**DOPAMINERGIC NEURODEGENERATION IN THE SUBSTANTIA NIGRA: EXPLORING THE PATHOLOGICAL CASCADE TRIGGERED BY ARSENIC**

**Abstract:**

Parkinson's disease (PD), characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), is a debilitating neurodegenerative disorder. While genetic factors contribute, environmental toxins like Arsenic (As) have been implicated in PD pathogenesis. This review examines the current understanding of arsenic-induced dopaminergic neurodegeneration, focusing on the specific pathological mechanisms triggered by arsenic exposure within the SNpc. A comprehensive literature search was conducted using databases such as PubMed, Scopus, and Web of Science. Search terms included "arsenic," "dopaminergic neurons," "substantia nigra," "neurodegeneration," "Parkinson's disease," "oxidative stress," "inflammation," "mitochondrial dysfunction," and "protein aggregation." Studies included were prioritized based on their relevance to arsenic's effects on dopaminergic neurons in the SNpc and the underlying cellular and molecular mechanisms. Exposure to arsenic induces a cascade of pathological events in dopaminergic neurons of the SNpc. Key mechanisms include: (1) **Oxidative stress:** Arsenic promotes the generation of reactive oxygen species (ROS), leading to lipid peroxidation, DNA damage, and protein oxidation. (2) **Mitochondrial dysfunction:** Arsenic disrupts mitochondrial respiration, impairs ATP production, and increases ROS generation, further exacerbating oxidative stress. (3) **Inflammation:** Arsenic activates microglia and astrocytes, leading to the release of pro-inflammatory cytokines that contribute to neuronal damage. (4) **Protein aggregation:** These interconnected pathways ultimately compromise neuronal function and survival, resulting in dopaminergic neurodegeneration. **In conclusion,** Arsenic exposure represents a significant environmental risk factor for dopaminergic neurodegeneration. Understanding the precise molecular mechanisms through which arsenic triggers neuronal damage in the SNpc is crucial for developing effective preventative and therapeutic strategies to mitigate the risk of Parkinson's disease and other related neurodegenerative disorders. Further research is warranted to investigate potential interventions targeting the specific pathways activated by arsenic, such as antioxidant therapies, anti-inflammatory agents, and strategies to promote mitochondrial health and protein homeostasis.

**Keywords:** *Arsenic, dopaminergic neurodegeneration, substantia nigra, mitochondrial dysfunction, neuroinflammation,*

**Introduction**

Arsenic, a naturally occurring element and a ubiquitous environmental toxicant, represents a significant and pressing global health challenge (Jiang et al., 2023). Its widespread presence in soil, water sources (both surface and groundwater), and air, often stemming from both natural geological sources and anthropogenic activities such as mining and industrial processes, makes human exposure virtually unavoidable in many regions (Oyovwi et al., 2025; Beckers and Rinklebe, 2017). Chronic exposure to arsenic, even at relatively low levels deemed acceptable by regulatory bodies, has been increasingly linked to a wide array of adverse health effects, extending far beyond the traditionally recognized dermatological and carcinogenic consequences. Among these emerging concerns is an alarming association with the development and progression of neurodegenerative diseases. Notably, epidemiological studies and experimental research have implicated arsenic exposure in the emergence of Parkinson's-like symptoms, including tremors, rigidity, and bradykinesia (Aldaajani et al., 2024; Afsheen et al., 2024; Chen et al., 2023). This association raises serious concerns about arsenic's potential to induce dopaminergic neurodegeneration, the hallmark of Parkinson's disease. The loss of dopamine-producing neurons in specific brain regions is a critical factor in the debilitating motor impairments characteristic of the disease.

This review focuses on dissecting the specific mechanisms by which arsenic targets the substantia nigra, the brain region most severely affected in Parkinson's disease, and triggers the complex cascade of events ultimately leading to neuronal damage and dysfunction. The study will explore the role of oxidative stress, mitochondrial dysfunction, inflammation, and protein misfolding, among other potential contributing factors, in arsenic-induced neurotoxicity. Understanding these intricate pathological pathways at the molecular and cellular levels is crucial for developing effective preventative measures, such as improved water filtration technologies and remediation strategies, and for designing targeted therapeutic interventions aimed at mitigating the neurotoxic effects of arsenic exposure and potentially slowing the progression of neurodegenerative diseases. Ultimately, a comprehensive understanding of arsenic's neurotoxic mechanisms is essential for safeguarding public health and reducing the global burden of arsenic-related neurological disorders.

**The Substantia Nigra and Dopamine Production**

**The substantia nigra, a key structure nestled within the midbrain, plays a pivotal role in a diverse array of functions, most notably movement, reward processing, and various other cognitive operations (**Wang et al., 2024)**. Its name, Latin for "black substance," derives from the dark pigmentation visible macroscopically, a consequence of the high concentration of neuromelanin within its dopaminergic neurons (**Chandler et al., 2019)**. This complex structure is anatomically and functionally divided into two primary compartments: the pars compacta (SNpc) and the pars reticulata (SNpr). The SNpc is characterized by its dense population of dopaminergic neurons, specialized cells responsible for the synthesis and release of dopamine, a neurotransmitter universally recognized for its vital role in the orchestration of smooth, coordinated motor control.** **These dopaminergic neurons of the SNpc extend their axons primarily to the dorsal striatum (comprising the caudate and putamen), forming the nigrostriatal pathway. This pathway is critically involved in influencing the initiation, planning, and execution of voluntary movements. Dopamine released into the striatum acts on D1 and D2 receptors, modulating the activity of striatal neurons and ultimately influencing the output of the basal ganglia. The SNpr, in contrast to the SNpc, acts as a major output nucleus of the basal ganglia. It receives inhibitory input from the striatum and globus pallidus, and in turn, projects to downstream targets in the thalamus and brainstem. Through these projections, the SNpr exerts a powerful influence on motor control, eye movements, and various behavioral functions by modulating the activity of thalamocortical circuits and brainstem motor nuclei.** **Beyond its established role in motor control, the dopaminergic neurons originating in the substantia nigra are fundamentally involved in the brain's complex reward system (**Miranda et al., 2025)**. Dopamine release, particularly in response to rewarding stimuli such as food, social interaction, or even addictive substances, mediates feelings of pleasure, motivation, and reinforcement. The nucleus accumbens, a critical brain region within the ventral striatum and a key component of the reward pathway, receives substantial dopaminergic input. Dopamine release in the nucleus accumbens reinforces behaviors associated with these rewards, thereby contributing significantly to learning, habit formation, and the development of addictive behaviors. This intricate interplay underscores the importance of dopamine in shaping our motivations and driving our actions (**Oleson et al., 2021; Wise and Robble, 2020; Volkow et al., 2017)

**Furthermore, dopamine's influence extends beyond reward processing to encompass a broader spectrum of cognitive processes. Dopamine modulates neuronal activity in the prefrontal cortex, a brain region crucial for higher-order cognitive functions such as attention, working memory, cognitive flexibility, and decision-making (**Boyle et al., 2024)**. Optimal dopamine levels are essential for maintaining focus, holding information in mind, and making sound judgments. Consequently, deficiencies or imbalances in dopamine signaling within the substantia nigra and its target regions can lead to a wide range of neurological and psychiatric disorders, including Parkinson's disease, schizophrenia, attention-deficit/hyperactivity disorder (ADHD), and addiction.** **Maintaining dopamine homeostasis within the substantia nigra is paramount for the long-term health and survival of its dopaminergic neurons. These neurons are particularly vulnerable to oxidative stress and the accumulation of toxic byproducts of dopamine metabolism (**Watanabe et al., 2024; Salvatore, 2024; Oyem et al., 2021; Iarkov et al., 2020)**. Disruptions in dopamine synthesis, vesicular storage, reuptake, or enzymatic degradation can lead to elevated levels of reactive oxygen species and the formation of cytotoxic compounds, ultimately damaging or destroying these vulnerable cells (**Shrestha et al., 2022; Udi et al., 2022)**. This progressive neuronal loss is a defining pathological feature of Parkinson's disease, a debilitating neurodegenerative disorder characterized by the gradual and irreversible degeneration of dopaminergic neurons in the SNpc. The resulting dopamine deficiency manifests clinically as the hallmark motor symptoms of tremor, rigidity, bradykinesia (slowness of movement), and postural instability (**Kumar et al., 2022)**. Therefore, a deeper understanding of the molecular mechanisms that govern dopamine production, metabolism, and transport, as well as the cellular processes that protect dopaminergic neurons from degeneration, is of paramount importance for developing effective treatments and preventative strategies for neurodegenerative disorders affecting the substantia Nigra and, more broadly, the aging brain.**

**Arsenic Exposure and Neurotoxicity: An Overview**

Arsenic exposure represents a significant and widespread environmental health threat impacting populations globally (Saxena, 2025; Podgorski and Berg, 2020). This exposure stems from a multitude of sources, including alarmingly high levels of arsenic contamination in drinking water, particularly in regions with naturally occurring arsenic-rich geological formations. Industrial emissions from activities such as coal-fired power plants and manufacturing processes also contribute significantly to arsenic burden in the environment, further polluting air, soil, and water resources. Dietary staples, notably rice grown in arsenic-contaminated soils, can also serve as a major pathway for human exposure. Furthermore, occupational exposure poses a substantial risk to workers in industries like mining, smelting operations, pesticide manufacturing, and agriculture, where arsenic-containing compounds are handled or present in the work environment (Kumar et al., 2024; Rahman and Singh, 2019). Following ingestion or absorption, arsenic undergoes complex metabolic transformations within the body. These processes involve enzymatic reactions that convert inorganic arsenic species into methylated forms, which are then either excreted or further metabolized. A significant portion of ingested arsenic accumulates in various tissues and organs, including the liver, kidneys, skin, and disturbingly, the brain. This accumulation contributes to the long-term toxicity associated with chronic arsenic exposure. The toxicity of arsenic arises from a complex interplay of mechanisms at the cellular and molecular level. A prominent mechanism involves the generation of reactive oxygen species (ROS), leading to oxidative stress that damages cellular components such as DNA, lipids, and proteins. Arsenic also disrupts mitochondrial function, impairing cellular energy production and contributing to cellular dysfunction and apoptosis. Furthermore, arsenic interferes with protein folding processes, leading to the accumulation of misfolded proteins and triggering cellular stress responses, including the unfolded protein response (UPR). These diverse mechanisms collectively contribute to widespread cellular damage and ultimately contribute to the pathogenesis of various diseases (El-Ghiaty and El-Kadi, 2023; Zhang et al., 2022; Palma-Lara et al., 2020).

A growing body of epidemiological and experimental evidence strongly suggests a compelling link between chronic arsenic exposure and the development of various neurological disorders. Studies have implicated arsenic exposure in cognitive impairment, memory deficits, peripheral neuropathy (nerve damage), and an increased risk of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease (Obukohwo et al., 2024; Nabi and Tabassum, 2022; Thakur et al., 2021; Sharma et al., 2020). The potential for developmental neurotoxicity, impacting cognitive and behavioral development in children, is also a significant concern. Given the ubiquitous nature of arsenic in the environment and the potential for long-term neurological consequences, there is a critical need for further research to elucidate the precise mechanisms underlying the neurotoxic effects of this environmental contaminant. This includes investigating the effects of low-dose arsenic exposure, the impact on specific brain regions, and the potential for preventative and therapeutic interventions to mitigate arsenic's neurotoxic effects. Further research is also needed to develop effective strategies for reducing arsenic exposure through improved water treatment technologies, safer industrial practices, and dietary modifications.

**Arsenic-Induced Dopaminergic Neurodegeneration: The Pathological Cascade**

1. **Oxidative Stress:**

Arsenic, a ubiquitous environmental contaminant, is now widely acknowledged as a potent neurotoxicant with far-reaching health implications (Dubey et al., 2025). While its toxicity is well-documented across various organ systems, the nervous system is particularly susceptible, with the dopaminergic neurons residing in the substantia nigra pars compacta exhibiting a pronounced vulnerability to arsenic-induced damage (Basu et al., 2023). The substantia nigra, a critical brain region involved in motor control, reward, and motivation, is specifically affected, potentially leading to neurological disorders resembling Parkinson's disease. A central mechanism underlying arsenic's neurotoxic effects and the subsequent degeneration of dopaminergic neurons is the induction of oxidative stress (Meder et al., 2019). Arsenic exposure disrupts the delicate balance between the production of free radicals and the body's ability to neutralize them. Specifically, arsenic promotes the excessive generation of both reactive oxygen species (ROS), such as superoxide and hydroxyl radicals, and reactive nitrogen species (RNS), including nitric oxide and peroxynitrite, within the substantia nigra. This surge in ROS and RNS overwhelms the endogenous antioxidant defenses of dopaminergic neurons, which are inherently less equipped to handle oxidative challenges compared to other cell types. This oxidative burden initiates a cascade of detrimental cellular damage (Oyovwi et al., 2024; Chaudhary et al., 2023). Lipids within neuronal membranes undergo peroxidation, compromising their integrity and function. Proteins are oxidized, leading to misfolding, aggregation, and ultimately, loss of function. Furthermore, DNA, the genetic blueprint of the cell, suffers damage, impairing its ability to replicate and repair. Collectively, these oxidative modifications disrupt crucial cellular processes, impairing the survival, and compromising the function of these critical dopaminergic neurons. This gradual loss of dopaminergic neurons contributes to the neurological deficits observed in arsenic-exposed individuals. The role of oxidative stress in arsenic-induced neurodegeneration is consistently supported by a wealth of evidence. In vitro studies utilizing cell culture models of dopaminergic neurons demonstrate that arsenic exposure leads to a significant increase in ROS/RNS production, followed by observable cellular damage and ultimately, cell death (Sadiq, 2023; He et al., 2017; Pisoschi et al., 2021). Similarly, in vivo animal studies, where animals are exposed to arsenic through various routes of administration, corroborate these findings. These studies consistently link arsenic exposure to elevated levels of oxidative stress markers in the substantia nigra, along with a demonstrable loss of dopaminergic neurons and associated motor deficits. Therefore, the convergence of evidence from both in vitro and in vivo models strongly implicates oxidative stress as a central and critical pathological event in the detrimental neurodegenerative process triggered by arsenic exposure. This understanding is crucial for developing potential therapeutic strategies aimed at mitigating the neurotoxic effects of arsenic and protecting vulnerable dopaminergic neurons.

1. **Mitochondrial Dysfunction:**

Arsenic exposure is emerging as a significant environmental risk factor implicated in dopaminergic neurodegeneration, exhibiting striking similarities to the neuropathological characteristics associated with Parkinson's disease (PD) (Pan-Montojo et al., 2020). A key pathway underlying this neurotoxic effect is the disruption of mitochondrial function. Arsenic compromises the intricate machinery of mitochondria, specifically targeting the electron transport chain (ETC), a vital series of protein complexes responsible for cellular energy production through oxidative phosphorylation. This disruption of the ETC results in a ripple effect of adverse consequences. Firstly, it significantly impairs the production of ATP, the cell's primary energy source, leading to energy deficits that compromise neuronal function and viability (Zuo at el., 2024; Mondal et al., 2022; Anand et al., 2020). Simultaneously, arsenic-induced ETC dysfunction triggers a marked increase in the generation of reactive oxygen species (ROS), highly reactive molecules that can damage cellular components. This surge in ROS overwhelms the endogenous antioxidant defense systems, resulting in a state of oxidative stress. This oxidative stress further exacerbates cellular damage, contributing to lipid peroxidation, protein oxidation, and DNA damage. Moreover, arsenic can directly inflict damage on mitochondrial DNA (mtDNA), the genetic material essential for the proper functioning and maintenance of mitochondria. This mtDNA damage further impairs mitochondrial function and contributes to the overall cellular stress. The cell normally employs mitophagy, a quality control mechanism, to selectively remove damaged and dysfunctional mitochondria. However, arsenic exposure also dysregulates mitophagy, impairing the cell's ability to eliminate these compromised organelles. The resulting accumulation of dysfunctional mitochondria amplifies their cytotoxic effects, contributing to a vicious cycle of energy depletion, oxidative stress, and ultimately, the degeneration of dopaminergic neurons, mirroring the pathological features observed in Parkinson's disease (Ghosh and Sil, 2023; Mahadik et al., 2024; Ulhassan et al., 2022). Consequently, therapies aimed at mitigating mitochondrial dysfunction and oxidative stress may hold promise in preventing or delaying arsenic-induced neurodegeneration.

1. **Protein Misfolding and Aggregation**

A crucial mechanism underlying neurotoxicity centers around the disruption of protein homeostasis, the delicate balance between protein synthesis, folding, and degradation (Ajmal, 2023). Specifically, arsenic exposure induces the misfolding of alpha-synuclein (α-syn), a protein highly expressed in neurons and implicated in synaptic transmission. This misfolding then triggers a self-assembly process, leading to the aggregation of α-syn into insoluble oligomers and fibrils. This aberrant protein accumulation is not merely a consequence of arsenic exposure; it is a driver of pathology. The aggregated α-syn forms Lewy body-like inclusions within dopaminergic neurons, the very cells that are selectively vulnerable in PD. These inclusions, although not identical to the Lewy bodies found in Parkinson's brains, mimic their pathological features and are believed to contribute to neuronal dysfunction and death (Roy et al., 2024; Murphy and McKernan, 2022). Furthermore, arsenic exacerbates the problem by compromising the cell's intrinsic ability to clear these misfolded proteins. It impairs the function of critical protein degradation pathways, most notably the ubiquitin-proteasome system (UPS) and autophagy. The UPS is responsible for targeting and degrading misfolded and damaged proteins, while autophagy involves the engulfment and degradation of larger protein aggregates and organelles. By hindering these pathways, arsenic prevents the efficient removal of toxic α-syn aggregates, allowing them to accumulate within neurons. This detrimental combination – increased protein misfolding coupled with decreased protein clearance – creates a vicious cycle of α-syn aggregation and toxicity. The escalating accumulation of toxic α-syn oligomers and fibrils disrupts cellular processes, initiates oxidative stress, impairs mitochondrial function, and ultimately contributes to the progressive degeneration of vulnerable dopaminergic neurons in the substantia nigra, the brain region primarily affected in Parkinson's disease. Therefore, arsenic exposure can be considered a significant environmental risk factor that promotes the development of Parkinson's-like pathology by disrupting protein homeostasis and triggering dopaminergic neurodegeneration (Krishnamurthy et al., 2022; Chen et al., 2024; Saha et al., 2022). Further research into the precise mechanisms of arsenic-induced protein misfolding and degradation impairment is crucial for developing effective preventative and therapeutic strategies to mitigate the risk and progression of Parkinson's disease.

1. **Neuroinflammation**

Arsenic exposure initiates a complex sequence of cellular and molecular events ultimately culminating in dopaminergic neurodegeneration, and neuroinflammation emerges as a critical driver of this detrimental process (Das et al., 2025; Rezaei et al., 2024). The pathophysiology commences with the introduction of arsenic into the neural environment, which acts as a potent trigger for the activation of microglia and astrocytes. These cells, the brain's intrinsic immune sentinels, are rapidly mobilized to counteract the perceived threat. Upon activation, microglia and astrocytes transition from their quiescent states and begin to orchestrate an inflammatory response, releasing a diverse array of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, and chemokines like MCP-1 and RANTES. These signaling molecules act as amplifiers, recruiting additional immune cells and perpetuating a self-sustaining cycle of neuroinflammation. While initially intended as a protective mechanism to neutralize the arsenic and repair potential damage, the chronic and uncontrolled nature of this neuroinflammation becomes profoundly destructive. The sustained release of inflammatory mediators creates a hostile microenvironment for dopaminergic neurons, rendering them increasingly susceptible to oxidative stress, excitotoxicity, and mitochondrial dysfunction. Consequently, these vulnerable neurons undergo progressive damage, characterized by impaired function, structural deterioration, and ultimately, cell death. This loss of dopaminergic neurons directly contributes to the progression of neurodegenerative diseases, highlighting the paradoxical role of neuroinflammation in exacerbating the neurodegenerative process it was initially meant to mitigate. Therefore, understanding the intricate interplay between arsenic exposure, neuroinflammation, and dopaminergic neurodegeneration is crucial for developing targeted therapeutic strategies aimed at preventing or slowing the progression of arsenic-induced neurological disorders (Anderson et al., 2023; Rahman et al., 2020; Matejuk and Ransohoff, 2020; Morris et al., 2018).

1. **Excitotoxicity**

The mechanism by which arsenic contributes to this neurodegeneration is complex and involves a pathological cascade where excitotoxicity plays a pivotal and potentially initiating role.

Specifically, arsenic disrupts the delicate balance of normal glutamate signaling within the brain. Glutamate, a major excitatory neurotransmitter, is crucial for learning, memory, and synaptic plasticity. However, arsenic can interfere with the proper uptake and metabolism of glutamate, leading to an abnormal and prolonged presence of this neurotransmitter in the synaptic cleft. This, in turn, causes an overstimulation of glutamate receptors, particularly NMDA receptors, located on the surface of neurons. This excessive and sustained stimulation triggers excitotoxicity, a destructive process wherein neurons are damaged or killed due to the prolonged and unrestrained activation of excitatory neurotransmitters like glutamate. Think of it like constantly revving an engine at its redline – eventually, something will break (de Paula Arrifano et al., 2023; Carmona et al., 2021; Udi et al., 2018).

A particularly critical consequence of this excitotoxicity is the dysregulation of intracellular calcium levels. Under normal physiological conditions, intracellular calcium concentration is tightly controlled. However, the over-activation of glutamate receptors allows a massive influx of calcium ions into the neuron. This surge of calcium sets off a cascade of damaging downstream events. The elevated intracellular calcium activates a variety of calcium-dependent enzymes, such as calpains and phospholipases, which can degrade proteins, lipids, and DNA, further contributing to neuronal damage. Furthermore, the excess calcium triggers the generation of reactive oxygen species (ROS), highly unstable molecules that cause oxidative stress. ROS damage cellular components like mitochondria, DNA, and proteins, exacerbating the cytotoxic effects. This combined damage from enzyme activation and oxidative stress ultimately leads to neuronal dysfunction and death, preferentially targeting dopaminergic neurons and contributing to the progressive degeneration observed in arsenic-induced neurodegeneration. This process highlights how arsenic exposure can significantly impact neuronal health and contribute to the pathogenesis of neurological disorders (Vázquez Cervantes et al., 2023; Garza-Lombó et al., 2018).

**Genetic and Environmental Factors Influencing Arsenic Neurotoxicity**

Arsenic neurotoxicity presents a significant public health challenge, characterized by a complex interplay of genetic predispositions and environmental exposures that ultimately determine an individual's vulnerability to arsenic-induced neurodegeneration (Vázquez Cervantes et al., 2023; Halvorsen, 2022). At the heart of this variability lies genetic polymorphism, where differences in gene sequences coding for key enzymes involved in arsenic metabolism and detoxification pathways significantly impact an individual's ability to process and eliminate this potent neurotoxin. Individuals inheriting less efficient versions of these detoxification genes may experience a slower rate of arsenic clearance, leading to increased accumulation in the brain and a heightened risk of neurological damage. However, genetic susceptibility is only one piece of the puzzle. The impact of environmental factors plays a crucial role in modulating arsenic's neurotoxic potential. Co-exposure to other neurotoxic substances commonly found in contaminated environments, such as lead (Pb) or manganese (Mn), can synergistically exacerbate the detrimental effects of arsenic on the nervous system. This combined exposure may overwhelm the brain's defenses, accelerating neurodegeneration and leading to more severe neurological outcomes. Moreover, an individual's nutritional status significantly influences their vulnerability to arsenic neurotoxicity. Deficiencies in essential micronutrients, particularly those involved in antioxidant defense mechanisms and detoxification processes, can compromise the body's ability to combat the oxidative stress and cellular damage induced by arsenic. For example, inadequate intake of selenium, zinc, or certain vitamins may weaken neuronal protection and enhance arsenic's neurotoxic effects (Wu et al., 2025; Udi et al., 2023; Zulfiqar et al., 2021; Kaur et al., 2021).

Therefore, a comprehensive understanding of the intricate interplay between genetic factors, environmental exposures, and nutritional status is paramount for accurately identifying populations at high risk of developing arsenic-induced neurological disorders. By unraveling these complex interactions, the study can develop targeted and effective mitigation strategies, including nutritional interventions, exposure reduction programs, and potentially even personalized medicine approaches, to minimize the devastating neurological consequences of arsenic exposure and protect vulnerable populations.

**Animal Models of Arsenic-Induced Dopaminergic Neurodegeneration**

Animal models are indispensable tools in biomedical research, and rodents, especially mice and rats, are frequently used to investigate arsenic-induced dopaminergic neurodegeneration. Several factors contribute to their widespread adoption. First, their relatively short lifespans allow researchers to observe the progression of neurodegenerative changes within a feasible timeframe (Eduviere et al., 2024). Second, their ease of handling and maintenance in a laboratory setting facilitates large-scale studies ((Anderson et al., 2023). Third, their genetic similarity to humans, despite obvious differences, makes them valuable for translating findings to human health. Specifically, these models enable researchers to examine the damaging effects of arsenic exposure on the nigrostriatal pathway, a crucial neural circuit heavily implicated in motor control and significantly affected in Parkinson's disease (Kaur et al., 2021; Andrew et al., 2017). By exposing rodents to controlled doses of arsenic, researchers can dissect the molecular and cellular events leading to the degeneration of dopaminergic neurons in the substantia nigra, which project to the striatum. However, it is essential to acknowledge that each animal model possesses its own inherent strengths and limitations. For example, different rodent strains exhibit varying degrees of susceptibility to arsenic toxicity. This variability can influence the observed neurodegenerative outcomes and necessitates careful strain selection and consideration during data interpretation. Crucially, rodent models cannot fully replicate the intricate complexity of the human brain, the diverse genetic background of human populations, or the prolonged, often decades-long, exposure scenarios typical of chronic arsenic poisoning in humans. Factors such as differences in metabolism, blood-brain barrier permeability, and the presence of protective mechanisms can contribute to discrepancies between rodent models and human disease.

Despite these limitations, animal studies have proven instrumental in elucidating key mechanisms underlying arsenic's neurotoxic effects (Orororo et al., 2022). These studies have revealed that arsenic exposure triggers a cascade of detrimental events within dopaminergic neurons. These include the generation of excessive oxidative stress, leading to cellular damage; mitochondrial dysfunction, impairing energy production; the activation of inflammatory pathways, exacerbating neuronal injury; and disruptions in the synthesis, storage, and transport of dopamine, ultimately affecting neuronal function. These mechanistic insights highlight the selective vulnerability of dopaminergic neurons to arsenic-induced damage and provide potential targets for neuroprotective interventions. Through continued refinement and careful interpretation, animal models remain essential for advancing the understanding of arsenic neurotoxicity and for developing strategies to mitigate its harmful effects on human health.

**Potential Therapeutic Strategies**

Addressing arsenic-induced neurotoxicity presents a significant challenge that necessitates a multifaceted therapeutic approach. Several potential strategies are currently under exploration, each targeting different aspects of arsenic's damaging impact on the nervous system. One primary approach is chelation therapy, which aims to remove arsenic from the body. By administering chelating agents, arsenic ions are bound and excreted, thereby reducing the overall arsenic burden and consequently mitigating its neurotoxic effects. While chelation can be effective, it's crucial to consider the timing and potential side effects of these therapies. In parallel with arsenic removal, researchers are actively investigating antioxidant and neuroprotective agents (Althobaiti, 2024; Udi et al., 2023; Bjørklund et al., 2017). Arsenic exposure generates significant oxidative stress, leading to cellular damage, particularly in vulnerable neurons. Supplementation with antioxidants aims to neutralize free radicals and reduce oxidative damage (Udi et al., 2025; Pisoschi et al., 2021). Furthermore, neuroprotective agents are being studied for their ability to safeguard neurons, enhance their resilience to arsenic-induced insults, and promote neuronal survival. Given the critical role of mitochondria in neuronal energy production and overall cellular function, targeting mitochondrial dysfunction is another promising avenue for intervention. Arsenic can disrupt mitochondrial activity, leading to energy deficits and increased free radical production. Therapies aimed at restoring mitochondrial function, improving electron transport chain efficiency, and reducing mitochondrial oxidative stress hold significant potential. Furthermore, modulating neuroinflammation is considered a vital component of therapeutic strategies. Arsenic exposure triggers an inflammatory response in the brain, contributing to the progression of neurological damage. By targeting inflammatory pathways and reducing the production of pro-inflammatory molecules, it may be possible to mitigate the detrimental effects of neuroinflammation and promote neuroprotection.

Looking ahead, future research should focus on combining these approaches in synergistic ways to achieve optimal outcomes. This might involve combining chelation therapy with antioxidant supplementation or targeting both mitochondrial dysfunction and neuroinflammation simultaneously. Furthermore, there is a need for developing novel therapies that specifically target the complex mechanisms underlying arsenic-induced neurotoxicity. This includes identifying new drug targets, exploring gene therapy approaches, and developing personalized treatment strategies based on individual risk factors and genetic predispositions. Ultimately, a deeper understanding of the intricate interplay of factors contributing to arsenic neurotoxicity will pave the way for more effective and targeted therapeutic interventions.

**Conclusion**

In conclusion, the neurodegenerative effects of arsenic on dopaminergic neurons are a complex web of interconnected pathological events. This multifaceted process involves a cascade of detrimental mechanisms, including oxidative stress stemming from an overproduction of reactive oxygen species, disruption of mitochondrial function and energy production, impairment of protein homeostasis leading to the accumulation of misfolded proteins, and the activation of inflammatory pathways within the brain. These factors synergistically contribute to the gradual but ultimately irreversible death of dopamine-producing neurons, which are critical for motor control, reward processing, and various other essential functions. While significant strides have been made in unraveling the intricacies of arsenic's neurotoxic mechanisms, critical gaps persist in our understanding. Notably, the precise molecular targets of arsenic within different brain regions, particularly those related to dopamine synthesis and signaling, remain to be fully identified. The role of epigenetic modifications, specifically how arsenic exposure alters gene expression patterns and contributes to long-term neurodegenerative changes, also requires further investigation. Furthermore, the long-term consequences of chronic, low-level arsenic exposure, a scenario relevant to many populations worldwide, need to be thoroughly assessed to understand the subtle yet potentially debilitating effects on brain health and cognitive function.

To address these knowledge gaps and pave the way for effective prevention and treatment strategies, future research should focus on several key areas. First, a more detailed characterization of the specific molecular targets of arsenic in the brain is essential, utilizing advanced techniques such as proteomics and transcriptomics. Second, investigating the contribution of epigenetic modifications, including DNA methylation and histone acetylation, to arsenic-induced neurodegeneration will provide valuable insights into the long-term neurological consequences. Third, longitudinal studies are needed to assess the impact of chronic, low-level arsenic exposure on cognitive function, motor skills, and the overall risk of developing neurodegenerative diseases later in life. Fourth, exploring potential neuroprotective compounds capable of mitigating oxidative stress, restoring mitochondrial function, or promoting protein clearance holds promise for therapeutic intervention. Finally, developing more sensitive and specific biomarkers for the early detection of arsenic-related neurotoxicity will enable timely intervention and potentially prevent irreversible neuronal damage. Ultimately, a multi-pronged approach is crucial for mitigating the devastating neurological consequences of arsenic exposure. Emphasizing prevention through rigorously minimizing arsenic exposure via contaminated water and food sources remains the most effective strategy. This includes implementing stringent water quality standards, developing effective arsenic removal technologies, and promoting awareness about the potential health risks associated with contaminated food products. Concurrently, early intervention strategies targeting key pathological mechanisms, such as oxidative stress and inflammation, are vital for slowing down or even preventing the progression of neurodegeneration in individuals already exposed to arsenic.

**DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

Author hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

**COMPETING INTERESTS**

Author has declared that no competing interests exist.

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