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Review Article

Mechanisms Pertaining to Arsenic Toxicity

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ABSTRACT

Arsenic is an environmental pollutant and its contamination in the drinking water is considered as a serious worldwide environmental health threat. The chronic arsenic exposure is a cause of immense health distress as it accounts for the increased risk of various disorders such as cardiovascular abnormalities, diabetes mellitus, neurotoxicity, and nephrotoxicity. In addition, the exposure to arsenic has been suggested to affect the liver function and to induce hepatotoxicity. Moreover, few studies demonstrated the induction of carcinogenicity especially cancer of the skin, bladder, and lungs after the chronic exposure to arsenic. The present review addresses diverse mechanisms involved in the pathogenesis of arsenic-induced toxicity and end-organ damage.

Key words: Arsenic, carcinogenicity, cardiovascular dysfunction, diabetes, hepatotoxicity, nephrotoxicity, neurotoxicity

INTRODUCTION

Arsenic is a naturally occurring element that ubiquitously exists in both organic and inorganic form in the environment. Arsenic contamination is an issue of concern worldwide and it is a considerable risk factor in various countries including Bangladesh, Taiwan, India, Mexico, China, Chile, Argentina, and USA. Human exposure to arsenic is either through oral route involving contaminated food and water or through inhalation that majorly covers exposure to agricultural pesticides and mining activities. According to World Health Organization (WHO) fact sheet in 1999, arsenic contamination is considered as major public health issue requiring correction measures on emergency basis.[1] The WHO guidelines describe safety limit of arsenic at 10 μg/l and a maximum permissible limit of 50 μg/l of drinking water.[2] Over 200 million people are at risk worldwide, out of which more than half are residing in Bengal Delta Plain including West Bengal and Bangladesh.[3] The arsenic content in this area has been found to be 800 μg/l of drinking water.[4] The chronic poisoning caused by high levels of arsenic in well waters has led to public health emergency in Bangladesh.[5,6] In Taiwan, chronic arsenic exposure through well waters has led to peripheral vascular disease called as black foot disease.[7] Arsenic exists in the environment as pentavalent (As^{5+}, arsenate) and trivalent (As^{3+}, arsenite) forms, and arsenite has been considered to be more toxic when compared with arsenate.[8] On absorption, arsenic is stored in liver, kidney, heart, and lungs. The lower amount of arsenic is observed in muscles and neuronal tissues.[9] The accumulation of arsenic in these tissues is associated with many disorders including cancer, diabetes, hepatotoxicity, neurotoxicity, and cardiac dysfunction. Arsenic metabolism is important for its toxicity and it exerts its toxicity by inhibiting around 200 enzymes involved in cellular energy pathways and DNA synthesis and repair, etc.[10] It is metabolized by reduction and methylation reactions, catalyzed by glutathione-S-transferase omega-1

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(GSTO1) and arsenic (III) methyltransferase (AS3MT) involving methylation of arsenic via one-carbon metabolism by S-adenosyl methionine (SAM) as methyl donor and requiring reduced glutathione (GSH) as electron donor in reductase reaction. GSTO1 reduces methylarsonate [MA(V)] and arsenate [As(V)] to methylarsonite [MA(III)] and arsenite [As(III)], respectively, and these toxic trivalent arsenicals formed during reduction are detoxified by AS3MT to methylarsonate [MA(V)] and dimethylarsinate [DMA(V)], which are less toxic pentavalent arsenicals.[11] Acute arsenic poisoning is associated with nausea, vomiting, abdominal pain, and severe diarrhea.[10] Chronic ingestion of arsenite through contaminated water results in accumulation of arsenite and MA(III) in vital organs and tissues leading to the incidence of atherosclerosis, hypertension, ischemic heart diseases, diabetes, hepatotoxicity, nephrotoxicity, and cancer of the skin, bladder, and lungs.[12-17] The present review critically discussed the mechanisms involved in the pathogenesis of arsenic-induced toxicity and end organ damage.

ARSENIC-INDUCED CARDIOVASCULAR DYSFUNCTION

Long-term exposure to inorganic arsenic may cause various cardiovascular disorders such as atherosclerosis, hypertension, ischemic heart diseases, and ventricular arrhythmias.[12-14,18] Arsenite stimulates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase present in the plasma membrane of vascular endothelial cells and vascular smooth muscle cells (VSMC) to increase the generation of reactive oxygen species (ROS) such as superoxides and hydrogen peroxide.[19,20] ROS generated during arsenite exposure couples with nitric oxide (NO) to form peroxynitrite, a strong oxidant implicated in the upregulation of inflammatory mediator such as cyclooxygenase-2.[21] ROS generated during arsenite exposure increases the expression of atherosclerosis related genes such as heme oxygenase-1 (HO-1), monocyte chemo-attractant protein (MCP-1), and interleukin-6 (IL-6) and thus its exposure promotes the attachment, penetration, and migration of monocytes in VSMC.[22] Arsenic alters focal adhesion proteins in VSMCs leading to their proliferation and migration.[23] Further, arsenic increases the synthesis of inflammatory mediators such as leukotriene E_4 (LTE_4) and prostacyclin, tumor necrosis factor-alpha and nuclear factor kappa B in vascular endothelial cells to induce the pathogenic process of atherosclerosis.[24,25] Moreover, arsenic causes neurogenic inflammation of the blood vessel by increasing the release of substance P and endothelial neurokinin-1.[26] Furthermore, arsenic activates protein kinase C alpha, which causes phosphorylation of beta-catenin and thus reverses the association between vascular endothelial cadherin and beta-catenin, along with the formation of actin stress fibers resulting in increased intercellular gap formation and permeability of the endothelium.[27] Arsenite has been reported to decrease the activity of endothelial nitric oxide synthase (eNOS) and Akt/protein kinase B, which subsequently decreases the bioavailability of NO that may lead to vascular endothelial dysfunction and associated cardiovascular complications.[28,29] Arsenite mediates vasoconstriction of the blood vessels by phosphorylating myosin light chain kinase (MLCK) and increases calcium sensitization leading to hypertension.[30] Chronic exposure to arsenic induces oxidative stress and alters the release of vasoactive mediators in blood vessel leading to elevation of blood pressure.[31] Arsenic trioxide develops ventricular arrhythmia by inducing prolonged Q-T interval and action potential duration.[18,32] Taken together, it may be suggested that arsenic induces cardiovascular dysfunction by inducing high oxidative stress, reducing the activation of eNOS and enhancing the phosphorylation of MLCK, which may be targeted for preventing arsenic exposure-associated cardiovascular complications [Figure 1]. Recently, a couple of studies from our laboratory demonstrated that treatment with either bis-(maltolato) oxovanadium, an inhibitor of protein tyrosine phosphatase, or rosiglitazone, an agonist of peroxisome proliferator activated receptor-gamma (PPAR-γ) markedly ameliorated sodium arsenite-induced vascular endothelial dysfunction in rats by enhancing the integrity of vascular endothelium, improving endothelium-dependent relaxation and reducing oxidative stress.[33,34]

ARSENIC-INDUCED DIABETES MELLITUS

The prolonged exposure to arsenic causes decreased expression of PPAR-γ, which may reduce the sensitivity

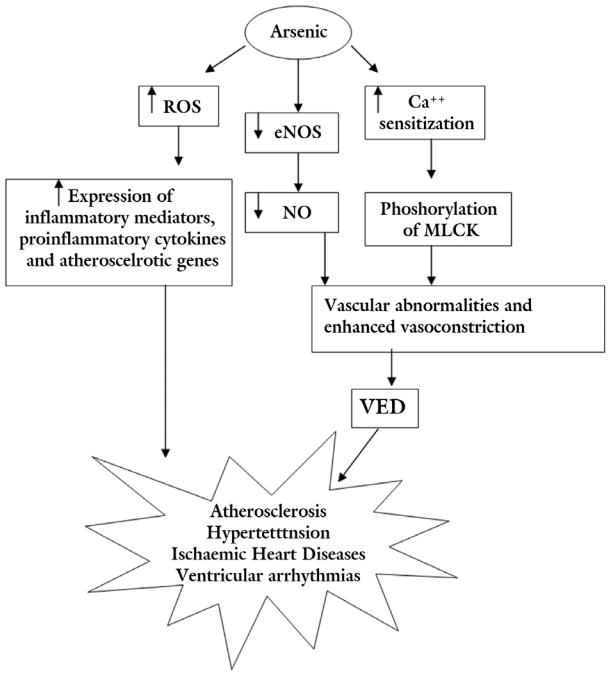


Figure 1: Pathological mechanisms involved in arsenic-induced cardiovascular dysfunction

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of insulin that is responsible for the induction of type II diabetes by arsenic.[35] Arsenite replaces a phosphate group from adenosine triphosphate (ATP) forming ADP-arsenate, which slows down the metabolism of glucose, interrupts the production of energy, and interferes with the ATP-dependent insulin secretion.[36] Moreover, arsenite has high affinity for sulfhydryl groups and hence form covalent bonds with the disulfide group of insulin, insulin receptors, glucose transporter, and enzymes involved in glucose metabolism.[36] An interesting biphasic response in glucose metabolism due to arsenic exposure was found through glucocorticoid receptor-mediated transcription with hyperglycemic effect at low concentration (<120 ppb) and hypoglycemia at high concentration (>120 ppb).[37] In addition, the chronic exposure to arsenic may cause hypoglycemia due to significant decrease in glucose-6-phosphatase activity in both liver and kidney.[38] Sodium arsenite has been suggested to downregulate the expression of insulin mRNA.[39] The long-term exposure to inorganic arsenic increases oxidative stress leading to overexpression of various stress mediators such as NF-κB, c-Jun-N-terminal kinase/stress-activated protein kinase (JNK/SAPK) and hexosamine that cause insulin resistance and dysfunction of beta cells of islets of Langerhans.[40] The trivalent arsenicals such as inorganic arsenic [iAs (III)], dimethylarsinous acid [DMA (III)], and monomethylarsonous acid [MMA (III)] suppress the phosphorylation of Akt/protein kinase B by inhibiting the activity of 3-phosphoinositide-dependent kinase-I (PDK-1) that causes significant inhibition of insulin-dependent glucose uptake and hence results in hyperglycemia.[40,41] Together, these studies suggest that decreased expression of PPAR-γ, interference in ATP-dependent insulin secretion, altered glucocorticoid receptor mediated transcription, and inhibition of PDK-1 are involved in the induction of arsenic-associated diabetes, which can serve as potential targets to modulate arsenic-induced diabetes [Figure 2].

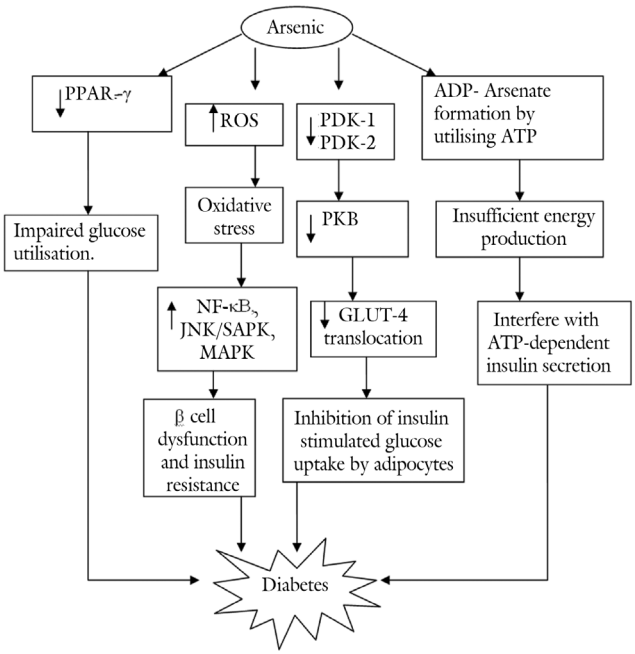


Figure 2: Pathological mechanisms involved in arsenic-induced diabetes

ARSENITE-INDUCED NEUROTOXICITY

Brain is a soft target for arsenic toxicity as it freely crosses blood-brain barrier.[42,43] Arsenic exposure is associated with wide range of neurological complications in humans such as impaired memory, poor concentration, Parkinson's disease, Guillain-Barre like neuropathy, verbal comprehension, encephalopathy, and peripheral neuropathy.[44-49] The mechanism postulated for arsenic-induced neurotoxicity majorly involve oxidative stress with increased reactive oxygen species, lipid peroxides along with decrease in superoxide dismutase, and reduced glutathione levels.[50] Arsenic exposure has been reported to alter metabolism of various neurotransmitters such as monoamines, acetylcholine, gamma amino butyric acid, and glutamate.[51] In a recent study, a significant reduction in monoamines such as adrenaline, nor-adrenaline, dopamine, and serotonin has been observed in corpus striatum, frontal cortex, and hippocampus areas of brain on chronic arsenic exposure.[42] Arsenite-mediated neurotoxicity involves induction of apoptosis in the cerebral neurons by activating p38 mitogen-activated protein kinase (p38MAPK) and JNK3 pathways.[52] Moreover, arsenic exposure induces neurotoxicity by causing destabilization and disruption of cytoskeletal framework, eventually leading to axonal degeneration.[53] The deficiency of thiamine (vitamin B1) is well known to induce neuronal complications. It is worthwhile to note that arsenic causes thiamine deficiency and inhibits pyruvate decarboxylase, which elevates blood pyruvate and hence causes encephalopathy.[47] Arsenic-induced oxidative stress in the brain causes oxidative DNA damage and subsequent brain cell death and induces the degeneration of dopaminergic neurons resulting in Parkinson like symptoms.[45,46] Acute arsenic toxicity decreases acetyl cholinesterase activity and hence causes cholinergic crisis like situation with altered mental status and weakness, which can be associated with peripheral neuropathy, neuropsychiatric abnormalities, and extrapyramidal disorders.[54] Moreover, arsenic affects the peripheral nervous system by disrupting the neuroskeletal integrity and thus markedly diminishes the nerve conduction velocity in the peripheral nerves to cause peripheral neuropathy.[49] The exposure to arsenic and its metabolites monomethylarsonic acid and monomethylarsonous acid suppresses the NMDA receptors in hippocampus, which play a pivotal role in synaptic plasticity, learning, and memory, leading to neurobehavioral disorders and cognitive dysfunction.[55,56] The chronic arsenic exposure is associated with morphological changes in axons and nerve fibers of the striatum which disturbs central structural organization.[57] Hence, oxidative stress,

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induction of thiamine deficiency, and inhibitions of pyruvate decarboxylase, acetyl cholinesterase, reduction in biogenic monoamines seem to play a pivotal role in arsenic-induced neurotoxicity [Figure 3]. 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. However, these have been able to provide deep insight into pathophysiological mechanisms involved in arsenic induced neurotoxicity.

ARSENIC-INDUCED NEPHROTOXICITY AND HEPATOTOXICITY

Arsenic concentrates in the kidney during its urinary elimination that affects the function of proximal convoluted tubules.[58,59] Arsenic-induced oxidative stress increases the expression of HO-1 and MAPK, which by regulating various transcription factors such as activator protein-1 (AP-1), activating transcription factor-2 (ATF-2), and Elk-1 lead to renal toxicity.[59,60] Acute renal dysfunction due to arsenic exposure is characterized by acute tubular necrosis and cast formation with increase in blood urea nitrogen and creatinine levels.[61] This arsenic-induced renal toxicity can be attenuated by *Curcuma aromatica* and *Corchorus olitorius*.[62,63] The kidney and liver are the primary targets for arsenic-induced toxicity, where the highest level of arsenic is detected in the liver than kidney.[64] Arsenite increases the generation of ROS, which enhances lipid peroxidation and cellular damage in both hepatic and renal tissue.[65] Chronic arsenic-mediated oxidative stress activates JNK and p38 MAPK and induces apoptosis in the hepatocytes.[66-68] Further, arsenic-induced oxidative stress induces hepatic apoptosis by upregulation of pro-apoptotic proteins.[69] A recent study has well documented that arsenite-induced apoptotic progression is aggravated by folate deficiency.[70] Arsenic exposure leads to the incidence of hepatotoxicity as manifested by increase in the levels of total bilirubin, alanine aminotransferase, aspartate aminotransferase, and malionaldehyde.[71] Hence, oxidative stress, apoptosis,and upregulation of transcription factors such as AP-1, ATF-2, and Elk-1 are the prospective target sites for arsenite-induced nephrotoxicity and hepatotoxicity [Figure 4].

Arsenic-induced carcinogenicity

The trivalent form of arsenic exhibits greater genotoxic effects than the pentavalent counterparts as it could be easily taken up by the cells.[72] Although the exact molecular mechanism of arsenic carcinogenicity is not well understood, arsenic has been shown to possess tumor-promoting properties by inducing intracellular signal transduction, activating transcription factors, and changing the expression of genes that are involved in cell growth, proliferation, and malignant transformation. Further, it is has been postulated that arsenic induces MAPK signal transduction, which activates transcription factors such as AP-1 and NF-kB to alter various gene expression profile that may account for the induction of arsenic-associated carcinogenicity.[73] Arsenic causes focal adhesion kinase activation, which mediates several downstream signaling pathways such as integrin, Src, Rho, Grb2, EGFR, ERK, and cadherins. These pathways are involved in cell adhesion, cell migration, cell survival, cell cycle control, carcinogenesis, and tumor cell necrosis.[74] DMA(V) and

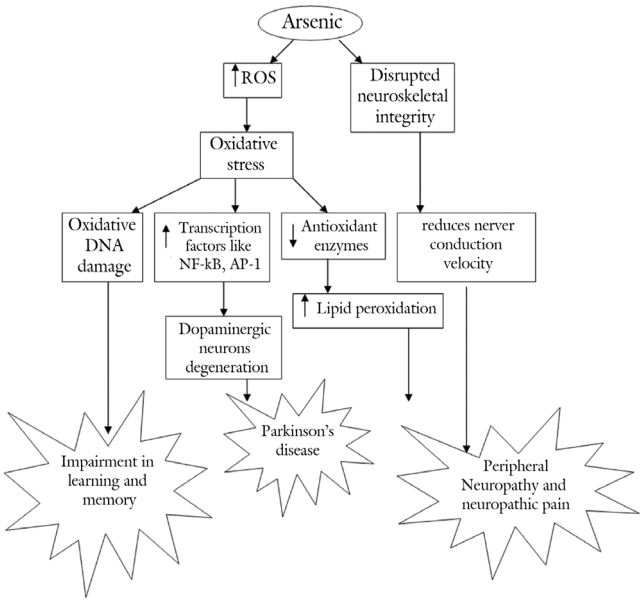


Figure 3: Pathological mechanisms involved in arsenic-induced neurotoxicity

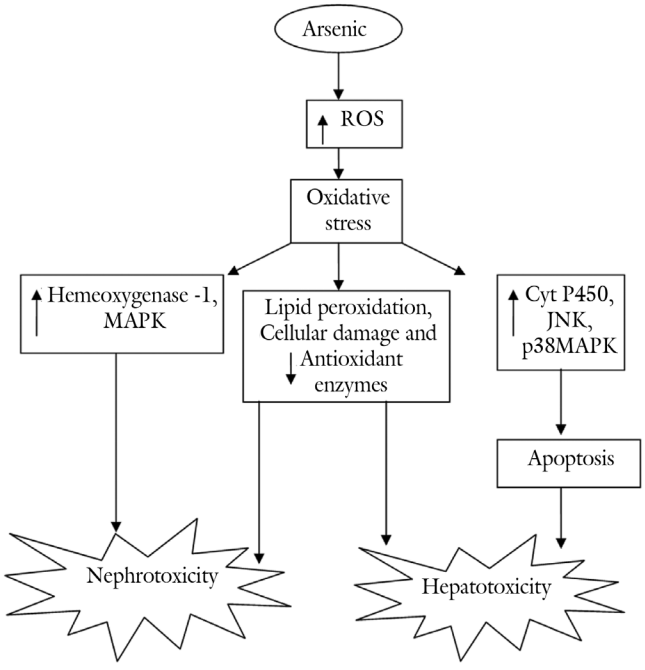


Figure 4: Pathological mechanisms involved in arsenic-induced hepatotoxicity and nephrotoxicity

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TMAO(V) generate oxidative stress and cause an elevation of 8-hydroxydeoxyguanosine, a marker of oxidative DNA damage, which stimulates cell proliferation and induces carcinogenicity.[75,76] Arsenic provokes proliferation of bladder epithelial cells and upregulates proto-onco-gene expression such as c-fos, c-jun, and EGR-1, which may collectively contribute to bladder cancer.[77] Smoking has been shown to potentiate the effect of arsenic on the risk of bladder and lung cancer because both can act synergistically to cause DNA damage.[78,79] Arsenic induces skin cancer by acting synergistically with sunlight and blocking DNA repair, stimulating angiogenesis, altering DNA methylation patterns, dysregulating cell cycle control, and blocking physiological apoptosis.[80] Oxidative stress seems to be the main culprit for arsenic-induced carcinogenicity, which can be prevented by antioxidants such as vitamin E, melatonin, and curcumin.[81,82] Taken together, various possible modes of carcinogenic action of arsenic proposed till date are increased oxidative stress, direct genotoxic effects, altered expression of growth factors, and altered DNA repairing mechanisms [Figure 5].

CONCLUSION

The chronic exposure to arsenic through contaminated water may account for various health intimidations. Arsenic increases oxidative stress, upregulates proinflammatory cytokines and inflammatory mediators, inactivates eNOS, and causes phosphorylation of MLCK to induce cardiovascular abnormalities. The decreased expression of PPAR-γ, interference in ATP-dependent insulin secretion, altered glucocorticoid receptor-mediated transcription, and inhibition of PDK-1 are the pathological events associated with arsenic-induced diabetes. Further, oxidative stress, inhibition of pyruvate decarboxylase, and acetyl cholinesterase seem to play a pivotal role in arsenic-induced neurotoxicity. Moreover, arsenic induces nephrotoxicity and hepatotoxicity by increasing oxidative stress and apoptosis. Furthermore, arsenic exposure may cause carcinogenicity as it increases oxidative DNA damage and chromosomal aberration and interferes with cellular signaling pathways. Targeting and modulating the aforementioned key pathological signaling mechanisms may provide novel pharmacological interventions to halt arsenic exposure-associated disorders.

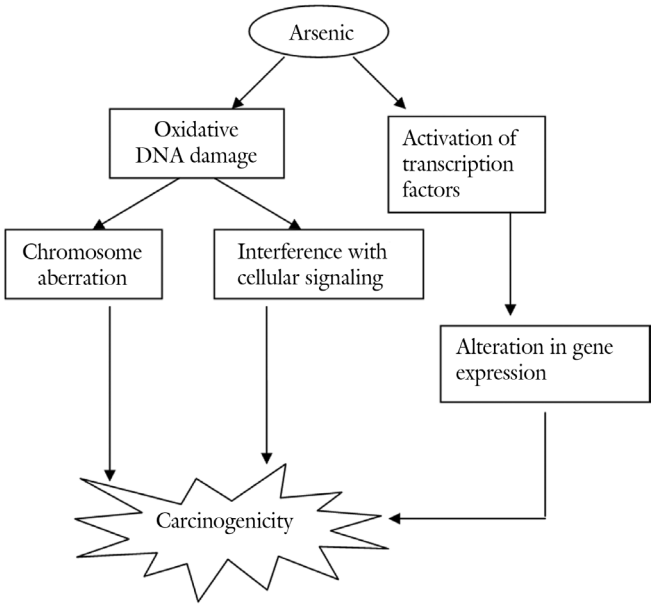


Figure 5: Pathological mechanisms involved in arsenic-induced carcinogenicity

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