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Neurotoxic Heavy Metals in the Human Brain - V. The Arsenic - Alzheimer Connection

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Abstract

Arsenic (As) is a naturally occurring, highly toxic element found in soil, water, and minerals. It exists in inorganic (more toxic) and organic (less toxic) forms. Epidemiological and experimental evidence suggests that chronic exposure to As is a significant environmental risk factor for the development and progression of Alzheimer's disease (AD). In this article, the sources of exposure to As are reviewed including environmental risks and occurrence in drinking water. The three key pathological risks are set forth, and the metabolism of As and its access to the brain are discussed. The nine As-induced neurotoxicity mechanisms in AD are analyzed to establish the connectivity of As to AD. Further, the management and treatment of As-induced neurological deficits are addressed. Lastly, the As classification and its regulatory limits are summarized.

Abbreviations

AD: Alzheimer's disease; AL: Action level; APP: Amyloid precursor protein; ATSDR: (U.S.) Agency for Toxic Substances and Disease Registry; BAL: British anti-Lewisite; BBB: Blood-brain barrier; CNS: Central nervous system; EPA: (U.S.) Environmental Protection Agency; ER: Endoplasmic reticulum; EU: European Union; FDA: (U.S.) Food & Drug Administration; GBA: Gut-brain axis; GBB: Gut-brain barrier; IARC: International Agency for Research on Cancer; IDLH: Immediately dangerous to life and health; LOC: Level of concern; NDD: Neurodegenerative diseases; NFT: Neurofibrillary tangles; NIEHS: (U.S.) National Institute for Environmental Health Sciences; NIOSH: (U.S.) National Institute for Occupational and Health; OS: Oxidative stress; OSHA: (U.S.) Occupational Safety and Health Administration; PD: Parkinson's disease; PEL: Permissible exposure limit; REL: Recommended exposure limit; ROS: Reactive oxygen

species; TWA: Time-weighted average; WHO: World Health Organization.

Chemical elements: Al: Aluminum; As: Arsenic; As0 (metalloid); As_2O_3: As trioxide; AsIII (Arsenite); AsV (Arsenate); AsH3: Arsine gas; ATP: Adenosine triphosphate; Ca: Calcium; Cd: Cadmium; C12H15AsN6OS2: DMSA: Dimercaptosuccinic acid; Fe: Iron; FeAs: Arsenopyrite; Fl: Fluoride; Hg: Mercury; iAS; inorganic As; Melarsoprol; O: Oxygen; Pb: Lead; S: Sulfur.

Drugs cited: British anti-Lewisite; Curcumin; Dimercaprol; Garlic acid; Genistein; Penicillamine; Quercetin; Resveratrol; Succimer; Thymoquinone.

Diseases mentioned: Alzheimer's disease; Arsenicosis; Cancer (bladder, kidneys, liver, lungs, nasal cavity, prostate, skin); H1N1 or swine flu; Parkinson's disease.

Keywords

Arsenic poisoning; Environment-disease interactions; Memory and cognitive impairment; Neurodegenerative diseases; Neurotoxicity; Oxidative stress; Poisoning; Reactive oxygen species.

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Arsenic (As) is a naturally occurring, highly toxic element found in soil, water, and minerals. It exists in inorganic (more toxic) and organic (less toxic) forms. It is used in industrial wood preservatives, electronics, ammunition, and glass manufacturing while environmental detection involves water testing and soil sampling. Epidemiological and experimental evidence suggests that chronic exposure to As is a significant environmental risk factor for the development and progression of AD. Recent population-based studies have identified a dose-response relationship between higher As levels in groundwater and an increased risk of AD. Chronic exposure, often via contaminated water or food (rice), is managed by bioremediation and treated with chelation.

Introduction

The human brain is particularly susceptible to the toxic effects of heavy metals, such as Aluminum (Al), Cadmium (Cd), Lead (Pb), Mercury, (Hg), and Arsenic (As). It has been proven that these compounds can damage the central nervous system (CNS) and lead to cognitive and behavioral impairments. Such environmental chemicals are well known to be neurotoxic or involved in the onset and progression of neurodegenerative diseases (NDD). These risk factors have been recognized to have a significant role in the development of Alzheimer's disease (AD). Among them, infections, diet, air pollution, and metal exposure are primarily considered. (For Al, CD, Pb, and Hg, refer to articles 1-4 in this series.) This article is exclusively concerned with As.

Exposure risks

Environmental issues

Naturally occurring sources of human exposure include volcanic ash, weathering of minerals and ores, and mineralized groundwater. As is also found in food, water, soil, and air. It is absorbed by all plants, but is more concentrated in leafy vegetables, rice, apple and grape juice, and seafood. An additional route of exposure is inhalation of atmospheric gases and dusts.

In addition, As hotspots are related to both frequent fertilization and close distance to mining activities. Chronic exposure to As, particularly through contaminated drinking water and food, has also been linked to long-term impacts on cognitive function, including reduced verbal IQ and memory. Studies in mainland China found that soil arsenic concentrations were positively correlated with AD mortality rates.

Occurrence in drinking water

Naturally occurring As in groundwater is the most common source of chronic exposure worldwide. Around one-third of the world's population drinks water from groundwater resources. Of this, about 10% (approximately 300 million people) obtain water from groundwater resources that are contaminated with unhealthy levels of As or Fluoride (Fl). These trace elements derive mainly from minerals and ions in the ground.

As in groundwater is of natural origin and is released from the sediment into the groundwater as caused by the anoxic conditions of the subsurface. Many countries and districts in Southeast Asia (Bangladesh, Cambodia, China, India, Pakistan, Thailand, Vietnam) have geological environments that produce groundwater with a high As content. As-induced toxicity may occur at relatively low concentrations with chronic exposure.

In the U.S., As is most found in the ground waters of the southwest, the Dakotas, Michigan, Minnesota, New England, and Wisconsin. Increased levels of skin cancer have been associated with As exposure in Wisconsin, even at levels below the 10 ppb drinking water standard. Millions of private wells have unknown As levels and, in some areas, more than 20% of the wells may contain levels that exceed established limits. Low-level exposure to As at concentrations of 100 ppb (i.e., ten times above the 10 ppb drinking water standard) compromises the initial immune response to the H1N1 or swine flu infection (a type of influenza A virus). People exposed to As in their drinking water may be at increased risk for more serious illnesses or death from the virus.

Some Canadians are drinking water that contains inorganic As from private dug–well waters that are most at risk for containing inorganic As. For such wells, preliminary well water analysis typically does not test for As.

Epidemiological evidence from Chile has shown a dose-dependent connection between chronic As exposure and various forms of cancer, when other risk factors (such as cigarette smoking) are present as As is itself a constituent of tobacco smoke. These effects have been demonstrated at contaminations less than 50 ppb.

An effective and inexpensive method to avoid As contamination is to sink wells 500 feet or deeper to reach purer waters. A recent 2011 study funded by the U.S. National Institute of Environmental Health Sciences (NIEHS)' Superfund Research Program shows that deep sediments can remove As and take it out of circulation. In this process, called adsorption, As sticks to the surfaces of deep sediment particles and is naturally removed from the ground water. Also, chaff-based filters have recently been shown to reduce the As content of water to 3 µg/L; this may find applications in areas where the potable water is extracted from underground aquifers.

Epidemiological studies have suggested a correlation between chronic consumption of drinking water contaminated with As and the incidence of all leading causes of mortality. Analyzing multiple epidemiological studies on inorganic As exposure suggests a small but measurable increase in risk for bladder cancer at 10 ppb. It is also causative in the pathogenesis of diabetes.

Early life exposure

Exposure during birth or young adulthood is particularly strongly associated with an elevated risk of developing AD later in life.

Key pathological links

As exposure induces the primary neuropathological hallmarks of AD:

• **Amyloid-beta (Aβ) accumulation:** As enhances the expression of amyloid precursor protein (APP) and the

activity of the BACE1 enzyme, leading to increased Aβ production and plaque formation.

• **Tau hyperphosphorylation:** Exposure to As activates kinases like GSK3β and JNK3, which cause the abnormal phosphorylation of tau protein, leading to the formation of neurofibrillary tangles (NFT).

• **Neuronal loss:** Chronic exposure can lead to necroptosis and granular vacuolar degeneration in critical memory regions like the entorhinal cortex and hippocampus.

As metabolism and access to the brain

As is a ubiquitous metalloid element and is one of the few that can be metabolized inside the human body. It exists in three valence states, As0 (metalloid), As^{III} (arsenite), and As^{V} (arsenate), and as AsH3 (arsine gas). In water, it is mainly found in the form of arsenite and arsenate ion, while, in the Earth's crust, it is often conjoined with Sulfur (S), mostly as arsenopyrite (FeAsS), or with other metals. It can also be found in the air, coupled with Oxygen (O) in the form of As trioxide (As_2O_3). Drinking water is the main source of As contamination, followed by food ingestion and air breathing. (Sidebar 1 provides additional details on the physicochemical properties of As.)

Metabolism

As^{III} and As^{V} are defined as inorganic As (iAs), and they represent the principal toxic contaminant form. However, when taken into the body, they undergo a metabolic processing, forming various adducts. Over the years, several hypotheses have been suggested as to how As is processed although the exact mechanism remains somewhat unclear.

Access to the brain

It has been evidenced that As and its metabolites can accumulate in several organs of the human body (the kidneys and the liver are the primary deposition sites), manifesting their toxicity. The concentration found in the brain is not comparable with that found in the above two organs but it remains significant. The high concentration of As deposited in the brain can be explained by the property of As to disrupt and pass through the blood-brain barrier (BBB). Indeed, several works report that As exposure induces damage to the BBB, with a decrease in the tight junctions.

As-induced neurotoxicity mechanisms in AD

The following biological mechanisms encompass the ways causing As-induced neurotoxicity mechanisms in AD:

Endoplasmic reticulum stress

Current evidence suggests a relationship between endoplasmic reticulum (ER) stress and As-induced NDD via accumulation of misfolded proteins, which results in neurotoxicity and cell death. It has recently been described that As-mediated ER stress and neurotoxicity are associated with early neurodevelopment.

Apoptosis

As toxicity involves apoptosis as a common phenomenon of cell death. As-induced neuronal cell death involves activation of autophagy-dependent apoptosis through inactivation.

Impaired proteostasis

Protein quality control systems, also known as protein homeostasis or simply proteostasis, play a significant role in cellular physiological functions. Impairment in proteostasis leads to aberrant deposition of protein aggregates, which are characteristics of many NDD such as Aβ aggregate in AD. Compelling evidence from

recent studies suggests that chronic exposure to inorganic As can disrupt protein quality control and clearance systems, which contribute to the pathobiology of proteinopathic brain disorders such as AD. As-mediated post-translational modifications of proteins and disruptions of ubiquitination may culminate in impairment in proteostasis.

Impaired calcium signaling

As-induced mitochondrial dysfunction causes a decline in ATP generation, which is responsible for ER stress, leading to Calcium (Ca) build-up in intracellular compartments and impairment in CA, most likely due to a lack of recovery systems. Altered Ca signaling can cause cognitive impairment or the development of tau hyperphosphorylation by activating protein kinases. Hyperphosphorylated tau and amyloid aggregates interact with mitochondria, leading to the establishment of a vicious cycle of energy deprivation and proteostasis.

Induction of oxidative stress in AD

Oxidative stress (OS) is a phenomenon in cells and tissues caused by an imbalance between the production and accumulation of ROS and the ability of biological systems to detoxify these reactive products. The brain is considered the organ the most prone to suffer from OS, and this is due to both structural and functional characteristics. In fact, the brain is rich in peroxidable lipids, and it is very exposed to O because of its high metabolic activity. It alone consumes 20% of the breathing-derived O. Moreover, cells in the brain are long-lasting, and there is low cell renewal, making them sensitive to accumulate oxidative damage. Oxidative damage happens physiologically during aging, but high oxidation levels or persistent exposure define OS, which is a common feature in all NDD. In AD, OS is a prodromic event that participates in membrane damage, cytoskeleton alterations, and cell death.

As-induces OS, followed by DNA damage, ER stress and mitochondrion dysfunction, which subsequently trigger apoptosis. Se–As complex inhibits OS, and Cd–Se prevents ROS production, DNA damage, and apoptosis. Additionally, Zn–Cd complex activates mitochondrial stabilization and inhibits OS and apoptosis.

A relationship between amyloid-beta (Aβ) and OS was demonstrated. Specifically, OS seems to promote as well as contribute to Aβ formation. Fewer, but consistent, evidence demonstrated the same interaction for OS and hyperphosphorylated tau.

Hence, in the AD context, As effects on amyloidogenesis and tau hyperphosphorylation, along with the induction of OS, can contribute to reinforce the vicious cycle responsible for neurodegeneration.

As and ferroptosis in AD

Ferroptosis is an Iron (Fe)-dependent form of cell death, in which OS has a central role. Recent studies have shown that ferroptosis is closely related to the pathophysiological processes of many diseases, including AD. Many compounds with the potential to induce ferroptosis have been developed in recent times. Fe deposition in the brain of AD patients is observed in the cortex, hippocampus, and basal ganglia. Fe metabolism dysregulation in AD seems to undergo a detrimental cycle. Finally, Aβ can reduce Fe. Moreover, hyperphosphorylation of tau protein causes its loss of function.

As and DNA methylation in AD

Alterations in DNA methylation in the AD context have been the subject of study for years, and they seem to have a central role in the pathological development of AD. It was also proved that As affects DNA methylation directly, regulating the activity of factors involved in DNA methylation. Nonetheless, no

investigations to date have specifically addressed whether this epigenetic alteration involves AD-related genes, including those already known to undergo hypomethylation in the context of AD. Moreover, evidence collected in different contexts reports both hypo- or hypermethylation after As exposure, meaning that more complicated mechanisms can mediate epigenetic effects of As exposure.

Ecotoxicity

As is bioaccumulative in many organisms, marine species in particular, but it does not appear to biomagnify significantly in food webs. In polluted areas, plant growth may be affected by root uptake of arsenate, which is a phosphate analog and therefore readily transported in plant tissues and cells. In polluted areas, uptake of the more toxic arsenite ion (found more particularly in reducing conditions) is likely in poorly drained soils.

Biological mechanism

As toxicity comes from the affinity of As (III) oxides for thiols. As disrupts ATP production through several mechanisms. Hydrogen peroxide production is increased, which, it is speculated, has potential to form ROS and OS. These metabolic interferences lead to death from multi-system organ failure. The organ failure is presumed to be from necrotic cell death, not apoptosis, since energy reserves have been too depleted for apoptosis to occur.

The Arsenic-Alzheimer's connectivity

As exposure represents a significant environmental risk factor in the pathogenesis of AD. Due to its ability to disrupt the BBB, As can accumulate in the brain and contribute to AD development through multiple mechanisms. Specifically, As promotes amyloidogenesis and the formation of NFT. Further studies should analyze As metabolism and the associated neurodegenerative effects in contexts of altered antioxidant and/or methylation potential. Following As exposure, the brain's redox balance is disrupted, resulting in OS and promoting ferroptosis, a specific mechanism of cell death that appears to be relevant to AD. Moreover, several works revealed that As decreases DNA methylation in the brain and interferes with the DNA methylation process, possibly altering gene expression and contributing to cognitive decline. Poor evidence directly connects the impact of As on DNA methylation to AD, but the causal effect of DNA methylation has already been demonstrated in the past decades. There is support for the possibility of a causal relationship between As exposure and the onset of AD, although further studies are needed to elucidate the molecular mechanisms underlying As-induced neurotoxicity and to develop targeted therapeutic strategies aimed at mitigating its contribution to AD pathology.

Management and treatment of As-induced neurological deficits

Bioremediation

Occupational exposure and As poisoning may occur in people working in industries involving the use of inorganic As and its compounds, such as wood preservation, glass production, nonferrous metal alloys, and electronic semiconductor manufacturing. Inorganic As is also found in coke oven emissions associated with the smelter industry.

Physical, chemical, and biological methods have been used to remediate As contaminated water. Bioremediation is said to be cost-effective and environmentally friendly. Bioremediation of ground water contaminated with As aims to convert Arsenite (the dominant form in hypoxic-to-anoxic environments), the toxic form of As to humans, to arsenate (the dominant form of arsenic in surface water). Arsenite is more soluble and mobile than

arsenate. Many species of bacteria can transform Arsenite to arsenate in anoxic conditions by using Arsenite as an electron donor. This is a useful method in ground water remediation. Another bioremediation strategy is to use plants that accumulate As in their tissues via phytoremediation but the disposal of contaminated plant material needs to be considered.

Although the epidemiological reports and experimental evidence clearly demonstrate that high exposure to As results in abnormalities in the developing brain and cognitive deficits in adults, the specific management strategy that can effectively address As-induced neurological deficits is yet to be developed. However, certain approaches such as administration of biological trace elements – Zinc (Zn) and Selenium (Se) -, antioxidants and As chelators, high-protein diets, and exposure to an enriched environment could be the possible strategies that can ameliorate As-induced systemic deficits. The forefront strategy that has been shown to be effective in alleviating As-induced toxic effects is the dietary inclusion of trace elements such as Zn and Se. Zn can prevent As-induced neurotoxicity in fish models by preserving the BBB and attenuating apoptosis and autophagy dysfunction. In several other studies with common carp, Zn supplementation also has been shown to be effective in protecting against As-induced toxicity in the heart, kidney, liver, spleen, and pancreas.

Early-stage Zn supplementation in pregnant women can prevent preterm birth induced by As toxicity. On the other hand, Se co-administration can protect against As-induced behavioral deficits in rats through a mechanism involving anti-inflammation, antioxidation, and anti-apoptosis.

Acute As poisoning is treated with chelating agents such as British anti-lewisite (BAL) Dimercaprol and Succimer (DMSA), which bind to the metal to aid excretion from the body. BAL is prescribed in doses of 5 mg/kg up to 300 mg every 4 hours for the first day, then every 6 hours for the second day, and finally every 8 hours for 8 additional days. However, the (U.S.) Agency for Toxic Substances and Disease Registry (ATSDR) states that the long-term effects of As exposure cannot be predicted. Blood, urine, hair, and nails may be tested for As; however, these tests cannot foresee possible health outcomes from the exposure. Long-term exposure and consequent excretion through urine have been linked to bladder and kidney cancer in addition to cancer of the liver, prostate, skin, lungs, and nasal cavity.

In addition to biological trace elements, food-derived bioactive compounds that can attenuate OS and inflammation have protective potential against As-induced tissue damage. The most notable of the natural compounds are Curcumin, Quercetin, Gallic acid, Genistein, Resveratrol, and Thymoquinone, whose protective effects against As toxicity have been supported by multiple studies in animals. However, extrapolation of the beneficial effects of these compounds from preclinical evidence to clinical patients requires further validation.

Access to a high-protein diet also can help mitigate As toxicity. Evidence suggests that ensuring an enriched environment can be a prospective strategy against As-induced neurological problems, probably by alleviating depression and stress. Moreover, conventional therapy that uses various chelating agents such as BAL, Dimercaprol, Dimercaptosuccinic acid (DMSA), and Penicillamine still may benefit As-induced neurological deficits.

Beyond the management strategies outlined above, preventive measures such as access to As-free drinking water, avoiding occupational exposure to As, avoiding risk factors to neurological disorders, and provision of nutritious foods need to be considered for the ultimate prevention of As-induced health consequences, including neurological deficits.

Classification and regulatory limits

Classification

The International Agency for Research on Cancer (IARC) recognizes As and its inorganic compounds as group 1 carcinogens. The European Union (EU) lists As-trioxide, As-pentoxide, and As-arsenate salts as category 1 carcinogens and classifies elemental As, As sulfate, and trioxide compounds as "toxic and dangerous for the environment".

Further, As is known to cause arsenicosis when present in drinking water, the most common species being Arsenate and Arsenite.

Regulatory limits

In the U.S., since 2006, the maximum concentration in drinking water allowed by the (U.S.) Environmental Protection Agency (EPA) is 10 ppb and the (U.S.) Food & Drug Administration (FDA) has set the same standard in 2005 for bottled water. The New Jersey's Department of Environmental Protection has set a drinking water limit at half that amount (5 ppb) in 2006. The immediately dangerous to life and health (IDLH) value for As metal and inorganic As compounds is 5 mg/m3 (5 ppb). The (U.S.) Occupational Safety & Health Administration (OSHA) has set the permissible exposure limit (PEL) to a time-weighted average (TWA) of 0.01 mg/m3 (0.01 ppb), and the (U.S.) National Institute for Occupational Safety & Health (NIOSH) has set the. recommended exposure limit (REL) to a 15-minute constant exposure of 0.002 mg/m3 (0.002 ppb). The PEL for organic As compounds is a TWA of 0.5 mg/m3 (0.5 ppb).

In 2008, based on its ongoing testing of a wide variety of American foods for toxic chemicals, the FDA set the level of concern (LOC) for inorganic As in apple and pear juices at 23 ppb, based on non-carcinogenic effects, and began blocking importation of products in excess of this level; it also required recalls for non-conforming domestic products. Testing by Consumer Reports showed inorganic As at levels slightly above 10 ppb, and the organization urged parents to reduce consumption. In July 2013, on consideration of consumption by children, chronic exposure, and carcinogenic effect, the FDA established an action level (AL) of 10 ppb for apple juice, the same as the drinking water standard.

Evidence-based public health advocates also recommend that, given the lack of regulation or labeling for As in the U.S., children should eat no more than 1.5 servings per week of rice and should not drink rice milk as part of their daily diet before age 5. The 2014 World Health Organization (WHO) Advisory Conference considered limits of 200–300 ppb for rice.

Conclusions and take-aways

- As is a naturally occurring, highly toxic element found in soil, water, and minerals. It exists in inorganic (more toxic) and organic (less toxic) forms.
- Epidemiological and experimental evidence suggests that chronic exposure to As is a significant environmental risk factor for the development and progression of AD. There is a dose-response relationship between higher As levels in groundwater and an increased risk of AD.
- The human brain is particularly susceptible to the toxic effects of heavy metals and it has been proven that these compounds can damage the central nervous system and lead to cognitive and behavioral impairments.
- Naturally occurring sources of human exposure include volcanic ash, weathering of minerals and ores, and mineralized groundwater. As is also found in food, water,

soil, and air. It is absorbed by all plants, but is more concentrated in leafy vegetables, rice, apple and grape juice, and seafood. An additional route of exposure is inhalation of atmospheric gases and dusts. In addition, As hotspots are related to both frequent fertilization and close distance to mining activities. Chronic exposure to As, particularly through contaminated drinking water and food, has also been linked to long-term impacts on cognitive function, including reduced verbal IQ and memory. Studies in mainland China found that soil arsenic concentrations were positively correlated with AD mortality rates.

- Naturally occurring As in groundwater is the most common source of chronic exposure worldwide.
- Epidemiological studies have suggested a correlation between chronic consumption of drinking water contaminated with As and the incidence of all leading causes of mortality.
- Exposure during birth or young adulthood is particularly strongly associated with an elevated risk of developing AD later in life.
- Health consequences of As exposure represent one of the devastating setbacks of environmental pollution in human history. As extends its toxic effects to a number of vital organs, including the brain, where it causes neurodevelopmental abnormalities in childhood and cognitive deficits in adults.
- The key neuropathological hallmarks of AD are: Amyloid-beta (Aβ) accumulation, tau hyperphosphorylation, and neuronal loss.
- When taken into the body, inorganic and organic As undergo a metabolic processing, forming various adducts. While several hypotheses have been suggested as to how As is processed, the exact mechanism remains somewhat unclear.
- As and its metabolites can accumulate in several organs of the human body. The high concentration of As deposited in the brain can be explained by the property of As to disrupt and pass through the blood-brain barrier with a decrease in the tight junctions.
- As induces neurotoxicity in AD through oxidative stress, neuroinflammation, mitochondrial dysfunction, epigenetic changes, and disruption of the gut microbiome, which in turn destroys the gut-brain barrier and promotes AD-like effects.
- Besides its contribution to the formation of amyloid plaques and neurofibrillary tangles, other mechanisms exist through which As can impact neurodevelopment, e.g., interference with synaptic transmission, induction of mitochondrial dysfunction, oxidative stress, inflammation, apoptosis, ferroptosis, and epigenetic alterations.
- Mitochondria are the main target in As-mediated neurotoxicity. As influences tau hyperphosphorylation in AD and hyperphosphorylated tau aggregates and acts on mitochondria, triggering energy deficit.
- The As-induced neurotoxicity mechanisms in AD include: Endoplasmic reticulum stress, apoptosis, impaired protein homeostasis, impaired Calcium signaling, induction of oxidative stress, ferroptosis, and DNA methylation in AD.
- Although the underlying precise mechanisms of As-induced neurotoxicity have not yet been determined, the changes caused by As exposure coincide with the pathological progression, clinical symptoms, and biochemical features of AD.
- As can accumulate in the brain and contribute to AD development through multiple mechanisms (promotion of amyloidogenesis, formation of neurofibrillary tangles, disruption of the brain′s redox balance, oxidative stress,

promotion of ferroptosis, decrease of DNA methylation, and interference with the DNA methylation process, possibly altering gene expression and contributing to cognitive decline.

- There is support for the possibility of a causal relationship between As exposure and the onset of AD, although further studies are needed to elucidate the molecular mechanisms underlying As-induced neurotoxicity and to develop targeted therapeutic strategies aimed at mitigating its contribution to AD pathology.
- While acute As toxicity can be managed by clinical use of specific antidotes, existing strategies to manage chronic As exposure are supportive only.
- As and its inorganic compounds have been recognized as group 1 carcinogens and classified as toxic and dangerous for the environment. Further, As is known to cause arsenicosis when present in drinking water, the most common species being arsenate and arsenite.
- Regulatory limits have been established by several countries.

Sidebar 1 – Physicochemical properties of Arsenic

Arsenic (As; atomic number 33) is a notoriously toxic metalloid. It occurs naturally in many minerals, usually in combination with sulfur (S) and metals, but also as a pure elemental crystal. It exists in inorganic (more toxic) and organic (less toxic) forms but also has various allotropes. (Allotropes are different structural forms of the same element in the same physical state - solid, liquid, or gas - resulting from atoms bonding in different arrangements.) Organic forms are produced by biological activity, mostly in surface waters, but are rarely quantitatively important. They may also occur where waters are significantly impacted by industrial pollution.

The primary uses of As (car batteries, ammunition, semiconductor dopant, pesticides, herbicides, insecticides, etc.) are declining with the increasing recognition of its persistent toxicity. The U.S. Environmental Protection Agency (EPA) states that " all As forms are a serious risk to human health". Also, the U.S. Agency for Toxic Substances and Disease Registry (ATSDR) ranked As number 1 in its 2001 prioritized list of hazardous substances. Further, As is classified as a group-A carcinogen.

Physical characteristics

The three most common As allotropes are grey, yellow, and black, with grey being the most common. Grey-As is brittle, yellow-As is soft and waxy, and black-As is glassy and brittle. As sublimes upon heating at atmospheric pressure, converting directly to a gaseous form without an intervening liquid state.

As occurs naturally as a single stable isotope, 75As. Synthetic radioisotopes are known from 64As to 95As, as well as at least 11 isomers. (Isomers are molecules with the same molecular formula but different structural arrangements or spatial orientations, resulting in distinct chemical and physical properties.) The most stable of these isotopes are 73As (half-life: 80.30 days) and 74As (17.77 days), followed by 71As (65.30 hours), 77As (38.79 hours), 76As (26.24 hours), and 72As (26.0 hours). All others have half-lives under 100 minutes and most under one minute.

Chemical characteristics

Although stable in dry air, As forms a golden-bronze tarnish upon exposure to humidity, which eventually becomes a black surface layer. When heated in air, it oxidizes and the fumes from this reaction have an odor resembling garlic. It burns in Oxygen (O) to form As-trioxide and As- pentoxide, and in Fluorine (Fl) to give As-pentafluoride. It makes As-acid with concentrated Nitric oxide (NO) and As-trioxide with concentrated

Sulfuric acid (H2SO4); however, it does not react with water, alkalis, or non-oxidizing acids. Also, As reacts with metals to form arsenides.

Occurrence and production

Arsenic is the 53rd most abundant element in the Earth's crust and the 22nd most abundant element in seawater. It ranks 41st in abundance in the universe. Most arsenic refinement operations in the U.S. and Europe have closed over environmental concerns.

Medical use

During the 17th, 18th, and 19th centuries, a number of As compounds were used as medicines for treating diseases such as cancer, psoriasis, and syphilis (now superseded by modern antibiotics). However, arsenicals such as Melarsoprol are still used for the treatment of sleeping thickness (African trypanosomiasis) despite their severe toxicity, since the disease is almost uniformly fatal if untreated. In 2000, the U.S. Food & Drug Administration (FDA) approved As-trioxide for the treatment of patients with acute promyelocytic leukemia that is resistant to all-trans retinoic acid. A 2008 paper reports success in locating tumors using As-74 (a positron emitter). This isotope produces clearer positron emission tomography (PET) scan images than the previous radioactive agent, Iodine-124. Nanoparticles of As have shown the ability to kill cancer cells with lesser cytotoxicity than other As formulations.

Heredity

As has been linked to epigenetic changes, which are heritable changes in gene expression that occur without changes in DNA sequence. These include DNA methylation, histone modification, and RNA interference. Toxic levels of As cause significant DNA hypermethylation of the tumor suppressor genes p!6 and p53, thus increasing the risk of carcinogenesis. Studies investigating As as an epigenetic factor can be used to develop precise biomarkers of exposure and susceptibility.

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