissue respiration are characterized by the enzymes and co-enzymes of the pyruvate dehydrogenase complex (pyruvate decarboxylase, dihydrolipoyl transacetylase, dihydrolipoyl dehydrogenase, thiamine pyrophosphate, lipoic acid, coASH, FAD, NAD^{+}). The attack of dihydrolipoic acid in the pyruvate dehydrogenase com-plex as represented in Figure 2, will alter the enzymes dihydrolipoyl dehydrogenase and dihydrolipoyl transacetylase thereby affecting the conversion of lipoic acid to acetyl

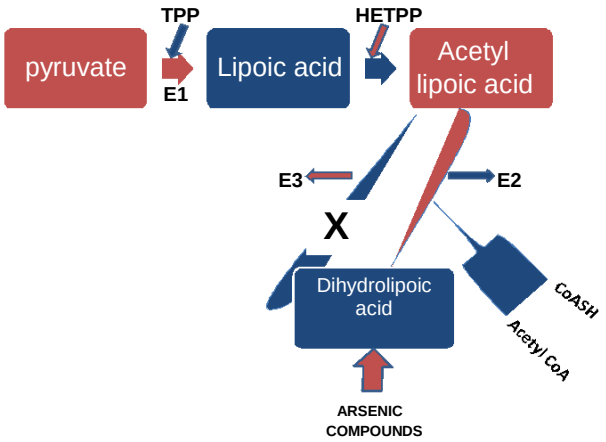

Figure 2. Schematic showing arsenic mechanism of impairing tissue respiration (E1: pyruvate decarboxylase, E2: dihydrolipoyl transacetylase, E3: dihydrolipoyl dehydrogenase, TPP: thiamine pyrophosphate, HETPP: hydroxyethyl-TPP,).

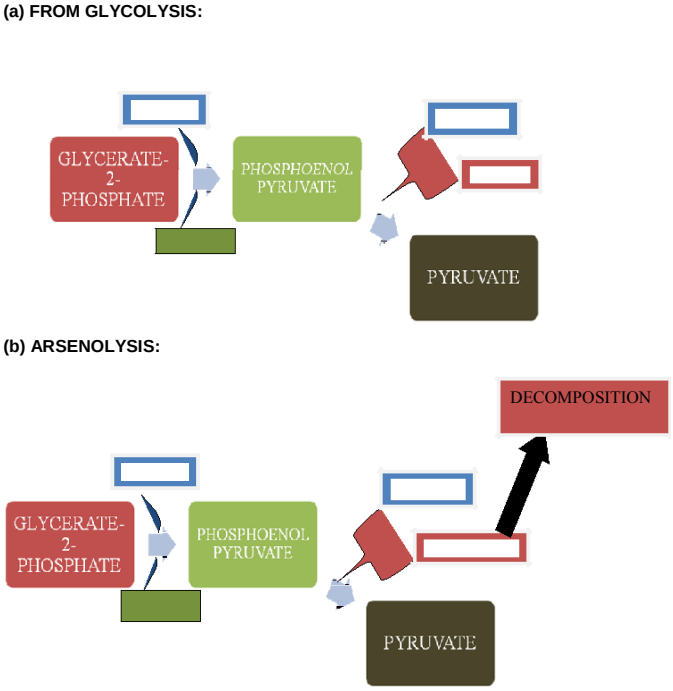

Figure 3. Schematic showing arsenic substitution for phosphorous in energy loss in metabolising cell.

lipoic acid and in turn acetyl CoA.

The role of mitochondria as a genotoxic target of arsenic is also not quite understood even though arsenic has been shown to alter mitochondrial membrane potential and induce apoptosis in various human cancer cells (Woo et al., 2002; Ivanov and Hei, 2004).Yet, in a study using enucleation and fusion techniques and the human-hamster hybrid (A_L) cells, mitochondria was shown to be a direct target of arsenic-induced genotoxicity in mammalian cells with peroxynitrite anions as important mediators in the process (Liu et al., 2005).

Nevertheless, reversion assays with Salmonella typhimurium fails to detect mutations induced by arsenic compounds even though *in vitro* experiments with several inorganic and organic arsenicals have evidence of their clastogenic effects in several cell types (Tchounwou et al., 2004). Another mechanism of arsenic toxicity is the methylation of inorganic arsenic which occurs in most though not all mammalian species. There is equally variation in the rate and extent of methylation between species and between human populations (Vahter, 1994, 1999 and 2000; Hughes, 2002).

According to Yamanaka et al. (2004), many recent *in vitro* studies have demonstrated that DMA^{3+} is more genotoxic than inorganic arsenic resulting in the proposition that DMA^{3+} rather than inorganic arsenic may be causative specie in arsenic carcinogenesis. Furthermore, possible mechanisms of oxidative damage induced by DMA^{3+} include iron-dependent oxidative-DNA damaged based on iron release from ferritin and DNA damage mediated by reactive oxygen species which are generated directly from DMA^{3+}. Reactive oxygen species (ROS) are key players in the induction of oxidative stress in cells and exposure to arsenic generates nitric oxide (NO) and superoxide anions(O_2^-) which are subsequently converted to more damaging species such as hydroxyl radical (OH). With the reaction and interaction of these reactive species with target molecules, oxidative stress, lipid peroxidation, DNA damage and the activation of signalling cascades associated with tumor promotion and/or progression occurs (Shi et al., 2004).

Arsenic has also been implicated in the inhibition of dehydrogenase and stimulation of mitochondrial adenosine triphosphatase activity by the uncoupling of oxidative phosphorylation. Some hypothesis have suggested that arsenic can replace phosphorous in many biochemical reactions and thus inhibit ATP formation during glycolysis (Wexler, 1998) by substituting phenylarsonic acid (As(v)) for phosphorous in most biochemical reactions thereby replacing stable phosphorous anion in phosphate with less stable As(v)) (anion in a process known as arsenolysis.

In Figure 3, where usually, ADP phosphorylates into ATP, in the presence of arsenic, ADP- arsenate is formed which undergoes spontaneous and irreversible decomposition resulting in the loss of energy by the metabolizing cell. The uncoupling of oxidative phosphorylation decreases cellular respiration and increases free radical production leading to hepatotoxicity and porphyrinuria which are commonly associated with acute exposure to arsenic and with low dose chronic exposure (Figure 4).

ACUTE TOXICITY

Oral exposure to arsenic, usually dosage greater than 70 mg is the common cause of the manifestation of symptoms associated with acute toxicity of arsenic. The acute

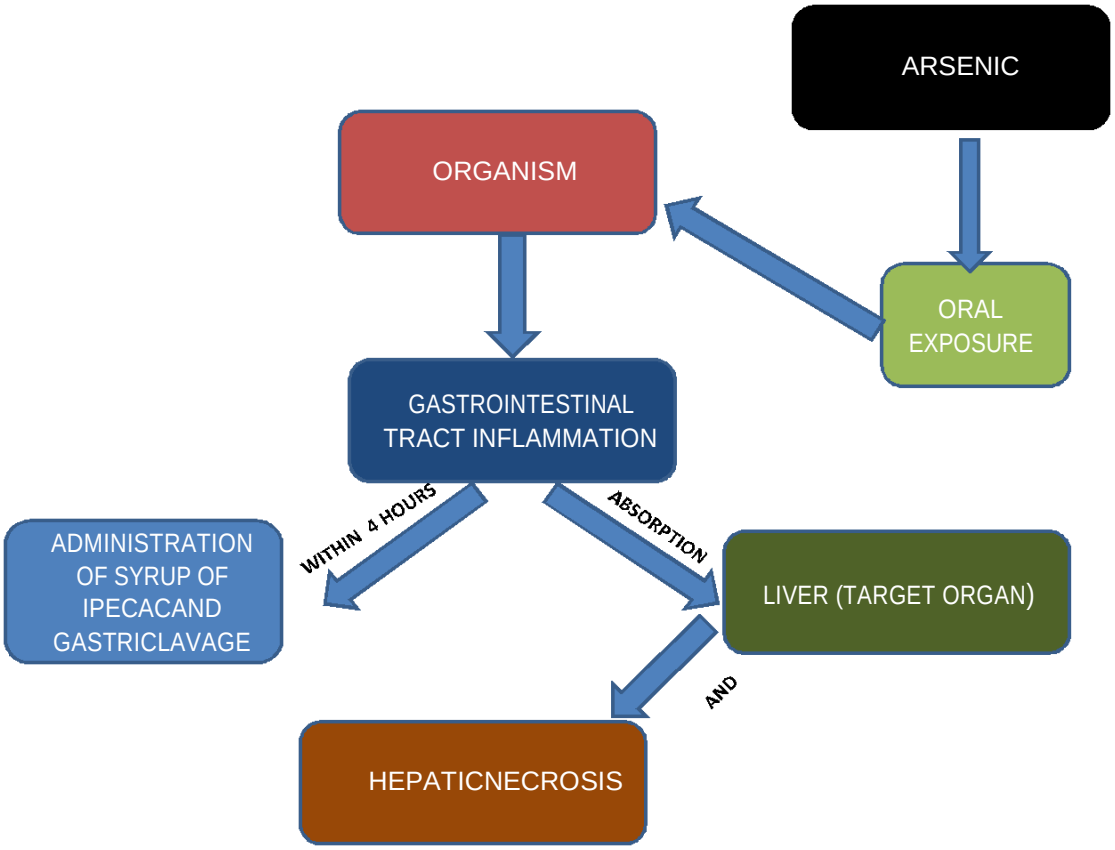

Figure 4. Elimination of arsenic using syrup of ipecac and gastric lavage resulting in reduction of arsenic availability for toxication at target site.

Table 1. Effects observed in humans and laboratory animals after acute exposure to arsenic.

System	Effect
Heart	Cardiac arrhythmias
Blood forming elements	Anaemia, leucopoenia
Peripheral nervous systems	Sensory loss
Gastrointestinal tract	Nausea, gastrointestinal distress and diarrhoea

Table 2. Effects observed in humans and laboratory animals after chronic arsenic exposure.

System	Effect
Skin	Skin lesions
Cardiovascular	Blackfoot disease
Nervous	Peripheral neuropathy, encephalopathy
Hepatic	Hepatomegaly, cirrhosis altered heme metabolism
Haematological	Bone marrow depression
Endocrine	Diabetes
Renal	Proximal tubule degeneration, papillary and coritical necrosis

Source: Hughes, M. (2002).

clinical effects from exposure to arsenic vary with the type and the state of the arsenical involved, the time – dose relationship, age, medical condition, etc.

Symptoms from a toxic dose may appear as soon as 8 min if in solution or may be delayed up to 10 h if it is a solid taken with a meal (Dickerson, 1980). This is due to the extreme irritation caused by this xenobiotic to the mucous membranes in the organism.

CHRONIC TOXICITY

Chronic exposure to arsenic affects different systems within the body. Oral exposure resulting in chronic toxicity could produce skin lesions characterized by hyperpigmentation, hyperkeratosis and hypopigmentation in humans (Tables 1 and 2).

CARCINOGENICITY

Arsenic carcinogenesis is a major concern. Arsenic is classified as a human carcinogen causing tumors of the skin, lung, urinary bladder, liver, prostate, kidney and other sites. The carcinogenic potential of arsenic was recognized over 110 years ago by Hutchison, who observed an unusual number of skin cancer occurring in patients treated for various diseases with medical arsenicals (Klaassen, 2008). In keratinocytes, arsenic is shown to enhance mitogenesis and the expression of nuclear and cell membrane proliferation markers (Bur- leson et al., 1996; Germolec et al., 1998). Like the skin, the urinary bladder is a major target for arsenic-induced cancers in humans. The induction of AP-1 by arsenic in the bladder is shown to result in uroepithelial proliferation and is held crucial to the manifestation of arsenic-induced bladder cancer (Simeonova et al., 2000). Transplancental arsenic carcinogenesis in mice has been recently established. Klaassen (2008), reported information of short – term ex-posure of pregnant rodent from gestation day 8 to 18 which is usually a period of generally great sensitivity to chemical carcinogenesis.

This exposure produced tumours in the liver, adrenal, ovary and lung of offspring as adult. Similarly, in utero exposure to arsenic induces lung cancer in female offsprings though the over-expression of -fetoprotein, epidermal growth factor receptor, L- myc and metallothionein-1 in the fetal lung (Shen et al., 2007).

The potential role for arsenic in prostate cancer is supported by evidence of prostate epithelial cell sensitivity to malignant transformation induced by in organic arsenic (Benbrahim-Tallaa and Waalkes 2008).

Conclusion

Arsenic as constituent elements of natural waters should basically induce no toxic effect as it should be occurring in tolerable amounts. However, man's continuous activities mediate the efflux of this element into the atomspher and environment thus increasing its availability. The biomethylation of arsenic had been considered a detoxification mechanism (Vahter, 2002). However, based on data from various scientific studies, biomethylation is now suspected to be a toxification mechanism and no longer a mechanism for detoxification (Yamanaka et al., 2004) although this evidence is limited to the knowledge of MMA^{3+} or DMA^{3+} *in vivo* for a sufficient period of time and quantity to induce toxicity at target sites (Schoen et al., 2004). Recently, Arsenic has been discovered as an Endocrine Disruptor (Davey et al., 2008).

Despite the toxic effects of arsenic in these organs, arsenic is shown effective in chemotherapy. These include Arsenic trioxide combination therapy with chemoherapy/all-trans retinoic acid (ATRA) in the treatment of relapsed or refractory acute promyelocytic leukaemia (Shen et al., 1997; Ghavamzadeh et al., 2006).

Several mechanisms of arsenic toxicity have been established *in vitro*. However, the exact dose and time at which it would induce tumorigenicity *in vivo* is still yet to be adequately understood. With the various organs discovered to be affected by this element, the need for further scientific research and caution is required in the use of arsenic in chemotherapy considering the poor understanding of its various mechanisms of exerting toxicity.

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