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Role of Arsenic in the Development of Neurodegenerative Diseases and Memory Impairment

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ABSTRACT
Arsenic is a naturally occurring toxic metalloid present worldwide. Arsenic in its inorganic form is the most hazardous and is responsible for causing different diseases like cancer, skin disease, and many neurological disorders in humans which can be demonstrated by several experimental models. Contamination of the drinking water by metal toxins has been a major problem worldwide in which arsenic is one of the major. For the past few decades, there has been increased concern about the health risk due to arsenic and lots of epidemiological studies have been done suggesting an arsenic role in developing neurotoxicity. They also suggest the neurological damage caused by arsenic in children. In this current work, we are trying to explore the different mechanisms involved in arsenic neuropathy and the effects of arsenic-contaminated water on the spatial memory, frontal cortex, and hippocampal ultra-structures, and many other different regions of the brain disrupted by arsenic. Additionally, this review will guide the viewer to determine their future directions for the remission of developing arsenic neuropathy.
Keywords: Arsenic · Oxidative stress · Neurotoxicity · Frontal cortex · Hippocampus

I. INTRODUCTION

Arsenic, a metalloid occurring worldwide found in the environment from various natural and anthropogenic sources [1] at an average concentration of 1.8 ppm [2]. Arsenic is first of all the toxicants posing a significant known or direct and indirect potential threat to humans [3]. It is a co-carcinogen and in lower concentration also known to increase cognitive impairment [4]. It exists both in plants and animals, naturally, it occurs in its organic form which is less toxic [5]. Most exposure to humans occurs from the consumption of water in the form of inorganic arsenic (iAs) i.e., arsenite (As [III]) and arsenate (As[V]), which is abundantly available in water and the most toxic form of arsenic [6]. The presence of arsenic in the groundwater is a major health problem globally, due to its various ailing effects [7, 8, 9]. Therefore, the identification of new regions with arsenic contamination in Asia has aroused great concern, as the large population is at risk of exposure [10, 11, 12]. Around 140 million people all over the world are exposed to arsenic-contaminated water [13]. Besides, its anthropogenic uses as an alloy, different semiconductor, transistors, metal adhesives and pigment factories [14, 15], mining, fossil fuels burning, natural weathering, and volcano eruptions also introduce arsenic to the environment [16] and therefore the presence of arsenic in the environment enhances the risk of exposure to humans which arises a need to explore its possible clinical effects and its various other links and other environmental sources.

Consumption of arsenic-containing water above 50g/l during pregnancy enhances the risk of fetal loss [17, 18]. It is also found to enhance immune suppression and incident to various infectious diseases in both mother and child [18, 19]. Peripheral neuropathies are quite common in arsenic-exposed individuals [20]. Neurological deficits in children and adults have been reported as the consequences of environmental and occupational exposure to arsenic [21, 22]. Arsenic exposure (>10 µg/L), the permissible water arsenic concentration considered safe by the WHO which can lead to declines in its different ailing effects.

1.1 Arsenic metabolism

The most common valence state of inorganic arsenic (AsV) is its arsenate form whereas arsenite is potentially found in groundwater in the form of sodium arsenite (Na3AsO3) due to the interaction with aquifer minerals and physiochemical conditions favoring its release.

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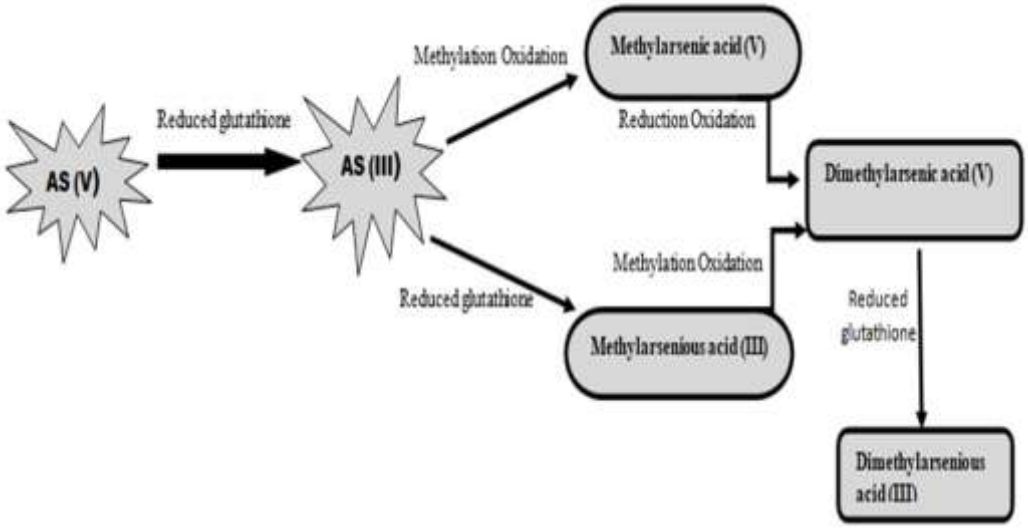

Figure 1. Proposed metabolic pathway of conversion of inorganic arsenic to organic arsenic

The proposed metabolic pathway of Arsenic is shown in Figure1 [23, 24]. Glutathione conjugation and Oxidative methylation are known to be the primary pathways of Arsenic metabolism [25]. Inorganic Arsenic (V) is reduced to Arsenic (III). Inorganic Arsenic (III) is methylated to methyl arsenic acid (V) and methylarsenious acid (III) which is reduced and methylated to Dimethylarsenic acid respectively. Dimethylarsenic acid formed by oxidation and reduction of As(III) and As(v) forms Dimethylarsenious acid (III).

Higher occurrence of skin lesions, cancer, neurological disorders, impairment of psychological and mental health, cardiovascular disorders, and infertility problems are reported in countries like Colombia, Argentina, Japan, Mexico, Bangladesh, and Taiwan where consumption of groundwater is high [26, 27, 28, 29, 30, 31]. Rising evidence of animal and human studies indicates that arsenic has toxic effects on the central and peripheral nervous systems [32, 33]. Presently, the concern over the increasing neurotoxicity of arsenic has been raised. [34, 35]. Development of physiological abnormalities including decreased growth rate, neural defects, malformation [36, 37, 38], and other behavioral changes as arsenic can directly reach the brain as it can cross the blood-brain barrier and placental barrier freely [39, 40, 41, 42, 43]. Several epidemiological studies have demonstrated that arsenic exposure leads to poor, impaired cognitive, and neuropsychological functioning suggesting its role in brain dysfunctions [44- 47]. Infertility, Neural tube defects, neonatal deaths, spontaneous abortion were reported in pregnant women consuming water contaminated with high arsenic content [36, 48, 49, 50]. Arsenic levels are also found in the breast milk of Bangladeshi women which can adversely affect the infant's health [51]. This finding suggests arsenic may cause impaired fetal growth and can also affect infant health adversely. The underlying mechanism of arsenic-induced neurotoxicity is not clearly known, though several mechanisms have been proposed from various animal and human studies. Arsenic metabolites cause the inactivation of the enzymes involved in the cellular pathways as well as the formation and repair of DNA is the target of the metabolites formed [52], oxidative stress, thiamine deficiency, and decreased acetylcholinesterase activity are some of the mechanisms involved in the arsenic-induced neurotoxicity.

II. EXPERIMENTAL AND EPIDEMIOLOGICAL EVIDENCES OF ARSENIC INDUCED NEUROTOXICITY

2.1 Experimental evidences

Long-term arsenic exposure to humans has been associated with impaired intellectual function in children and adults. Various In vitro and In vivo studies have been conducted as epidemiological evidence of As-induced impaired cognition.

Several studies have been conducted that in mice providing evidence for the toxic effects of arsenic on the entire brain [53, 54] and its discrete regions [55, 56]. Studies also support the evidence that assures the effect of acute and chronic exposure of arsenic develops deficits in spatial

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working memory, short term, and long term memory impairment, and damaging different neurological regions responsible for memory impairment. The study indicates the effects of arsenic-containing drinking water on different regions of brain hippocampal ultra-structures, spatial memory, and N-methyl-d-aspartate receptor expression in SD rats [57]. Some studies also indicate that Postnatal exposure to low-concentration of arsenic induces autism-like behavior and affects the frontal cortex in the brain of rats [58].

A. Anwar-Mohamed et. al. investigated and found that acute arsenite (As(III)) exposure can lead to a decrease in cytosolic phospholipase A2 (cPLA2) with a subsequent decrease in brain catalytic activity of mice. It also alters CYP epoxygenases and CYP -hydroxylases, increases expression of cyclooxygenase-2 (COX-2), 5-lipoxygenase (5-LOX), and 15-LOX mRNA while decreasing prostaglandins F2 (PGF2) and PGJ2. This altered state of the different enzymes affects brain development and neurochemistry [59].

2.2Epidemiological evidences

Many Epidemiological investigations found that low level and chronic exposure to arsenic can be broadly related to serious toxic effects on intellectual functions and early exposure to arsenic can cause full memory deficit by interfering with different brain functions.

In children, adverse neurobehavioral outcomes have been associated with acute and chronic arsenic exposure. A meta-analysis in arsenic-exposed children indicated intelligence deficits; considering 4 cross-sectional studies in China on arsenic exposure and IQ effects, this analysis found that the overall mean IQ score of children who lived in arsenic-exposed areas was more than 6 points lower than the mean score in unexposed children.36 Indeed, a growing number of studies are confirming intellectual deficits associated with arsenic exposure in children as young as 5 years of age [60-68].

A cross-sectional study conducted on older age relates to chronic arsenic exposure in adolescents. The study found that adolescent exposure to the arsenic-contaminated water in early life performed poorly in 3 of 4 neurological subtests when compared with the unexposed control groups, indicating an alteration in neurobehavioral development in later life might be due to the exposure during childhood exposure [69].

A study on the geriatric population exposed with long term low-level arsenic exposure (average 6.33 mg/L), estimated by the geographic information system (GIS)-based models was significantly associated with impaired executive functioning, slower processing speed, diminished visuospatial skills, poorer global cognition, slower processing speed, reduced language and reduced short term memory [70].

A study on 6-8year old school children in Mexico suggested that arsenic toxicity can lead to different neurological alterations including memory, problem-solving ability, and attention span [63]. A longitudinal cohort study was conducted on children in Bangladesh suggested that there was a reduction in verbal IQ and full-scale IQ associated with arsenic exposure [71].

Urinary arsenic has been inversely associated with full and verbal IQ in 6-8yr old children in Mexico [60]. Finally, arsenic in drinking water has been associated with decreased full IQ scores in children 6- to 10 years of age [62]. In a meta-analysis, including 15 studies evaluating the effect of arsenic on neurodevelopment, in which 13 articles showed a significant effect on neurodevelopment in children of age between 5-15years. In separate meta-analysis assessing arsenic exposure in urine (n ¼ 6) and those that studying drinking water (n ¼ 4), observed that combined effect suggests that a 50% increase in arsenic level in urine would cause a reduced IQ level by 0.39 points, whereas 50% increase in water causes a significant reduction in full-scale IQ by 0.65 points [72]. The timing of exposure to arsenic seems to affect the outcome.

In a study that directly quantified water arsenic exposure, above-median early prenatal maternal arsenic exposure in drinking water was found to be associated with a decreased verbal IQ in children, and late gestational maternal arsenic exposure was associated with a decreased performance IQ in children at 5 years of age [51].

III. MECHANISMS INVOLVEMENT IN NEURODEGENERATION AND MEMORY IMPAIRMENT OF ARSENIC

3.1Oxidative stress and intracellular pathways activation : In vivo studies have demonstrated that high iAs concentration (i.e., 4 mg/L), leads to neurological damage-inducing oxidative stress and decreased amount of superoxide dismutase, 8-nitroguanine and peroxiredoxin 2 and expression in the neurological tissue of exposed rodents [73],

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glutathione after exposure to 50mg/L [74] and increased expression of superoxide anion, singlet oxygen, hydrogen peroxide, hydroxyl radical, and peroxyl radicals in different cells [75, 76, 77]. The main signal transduction pathways altered by ROS are: (i) the tyrosine phosphorylation system; (ii) transcription factor families, including the activating protein-1 (AP-1) and nuclear factor-kB (NF-kb); and (iii) mitogen-activated protein kinases (MAPKs) like ERK1/2 [78].

3.2 Pro-inflammatory mediators: Fry et al., found that iAs in concentrations higher than 10mg/L are known to cause overexpression of NF-Kb and IL-1B in the umbilical cord of newborns which causes the overproduction of the inflammatory mediators in urothelial cells [79]. An increase in different inflammatory markers – such as TNF-a, IL-1a, IL-8, and IL6 are also get increased in human and rodents peripheral blood [80, 81, 82].

3.3 Neurotransmitter synthesis and regulation: Arsenic has been found to produce decreased levels of different neurotransmitters, such as norepinephrine (NE), epinephrine (EPN), Dopamine (DA), serotonin (5-HT), and acetylcholine in the different regions of rats brain exposed to sodium arsenite(20mg/L p.o) [83], whereas glutamate expression also gets reduced in the brain when rats are being exposed to sodium arsenite(70mg/L) [84]. As arsenic activates multiple pro-inflammatory signaling pathways which in turn activates indoleamine 2,3-dioxygenase or IDO leading to a reduction in serotonin availability increasing KP's (kynurenine pathway) intermediates which negatively modulates the release of different neurotransmitters including Ach, dopamine, GABA, and glutamate [85]. Therefore, KP impairment may impose a negative impact on the brain and can lead to many neurological and neurodegenerative diseases and also cognitive deficits [86].

3.4 Mitochondrial Dysfunction: There are several studies that support the damage in the mitochondrial region of the brain region by arsenic at different concentrations in rats that are 2 mg /kg BW for 10 weeks [87], 2.5 mg /Kg BW for 4weeks [88], 20 mg/Kg BW for 28 days [89], 10 mg/ kg BW for 16 weeks [90] and 100 ppm for GD 6 to PND 21, 28 and 3 months [91] and found that there is an increase in ROS, lipid peroxidation in the frontal cortex and hippocampus region of the brain and reduced content of GSH, MnSOD and CAT, GPx and GST in rats and pups respectively in the mitochondria of the cerebral cortex, cerebellum and hippocampus regions of the brain.

3.5 Autophagy impairment: Studies show that autophagy plays an important role in regulating pathophysiology [92], as there are many neurodegenerative diseases associated with impaired autophagy such as Parkinson's, Autism, Alzheimer's, and Huntington's where defective BBB plays a major role [93]. Ram Kumar Manthari et.al. found that the leaky BBB in the cerebral cortex and hippocampus may facilitate the transfer of As and induces autophagy by inhibiting PI3K/Akt/mTOR signaling pathway that causes the rats at PND21 more vulnerable to As-induced neurotoxicity [94]. Qi etal., found that sodium arsenite (0.25mM) inhibited autophagy in human bronchial epithelial cells [95].

3.6 Ultra-structural changes in Brain and accumulation of proteins: Ultrastructural changes in neurons and endothelial cells in the hippocampus, found when the rats are being chronically exposed to sodium arsenite. The expressions of NMDAR subunits in the hippocampus were decreased and there was a reduction in NR2A mRNA levels in the hippocampus after arsenic exposure [96]. Many In vitro and In vivo studies showed that the metabolites induce tau protein hyperphosphorylation, which is acytoskel biomarker for different neurological disorders [97,98]. As arsenic is known to cause oxidative stress which can lead to lead to the activation of kinases, including GSK-3and p38, which phosphorylates tau proteins leading to disassembling of microtubules and is responsible for the formation of tau oligomers [99]. Sodium arsenite has also been reported to decrease PPARg expression while increasing TNF-a and NF-kb contributing to the formation of reactive species and Ab oligomers.

3.7 Impaired expressions of proteins: Studies have shown that arsenic in its trioxide form at 0.15 mg or 1.5 mg or 15 mg doses when administered from gestational to lactational and continued to the pups till PND42 in

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drinking water causes declined mRNA expression of TJ proteins, Occludin protein, PI3K, Akt, mTOR, and p62 [94].

3.8 **Endoplasmic reticulum stress:** Endoplasmic reticulum stress: Accumulation of misfolded proteins triggers unfolded protein response (UPR). An impaired UPR, leading to apoptosis. In brain protein aggregation, improper synaptic function, impair signal transduction contributes to the development of several neurodegenerative diseases. AD, PD, HD, and ALS besides their protein folding and aggregation are also characterized by increased ER stress and UPR activation [100]. The ability of sodium arsenite and metabolites in rat liver cells was also demonstrated [101]. Bolt et al. established that In vitro 1.5mM sodium arsenite activates the ER stress in three-pathways: protein kinase-like endoplasmic reticulum kinase (PERK), inositol requiring enzyme (IRE-1) in human B lymphoblastoid cell line, and activating transcription factor 6 (ATF6) [102]. Chiu et al. found that programmed cell death was induced on exposure to arsenic trioxide through the stimulation of ER stress. It was also found to suppresses the ubiquitin-proteasome system and Akt/mTOR signaling pathways in human sarcoma cells [102, 103].

Studies indicate that arsenic-induced ER stress is associated with both ROS-dependent and ROS-independent pathways, and includes phosphorylation of eIF2a (the translation initiation factor) and over-expression of chaperones [101,104,105]. Also, involve activation of JNK/Erk pathway has been found to be involved in ER-related cellular apoptosis [104].

Some of the In vitro studies account that iAs also disrupt mitochondrial membrane potential, increasing intracellular calcium level and increased cytochrome C level and impair Akt expression and activation leading to arise different mechanisms for the development of arsenic toxicity activation [106,107,104].

IV. CONCLUSION

Several experiments have been conducted in the last few decades which shows arsenic is one of the major toxinscontaminating water and it seems that it is the major cause behind many neurodegenerative diseases and cognitive impairment in adults as well as in children. On analysis, the mechanism underlying the neurotoxicity include neurotransmitter synthesis and their transmission, Protein accumulation and their impaired expressions, increased oxidative stress, production of pro-inflammatory mediators, impaired autophagy. Based on these, we can conclude that arsenic via the above-discussed mechanisms may lead to imposing neurotoxic effects on different regions of the brain that may lead to neurodegeneration and cognitive impairment.

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