

Arsenic toxicity

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<i>Classification and external resources</i>	
ICD-10	T57.0 ^[1]
ICD-9	985.1 ^[2]

Arsenic and many of its compounds are especially potent poisons. Arsenic disrupts ATP production through several mechanisms. At the level of the citric acid cycle, arsenic inhibits pyruvate dehydrogenase and by competing with phosphate it uncouples oxidative phosphorylation, thus inhibiting energy-linked reduction of NAD⁺, mitochondrial respiration, and ATP synthesis. Hydrogen peroxide production is also increased, which might form reactive oxygen species and oxidative stress. These metabolic interferences lead to death from multi-system organ failure (see arsenic poisoning) probably from necrotic cell death, not apoptosis. A post mortem reveals brick red colored mucosa, due to severe hemorrhage. Although arsenic causes toxicity, it can also play a protective role.^[3]

Exposure

The oxides of arsenic are the most common threat since arsenite and arsenate salts are the most toxic. These forms are components of geologic formations and are extracted into the ground water. Thus although arsenic poisoning can be related to human activities such as mining and ore smelting, the most serious problems are natural, resulting from water wells drilled into aquifers that have high concentrations of arsenic. "Inorganic arsenic" (arsenate and arsenite salts) are more harmful than organic arsenic exposure.^[4]

Organic arsenic is 500 times less harmful than inorganic arsenic,^[5] and is a minor problem compared to the groundwater situation which affects many millions of people. Food is a source of the less toxic organic arsenic, with the predominant source being seafood.

Kinetics

The two forms of inorganic arsenic, reduced (trivalent As (III)) and oxidized (pentavalent As(V)), can be absorbed, and accumulated in tissues and body fluids.^[6] In the liver, the metabolism of arsenic involves enzymatic and non-enzymatic methylation, the most frequently excreted metabolite ($\geq 90\%$) in the urine of mammals is dimethylarsinic acid (or Cacodylic acid) (DMA(V)).^[7] Dimethylarsenic acid is also known as Agent Blue and was used as herbicide in the American war in the South-East Asian country of Viet Nam.

In humans inorganic arsenic is reduced nonenzymatically from pentoxide to trioxide, using glutathione (GSH) or it is mediated by enzymes. Reduction of arsenic pentoxide to arsenic trioxide increases its toxicity and bio availability, . Methylation occurs through methyltransferase enzymes. S-adenosylmethionine (SAM) may serve as methyl donor. Various pathways are used, the principal route being dependent on the current environment of the cell.^[8] Resulting metabolites are monomethylarsonous acid (MMA(III)) and dimethylarsinous acid (DMA(III)).

Methylation had been regarded as a detoxification process. While in fact reduction from +5 As to +3 As may be considered as a bioactivation instead.^[9] Another suggestion is that methylation might be a detoxification if "As(III) intermediates are not permitted to accumulate" because the pentavalent organoarsenics have a lower affinity to thiol groups than inorganic pentavalent arsenics.^[8] Gebel (2002) stated that methylation is a detoxification through accelerated excretion.^[10] With regard to carcinogenicity it has been suggested that methylation should be regarded as a toxification.^{[11][12][13]}

Arsenic, especially +3 As, binds to single, but with higher affinity to vicinal sulfhydryl groups, thus reacts with a variety of proteins and inhibits their activity. It was also proposed that binding of arsenite at nonessential sites might contribute to detoxification.^[14] Arsenite inhibits members of the disulfide oxidoreductase family like glutathione reductase^[15] and thioredoxin reductase.^[16]

The remaining unbound arsenic ($\leq 10\%$) accumulates in cells, which over time may lead to skin, bladder, kidney, liver, lung, and prostate cancers.^[7] Other forms of arsenic toxicity in humans have been observed in blood, bone marrow, cardiac, central nervous system, gastrointestinal, gonadal, kidney, liver, pancreatic, and skin tissues.^[7]

Mechanism

Arsenite inhibits not only the formation of Acetyl-CoA but also the enzyme succinic dehydrogenase. Arsenate can replace phosphate in many reactions. It is able to form Glc-6-Arsenate in vitro; therefore it has been argued that hexokinase could be inhibited.^[17] (Eventually this may be a mechanism leading to muscle weakness in chronic arsenic poisoning.) In the glyceraldehyde-3-P-dehydrogenase reaction arsenate attacks the enzyme-bound thioester. The formed 1-arseno-3-phosphoglycerate is unstable and hydrolyzes spontaneously. Thus, ATP formation in Glycolysis is inhibited while bypassing the phosphoglycerate kinase reaction. (Moreover, the formation of 2,3-bisphosphoglycerate in erythrocytes might be affected, followed by a higher oxygen affinity of hemoglobin and subsequently enhanced cyanosis) As shown by Gresser (1981), submitochondrial particles synthesize Adenosine-5'-diphosphate-arsenate from ADP and arsenate in presence of succinate. Thus, by a variety of mechanisms arsenate leads to an impairment of cell respiration and subsequently diminished ATP formation.^[18] This is consistent with observed ATP depletion of exposed cells and histopathological findings of mitochondrial and cell swelling, glycogen depletion in liver cells and fatty change in liver, heart and kidney.

Experiments demonstrated enhanced arterial thrombosis in a rat animal model, elevations of serotonin levels, thromboxane A₂ and adhesion proteins in platelets, while human platelets showed similar responses.^[19] The effect on vascular endothelium may eventually be mediated by the arsenic-induced formation of nitric oxide. It was demonstrated that +3 As concentrations substantially lower than concentrations required for inhibition of the lysosomal protease cathepsin L in B cell line TA3 were sufficient to trigger apoptosis in the same B cell line, while the latter could be a mechanism mediating immunosuppressive effects.^[20]

Carcinogenicity

It is still a matter of debate whether DNA repair inhibition or alterations in the status of DNA methylation are responsible for the carcinogenic potential of As. As vicinal sulfhydryl groups are frequently found in DNA-binding proteins, transcription factors and DNA-repair proteins, interaction of arsenic with these molecules appears to be likely. However, in vitro, most purified DNA repair enzymes are rather insensitive to arsenic, but in cell culture, As produces a dose-dependent decrease of DNA ligase activity. This might indicate that inhibition of DNA repair is an indirect effect due to changes in cellular redox levels or altered signal transduction and consequent gene expression.^[21] In spite of its carcinogenicity, the potential of arsenic to induce point mutations is weak. If administered with point mutagens it enhances the frequency of mutations in a synergistic way.^[22]

Its comutagenic effects may be explained by interference with base and nucleotide excision repair, eventually through interaction with zinc finger structures.^[23] DMA showed to effectuate DNA single strand breaks resulting from inhibition of repair enzymes at levels of 5 to 100 mM in human epithelial type II cells.^{[24][25]}

+3 MMA and +3 DMA were also shown to be directly genotoxic by effectuating scissions in supercoiled Φ X174 DNA.^[26] Increased arsenic exposure is associated with an increased frequency of chromosomal aberrations,^[27] micronuclei^{[28][29]} and sister-chromatid exchanges. An explanation for chromosomal aberrations is the sensitivity of the protein tubulin and the mitotic spindle to arsenic. Histological observations confirm effects on cellular integrity, shape and locomotion.^[30]

+3 DMA is able to form reactive oxygen species (ROS) by reaction with molecular oxygen. Resulting metabolites are the dimethylarsenic radical and the dimethylarsenic peroxy radical.^[31] Both +5 DMA and +3 DMA were shown to release iron from horse spleen as well as from human liver ferritin if ascorbic acid was administered simultaneously. Thus, formation of ROS can be promoted.^[32] Moreover, arsenic could cause oxidative stress by depleting the cell's antioxidants, especially the ones containing thiol groups. The accumulation of ROS like the cited above and hydroxyl radicals, superoxide radicals and hydrogen peroxides causes aberrant gene expression at low concentrations and lesions of lipids, proteins and DNA in higher concentrations which eventually lead to cellular death. In a rat animal model, urine levels of 8-hydroxy-2'-desoxyguanosine (as a biomarker of ROS DNA damage) were measured after treatment with DMA. In comparison to control levels, they turned out to be significantly increased.^[33] This theory is further supported by a cross-sectional study which found elevated mean serum lipid peroxides (LPO) in the As exposed individuals which correlated with blood levels of inorganic arsenic and methylated metabolites and inversely correlated with nonprotein sulfhydryl (NPSH) levels in whole blood.^[34] Another study found an association of As levels in whole blood with the level of reactive oxidants in plasma and an inverse relationship with plasma antioxidants.^[35] A finding of the latter study indicates that methylation might in fact be a detoxification pathway with regard to oxidative stress: the results showed that the lower the As methylation capacity was, the lower the level of plasma antioxidant capacity. As reviewed by Kitchin (2001), the oxidative stress theory provides an explanation for the preferred tumor sites connected with arsenic exposure.^[11] Considering that a high partial pressure of oxygen is present in lungs and +3 DMA is excreted in gaseous state via the lungs this seems to be a plausible mechanism for special vulnerability. The fact that DMA is produced by methylation in the liver, excreted via the kidneys and latter on stored in the bladder accounts for the other tumor localizations.

Regarding DNA methylation, some studies suggest interaction of As with methyltransferases which leads to an inactivation of tumor suppressor genes through hypermethylation, others state that hypomethylation might occur due to a lack of SAM resulting in aberrant gene activation.^[36] An experiment by Zhong et al. (2001) with arsenite-exposed human lung A549, kidney UOK123, UOK109 and UOK121 cells isolated eight different DNA fragments by methylation-sensitive arbitrarily primed PCR.^[37] It turned out that six of the fragments were hyper- and two of them were hypomethylated.^[37] Higher levels of DNA methyltransferase mRNA and enzyme activity were found.^[37]

Kitchin (2001) proposed a model of altered growth factors which lead to cell proliferation and thus to carcinogenesis.^[11] From observations, it is known that chronic low-dose arsenic poisoning can lead to increased tolerance to its acute toxicity.^{[22][38]} MRP1-overexpressing lung tumor GLC4/Sb30 cells poorly accumulate arsenite and arsenate. This is mediated through MRP-1 dependent efflux.^[39] The efflux requires GSH, but no As-GSH complex formation.^[40]

Although many mechanisms have been proposed, no definite model can be given for the mechanisms of chronic arsenic poisoning. The prevailing events of toxicity and carcinogenicity might be quite tissue-specific. Current consensus on the mode of carcinogenesis is that it acts primarily as a tumor promoter. Its co-carcinogenicity has been demonstrated in several models. However, the finding of several studies that chronically arsenic-exposed Andean populations (as most extremely exposed to UV-light) do not develop skin cancer with chronic arsenic exposure, is puzzling.^[41]

Heat shock response

Another aspect is the similarity of arsenic effects to the heat shock response. Short-term arsenic exposure has effects on signal transduction inducing heat shock proteins with masses of 27,60,70,72,90,110 kDa as well as metallotionein, ubiquitin, mitogen-activated [MAP] kinases, extracellular regulated kinase [ERK], c-jun terminal kinases [JNK] and p38.^{[30][42]} Via JNK and p38 it activates c-fos, c-jun and egr-1 which are usually activated by growth factors and cytokines.^{[30][43][44]} The effects are largely dependant on the dosing regime and may be as well inverted.

As shown by some experiments reviewed by Del Razo (2001), ROS induced by low levels of inorganic arsenic increase the transcription and the activity of the activator protein 1 (AP-1) and the nuclear factor- κ B (NF- κ B) (maybe enhanced by elevated MAPK levels), which results in c-fos/c-jun activation, over-secretion of pro-inflammatory and growth promoting cytokines stimulating cell proliferation.^{[42][45]} Germolec et al. (1996) found an increased cytokine expression and cell proliferation in skin biopsies from individuals chronically exposed to arsenic-contaminated drinking water.^[46]

Increased AP-1 and NF- κ B obviously also result in an up-regulation of mdm2 protein, which decreases p53 protein levels.^[47] Thus, taking into account p53's function, a lack of it could cause a faster accumulation of mutations contributing to carcinogenesis. However, high levels of inorganic arsenic inhibit NF- κ B activation and cell proliferation. An experiment of Hu et al. (2002) demonstrated increased binding activity of AP-1 and NF- κ B after acute (24 h) exposure to +3 sodium arsenite, whereas long-term exposure (10–12 weeks) yielded the opposite result.^[48] The authors conclude that the former may be interpreted as a defense response while the latter could lead to carcinogenesis.^[48] As the contradicting findings and connected mechanistic hypotheses indicate, there is a difference in acute and chronic effects of arsenic on signal transduction which is not clearly understood yet.

Oxidative stress

Studies have demonstrated that the oxidative stress generated by arsenic may disrupt the signal transduction pathways of the nuclear transcriptional factors PPAR's, AP-1, and NF- κ B,^{[7][48][49]} as well as the pro-inflammatory cytokines IL-8 and TNF- α .^{[7][48][49][50][51][52][53][54]} The interference of oxidative stress with signal transduction pathways may affect physiological processes associated with cell growth, metabolic syndrome X, glucose homeostasis, lipid metabolism, obesity, insulin resistance, inflammation, and diabetes-2.^{[55][56][57]} Recent scientific evidence has elucidated the physiological roles of the PPAR's in the ω -hydroxylation of fatty acids and the inhibition of pro-inflammatory transcription factors (NF- κ B and AP-1), pro-inflammatory cytokines (IL-1, -6, -8, -12, and TNF- α), cell4 adhesion molecules (ICAM-1 and VCAM-1), inducible nitric oxide synthase, proinflammatory nitric oxide (NO), and anti-apoptotic factors.^{[7][50][55][57][58]}

Epidemiological studies have suggested a correlation between chronic consumption of drinking water contaminated with arsenic and the incidence of Type 2-diabetes.^[7] The human liver after exposure to therapeutic drugs may exhibit hepatic non-cirrhotic portal hypertension, fibrosis, and cirrhosis.^[7] However, the literature provides insufficient scientific evidence to show cause and effect between arsenic and the onset of diabetes mellitus Type 2.^[7]

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