Review Article

SYSTEMIC HEALTH EFFECTS ASSOCIATED WITH SODIUM ARSENITE EXPOSURE: A REAPPRAISAL

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Abstract: *Sodium Arsenite is a potent toxic mutagenic and xenobiotic metalloid that has been increasing in the environment as a significant pollutant. Contamination of drinking water by chemicals containing arsenic is still a serious public health issue. Prolonged exposure to sodium arsenite can lead to several health problems, including irregularities in the cardiovascular system, diabetes, nephrotoxicity, neurotoxicity, hearing loss, haematological diseases, hepatotoxicity, and infertility. Sodium arsenite is a multi-site carcinogen that can cause cancers in the skin, kidney, colon, lung, and uterus, among other tissues. Numerous research investigations have demonstrated that the toxicity of arsenic is contingent upon various elements such as exposure level, frequency, duration, biological species, age, gender, genetic susceptibilities, and nutritional status. Arsenic exposure has been linked to several consequences, such as apoptosis, cell growth, and alteration of signal transduction pathways. This implies that Arsenite might have incredibly wide impacts rather than targeted effects. Furthermore, several epidemiological studies have documented the exposure sources and the worldwide impacts of arsenic, but the exact method by which it affects various systems, including cancer, is still unknown. More research is needed to give a more precise knowledge of the underlying mechanism.*

Keywords: Exposure, Health, Mechanism, Sodium Arsenite, System

Introduction

Arsenic is a naturally occurring element in the environment in both organic and inorganic forms. It is challenging to find arsenic in its pure form; instead, it can be found as a salt of sodium, potassium, or calcium or as a chemically unstable sulphide or oxide in both trivalent and pentavalent oxidation states. Arsenic exposure in humans is a serious public health risk. Arsenic is a metalloid widely found in soil, air, and water (Järup, 2003), making it a worldwide environmental contaminant of concern. When arsenic compounds are found in more significant quantities in the environment due to manmade or natural sources, it poses a risk to occupational and environmental health. Arsenic and its derivatives are constantly being released into the environment due to various dynamic processes caused by natural and human activity (Rodrıguez et al., 2002; Tchounwou et al., 2003). Because of the weathering of rocks, combustion of fossil fuels, smelting of ores, and other processes, arsenic levels in the environment are constantly rising. Another factor that has helped disseminate arsenic throughout the ecosystem is coal burning (Rodríguez et al., 2002). Over 80% of compounds containing arsenic are utilized in the production of agricultural products, including but not limited to pesticides, herbicides, fungicides, algaecides, sheep dips, wood preservatives, dyes, and medications for the treatment of tapeworms in sheep and cattle (Tchounwou et al., 2003). Human exposure to arsenic has also been documented by eating contaminated food, especially seafood, and using traditional remedies (Hughes et al., 2011; Mandal and Suzuki, 2002).

Arsenic exposure is a persistent problem for a vast number of people worldwide. Exposure to sodium arsenite can happen through oral consumption, inhalation, skin contact, and, to a lesser extent, parenteral administration. The primary source of exposure for most people is their diet, with an average daily intake of roughly 50 μg of food. Soil, water, and air intake are typically far less. However, in regions where arsenic poisoning is present, exposure to these media may become substantial. Workers in industries such as wineries, ceramics, glass-making, smelting, pharmaceuticals, the production and use of pesticides, the preservation of wood, and semiconductor manufacturing may be exposed to significantly higher levels of arsenic (Armstrong et al., 1984). Hazardous waste sites (HWS) represent an additional potential pathway for arsenic exposure in humans. There are several ways to be exposed at these locations, such as breathing in airborne dust, consuming tainted water or soil, or coming into contact with it through the food chain.

After absorption, arsenic is retained in the heart, lungs, liver, and kidney. Muscles and neural tissues have lower levels of arsenic. Arsenic buildup in these tissues is linked to several

illnesses, such as diabetes, cancer, hepatotoxicity, neurotoxicity, and heart problems. Arsenic toxicity mostly depends on its metabolism, which is carried out by blocking around 200 enzymes involved in DNA synthesis and repair, cellular energy routes, and other processes. When arsenite and MA(III) are consumed over an extended period through tainted water, arsenite and MA(III) build up in essential organs and tissues. This can cause atherosclerosis, hypertension, ischemic heart disease, diabetes, hepatotoxicity, nephrotoxicity, and skin, bladder, and lung cancer (Nielsen et al., 1996).

Arsenic contamination poses a serious risk in several nations, including Bangladesh, Taiwan, India, Mexico, China, Chile, Argentina, and the United States—the first reports date back to the mid-1980s. Of the 18 state districts in West Bengal, (Ghosh et al., 2017) tube wells were impacted; of the 64 districts in Bangladesh, 50 had been affected (as levels <10 - >10,000 μg/L). In Bangladesh and West Bengal alone, 150 million people might be in danger. Humans can become exposed to arsenic through inhalation, which primarily involves exposure to mining and agricultural pesticides, or oral routes that involve contaminated food and water. A 1999 World Health Organization (WHO) fact document (Geneva and Organization, 1999) states that arsenic contamination is a serious public health concern that needs immediate remediation. Exposure to arsenic has been linked to a higher risk of systemic health consequences as well as carcinogenic effects, according to several epidemiological studies (Shila et al., 2005). The processes underlying the pathophysiology of end organ damage and arsenic-induced toxicity were critically examined in the current review.

General Mechanism of Action of Sodium Arsenite

Arsenic affects cells in many ways, affecting several signal transduction pathways and producing a wide range of biological consequences, such as the induction of death, growth inhibition, encouragement or inhibition of differentiation, and inhibition of angiogenesis. The precise mechanism underlying arsenite's toxicity is unknown. Reactive oxygen species (ROS) production and DNA repair and methylation modifications are two of the hypothesized explanations (Shi et al., 2004). According to Qian et al. (2003), arsenite can also bind to thiol in proteins. Many protein activities are thought to be altered by thiol group binding and reactive oxygen species (ROS) production. As a result, the several signal transduction pathways that arsenite activates or inactivates may be responsible for its unique and varied actions (Qian et al., 2003).

Cell migration rates were decreased when cells were treated with sodium arsenite at sub-lethal doses. The formation and disintegration of focal adhesions is one of the events necessary for the complicated and dynamic process of cell migration. Cells have focal adhesions that bridge the extracellular matrix (ECM) and the actin cytoskeleton. Because many protein kinases have been localized to focal adhesions, these structures are considered significant locations of cell signaling events (Zamir and Geiger, 2001). It has been demonstrated that sodium arsenite affects a number of the signaling kinases (Ishrath et al., 2002) found in focal adhesions (Porter et al., 1999; Trouba et al., 2000; Yih et al., 2002). Because arsenite inhibits protein kinases involved in the regulation of focal adhesion, focal adhesion function is disrupted, leading to the reported lower cell migration rates. Sublethal concentrations of sodium arsenite have been shown to modify the distribution and number of focal adhesions, as well as the phosphorylation of focal adhesion proteins and cell adhesion to a substrate. However, total polymerized actin and the expression of focal adhesion proteins remain unaltered (Trouba et al., 2000). Larger-scale changes in the structure and signaling of focal adhesion structures could be anticipated to have a range of additional effects in cells, which could explain many of the observed arsenite effects. These effects include increased apoptosis, malignancy-associated characteristics, cell cycle arrest/inhibition of proliferation, and disruption of the cell cytoskeleton. This overview covers the fundamental mechanisms of systemic disorders linked to arsenic. Such information is essential for comprehending the scope of global health impacts linked to arsenic exposure, particularly for raising awareness among people who are severely at risk in work environments (Zamir and Geiger, 2001).

SYSTEMIC HEALTH EFFECTS AND THEIR MECHANISM

Nervous system

Arsenic impacts the body's organ systems, particularly the central nervous system (CNS). There have been reports of seizures, encephalopathy, peripheral neuropathies, and behavioral abnormalities in the nervous system (Vahidnia et al., 2007). The mature nervous system's central and peripheral components are neurotoxically affected by arsenic. There is mounting evidence that arsenic exposure is harmful to the developing nervous system as well, causing cultured growing neurons to undergo more apoptosis and less cell proliferation. Uncertainty persists regarding arsenic's impact on later neuron growth and shape. Arsenic and its inorganic constituents have long been known to be neurotoxic (Vahidnia et al., 2007). An extensive body of research has been done on peripheral neuropathy after arsenic exposure (Datta et al., 1979). It has been documented that long-term exposure to arsenic dust reduces peripheral nerve conduction velocity (Blom et al., 1985). A correlation has been documented between the consumption of arsenic and a higher likelihood of microvascular illnesses, such as neurological conditions (Chiou et al., 2005). Because arsenic causes cortical neurons to die, Gharibzadeh and Hoseini (2008) proposed that exposure to arsenic may increase the risk of Alzheimer's disease.

Arsenic readily penetrates the blood–brain barrier [25] and builds up in the brain, causing changes in behavior

(Tadanobu et al., 1990). While the specific target of arsenic in the brain remains unclear, research has demonstrated that basal ganglia are very susceptible (Richter et al., 2022; Rodrıguez et al., 2002). Studies have been conducted on the whole brain to learn more about the mechanism underlying arsenic-induced neurotoxicity.

Arsenic has been shown to have a noticeable impact on the hippocampus, cortex, and corpus striatum (Richter et al., 2022). The brain growth phase from postnatal days 4 to 10 is characterized by the delayed maturity of Purkinje cells and their poor migration (Dhar et al., 2007). Exposure to arsenic has been linked to learning and memory impairment in both adults and children (Farias et al., 2015). Research has also shown that rats exposed to arsenic exhibit altered motor behavior (Rodrıguez et al., 2002).

The effects of sodium arsenite on the initial phases of neurite formation and development were examined in a distinct investigation using differentiated PC12 cells. Arsenic affects early neurite outgrowth in vitro in concentration- and time-dependent ways. Newly developing PC12 cells exhibit decreased neurite generation, outgrowth, and complexity after five days of exposure to low micromolar concentrations of sodium arsenite. These findings imply that arsenic exposure can modify the regular course of morphological development, possibly leading to reduced long-term neuron functioning and disrupting early phases of neuron differentiation. The neuroprotective efficacy of curcumin, a polyphenolic antioxidant, has been studied in rats in light of ongoing arsenic exposure and related health risks, including neurotoxicity. Rats given arsenic (sodium arsenite, 20 mg/kg body weight, p.o., 28 days) showed a substantial reduction in locomotor activity (26%) and grip strength (26%) as well as rota-rod performance (82%), in comparison to controls. The binding of striatal dopamine receptors (32%) and tyrosine hydroxylase (TH) immunoreactivity (19%) in the striatum was likewise decreased in the rats treated with arsenic. Rats treated with arsenic showed higher levels of arsenic in the corpus striatum (6.5 fold), frontal cortex (6.3 fold), and hippocampus (7.0 fold). These increases were linked to increased oxidative stress in these brain regions, as evidenced by an increase in lipid peroxidation, protein carbonyl, and a decrease in glutathione levels and activity of superoxide dismutase, catalase, and glutathione peroxidase with varying effects (Blom et al., 1985).

Several investigations have been conducted to comprehend the biochemical processes underlying arsenic-induced neurotoxicity. Experimental studies exposing subjects to arsenic have discovered changed levels of dopamine, norepinephrine, and serotonin. These findings suggest that biogenic amines play a role in the neurotoxicity of arsenic (Tripathi et al., 1997). Arsenic neurotoxicity has been linked to impaired antioxidant defense and increased oxidative stress in the brain, in addition to effects on the catecholaminergic system (Flora et al., 2005). Increased production of free radicals by arsenic causes lipid peroxidation, protein carbonyls, and a reduction in the activity of superoxide dismutase and other antioxidant defense-related enzymes in the rat brain. In addition, arsenic has a strong affinity for GSH, which makes it more susceptible to oxidative stress by upsetting the balance between pro-oxidant and antioxidant homeostasis (Aposhian et al., 2000; Wang, 1996).

Rats exposed to chronic arsenic exposure showed decreased brain nitric oxide synthesis and increased reactive oxygen species generation (Zarazúa et al., 2006). There is great interest in determining if arsenic's neurotoxicity can be avoided, given that people are still exposed to it. Numerous neurotransmitters, including glutamate, acetylcholine, gamma amino butyric acid, and monoamines, have been shown to have different metabolisms when exposed to arsenic (Edmondson et al., 1988; Yadav et al., 2010). According to another study, long-term exposure to arsenic has been shown to significantly lower levels of monoamines in the corpus striatum, frontal cortex, and hippocampal regions of the brain, including adrenaline, nor-adrenaline, dopamine, and serotonin (Yadav et al., 2010). Arsenite-mediated neurotoxicity induces death in cerebral neurons by activating the JNK3 and p38 mitogen-activated protein kinase (p38MAPK) pathways (Namgung and Xia, 2001).

Exposure to sodium arsenite causes neurotoxicity through the disruption and instability of the cytoskeletal structure, eventually resulting in axonal degeneration (Vahidnia et al., 2008). It is commonly recognized that thiamine (vitamin B1) deficiencies result in neurological issues. Notably, arsenic inhibits pyruvate decarboxylase, which raises blood pyruvate and consequently results in encephalopathy and causes thiamine shortage (Rodrıguez et al., 2003). Parkinson-like symptoms can arise from arsenic-induced oxidative stress in the brain, which damages oxidative DNA, leads to the death of brain cells, and degenerates dopaminergic neurons (Felix et al., 2005). Acute arsenic toxicity can be linked to peripheral neuropathy, neuropsychiatric abnormalities, and extrapyramidal diseases because it reduces acetylcholinesterase activity, which results in a cholinergic crisis-like state with altered mental status and weakness (Patlolla and Tchounwou, 2005). Furthermore, arsenic damages the neuro-skeletal integrity of the peripheral nervous system, significantly reducing the nerve conduction velocity in the peripheral nerves and resulting in peripheral neuropathy (Bardullas et al., 2009). The hippocampal NMDA receptors, essential for synaptic plasticity, learning, and memory, are suppressed by exposure to arsenic and its metabolites monomethyl arsenic acid and monomethylarsonous acid. This results in neurobehavioral problems and cognitive impairment (Chen et al., 2005; Krüger et al., 2009). Chronic arsenic exposure disrupts the central structural architecture of the striatum by altering the morphology of its axons and nerve fibers (Rios et al., 2009; Tsou et al., 2005). Thus, pyruvate

decarboxylase, acetylcholinesterase, reduction in biogenic monoamines, oxidative stress, and induction of thiamine shortage all appear to be essential factors in arsenic-induced neurotoxicity [Figure 1].

The animal models of arsenic toxicity are associated with inconsistent neurotoxicity because of varying doses, duration, and different salts of arsenic used in various studies. On the other hand, these have offered a profound understanding of the pathophysiological pathways behind arsenic-induced neurotoxicity. In San Luis Potosi, Mexico, an across-sectional study (Hsueh et al., 1998) looked at the effects of lead, arsenic, and malnutrition on schoolchildren's neuropsychological functioning at ages six to nine.

Participants were 39 kids living 7 km upwind from the smelter (Martinez Zone) and 41 kids living 1.5 km inside a smelter complex (Morales Zone) with rising amounts of lead and arsenic. The Martinez children's urine had a lower geometric mean total arsenic concentration than the Morales children's. The Martinez group had a poorer socioeconomic position and lesser levels of educational achievement from both parents. Neuropsychological performance was evaluated using the Weschler Intelligence Scale for Children, Revised Version (WISC-RM). On the full-scale IQ exam and other neuropsychological subscores, the Morales kids' scores were lower than the Martinez kids.
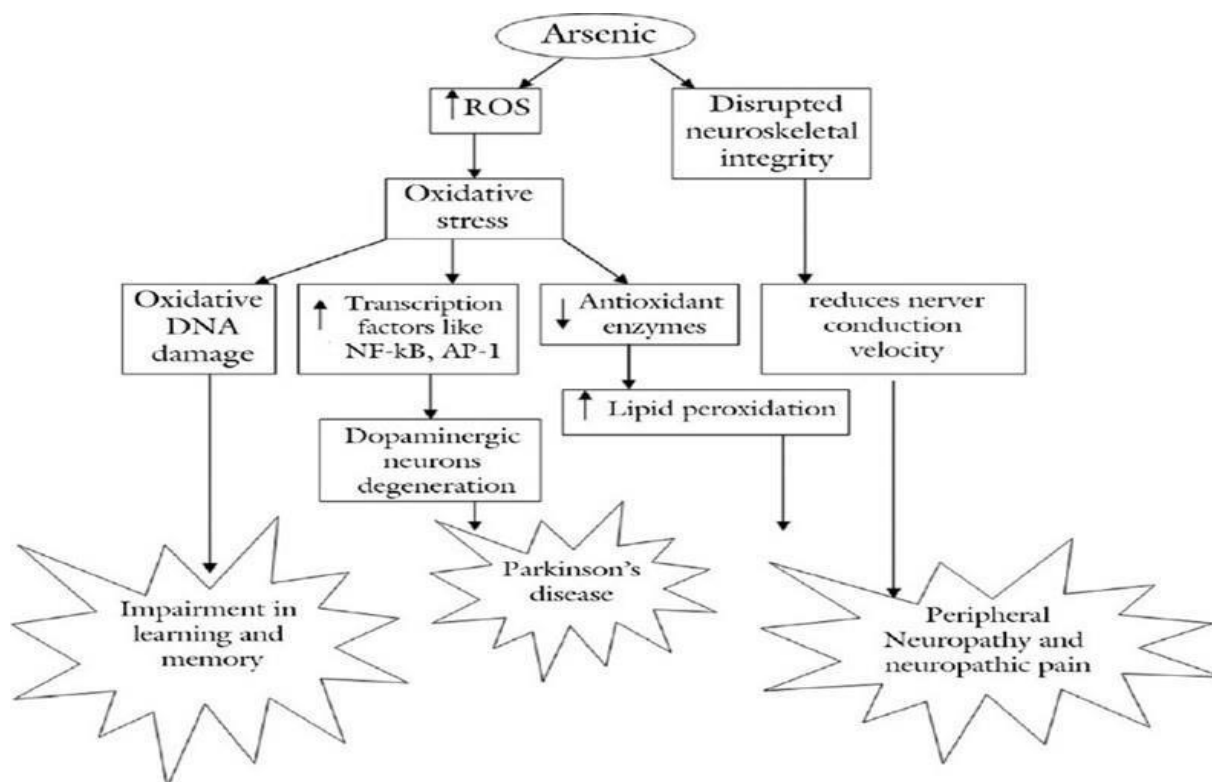

Fig 1. Pathology Mechanism involved in Nervous system

Cardiovascular Diseases Caused by Sodium Arsenite
Cardiovascular Diseases Caused by Sodium Arsenite Cardiovascular diseases are common among chimney sweeps, copper smelter workers, and glass blowers exposed to arsenic in their working environments in Japan (Hsueh et al., 1998). Ventricular arrhythmias, hypertension, atherosclerosis, and ischemic heart disease are only a few of the cardiovascular conditions that can result from prolonged exposure to inorganic arsenic (Nielsen et al., 1996). Venous endothelial cells and vascular smooth muscle cells (VSMC) have plasma membranes that contain nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. This enzyme is

stimulated by arsenite to produce more reactive oxygen species (ROS), including hydrogen peroxide and superoxide (Manna et al., 2008; Vahidnia et al., 2007; Yih et al., 2002). According to epidemiological research, long-term arsenic-contaminated drinking water consumption can uniquely affect the cardiovascular system. Increased mortality from cardiovascular disease and hypertension are two notable outcomes (Monrad et al., 2017).

A cross-sectional blood pressure assessment was conducted on 1,595 persons (over 30 years old) who had grown up in a Bangladeshi rural area. Due to the area's usage of tainted groundwater for drinking water—wells were drilled due to

surface water microbiological contamination—there was a significant degree of arsenic exposure. Every subject had the same food, way of life, and socioeconomic standing. No patients were using antihypertensive medication at the time of the research. The study discovered that elevated levels of arsenic in drinking water raised the prevalence and intensity of hypertension (Rehman et al., 2019). Heart disease mortality in Chile has been linked to environmental exposure to inorganic arsenic through drinking water (Zaldivar, 1980).

Extended Exposure to inorganic arsenic has been associated with a higher incidence of coronary heart disease. According to a recent study, fatal ischemic heart disease (ISHD) in Taiwan is correlated with a biological gradient of cumulative arsenic exposure from drinking artesian well water (Chen et al., 2005).

Prolonged exposure to arsenite produces reactive oxygen species (ROS), which elevate the expression of genes linked to atherosclerosis, including heme oxygenase-1 (HO-1), monocyte chemo-attractant protein (MCP-1), and interleukin-6 (IL-6). In VSMC, arsenic exposure also encourages monocyte adhesion, penetration, and migration. Arsenic also causes vascular endothelial cells to produce more inflammatory mediators, including prostacyclin, leukotriene E 4 (LTE 4), tumor necrosis factor-alpha, and nuclear factor kappa B, which might lead to the pathogenic process of atherosclerosis (Chen et al., 2005). The activity of Akt/protein kinase B and endothelial nitric oxide synthase (eNOS) is decreased by arsenite. This, in turn, lowers the bioavailability of NO and may cause vascular endothelial dysfunction and related cardiovascular problems (Tsou et al., 2005). Additionally, arsenic triggers the activation of protein kinase C alpha, which phosphorylates beta-catenin and consequently causes the association between vascular endothelial cadherin and beta-catenin to be reversed. Actin stress fiber formation also increases the formation of intercellular gaps and endothelium permeability. Arsenite increases calcium sensitivity, which causes hypertension, and phosphorylates myosin light chain kinase (MLCK), which causes vasoconstriction of the blood vessels (Lee et al., 2005). Prolonged exposure to arsenic causes oxidative stress and modifies the release of vasoactive mediators in blood vessels, which raises blood pressure (Cifuentes et al., 2009). When considered collectively, these data point to the possibility that arsenic causes cardiovascular dysfunction by raising oxidative stress, decreasing eNOS activation, and increasing MLCK phosphorylation. These effects may be addressed to minimize arsenic exposure-related cardiovascular problems.

Sodium Arsenite Induced Nephrotoxicity

The kidneys are the main organ responsible for excreting arsenic and converting pentavalent arsenic into trivalent arsenic, which is less soluble and more poisonous. The principal organs affected by arsenic-induced poisoning are the kidney and liver, with the kidney exhibiting the highest concentration of arsenic (Nandi et al., 2006). Similar to injury to other organs, capillary damage appears to be a fundamental event that results in various cellular expressions. Capillaries, tubules, and glomeruli in the kidney are among the areas where arsenic damage occurs (Tchounwou et al., 2003). Tubular cells also exhibit a significant amount of mitochondrial damage. Arsenite causes more reactive oxygen species (ROS) to be produced, which in turn causes more lipid peroxidation and cellular damage in renal tissue (Kokilavani et al., 2005). Acute tubular necrosis, cast formation, and elevated blood urea nitrogen and creatinine levels are indicative of acute renal failure brought on by arsenic exposure (Kimura et al., 2006). Renal toxicity is caused by activator protein-1 (AP-1), activating transcription factor-2 (ATF-2), and Elk- 1, among other transcription factors, which are regulated by HO-1 and MAPK, which are expressed more when arsenic-induced oxidative stress occurs (Kimura et al., 2006; Sasaki et al., 2007). Haematuria is made possible by the dilation of glomerular arterioles. Urine casts and proteinuria are symptoms of damaged proximal tubular cells. Although oliguria is a typical symptom, renal failure is a real possibility if acute arsenic poisoning is severe enough to cause shock and dehydration (Giberson et al., 1976). Haemodialysis is necessary to remove the arsenic that is linked to haemoglobin in cases of arsine-induced haemolysis, which is likely to result in acute tubular necrosis and partial or total renal failure. After recovery, interstitial fibrosis and thicker glomerular basement membranes may remain (Fowler and Weissberg, 1974).

Hepatoxicity

The main organ affected by arsenic-induced poisoning is the liver, which also has the highest arsenic concentration [61]. Increases in total bilirubin levels, alanine aminotransferase, aspartate aminotransferase, and malonaldehyde are signs of hepatotoxicity caused by exposure to arsenic (Jain et al., 2011). The oxidative stress caused by chronic arsenic stimulates p38 MAPK and JNK, which causes hepatocytes to undergo apoptosis (Flora et al., 2009). Arsenite-induced nephrotoxicity and hepatotoxicity may thus be caused by oxidative stress, apoptosis, and activation of transcription factors such AP- 1, ATF-2, and Elk-1. Furthermore, liver apoptosis is promoted by arsenic-induced oxidative stress through the overexpression of pro-apoptotic proteins (Hernández-Zavala et al., 1998). In one investigation, serum samples from seven people who had consumed arsenic through their drinking water showed elevated total bilirubins. Moreover, portal tract fibrosis, which sporadically results in portal hypertension and bleeding from oesophageal varices, has been identified by histological analysis of the livers of people who have been exposed to high quantities of arsenic over an extended period (Armstrong et al., 1984).

A study was conducted on the liver function of people living in three villages around Lagunera, Mexico. They identified hepatocellular injury markers in the blood activity of aspartate aminotransferase (SAT) and alanine aminotransferase (ALT) and cholestasis injury markers in the serum activity of gamma-glutamyl-transpeptidase (GGT) and alkaline phosphatase (ALP). The study's primary conclusions, which mainly were conjugated hyperbilirubinemia and elevated serum ALP activity, were connected to the amount of total arsenic in urine and suggested that people exposed to arsenic may have cholestasis (Hernández-Zavala et al., 1998). In West Bengal, India, patients with substantial hepatomegaly due to persistent arsenicosis did not have classic findings of elevated bilirubin or alkaline phosphatase. The investigation found minor portal fibrosis and cirrhosis in patients with a clinical diagnosis of chronic arsenic poisoning based on liver biopsy results (Santra et al., 1999).

Effects on Reproductive system

Adult male rats given sodium arsenite orally over an extended period may have changes in their reproductive systems, including decreased paired testicular mass, inhibition of testicular androgenesis, decreased gonadotrophin and testosterone concentrations, and increased adrenocortical activity. In male rats treated with arsenic, paired testicular mass, a helpful indicator of reproductive toxicity, decreased (Amankwah and Fasching, 1985; Tully et al., 2000). This decrease in testicular mass was consistent with the removal of germ cells. Since these enzymes are the leading players in testicular androgenesis, testicular steroidogenic events, $\Delta 5$, 3β-HSD, and 17β-HSD, have a crucial regulatory role (Guha Mazumder et al., 2001; Maity et al., 2018). The reduction in these enzymes caused by sodium arsenite treatment in this investigation is consistent with prior research findings that arsenic treatment inhibited testicular androgenesis (Russell et al., 2018). Because these testicular androgenic enzymes regulate testosterone production, a dose-dependent drop in the plasma and intratesticular concentrations of testosterone in rats treated with arsenic may result from their suppression (Guha Mazumder et al., 2001; Maity et al., 2018). Furthermore, as Low plasma levels of LH are a significant regulator of the activities of testicular androgenic enzymes; the suppression of these enzymes in rats treated with arsenic may also be the outcome (Mandal et al., 2013).

The decrease in the number of distinct generations of germ cells at stage VII of the spermatogenic cycle has been discovered to reflect the spermatogenic disease. The results of the previous study on arsenic in testicles were likewise supported by these results (Russell et al., 2018). Low gonadotrophin levels, for example, could cause the suppression of spermatogenesis. FSH and LH (Perreault et al., 2016). Quantitatively normal spermatogenesis in pubertal rats requires LH and FSH (Perreault et al., 2016). Arsenic-induced alterations in spermatogenesis may thus be attributed to decreased levels of LH and FSH and, as a result, decreased testosterone production. In addition, as a high level of testosterone in the testis is necessary for normal spermatogenesis as well as the maintenance of structural morphology and normal physiology of the seminiferous tubule, low intratesticular concentrations of testosterone may be the cause of the germ cell degeneration caused by arsenic treatment (Perreault et al., 2016).

The amount of arsenic found in drinking water across a large portion of West Bengal affected the ovarian steroidogenesis of Wister strain rats. Mature rats of the Wistar strain at the dioestrus phase were given a 0.4 ppm/rat/day dose for 16 and 28 days. Following this, the weight of the ovary, uterus, and vagina was measured, along with the enzyme activities of ovarian delta 5-3 beta-hydroxysteroid dehydrogenase (delta 5-3 beta-HSD) and 17 beta-hydroxysteroid dehydrogenases (17 beta-HSD), and plasma levels of LH, FSH, and estrogen. The activities of ovarian delta 5-3 beta-HSD and 17 beta-HSD were significantly reduced after 28 days of sodium arsenite treatment, and there was also a significant drop in the plasma levels of LH, FSH, and estrogen. A notable reduction in the weights of the ovary, uterus, and vagina was also observed throughout this treatment time; however, no noteworthy effect was observed on the parameters above after 16 days of treatment. In contrast to control rats, which had four days of a typical estrous cycle, rats treated with arsenic showed a protracted dioestrus phase in the oestrous cycle (Chaudhuri et al., 1999). In rats given arsenic, the amount of arsenic deposited in the uterus, ovary, vagina, and plasma was also observed. The findings of this study indicate that the length of arsenic treatment is a crucial component in its detrimental impact on ovarian functions at doses within the range seen in drinking water in various regions of West Bengal, India.

Despite research showing that arsenic and its methylated metabolites cross the placenta in both humans and experimental animals, relatively little focus has been placed on the possible effects of arsenic exposure on the human reproductive system, even though it has been linked to several detrimental health outcomes (Concha et al., 1998). There is evidence from human research that the children of workers at a Swedish copper smelter (where arsenic exposure was observed) and neighboring inhabitants may experience adverse reproductive effects. Mothers who worked in jobs requiring higher exposure levels gave birth to babies that were heavier than those who did not live near the smelting region (Nordstrom et al., 1979).

There was a discernible upward trend in the frequency of spontaneous abortions as residential and occupational exposure increased. Pregnant women who worked in jobs with high levels of exposure seemed to have a higher incidence of congenital abnormalities (Cifuentes et al., 2009). In Bulgaria, an area near a smelter with environmental contamination from several metals had significantly higher rates of congenital malformation death

and pregnancy toxemia than the national rates (Zaldivar and Ghai, 1980). Hungary has a higher incidence of spontaneous abortions and stillbirths than other countries when drinking water contaminated with arsenic is present (Börzsönyi et al., 1992). Three American investigations found negative impacts on reproduction, including an increase in mortality from spontaneous abortions (Aschengrau et al., 1989) and congenital cardiovascular malformations (Tabacova et al., 1994).

Developmental Toxicity

Animal research using single-injection or gavage treatments during embryogenesis provides the majority of the knowledge about the developmental toxicity of arsenic. Arsenic can cause growth retardation, deformity, and intrauterine death, according to data from research conducted on mice and rats. Neural tube anomalies, renal and gonadal agenesis, ocular problems, and rib deformities were among the typical patterns of malformations reported in injection trials. The consequences of developmental toxicity were contingent upon the arsenic dosage, method, species, and day of gestation at which the substance was delivered. The placenta can easily absorb arsenic. In embryo culture, a comparable developmental toxicity trend has been replicated. In studies using the gavage method, skeletal abnormalities, growth retardation, and intrauterine mortality were observed in mice. Three studies have employed long-term oral administration of drinkable water or feed before conception, as well as during the gestational and lactation phases. The consequences documented in these investigations included reduced litter sizes, growth retardation, and intrauterine and postnatal deaths. Living in an area with high levels of arsenic in drinking water was linked to both spontaneous abortion and stillbirth, according to an ecological study. There are links between exposure to arsenic emissions from a copper smelter and congenital disabilities, low birth weight, and spontaneous abortion, according to several studies conducted on people who work at or live close to the facility. One explanation for teratogenic consequences has been suggested: free radical damage (Tabacova et al., 1994). Neural tube abnormalities may be caused by impacts on cytoskeletal activities, cell death, proliferation of cells, placenta and embryonic vasculature, and nutrient transport, according to Shalat et al. (1996) (Shalat et al., 1996).

Effects on Respiratory System

A recent study found a correlation between the frequency of respiratory diseases and consuming water containing arsenic. There has previously been evidence from epidemiological studies conducted in Chile that arsenic exposure is linked to non-malignant respiratory consequences (Mazumder et al., 2000). In Bengal, West When 57% of the 156 patients who resided in communities affected by arsenic reported having a chronic cough, respiratory consequences were first observed in 1995 (Mazumder et al., 2000). According to survey data gathered

in Antofagasta and Chile between 1968 and 1972, consuming tainted water containing arsenic was linked to a higher cough frequency among 398 children. In a cross-sectional survey conducted in Antofagasta, 144 schoolchildren with skin lesions caused by arsenic were shown to have a 2.5-fold higher incidence of bronchopulmonary illness than children with normal skin (Borgoño et al., 1977). Additionally, compared to children living in the rest of Chile with low sodium arsenite concentration, the prevalence of bronchiectasis was shown to be 23 times higher in children with skin lesions caused by arsenic living in Antofagasta, which has a high concentration of arsenic in the environment (Zaldivar and Ghai, 1980).

There have also been reports of nonmalignant respiratory symptoms in copper smelter workers exposed to airborne arsenic from a few occupational studies carried out in Sweden during the 1950s. According to a study by Smith et al. (Smith et al., 1998), young men and women who reside in the same Arsenic-exposed region of Chile, which includes Antofagasta, has high relative rates of chronic obstructive pulmonary disease (COPD) mortality. Milton et al.'s study [97] of 94 people in Bangladesh who had skin lesions attributable to arsenic revealed a connection between long-term absorption of arsenic and chronic bronchitis. Arsenic is unique in that it appears to exacerbate respiratory diseases, both malignant and non-malignant, after consumption. Chronic bronchitis was described as a history of coughing up sputum on most days for at least three months in a row for longer than two years, together with the physical examination finding of chest rhonchi and crepitation. Men were more likely than women to have chronic bronchitis. To date, reports from Bangladesh, India, and Chile have shown a connection between non-malignant respiratory symptoms and ingested arsenic. Research from Taiwan, Chile, and Argentina with high levels of arsenic pollution demonstrates an apparent rise in the death rate from lung cancer (Milton et al., 2001).

Sodium arsenite as a carcinogen

The National Toxicology Programme (NTP), Occupational Safety and Health Administration (OSHA), United States Environmental Protection Agency (USEPA), and International Agency for Research on Cancer (IARC) have all designated arsenic as a human carcinogen. Skin, kidney, bladder, and lung tumors are linked to inorganic arsenic exposure in the population. The mechanism underlying arsenate's genotoxicity remains unknown despite numerous suggestions having been put up. One possibility is that arsenate inhibits enzymes replicating or repairing DNA, or it may function as a phosphate analog (Jacobson-Kram and Montalbano, 1985). Due to its easier cell absorption, the trivalent form of arsenic has more genotoxic effects than its pentavalent equivalent (ENTERLINE and MARSH, 1982). Lung cancer risk is the main carcinogenic effect in workers exposed to inhalation (Tchounwou, 1999). The primary

carcinogenic impact of oral exposure is an elevated risk of skin cancer. Exposure to arsenic has also been linked to an increased risk of many internal malignancies, primarily of the liver, kidney, lung, colon, and bladder (Jacobson-Kram and Montalbano, 1985). The digestive system, skin, liver, lung, kidneys, neurological system, and heart are all impacted by prolonged exposure to arsenic.

Exposure to inorganic arsenic raises the risk of cancer, as demonstrated by epidemiological research. While the precise molecular mechanism underlying arsenic's carcinogenicity remains unclear, arsenic has been demonstrated to exhibit tumour-promoting characteristics through the induction of intracellular signal transduction, the activation of transcription factors, and modifications in gene expression related to cell growth, proliferation, and malignant transformation. Arsenic-induced MAPK signal transduction has also been proposed as a possible mechanism for inducing arsenic-associated carcinogenicity (Jacobson-Kram and Montalbano, 1985). This process modifies the expression patterns of several genes by activating transcription factors such as NF-kB and AP-1. Reversion experiments using Salmonella typhimurium are unable to identify arsenic compound-induced mutations. Despite being viewed as mild mutagens in mammalian and bacterial cells, arsenic compounds show clastogenic characteristics in a variety of cell types both in vivo and in vitro (Jacobson-Kram and Montalbano, 1985; Tchounwou, 1999). These pathways have a role in carcinogenesis, adhesion of cells, migration of cells, survival of cells, control of the cell cycle, and necrosis of tumor cells (Liu et al., 2000).

Studies of in vitro cell transformation become a valuable tool for learning about the carcinogenic processes of arsenic toxicity when animal models are unavailable. Arsenic trioxide has been shown to cause DNA damage in human cells based on the comet assay (Schaumloffel and Gebel, 1998). Arsenical chemicals have also been demonstrated to cause amplification of genes, stop cells in their mitotic cycle, Impeding DNA repair causes the oxidative stress protein heme oxygenase and the c-fos gene to be expressed in mammalian cells (Yang and Frenkel, 2002). Arsenic stimulates the growth of bladder epithelial cells. It increases the expression of proto-on-genes, including EGR-1, c-jun, and c-fos, which may all work together to cause bladder cancer (Simeonova and Luster, 2000). In addition to inhibiting DNA repair, promoting angiogenesis, changing DNA methylation patterns, dysregulating cell cycle regulation, and preventing natural apoptosis, arsenic works with sunshine to cause skin cancer (Klein et al., 2007). An increased incidence of basal cell carcinoma was found in a case-control study of skin cancer conducted in Hungary, which was linked to elevated levels of atmospheric arsenic from coal burning. The difference between patients diagnosed before 1982 and those diagnosed after 1986 was more noticeable in the former. Antioxidants like vitamin E,

melatonin, and curcumin help avert oxidative stress, the primary cause of arsenic-induced carcinogenicity (Tapio and Grosche, 2006).

When considered collectively, the different hypothesized pathways of arsenic's carcinogenic action include elevated oxidative stress, direct genotoxic effects, changed growth factor expression, and altered DNA repair. Numerous theories have been put out to account for the carcinogenic properties of inorganic arsenic [75]. However, little is known about the molecular pathways by which this arsenic causes cancer. Previous research findings suggest that inorganic arsenic may function as a tumor promoter via altering signal transduction pathways linked to cell growth and proliferation rather than acting through traditional genotoxic and mutagenic mechanisms. It has been demonstrated that inorganic arsenic (III) alters the expression and DNA-binding properties of several essential transcription factors, such as activating protein-1 (AP-1), tumor suppressor 53 (p53) (129), and nuclear factor kappa B. Trivalent inorganic arsenic stimulates the mitogen-activated protein kinase (MAPK) cascade, which increases the production and phosphorylation of the two main AP1 constituents, c-Jun and c-Fos, and activates AP-1.

In a different investigation, Patterson et al., 2004. (Patterson et al., 2004) concluded that prolonged exposure to high concentrations of arsenic could increase the number of mitogenic signaling proteins in cells, enhancing the carcinogenic effects of arsenic. Several studies have shown that arsenic can disrupt cell signaling pathways, such as the p53 signaling pathway, which are commonly linked to the development and spread of a range of tumor types in experimental animal models and some human tumors. Numerous theories have been put out, such as changes in DNA methylation and repair and the production of reactive oxygen species (ROS) (Harris and Shi, 2003).

Conclusion

Exposure to arsenic is considered a significant public health concern, mainly because of its clear carcinogenic potential. It is still unknown, though, exactly how it works molecularly and at what does it impacts every system in the body. Understanding and applying the dose-response curve's shape at low ambient arsenic concentrations and the mode of carcinogenic action is crucial for risk assessment of environmental arsenic. Despite recent significant advancements, there is still no scientific agreement regarding the mode(s) of action of arsenic. Arsenic-induced chromosomal abnormalities, oxidative stress, altered DNA repair, altered DNA methylation patterns, altered growth factors, enhanced cell proliferation, promotion/progression, suppression of p53, and gene amplification have nine distinct potential mechanisms of action, according to the literature review. Three mechanisms of arsenic carcinogenesis—chromosomal abnormalities, oxidative

stress, and altered growth factors—now have some supporting data from experimental systems (human and animal cells) and human tissues. The mode-of-action studies, therefore, imply that arsenic may be promoting, advancing, or cocarcinogen in the process of carcinogenesis. Arsenic may be able to alter gene expression in people and experimental models, according to several studies. It is unknown exactly how sodium arsenite becomes poisonous.

Declarations

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