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Molecular Basis of Neurodegenerative Changes and Neurotoxicity Linked with Arsenic Exposure: A Review

Priyadarshini Soni[1], Rupesh Kumar Pandey[*2], Surbhi Gupta[3], Akansha Singh[4] Lubhan Singh[5]

[1]Reseach Scholar, Faculty of Pharmacy, Swami Vivekanand Subharti University, Meerut-250005
[*2, 4 & 5] Faculty of Pharmacy, Swami Vivekanand Subharti University, Meerut-250005
[3]School of Pharmacy, Bharat Institute of Technology, Meerut-250005

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Abstract

Background

Toxicity with metals like arsenic trioxide is a growing concern as they are responsible to leading neurological diseases. The neurological diseases that are increasing day by day are not specific to any age or gender.

Main Body

In this systematic review, we have collected scientific information related to toxicity of heavy metal which leads to neurological complications. Such an approach incorporates the environmental occurrence of arsenic trioxide, human exposure, clinical significance, impact on the brain, and the mechanisms involved. Mechanistic approach behind arsenic neurotoxicity is oxidative stress, disruption of vital cellular functions such as glutathione depletion and lipid peroxidation and impaired neurotransmitter signaling. Gaining an understanding about these pathways are necessary for creating solutions that effectively lessen the detrimental impacts of (As) exposure on human health. Arsenic exposure exhibits neurodegenerative changes in brain due to oxidative injury, mitochondrial impairments, glutamate excitotoxicity through glutamate transporters, and calcium dysregulation through ryanodine receptors modulation in the brain. Arsenic neurotoxicity has been studied for many years, but in order to comprehend their possible health advantages, their mechanistic significance has recently been investigated. In this review, we have discussed the mechanisms involved in arsenic trioxide mediated neurodegenerations.

Short conclusion

This review provides a summary on current prospective related to neurological consequences of arsenic trioxide. The findings highlights that a multimodal strategy is needed to reduce the health effects of arsenic exposure, including strict industrial process controls, food and water source monitoring, and public awareness programs.

Keywords: Ryanodine Receptor, Glutamate Transporter, Glutathione, Glutamate Excitotoxicity

1. Introduction

Human coming into contact with heavy metals (Pb, As, Hg, Cd, Zn, Ag, Cu, Fe, Cr, Ni, Pd) has been related to serious health issues that worsen with time and impact several major organs, including the liver, heart, brain, and kidneys. They cause disruptions to the neuronal reactions by interfering with the regular biological mechanisms. These are not biodegradable; thus, they linger longer and present long-term health hazards [Hamdy et al., 2019]. Amid the most dangerous metals reported in the natural form in the world is arsenic (As) [Ratnaik, 2003]. It is widely recognized that

arsenic (As) is an enormous environmental element that seriously impacts the condition of humans and other animals [Kurosawa et al., 2008]. There has been a long history of using arsenic including as a wood preservative, agricultural compounds, medicines, and uses in the semiconductor, metallurgical, glass, and mining industries also used as a homicidal agent and as a pigment. However, over the past 100 years, (As) has been utilized as an insecticide, and component of several goods [Hughes et al., 2011]. It has long been recognized and utilized in Persia and other ancient cultures as well as in traditional Chinese and Indian medicine other than this it was used as an eye shadow beauty product throughout the Roman Empire [Marsh, 1836]. Additionally, there is an extensive history of intentional poisoning with arsenic. Napoleon Bonaparte was arguably the most well-known victim of (As) poisoning. Based on a hair sample's neutron activation research, it appears that he was exposed on a regular basis in 1816 [Leslie and Smith, 1978]. Thus, elevated atmospheric arsenic levels have been identified as a significant concern to world health for humans [Karagas et al., 2002]. Diverse clinical diseases, such as neurotoxicity and immunotoxicity, can arise from exposure in the workplace and surroundings to metals and metalloids. Reportedly, (As) may migrate over the blood-brain barrier and accumulate into the various brain regions that can affects various neurological conditions [Nagaraja & Deiraju, 1994; Rodriguez et al., 2003; Islam at al., 2007; Palmieri et al., 2007; Duana et al., 2016]. In numerous nations throughout the world, groundwater has been found to contain arsenic (As) with concentrations higher than the 10 µg/L. WHO drinking water guideline standard [WHO, 2001] and the national regulatory criteria (50 µg/L) in Bangladesh and India [Ahmad et al., 2004]. Groundwater with arsenic is frequently linked to geology origins however, anthropogenic inputs can have a significant impact in some places. The implications of (As) poisoning are especially concerning in Asia. For instance, in West Bengal, India, and the Bengal Basin of Bangladesh [Bhattacharya et al., 1997; Bhattacharya et al., 2002; Bhattacharya et al., 2002; Bhattacharya et al., 2004; Bhattacharya et al., 2006; Mukherjee & Bhattacharya, 2001]. The greatest environmental health crisis has been identified as groundwater, putting at least 100 million people in danger of cancer and other diseases linked to (As) for example, in various parts of Madhya Pradesh and Chhattisgarh, in the Central Gangetic Plains of Uttar Pradesh, Bihar, Jharkhand, and the Brahmaputra valley in Assam, India [Mukherjee et al., 2006].

2. Material and Method

In this review, we have done systematic review from Cochrane database. We have reviewed more than 125 papers in which 90 papers are having relevance with regards to prospective of the neurological consequences of metal poisoning we used keywords as arsenic (As), reactive oxygen species (ROS), glutamate transporter (GLT-1) and ryanodine Receptors (RyR).

2.1 Environmental occurrence

In nature, (As) is a present as metalloid that can exist in both organic and inorganic forms. There are around 300 arsenic (As) minerals in the environment. Approximately 60% of them are arsenates, 20% are sulfides and sulphosalts, 10% are oxides, and the remaining percentage are arsenites, arsenides, and native elements and alloys of metals [Bowell & Parshley, 2001]. According to research, inorganic arsenic is more poisonous and has more detrimental effects on health. The ancient Greeks described two arsenic sulfide minerals, red-colored realgar (As4S4) and bright yellow orpiment (As_2S_3), but they thought of them as two completely different entities. For instance, arsenic trioxide (As_2O_3) is a white powder with no flavor or odor. It has an atomic number of 33 but is never found in its pure elemental state. Arsenic is released into soil and water through weathering, dissolution, and erosion. As-rich alluvial groundwater is global issue [Nriagu et al., 2007]. Drinking water contamination from natural sources is the main cause of arsenic toxicity in humans, as opposed to those derived through mines, smelting, or farming (pesticides or fertilizers) [Matschullat, 2000]. (As) is found in trace amounts in the air, food, soil, and ocean. Its concentration in the Earth's crust is typically 1.5–5 mg/kg. (As) happens in rocks, loose sediments, and soils at varying amounts. (As) concentrations in soils can range from 0.1 mg/kg to 40 mg/kg [Ure & Berrow, 1982]. Paints, fungicides, insecticides, pesticides, herbicides, wood preservatives, and cotton desiccants are among the industrial products made with arsenic. (As) is added to animal feed because it is a necessary trace element for certain animals. Crystals of gallium arsenide, additionally referred to as aluminum gallium

arsenide, are used in light-emitting diodes, semiconductors, lasers, and other transistors [Ratnaik, 2003].

2.2 Arsenic Exposure

Exposure to (As) can happen by ingestion of tainted drinking water, for example, additionally through inhalation and skin absorption. Arsenobentaine and arsenocholine, two generally innocuous chemical molecules found in food, are sources of arsenic. The most abundant organic sources are fish, seafood, and algae [Edmonds & Francesconi, 1987]. Arsenic-containing soil that is irrigated with water tainted with arsenic or agricultural products can introduce both organic and inorganic arsenic compounds into the plant food chain [Tamaki & Frankenberger, 1992]. The small intestine is the primary site of absorption by an electrogenic mechanism that involves a gradient of protons (H+) [Gonzalez et al., 1997]. The ideal pH for absorbing arsenic is 5.0 [Silver & Misra, 1984], but due to release of pancreatic bicarbonate, the pH in the environment of the small intestine is roughly 7.0 [Ratnaik & Barbour, 2000]. Hepatic biomethylation of the ingested arsenic produces less toxic but still somewhat harmful monomethylarsonic acid and dimethylarsinic acid. In three to five days, the urine may contain around half of the consumed dosage. Comparing monomethylarsonic acid to dimethylarsinic acid, the former is the more common urine metabolite (60–70%) [Thompson, 1993; Aposhian, 1997; Hopenhayen et al., 1993]. Additionally, a tiny quantity of inorganic arsenic is unchangedly expelled. Studies using atomic absorption spectroscopy that is electrothermal after acute poisoning reveal that the kidneys and liver have the highest quantity of arsenic. When arsenic is consumed over a prolonged duration of time, it builds up in the lungs, heart, liver, and kidneys and in smaller levels in the muscles, neurological system, gastrointestinal tract, and spleen [Benramdane et al., 1999; Negi et al., 2024].

2.3 Clinical Significance

The symptoms of arsenic poisoning that appear quickly include bloody diarrhea, encephalopathy, vomiting, and stomach discomfort. Cancer can result from excessive exposure, heart problems, numbness, diarrhea, thickening and darkening of the skin, as well as abdominal pain. Urine, blood, or hair tests are used to make the diagnosis. Arsenic works by modifying the way about 200 enzymes function [Ratnaik, 2003]. Abdominal pain, nausea, vomiting, and diarrhea are symptoms of food poisoning that might happen within hours of consuming substantial levels of arsenic. Hypovolemic shock can arise from substantial fluid loss brought on by bloody diarrhea. Additionally, problems with the heart and nervous system might result in heart failure, tachycardia or QT interval prolongation, confusion, seizures, brain swelling, coma, and even death. The most poisonous form of arsenic, arsine gas, can produce a multisystem illness that manifests two to twenty-four hours after inhalation. RBCs degeneration, headaches, weakness, breathing difficulties, kidney and liver malfunction, and gastrointestinal upset are among the symptoms [Mahajan, 2020]. Long-term consumption of lesser concentrations of arsenic results in skin alterations that are usually noticeable as hyperpigmentation (dark patches), however it can also sporadically happen as hypopigmentation (light patches) or as alternating regions of each. The palms and soles of certain people's feet may become generally thicker, or there may be isolated regions of thicker skin. Liver and spleen enlargement, heart disease, diabetes, cognitive decline, and portal vein damage (portal hypertension and non-cirrhotic portal fibrosis) are some other significances of prolonged exposure [Martinez-Castillo et al., 2021; Chen & Costa, 2021]. Squamous cell carcinoma in situ is the most frequent type of skin cancer caused by arsenic poisoning, and it usually develops two to twenty years after exposure [Santa Cruz & Gru, 2021].

2.4 The Impact of As_2O_3 exposure to brain functions

Water tainted with (As) at quantities as low as 10–50 parts per billion can result in Polyneuropathy from long-term exposure [Mochizuki et al., 2019]. This results in a deficit that is primarily seen in sensory fibers and less so in motor fibers [Ishii et al., 2018]. Furthermore, (As) exposure concentrations, acute or chronic factors can potentially cause organ damage. The primary target of (As) in the nervous system is peripheral neuropathy resembling Guillain-Barré syndrome [Goddard et al., 1992] initially the neuropathy is sensory and is treated with glove and stocking anesthesia. Toxic effects also include altered behavior, disorientation, and loss of memory [Schenk & Stolk, 1967]. Cognitive impairment is another sign of (As) poisoning [Morton & Caron, 1989]. In a comprehensive research 8102 males and females who had

long-term exposure to well water tainted with arsenic, an elevated prevalence of cerebrovascular illness, particularly cerebral infarction, was noted [Chiou et al., 1997]. Increasing evidence also suggests that arsenic may cause lipid peroxidation in the brain by producing free radicals and reactive oxygen species (ROS), which can disrupt the functions of the enzymes that make up the antioxidant defense mechanism [Rao & Avani, 2004].

2.5 Arsenic Trioxide Neurotoxicity Mechanisms

Some pathways that appear to be important in As-induced neurotoxicity include oxidative stress, thiamine shortage, and reduced acetyl cholinesterase activity [Dwivedi & Flora, 2011; Singh et al., 2011].

2.5.1 Oxidative Stress

Reactive oxygen species (ROS) are synthesized by arsenic trioxide by a multitude of routes:

2.5.1.a Mitochondrial dysfunction

The capacity of (As) to bring about oxidative damage and mitochondrial dysfunction is one among the most significant processes underlying its neurotoxicity [Chandravanshi et al., 2018; Prakash & Kumar, 2016]. An important source of reactive oxygen species (ROS) in cells is the electron leak from the electron transport chain of the mitochondria.

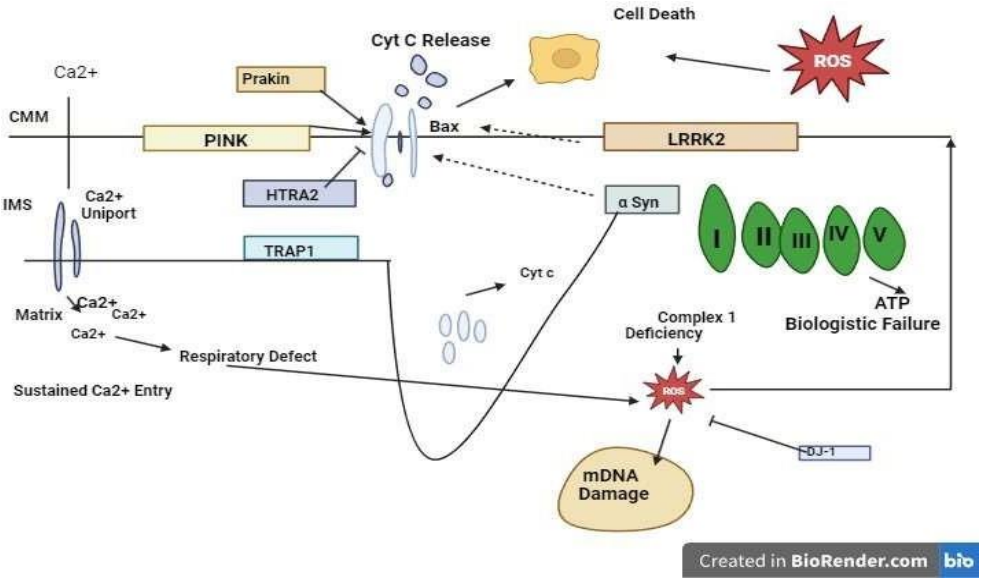

Fig. 1 Oxidative stress, Mitochondrial Dysfunction and Neurodegenerative changes

Antioxidant keep mitochondrial ROS levels steady in a physiological setting, but when a person is injured or elderly, their body produces more ROS [Halliwell 7 Cross, 1994; Forman, 2016]. The nicotinamide adenine dinucleotide phosphate (NADPH)-dependent oxidases (NOX) and the NO synthases (NOS) are the other sources of ROS/ reactive nitrogen species (RNS) [Culotta et al., 2006]. Oxidative stress results from an inconsistency between rising ROS/RNS levels and their metabolism or detoxification and lead to oxidative modifications of biomolecules connected to the loss of function of proteins, damage to organelles and even cell death [Forman, 2016]. Within the rat brain, arsenic raised the amounts of reactive oxygen species (ROS) and reduced the activity of mitochondrial complexes I, II-III, and IV [Chandravanshi et al., 2014]. Lipid bilayer damage is brought carried out by the buildup of ROS, which also results in mitochondrial enlargement and a decrease in membrane potential. Additionally, it has been established that mitochondrial malfunction and oxidative stress could perhaps lead to neurodegeneration (Fig.1) [Srivastava et al., 2014].

2.5.1.b Glutathione Depletion

Glutathione works to protect cells from harm by neutralizing dangerous chemicals produced during the process of producing energy. In addition, it is involved in the synthesis of proteins, DNA, and other critical cellular components also in the metabolism of drugs. Red blood cell death is typically the outcome of mild glutathione

synthetase deficiency (hemolytic anemia) [Al-Jishi et al., 1999; Ben Ameur et al., 2015]. Glutathione (GSH) thiol groups are linked by ATO, reducing GSH levels in cells. Since GSH is a major antioxidant that minimizes ROS, oxidative stress is made worse when it's reduced (Fig 2).

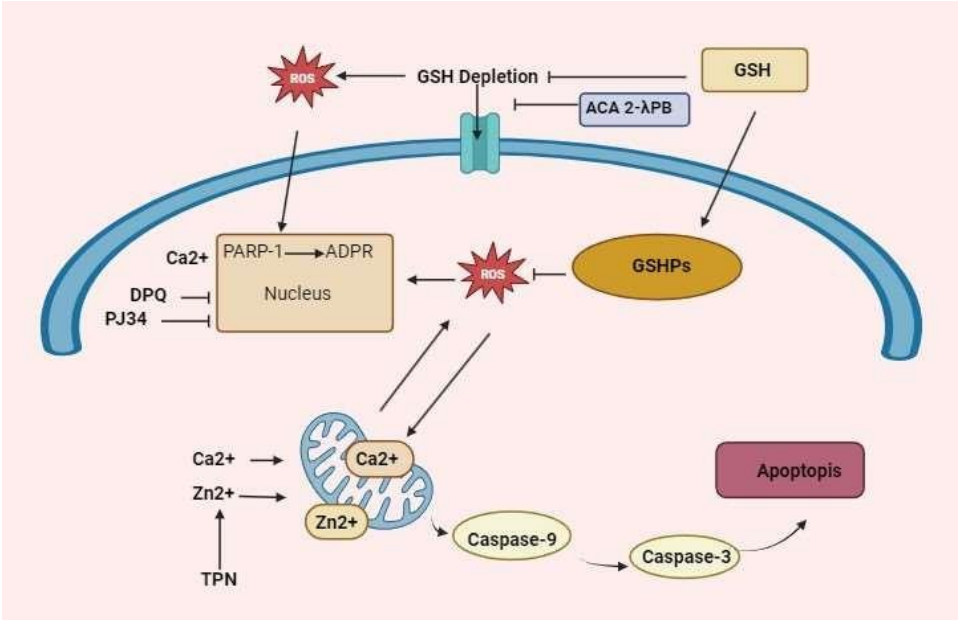

Fig. 2 Depletion of glutathione leads to oxidative stress.

2.5.1.c Metalloprotein Inhibition

Cellular inhibitors of matrix metalloproteinases (MMPs) are known as metalloprotease inhibitors. In several clinical circumstances, including inflammation, metabolic bone disease, cancer invasion, metastasis, and angiogenesis, the expression of MMPs is elevated. The subsequent items are some examples of diseases: Alzheimer's disease, rheumatoid arthritis, osteoarthritis, multiple sclerosis, periodontitis, hepatitis, glomerulonephritis, atherosclerosis, emphysema, asthma, autoimmune disorders of skin and dermal photoaging, uterine involution, corneal epithelial defects, bone resorption, tumor progression and metastasis.

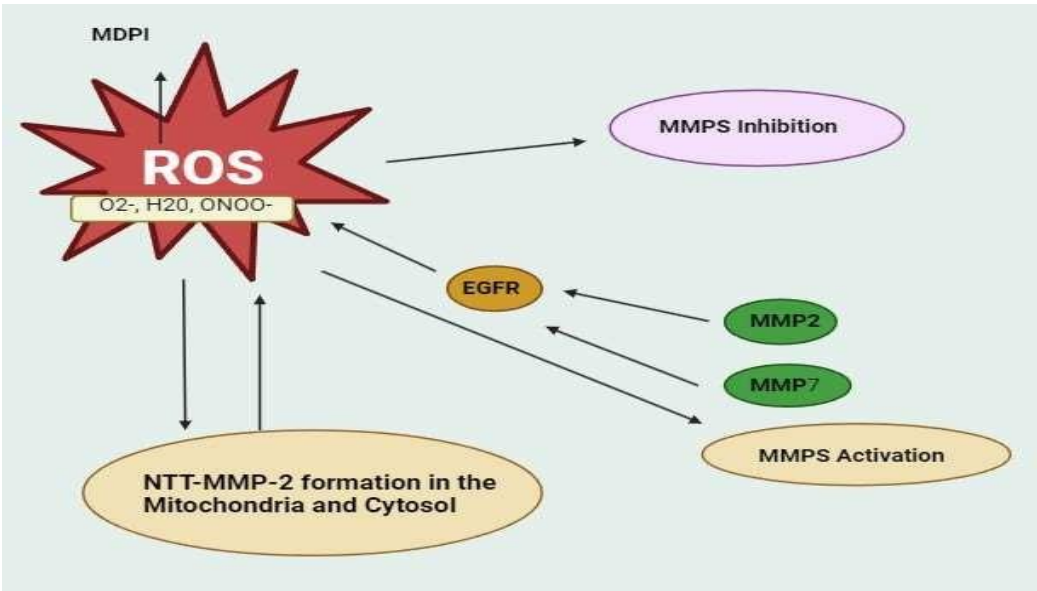

Fig. 3 Biomolecules Metalloproteins effects on ROS

Metalloproteins that typically scavenge ROS, such as catalase and superoxide dismutase (SOD), are inhibited

by ATO. This inhibition promotes the accumulation of ROS, which affects different areas of the cell (Fig.3) [Acharya et al., 2004; Whittaker & Ayscough, 2001].

2.5.1.d Lipid Peroxidation

Lipid oxidation, also known as lipid peroxidation, is a complicated chemical process that causes lipids to degrade oxidatively [Izdebska, 2016], leading to the production of derivatives of peroxide and hydroperoxide [Ayala et al., 1014]. Reactive oxygen species (ROS), a type of free radical, interact with lipids found in cell membranes. Lipid radicals, also known as lipid peroxides or lipid oxidation products (LOPs), are created consequently of this process. These LOPs then react with other oxidizing substances, setting off a series of events that cause oxidative stress and cell damage**.** Lipid peroxidation is caused by ROS attacking the lipids in membranes. Neuronal function can be affected by this process, which damages cell membranes, reduces their fluidity, and messes with ion gradients (Fig. 4).

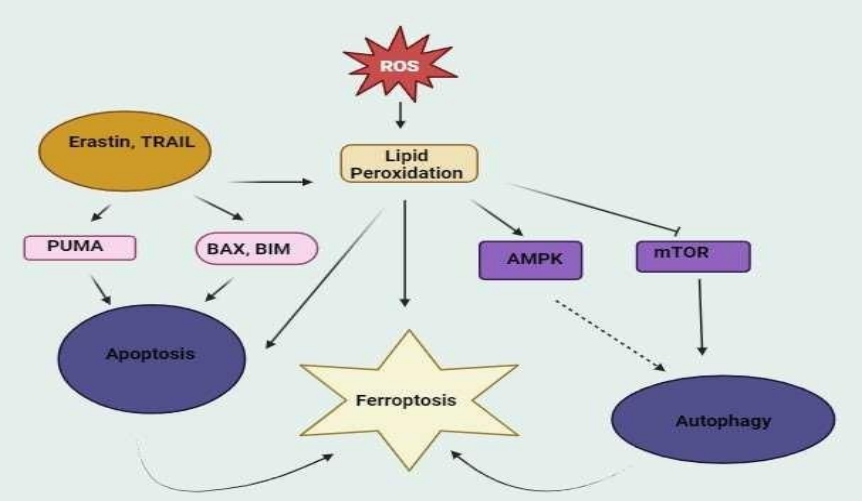

Fig. 4 Effects of ROS on Lipid Peroxidation

2.5.2 Disruption of Neurotransmitter Signaling Pathways

Arsenic trioxide generates neurotoxic effects by interfering with neurotransmitter systems.

2.5.2.a Glutamate Excitotoxicity

As a neurotransmitter—a substance that nerve cells employ to send signals to other cells—glutamate is the anion of glutamic acid. It is by far the most prevalent excitatory neurotransmitter in the nervous system of vertebrates [Meldrum, 2000].

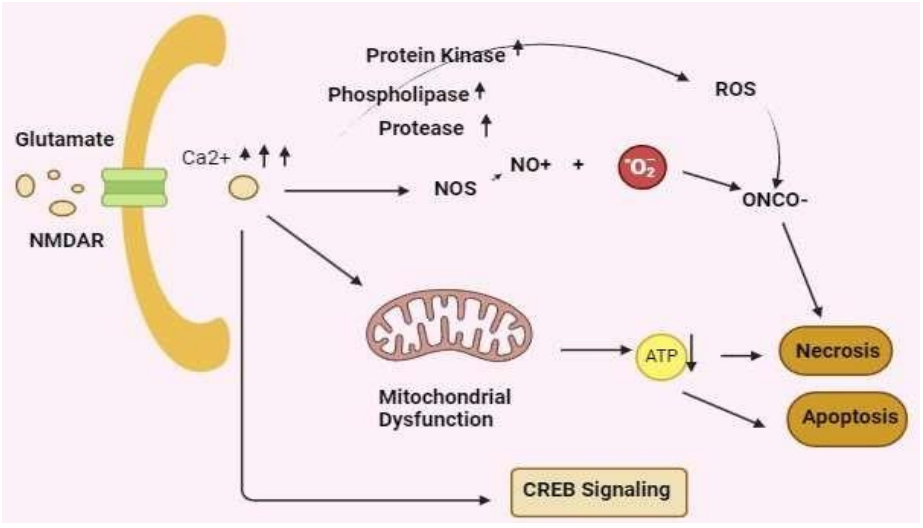

Fig. 5 Molecular Mechanism of Glutamate Toxicity

Their qualities make them particularly crucial for memory and learning. Metabotropic receptors cause gradual, persistent effects on their targets by acting through second messenger systems. Excessive glutamate receptor activation (such as NMDA receptors) results from ATO's enhancement of glutamate release and inhibition of its reuptake. Excitotoxicity results in calcium influx, mitochondrial malfunction, and neuronal death (Fig. 5).

2.5.2.b GABAergic Dysfunction

The primary inhibitory neurotransmitter in the developed central nervous system of mammals during development is GABA. Its main function in the neurological system is to decrease neuronal excitability [Kuriyama & Sze 1971; Boonsta et al., 2015].

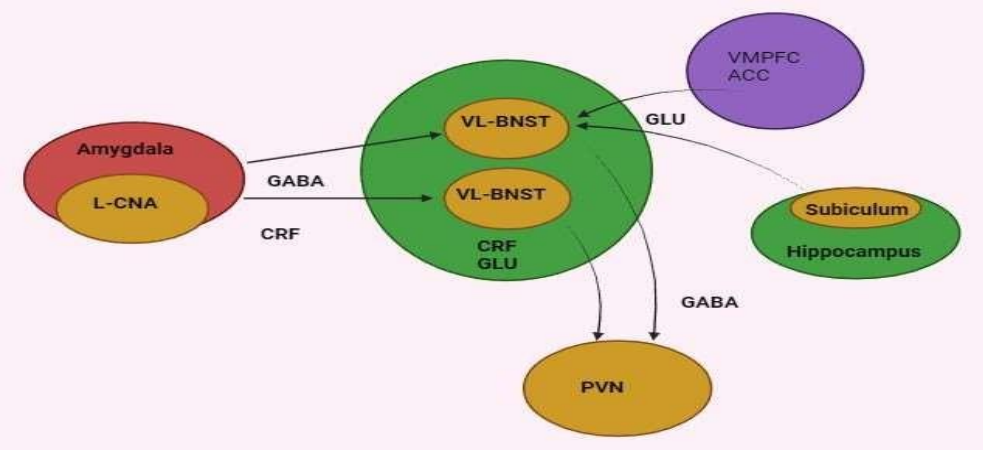

Fig 6 GABAergic Dysfunction in Neurotransmitter Signal Pathway

Through the inhibition of GABA production enzymes and the promotion of GABA release, ATO modifies GABAergic neurotransmission. Neural hyperexcitability is exacerbated by this imbalance between excitatory and inhibitory neurotransmission (Fig. 6).

2.5.2.c Dopaminergic and Serotonergic Disruption

Serotonin and dopamine are two substances that go throughout the body sending signals that impact our emotions. Our brains temporarily experience pleasure when dopamine is released. Though it works similarly to dopamine, serotonin produces a mood that lasts for a long time. With changes in neurotransmitter release and receptor sensitivity, ATO influences the dopaminergic and serotonergic systems. Mood disorders, cognitive decline, and motor dysfunction can result from this disruption [Li et al., 2020; Niu & Zhang, 2019; Chowdhury et al., 2021; Singh & Sharma, 2020; Singh & Sharma, 2017; Gupta et al., 2024; Singh et al., 2014; Danbolt, 2001].

2.6 Glutamate transporter (GLT-1)

To ensure that neurotransmission functioning properly and shield the brain from excitotoxicity, glutamate transporters are essential. These carriers are crucial because removing excess glutamate from the synaptic cleft, ensuring that neuronal transmission remains balanced. Excitatory amino acid transporters (EAAT), or glutamate transporters, are the primary glutamate transporters in the CNS. EAAT1 (also known as GLAST), EAAT2 (GLT-1), EAAT3 (EAAC1), EAAT4, and EAAT5 are the subclasses of EAAT that is a transport protein. Of these, the majority of glutamate absorption in the brain is caused by GLT-1 which is mostly expressed in astrocytes. In the transport process, glutamate is moved along with the co-transport of three sodium ions and one proton into both the counter-transport and the cell of one potassium ion out of the cell. Increased amounts of extracellular glutamate resulting from dysregulation of glutamate transporters can cause neurodegeneration and dysfunction in neurons. Transporters of glutamate have been linked to number of neurological conditions, such as epilepsy, Alzheimer's disease, and ischemic stroke, as demonstrated by numerous researches. For the purpose of controlling glutamate homeostasis and reducing the negative effects of excessive glutamate signaling in the

brain, it is imperative to comprehend the mechanisms and roles of glutamate transporters. [Robinson & Jackson, 2016; Fill & Copello, 2002].

2.7 Ryanodine Receptors

A class of intracellular calcium channels known as RyRs (ryanodine receptors) is present in many different types of cells, including neurons and muscle cells. They are necessary for calcium signaling, especially in the location of excitable cells implicated in the release of neurotransmitters and contraction of muscles. RyR is present in three different isoforms: RyR1, which is mostly found in skeletal muscle; RyR2, which is primarily found in cardiac muscle; and RyR3, which is expressed in a range of organs, including the brain. These big proteins, known as receptors, have several domains, one of which forms a pore and is in charge of allowing calcium to pass through the membrane. Calcium-induced calcium release (CICR), wherein a minor calcium influx causes a greater release of calcium from intracellular reserves, activates RyRs. This process is essential for synaptic neuronal transmission and excitation-contraction coupling in muscle cells. In order for skeletal muscle to contract, the appearance of calcium from the sarcoplasmic reticulum needs to be handled by a mediator RyR1. Calcium homeostasis during cardiac contraction and relaxation is mostly controlled by RyR2, which is mainly present in heart muscle cells. Though it has not received as much research, RyR3 is engaged in the plasticity of synapses and neuronal calcium signaling. It takes part in controlling the brain's synaptic strength and release of neurotransmitters. Determining the roles of RyR receptors in both healthy and pathological conditions requires an understanding of their structure and function. Pharmacologically targeting RyRs may present therapeutic prospects for diseases like cardiac arrhythmias and neurological conditions that are connected to calcium dysregulation [Marks, 2000; Fruen et al., 1997; Singh & Sharma, 2016].

3 Conclusion

In summary, significant health risks are connected to human exposure to heavy metals, such as arsenic (As), This may be harmful to important organ systems and physical functions. There are several ways to get exposed to arsenic: eating or drinking tainted water or food, breathing it in, and absorbing it through the skin. Both organic and inorganic forms can be hazardous, although inorganic arsenic is more dangerous. Long-term exposure to arsenic can result in a variety of health problems, including several types of cancer, heart disease, neurological conditions, and abnormalities of the skin. Arsenic neurotoxicity is caused by oxidative stress, disruption of neurotransmitter signaling pathways, and changes in calcium homeostasis that are mediated by ryanodine receptors and glutamate transporters, among other proteins. A multimodal strategy is needed to reduce the health effects of arsenic exposure, including strict industrial process controls, food and water source monitoring, and public awareness programs.

List of Abbreviations

As: Arsenic
WHO: World Health Organization
AS_4S_4: Arsenic Sulfide
AS_2S_3: Arsenic Trisulfide
AS_2O_3: Arsenic Trioxide
QT Interval Prolongation: Irregular heart rhythm
RBCs: Red blood cells
ROS: Reactive Oxygen Species
NADPH: Nicotinamide adenine dinucleotide phosphate
NOX: Nitrogen dependent oxidases
NOS: NO synthases
RNS: reactive nitrogen species
GSH: Glutathione
ATO: Arsenic Trioxide

MMPs: Matrix metalloproteinases
SOD: Superoxide dismutase
LOPs: Lipid oxidation products
NMDA receptors: N-methyl-D-aspartate receptor
GABA: Gamma-aminobutyric acid
EAAT: Excitatory amino acid transporters
GLT-1: Glutamate transporter
RyRs: Ryanodine Receptors
CICR: Calcium-induced calcium release

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