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A Systematic Review On Arsenic Induced Toxicity: Conventional To Modern Approach.

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Arsenic is a potent cardiovascular toxicant associated with numerous biomarkers of cardiovascular diseases in exposed human populations. Arsenic is also a carcinogen, yet arsenic trioxide is used as a therapeutic agent in the treatment of acute promyeloid leukaemia (APL). The therapeutic use of arsenic is limited due to its severe cardiovascular side effects. Many of the toxic effects of arsenic are mediated by mitochondrial dysfunction and related to arsenic's effect on oxidative stress and ischemia reperfusion injury. Therefore, we investigated the effectiveness of Ischemic preconditioning against arsenic induced cardiovascular dysfunction. ischemia-reperfusion injury (IRI) is a complex pathophysiological process causing postischemic organ dysfunction and cell death, leading to increased morbidity and mortality.1 Ischemic preconditioning (IPC), on the other hand, is the phenomenon whereby an organ supposedly becomes more resistant to IRI following multiple reversible episodes of ischemia and reperfusion effectively reverse mitochondrial dysfunction and oxidative stress in cardiovascular cells and tissues. In addition, we propose that IPC have the potential to improve the cardiovascular health of millions of people chronically exposed to elevated arsenic concentrations through contaminated water supplies or used to treat certain types of leukemAs. Importantly, we identify conceptual gaps in research and development of new mito-protective antioxidants and suggest avenues for future research to improve bioavailability of antioxidants and distribution to target tissues in order reduce arsenic-induced cardiovascular toxicity in a real-world context.

Keywords: Arsenic, ischemia-reperfusion injury (IRI), Ischemic preconditioning (IPC), cardiovascular, mitochondrial dysfunction

Introduction

Arsenic poisoning is a global health issue affecting millions of people worldwide through environmental and occupational exposure, as well as intentional suicide and homicide attempts. Although arsenic homicides commonly receive media publicity, the primary source of arsenic toxicity to the general population is by contaminated water, soil and food products (Bronkowska, et al., 2015). Arsenic (As) is a nearly tasteless odourless toxic metalloid element that is found ubiquitously in the environment. Arsenic comes in four common valence states: As(o), As(III), As(V) and Arsine gas and three common forms: inorganic salt, organic salt, and gaseous form. High arsenic (As) levels in food and drinking water, or under some occupational conditions, can precipitate chronic toxicity and in some cases cancer (Camacho, Welch, Sprando, & Hunt, 2023). Millions of people are exposed to unacceptable amounts of As through drinking water and food. Highly exposed individuals may develop acute, subacute, or chronic signs of poisoning, characterized by skin lesions, cardiovascular symptoms, and in some cases, multi-organ failure. Inorganic arsenide (III) and organic arsenicals with the general formula R-As^{2+} are bound tightly to thiol groups, particularly to vicinal dithiols such as dihydrolipoic acid (DHLA), which together with some seleno-enzymes constitute vulnerable targets for the toxic action of As. In addition, R-As^{2+}-compounds have even higher affinity to selenol groups, e.g., in thioredoxin reductase that also possesses a thiol group vicinal to the selenol (Barai, et al., 2017). Inhibition of this and other ROS scavenging seleno-enzymes explain the oxidative stress associated with arsenic poisoning. The development of chelating agents, such as the dithiols BAL (dimercaptopropanol), DMPS (dimercapto-propanesulfonate) and DMSA (dimercaptosuccinic acid), took advantage of the fact that As had high affinity towards vicinal dithiols (Chen, et al., 2022). Primary prevention by reducing exposure of the millions of people exposed to unacceptable As levels should be the prioritized strategy. However, in acute and subacute and even some cases with chronic As poisonings chelation treatment with therapeutic dithiols, in particular DMPS appears promising as regards alleviation of symptoms (Chan, et al., 2021). In acute cases, initial treatment with BAL combined with DMPS should be considered (Camacho, Welch, Sprando, & Hunt, 2023).

Conventional Use of Arsenic

Arsenic was used as a healing agent after Greek physicians such as Hippocrates and Galen popularised its use. Arsenic compounds became available as solutions, tablets, pastes, and in injectable forms (Dong, et al., 2023). Fowler's solution,

a 1% arsenic trioxide preparation, was widely used during the 19th century (Gonzalez, et al., 2015). As recently as 1958, the British Pharmaceutical and Therapeutic Products handbook edited by Martindale, listed the indications for Fowler's solution as: leukaemia, skin conditions (psorAsis, dermatitis herpetiformis, and eczema), stomatitis and gingivitis in infants, and Vincent's angina. Fowler's solution was also prescribed as a health tonic (Guidi, Martínez-López, Oliver, Sánchez-Vázquez, & Vera, 2023). Chronic arsenic intoxication from the long-term use of Fowler's solution caused haemangiosarcoma,10 angiosarcoma of the liver,11 12 and nasopharyngeal carcinoma.13 Arsenic was the primary treatment for syphilis until World War II. Arsphenamine (neoarsphenamine), a light-yellow compound containing 30% arsenic was used intravenously to treat syphilis, yaws, and some protozoan infections (Fan, et al., 2008).

Arsenic Exposure

Arsenic exposure occurs from inhalation, absorption through the skin and, primarily, by ingestion of, for example, contaminated drinking water. Arsenic in food occurs as relatively nontoxic organic compounds (arsenobentaine and arsenocholine). Seafood, fish, and algae are the richest organic sources (Hull, et al., 2021). These organic compounds cause raised arsenic levels in blood but are rapidly excreted unchanged in urine (Lee, et al., 2005). Arsenic intake is higher from solid foods than from liquids including drinking water. Organic and inorganic arsenic compounds may enter the plant food chain from agricultural products or from soil irrigated with arsenic contaminated water (Jakovljević, et al., 2023).

Arsenic Toxicity in Male Reproduction and Development.

Arsenic is an important environmental toxicant that affects the reproductive and developmental toxicity (van Geen, Ahmed, Seddique, & Shamsudduha, 2003). These toxic effects are influenced by the forms, sources, and routes, as well as doses and periods of arsenic exposure (Angon, et al.). *In vivo* studies demonstrated that inorganic arsenic, such as sodium arsenite, arsenic trioxide, and dimethyl arsinic acid, an arsenic metabolite, causes reproductive and developmental toxicity (Jeong & Ra, 2022). Prenatal exposure to inorganic arsenic by only i.p. or i.v. injection routes causes fetal malformation; in contrast, oral and inhalational exposure to inorganic arsenic affects fetal development, including growth retardation and fetal death (Ghosh, 2013). In drinking water, oral exposure to inorganic arsenic causes dysfunctions of spermatogenesis, reductions of testosterone and gonadotrophins, and disruptions of steroidogenesis. However, the reproductive and developmental toxicity of arsenic is poorly understood, and the molecular mechanism of arsenic-induced reproductive toxicity remains unclear (Giraud-Billoud, Campoy-Diaz, Muñoz, & Vega, 2022). Therefore, we further investigated some of the possible mechanisms that are affected by arsenic causing reproductive toxicity (Gonzalez, et al., 2015). The crucial mechanisms of arsenic-induced reproductive toxicity may be associated with hormonal regulation and function, binding to sperm, and regulation of steroidogenesis, as well as direct effects of testicular component cells (Guidi, Martínez-López, Oliver, Sánchez-Vázquez, & Vera, 2023).

Arsenic-induced neurotoxicity: a mechanistic appraisal.

The neurotoxic effects of *As* is an important issue since *As* exposure is a public health concern around the World. The epidemiological reports undoubtedly show that *As* affects intellectual and cognitive function during development and in adults (Chan, et al., 2021). Moreover, while *As* cannot be considered by itself a trigger of neurodegeneration there is evidence that suggests that it can increase the susceptibility to develop neurodegenerative disorders (Chen, et al., 2022). While there are toxicological and epidemiological studies that show the neurotoxic effects of *As* the mechanisms involved are still unclear (Lee, et al., 2005). In this review, we have summarized the current state of knowledge in regards to *As* metabolism and transport, and our current understanding of the molecular mechanisms involved in its neurotoxic effects. As summarized elsewhere (Li, et al., 2016). it is clear that more research is needed to clearly identify the mechanisms involved in the alterations in neurotransmission and cognitive/behavioral functions associated with developmental *As* exposure and the integrated role of neural cell populations (neurons and glia) (Lu, et al., 2014). In particular, a detailed exploration of the changes in epigenetic signatures and metabolism is still missing (bioenergetics, redox and neurotransmitter), which has the enormous potential to be used as biomarkers of disease mechanisms (Sachan, Pathania, Mahdi, Suvirya, & Singhai, 2021). Furthermore, the effect of aggregate exposures to the neurotoxicity of *As* has been poorly studied (Ravi, et al., 2023).

Molecular features in arsenic-induced lung tumours.

Arsenic poisoning through contaminated drinking water leading to arsenic-induced lung cancer is a major public health concern; consequently, the mechanisms underlying the carcinogenic effects of arsenic in lung cancer has become an important avenue of research. Undoubtedly, the biotransformation of As^{V} into As^{III} and its methylated conjugates plays a crucial role in arsenic carcinogenicity at both genetic and epigenetic levels (Sánchez-Bermejo, et al., 2014). Genetic changes are acquired mainly through the induction of ROS during the biotransformation process, while the competition for methyl groups between As^{V} detoxification enzymes and DMT's contribute to epigenetic abnormalities. Arsenic species directly modulate several oncogenic pathways - most notably the EGFR, PI3K/AKT and the NRF2/KEAP1

pathways - and these specific pathways apossess actionable targets for therapy in lung cancer (Jeong & Ra, 2022). A greater understanding of the molecular mechanisms governing arsenic-related lung tumorigenesis may therefore yield promising translatable findings (Yao, Yang, Zhang, Shi, & Zhang, 2022). Deep characterization of arsenic-related tumors and/or cell models at both the genetic and epigenetic levels, and the comparison of arsenic-related and unrelated SqCC tumors may provide such insights. On the other hand, mechanisms associated with anti-tumoral effects of As2O3 in the treatment of APL (not discussed in this review) should also be considered in order to increase the understanding of the molecular effects of arsenic in the human body. In conclusion, arsenic can induce specific alterations affecting pathways that drive malignant transformation in lung cells (Li, et al., 2016). Current evidence suggests that arsenic-induced lung tumors represent a unique class of lung cancer, based on histology and underlying molecular characteristics (Yang, et al., 2016).

Further characterization of the mechanisms by which arsenic affects its targets will certainly give support to preventing and/or reducing the effects of arsenic toxicity, especially among those populations chronically exposed to arsenic (Wang, Zhao, Mu, Guo, & Xing, 2021).

Arsenic-Induced Hepatic Toxicity

Arsenic is widely distributed in the environment due to its natural existence and anthropogenic activities (Valente, et al., 2022). Due to the presence of high levels of inorganic arsenic in ground water in many parts of the world, human health related disorders are of major concern (Sánchez-Bermejo, et al., 2014). High levels of arsenic has been reported in three districts Ballia, Varansi and Gazipur of Uttar Pradesh in the upper and middle Ganga plain, India (Singh, Mills, Asadi, & Testro, 2018).The soluble salts of arsenic including arsenate or arsenite are well absorbed (80 %) through the gastrointestinal tract and cause health effects in individuals. Further, individuals suffers from arsenicosis have high risk to develop other health related disorders including cardiovascular, hepatic, renal, gastrointestinal, neurological and reproductive problems and malignancies (Li, et al., 2021). Due to the accumulative properties of arsenic, deposition of high concentrations of arsenic in the liver, kidney, lungs, hair and nails have been well reported as a result of chronic exposure (Lee, et al., 2005)The trivalent form of arsenic is considered to be more toxic as compared to pentavalent form due to its ability to bind with the sulfhydryl groups of proteins and disrupt the enzyme activity (Shi, et al., 2023). In view of increasing risk of chronic arsenic toxicity, the World Health Organization has lowered the permissible limit of arsenic in drinking water from 50 lg/l to 10 lg/l [7]. The metabolic function of the liver is primarily responsible for detoxification of toxins and carcinogens. Druginduced liver injury may manifest as acute hepatitis, cholestasis, and further develop as liver cirrhosis. Reactive oxygen species (ROS) generated by metabolic intermediates of xenobiotics via induction of CYP450 families as well as activated inflammatory cells through NADPH oxidases promote the accumulation of lipid derived oxidation products that cause liver injury, resulting in cell necrosis [8]. Heavy metals have been found to be associated with various effects on blood biochemistry, enzymes and transport protein's activity [9, 10]. The over production of ROS may overwhelm the antioxidant defense mechanism and cause oxidative damage to cellular ingredients such as lipids, proteins and DNA; this in turn can impair cellular structure and function [11]. Recent research the acute and chronic toxicity of arsenic, not much is known about the sub chronic toxicity of arsenic on various parameters of blood and liver damage. Present study has therefore been carried out to investigate the hepato protective properties of amla in arsenic induced liver damage and oxidative stress in mice (Hull, et al., 2021).

Immunological profile of arsenic toxicity in carcinogenesis.

Arsenic contamination of drinking water sources is a major problem worldwide. Clinical implications of the prevalence of arsenic groundwater contamination are evidenced by an impact on the incidence of cancer, even at low exposure levels (Manna, Sinha, & Sil, 2007). This evidence suggests that the current guideline for maximum exposure to arsenic may still present a hazard to exposed populations (Mazumder, et al., 1992). Limiting the effects of arsenic exposure on at-risk populations may require the implementation of strategies to manage groundwater concentrations, such as nanofiltration, adsorption and bioremediation (Jeong & Ra, 2022). We have discussed a spectrum of molecular aberrations induced by arsenic. Arsenic exposure is closely associated with DNA damage through the production of ROS, which may provide a distinct molecular signature (Maiti, Banerjee, & Kanwar, 2022).

This type of oxidative damage can induce chromosomal instability including copy number alterations that lead to the amplification or deletion of certain loci, which has implications in carcinogenesis when an oncogene or tumour suppressor gene is involved (Nurchi, et al., 2020). Arsenic exposure can also induce epigenetic changes, including global hypomethylation by the depletion of the global methyl pool, leading to aberrant gene expression, as well as alterations in promoter CpG island methylation status. Furthermore, arsenic exposure is associated with changes in both coding and non-coding gene expression, which not only affects critical-protein activity in cells, but also the regulation of coding-genes, through disruptions in miRNA and possibly other non-coding gene levels. Interestingly, the regulatory functions of piRNAs overlap with known mechanisms of arsenic toxicity and chemotherapeutic effects, leading to the assumption

that piRNAs might play important roles in these mechanisms. However, our current understanding of the precise mechanism of arsenic-induced carcinogenesis is still far from comprehensive, and further work may look to characterize novel biological players involved (Mukhi, Rukmini, Ajay Manjrekar, Iyyaswami, & Sindhu, 2022).

Clinical Features

Most cases of acute arsenic poisoning occur from accidental ingestion of insecticides or pesticides and less commonly from attempted suicide. Small amounts (<5 mg) result in vomiting and diarrhoea but resolve in 12 hours and treatment is reported not to be necessary (Jakovljević, et al., 2023) The lethal dose of arsenic in acute poisoning ranges from 100 mg to 300 mg.45 The Risk Assessment Information System database states "The acute lethal dose of inorganic arsenic to humans has been estimated to be about 0.6 mg/kg/day".The clinical features initially invariably relate to the gastrointestinal system and are nausea, vomiting, colicky abdominal pain, and profuse watery diarrhoea. The abdominal pain may be severe and mimic an acute abdomen (Lee, et al., 2005). Excessive salivation occurs50 and may be the presenting complaint in the absence of other gastrointestinal symptoms.51 Other clinical features are acute psychosis, a diffuse skin rash, toxic cardiomyopathy,47 52 and seizures.50 Diarrhoea attributed to increased permeability of the blood vessels is a dominant feature. The voluminous watery stools are described as "choleroid diarrhoea". In cholera the stools are described as "rice water", but in acute arsenic poisoning, because of blood in the gastrointestinal tract, the term "bloody rice water" diarrhoea is used (Li, et al., 2021). The cause of death is massive fluid loss due to secretion from the gastrointestinal tract eventuating in severe dehydration, reduced circulating blood volume, and consequent circulatory collapse. On postmortem examination oesophagitis, gastritis, and hepatic steatosis are reported.47 Haematological abnormalities reported are haemaglobinuria, intravascular coagulation, bone marrow depression, severe pancytopenia, and normocytic normochromic anaemia and basophilic stippling (Rodriguez, et al., 2016). Renal failure was reported in four of eight sailors exposed to arsine (Salgado, et al., 2023). Respiratory failure and pulmonary oedema are common features of acute poisoning. The most frequent neurological manifestation is peripheral neuropathy that may last for as long as two years. The peripheral neuropathy may lead to rapid, severe ascending weakness, similar to Guillain-Barré syndrome, requiring mechanical ventilation (Ravi, et al., 2023). Encephalopathy is a common manifestation and the possibility of arsenic toxicity must be considered if the aetiology of encephalopathy is uncertain. Encephalopathy has occurred after intravenous administration of arsphenamines (Singh, Dwivedi, Yadav, Sharma, & Khattri, 2014). The basis for the encephalopathy is thought to be due to haemorrhage.58 Metabolic changes with acute arsenic poisoning are reported. Acidosis has occurred in a single patient47 and hypoglycaemia and hypocalcaemia in cattle. In acute poisoning the best indicator of recent ingestion (1–2 days) is urinary arsenic concentration (Song, et al., 2014)

Discussion and Conclusions

Arsenic toxicity remains a critical public health concern due to its widespread presence in the environment and its profound impact on human health. This study has elucidated several key aspects of arsenic toxicity, including its sources, mechanisms of action, and the resultant health effects. The primary sources of arsenic exposure include contaminated drinking water, industrial processes, and agricultural practices (Li, et al., 2016). Chronic exposure to arsenic, particularly in regions with high levels of arsenic in groundwater, poses significant health risks. Arsenic exerts its toxic effects through several mechanisms, including the generation of reactive oxygen species (ROS), interference with cellular respiration, and disruption of signal transduction pathways (Lu, et al., 2014). These mechanisms lead to oxidative stress, DNA damage, and apoptosis, contributing to the development of various diseases. Prolonged exposure to arsenic is associated with an increased risk of several adverse health outcomes, including cancers (skin, lung, bladder), cardiovascular diseases, neurotoxicity, and diabetes. The findings underscore the importance of continuous monitoring and regulation of arsenic levels in the environment. This research highlights the need for effective interventions to mitigate arsenic exposure. Potential measures include the development of advanced water purification systems, implementation of stricter regulatory standards, and public education campaigns to raise awareness about arsenic toxicity and its prevention. Further studies are necessary to fully understand the long-term effects of low-level arsenic exposure and to identify susceptible populations. Research should also focus on developing novel therapeutic strategies to counteract arsenic-induced damage and exploring the genetic and epigenetic factors that influence individual susceptibility to arsenic toxicity (Goodale, et al., 2019). A[rsenic toxicity requires a multifaceted approach that combines scientific research, public health initiatives, and policy interventions. By advancing our understanding of arsenic's toxic effects and implementing effective prevention and mitigation strategies, we can significantly reduce the burden of arsenic-related diseases and improve public health outcomes globally

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