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The mechanistic approach of arsenic mediated neurotoxicity-a concise review

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Abstract
Arsenic is a naturally occurring element that may be found in both inorganic and organic forms throughout the environment. It is believed that inorganic arsenic are particularly detrimental to human health. Human exposure to inorganic arsenic is mostly caused by polluted drinking water, despite the fact that food and water are the main sources of inorganic arsenic exposure for people. In Bangladesh, West Bengal, China, Taiwan, Thailand, Ghana, Argentina, Chile, Mexico, Hungary, Canada, the United Kingdom, and some parts of the United States, widespread arsenic pollution of groundwater has been documented. However, if arsenic enters the neonate, it may pass the blood-brain barrier (BBB) and have an immediate impact on the central nervous system (CNS). Tight connections between capillary endothelial cells in the brain and epithelial cells in the choroid plexus make up the BBB, a structure designed to keep proteins and other tiny molecules from interacting with the cerebrospinal fluid. Additionally, as succinyl coA is present in complex II of the electron transport chain, arsenic prevents the synthesis of succinyl CoA, hinders the generation of ATP in cells, and completely shuts off the energy supply. Neurotransmitters, which are in charge of facilitating cell-to-cell communication in the brain, are impacted by arsenic-induced neurotoxicity. Arsenic serves to induce dopamine and serotonin levels while inversely regulating norepinephrine levels. The arsenic impact alters the amounts of Ɣ-aminobutyric acid (GABA), glutamate, and other biogenic amines. As a result of the arsenic threat, the levels of various inflammatory indicators, including IL-6, TNF-α, IL-1, and IFN-Ɣ, as well as mitochondrial apoptotic markers like bax, bak, bid, and bim change in neural tissues. The goal of this review paper is to provide an in-depth investigation of the mechanistic approach to arsenic-mediated neurotoxicity.

Keywords: Arsenic, blood-brain-barrier, neurotransmitters, inflammation, apoptosis

Introduction
The periodic table displays arsenic, a metalloid, at position 33. It is a widely dispersed element of the earth's crust. Both organic and inorganic forms of arsenic are known to exist. In its inorganic form, arsenic is poisonous, even though in its organic state it is thought to be non-toxic. Compared to inorganic forms, which are highly reactive and set off a chain reaction in the body, organic forms are less toxic and less easily absorbed into the bloodstream (Carlin *et al*. 2016) [2]. Oxidative stress is brought on by an excess of arsenic in subcellular compartments. Exposure to arsenic, the main cause of oxidative stress, generates reactive oxygen species (ROS), which can harm amino acids, nucleic acids, proteins, and lipids in membranes. (Dat *et al*. 2000) [4]. This metalloid is also referred to as a xenobiotic because it is harmful to humans and lacks any physiological function. Food and drink are the most common ways that people are exposed to this metalloid. (Concha *et al*. 1998) [3]. Drinking water across much of the world has arsenic concentrations above advised exposure limits. According to a preliminary assessment by the World Health Organization (WHO), drinking water contaminated with arsenic affects at least 140 million people across 50 countries. Many countries, including China, India, Mexico, Bangladesh, Argentina, Chile, and the United States of America, have significant levels of naturally occurring arsenic in their groundwater. Arsenic poisoning has been linked to skin lesions, many cancers, and problems with the heart, lungs, and digestive system, among other disorders. This metalloid may result in encephalopathy, peripheral neuropathies, and neurological behavioral disorders. It has been linked to neuro-degeneration. Even though research in the fields of toxicology and epidemiology has demonstrated the harmful effects of arsenic on the brain, this field is still developing.

People who are exposed to arsenic have increased dramatically as a result of heavy metal poisoning in some aquifers and the growing number of people who rely on aquifers for their drinking water. The extraction of rare metals from deep strata has increased human exposure to heavy metals. When volcanic eruptions are combined with exposure to heavy metals, there is a significant chance that an individual will be exposed to these metals at levels that are often far higher than acceptable limits for human health. In human arsenic metabolism, trivalent arsenic (As3+) is oxidatively methylated to pentavalent arsenic (As5+). Trivalent arsenic's toxicity and carcinogenic qualities rise when it is produced through metabolism or another process. This means that different metabolic enzymes may emerge as a result of exposure to arsenic and its various metabolic phases. (Nagaraja and Desiraju 1994) [12]. The specific protein poisoning caused by arsenic is caused by its binding to reduced thiol in certain proteins. Additionally, these interactions lead to various metabolic disorders in some tissues. But treatment strategies for arsenic toxicity require these specific interactions (Dilda and Hogg 2007) [5]. However, once ingested, arsenic can cross the blood-brain barrier (BBB) and directly affect the central nervous system (CNS) in neonates. A protein called the blood-brain barrier (BBB) develops between the choroid plexus's epithelial cells and the brain's capillary endothelial cells. Although studies have shown that the BBB is ineffective at preventing the transport of arsenic to the central nervous system (CNS), it serves the purpose of preventing proteins and other small molecules from mingling with the CSF (Rai *et al*. 2010) [14]. Low-level, prolonged exposure to arsenic can harm the skin's development, the immune system, the reproductive system, neurological conditions, hypertension, diabetes, anaemia, and cardiovascular disease. The International Agency for Cancer Research (IRAC) states that arsenic, a known human carcinogen, can result in cancers of the kidney, liver, prostate, lung, bladder, and skin. Arsenic's toxicity has been extensively studied, but its cumulative effects on neurocognitive function have not. This study reviewed and synthesised research on the behavioural and psychological effects of long-term exposure to arsenic, particularly in infancy, from *in vitro*, animal, and epidemiological studies.

Sources of arsenic

There is a lot of arsenic in the soil, water, air, and crust of the earth. In the human body, it ranks as the twelfth most prevalent element. There are two types of compounds that contain arsenic: inorganic (iAs) and organic (iAs). Arsenite +3 (iAs iii) and arsenate +5 (iAsv) are the two oxidation states of iAs. iAs is used in the electronics industry, as an alloying agent, as a wood preservative, in agriculture, and in the treatment of leukaemia. In 50 different countries, at least 140 million people have been exposed to iAs at levels above the WHO-recommended exposure limit (10 ppb). In contaminated areas, the concentration of iAs in groundwater can exceed one billion parts per billion. (Carlin *et al*. 2016) [2].

Toxic Mechanisms

The most widely accepted theories regarding arsenic-induced neurotoxicity are the most fundamental ones, though numerous other theories have been put forth, the majority of which are derived from studies done on animals. By deactivating various enzymes, especially those involved in DNA synthesis, repair, and the cell energy system, metabolites inflict damage. Arsenic's neurotoxicity is caused by oxidative stress, reduced acetylcholinesterase activity, and thiamine deficiency (Ratnaike 2003) [15].

Brain Weight and Effects in Body

Several experimental studies involving individuals exposed to arsenic have demonstrated arsenic dependence in the body and brain weight losses (Luo *et al*. 2009) [11]. It is unknown why there have been decreases in body weight and brain size. Cross-fostering exposed pups to a mother who has not been exposed to arsenic was shown to reverse this tendency, despite one study finding that the weight loss of arsenic-exposed mice was not associated with reduced food intake (Garza-Lombó *et al*. 2018) [6]. The finding that mice exposed to arsenic had lower levels of triglycerides, even at low concentrations, in their breast milk is quite interesting (Kozul-Horvath *et al*. 2012) [10].

Clinical Neurological Symptoms

Arsenic in drinking water at levels as low as 10–50 parts per billion can cause peripheral neuropathy if exposed to it for an extended period of time. Motor fibres are less affected than sensory fibres by the ensuing damage. Peripheral nerve axonal degeneration was shown in sural nerve biopsies as a decrease in both tiny myelinated and unmyelinated fibres. Exposure of children to 50 parts per billion or higher of arsenic can cause CNS impairments, even though high concentrations of the metal are only known to cause problems for adults. While CNS impairments are less likely to heal, arsenic-induced peripheral neuropathy may eventually heal. Organ damage can result from both acute and chronic illnesses as well as from arsenic exposure at different levels (Singh *et al*. 2015) [16].

Effects on behavioral and neurocognitive elements

Epidemiological research has demonstrated that early exposure to arsenic causes deficits in verbal IQ, full-scale IQ, and memory; however, different studies have found different effects of the exposure on different cognitive domains. The most impacted functional domains in a long-term cohort study of Mexican children aged 11 to 13 in Oklahoma were memory, problem-solving, and attention span (Siripitayakunkit *et al*. 1999) [17]. On the other hand, full-scale IQ scores of children aged 6 to 10 who drink water tainted with arsenic have been found to be lower (Calderón *et al*. 2001) [1]. Similar research showed that Mexican children aged 12 to 8 had lower cognitive abilities after being exposed to arsenic.

Factors to Consider

The amount of damage is dependent on the target organ, exposure route, concentration, time, and total quantity. Patient characteristics like age, weight, and overall health have the potential to either worsen or lessen the negative effects of arsenic exposure (Kapaj *et al*. 2006) [9]. The blood-brain barrier's ability to shield the central nervous system is compromised by high concentration exposure, but damage can still be difficult to inflict even after prolonged exposure to low concentrations. Peripheral nerves are one organ among the injured that can be repaired. On the other hand, it is harder to regenerate the central nervous system. It is also necessary to take into account the effects of heavy metals other than arsenic. Lead, manganese, cadmium, chromium,

uranium, and manganese are some other hazardous heavy metals (Vibol, Hashim, and Sarmani 2015) [18].

Molecular mechanism

Reactive oxygen species (ROS) in cells are mostly produced by electron leaks in the mitochondrial electron transport chain. Antioxidant systems can sustain steady-state levels of mitochondrial ROS in a healthy environment, but older or less functional mitochondria produce more ROS per cell (Halliwell and Cross 1994) [7]. Reactive nitrogen species (RNS) can also originate from nicotinamide adenine phosphates (NAP) (Ng *et al*. 1999).

The electron leak from the mitochondrial electron transport chain is the main source of reactive oxygen species (ROS) in cells. Antioxidant systems can maintain steady-state levels of mitochondrial ROS in a healthy environment, but aged or dysfunctional mitochondria generate more ROS per cell. Reactive nitrogen species (RNS) can also originate from NAP.

Oxidative stress can lead to protein deterioration, tissue damage, and even cell death. Cells have both non-enzymatic and enzymatic antioxidant capabilities to lessen the possibility of oxidative stress. The elevated oxidative stress and low antioxidant defence content are made worse by the high rate of arsenic ingestion. Because the brain contains a lot of lipids and fatty acids, it is especially vulnerable to oxidative damage. It has been noted that in animal models, glial cell, and neuronal cultures exposed to iAS, oxidative stress increases in certain brain regions. The primary source of ROS generated by iAS is mitochondria.

In the rat brain, prolonged exposure to iAS damages mitochondrial complexes I, II, and IV, increasing ROS generation, protein carbonylation, and lipid peroxidation in addition to increasing mitochondrial oxidative stress. Moreover, exposure to iAS lowers levels of mitochondrial transcription factor A (tfam) and the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (pgc-1), which inhibits mitochondrial biogenesis. Moreover, iAS release peroxyl and dimethylarsine (dmah) radicals, which aid in the oxidation of waste products and encourage lipid peroxidation. The metabolites DMAIII and nascent, which can also generate radicals, are found in MMA III and seem to be more potent and toxicants. Furthermore, iAs activates the antioxidant transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2) via a non-canonical pathway. As a result, the Nrf2 suppressor kelch-like ECH-associated protein 1 (Keap1) is sequestered by the ubiquitin-binding protein/adaptor autophagic receptor sequestosome-1, also known as p62 (p62/SQSTM1). Metal-activated transcription factor 1 (MTF1) regulates the transcription of metallothionein I, which reduces the toxicity of isoamyloid precursors (iAs III) (He and Ma 2009).

Conclusion

The mechanistic approach to arsenic-mediated neurotoxicity has made it feasible to comprehend the underlying molecular and cellular mechanisms through which arsenic exposure can deteriorate neurological function and cause neurotoxicity.

Several key conclusions can be drawn from the mechanistic studies

1. Oxidative stress: Oxidative stress occurs in the brain as a result of reactive oxygen species (ROS) generation and antioxidant defence systems being thrown off balance by arsenic exposure. Excessive ROS concentrations may cause neurotoxicity by harming neurons and other brain cells.
2. Inflammation: The brain's inflammatory pathways are activated by exposure to arsenic, and this leads to the release of inflammatory cytokines and the mobilisation of immune cells. There is a connection between nervous system dysfunction and damage caused by chronic inflammation.
3. Disruption of neurotransmission: Arsenic alters neuronal signalling and communication by interfering with the brain's neurotransmitter systems. Research have demonstrated that exposure to arsenic changes the ratio of neurotransmitters, which are essential for healthy brain function and include glutamate, GABA, acetylcholine, and dopamine.
4. Mitochondrial dysfunction: Brain cells' mitochondrial efficiency can be lowered by exposure to arsenic. Cell damage and energy shortages can result from malfunctioning mitochondria, which are responsible for producing energy and controlling cellular metabolism.
5. Epigenetic modifications: Exposure to arsenic modifies histone modifications and other epigenetic processes in brain cells, including DNA methylation. Because they disrupt regular cellular processes and alter gene expression patterns, these changes may be neurotoxic.

Ultimately, the mechanistic method has provided insight into the intricate and varied impacts of arsenic on the brain. Understanding these pathways is essential to developing methods to reduce arsenic-induced neurotoxicity and shield people from its harmful effects. More investigation is needed to completely understand the particular biochemical mechanisms at play and pinpoint viable treatment targets.

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