BOHR International Journal of Neurology and Neuroscience
2025, Vol. 3, No. 1, pp. 1–6
DOI: 10.54646/bijnn.2025.22
www.bohrpub.com

REVIEW

Exposure to aluminum nanoparticles: Cognitive impairments and Alzheimer-like impact

Mojtaba Ehsanifar[1*†], Alireza Esmaeili[2], Akram Gholami[3] and Omid Ahmadi[3]

[1]Department of Environmental Health Engineering, Torbat Jam Faculty of Medical Sciences, Torbat Jam, Iran
[2]Department of Emergency Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[3]Department of Nursing, Torbat Jam faculty of Medical Sciences, Torbat Jam, Iran

***Correspondence:**
Mojtaba Ehsanifar,
Ehsanifar@gmail.com
†ORCID:
Mojtaba Ehsanifar,
0000-0003-1005-2501
Scopus ID: 57199997598

Received: 11 September 2024; **Accepted:** 11 December 2024; **Published:** 18 January 2025

Recent findings implicate aluminum (Al) as a contaminant in the cause of progressive damage to the structure and function of neurons, which can cause neuronal cell death and may lead to cognitive impairment, learning, and memory impairment in older adults, resembling the damage of Alzheimer's disease (AD). However, there is still no solid evidence to prove it. The idea of a role for Al in the origin, development, and severity of AD has existed for many years. Although the role of Al in AD is becoming increasingly clear, the underlying toxic mechanism remains unclear. This small review describes the morphological features and effects of Al exposure on neuronal cell death and cognitive challenges following exposure to Al nanoparticles.

Keywords: aluminum nanoparticles exposure, cognitive impairments, phosphorylated tau, Alzheimer's disease

Introduction

The continuous exposure to ambient nanoparticles is correlated with alterations in brain neurobehavioral, neurochemical, and pathological states, leading to reduced learning abilities in mice. Prior studies have explored central nervous system (CNS) disorders and neurobehavioral challenges resulting from oxidative stress and neuroinflammation caused by air pollution particles (1–4). These neurobehavioral changes encompass anxiety, depression, learning difficulties, and memory issues following exposure to air pollution (5–7). By the late 19th century, Al had become a staple material used extensively in various sectors, including automobiles, household products, building construction, military hardware, electrical conduits, aviation, and food processing, among others. As the Al industry continued to grow, concerns over occupational exposure to Al emerged, highlighting significant occupational health challenges related to its effect on the nervous system (8). Studies focusing on epidemiology have revealed that individuals subjected to Al exposure at their workplaces have a heightened susceptibility to mild cognitive impairments. These impairments often manifest as slower information processing, deficits in memory, and difficulties with spatial orientation (9–11). Additionally, in routine life, Al permeates the human body through various channels such as food and water intake, infant formulas, cleaning systems, antacids, materials that come into contact with food, dust, dialysis solutions, nutritional injections, vaccine components, deodorants, and beauty products, among others. Therefore, the consequences of Al pollution from environmental sources on human health warrant significant attention (12).

In a region of Spain renowned for its environmental pollution, a study evaluating metal contamination levels in breast milk in the Murcia region discovered that the

average Al concentration in the breast milk of women who had resided in industrial or mining zones for a duration exceeding five years surpassed the maximum levels advised by the World Health Organization, potentially posing a health hazard to mothers and their offspring (13). A forward-looking cohort study that meticulously analyzed the consequences of exposure to multiple metals during pregnancy and early childhood on the neurocognitive abilities of children aged 2–3 indicated that Al exposure during pregnancy can impair fine motor skills, adaptive and language growth, as well as social skills development (14), suggesting that prenatal exposure to Al may detrimentally affect neural development in children. Numerous in vivo and in vitro experiments have demonstrated that neuronal death induced by Al is a crucial mechanism by which its neurotoxic effects are exerted. Gaining a deeper insight into the fundamental signaling pathways of Al-induced neuronal cell death might offer valuable knowledge for minimizing ambient Al exposure. It would provide a theoretical framework for understanding the negative health implications of Al exposure. Presently, the neuronal cell death induced by Al is considered part of an actively regulated cell death (RCD) process. RCD is a contemporary term synonymous with programmed cell death, which holds a pivotal role in ensuring cellular equilibrium and the survival of multicellular life forms (15). The most vital form of RCD is apoptosis, but it also encompasses methods like necroptosis, autophagy, pyroptosis, and ferroptosis. This study aims to explore cognitive impairments and AD-like injuries due to occupational exposure to Al nanoparticles.

Literature review

While the neurotoxicologically effects of Al are somewhat known, previous studies have not fully addressed Al's interactions and its long-term effects on the brain and nervous system. This review fills these gaps by focusing on Al role in neurotoxicological effects and cognitive impairments. It also provides a more detailed exploration of Al's molecular mechanisms, which have been largely underexplored in earlier works. The integration of recent findings on the risks of Al chronic exposure further distinguishes this review from past analyses, offering a more comprehensive understanding of Al neurotoxicity.

Methodology

A methodical search was carried out across numerous databases such as PubMed, Scopus, and Web of Science. The focus was on specific terms like Al nanoparticle exposure, cognitive decline, phosphorylated tau, and their connection to Alzheimer's disease and Al toxicity. The review encompasses studies published from 2010 to 2023, ensuring coverage of up-to-date discoveries. Only peer-reviewed studies involving both animal and human models were considered. Research should specifically assess the impact of Al nanoparticles on cognition and Alzheimer's.

Cognitive impairments from exposure to Al

Al has become crucial in modern sectors, including electronics, aerospace, healthcare, and cosmetics. Its use in food-related products and additives highlights its widespread environmental presence. Al can be found in particulate matter like PM2.5, heightening exposure risks for people and workers. Studies suggest that exposure to Al nanoparticles is linked to cognitive impairments (16). Urine monitoring can reveal recent Al exposure events (17), while plasma analyses provide insights into both recent exposures and total body accumulation (18). Notably, after exposure ceases, plasma AL levels decrease at a gradual pace, indicating both prior and ongoing exposure (19). In retired individuals, AL serum concentrations were observed to be twice as high as those in a non-exposed control group, even a decade post-exposure (18). Plasma Al indicates body burden levels irrespective of current or past occupational exposure, influencing cognitive function differently across industries. Various studies highlight poor cognitive outcomes in occupational groups exposed to Al, such as Al welders (20, 21), smelters (22), and pot room employees (23, 24). A meta-analysis concerning occupational exposure suggests that urine Al, at levels below 135 μg/l, compromises cognitive abilities (16). Another research shows an inverse correlation between serum Al and results on cognitive and clock drawing tests (17). Furthermore, a comprehensive review found a strong positive association between elevated blood Al and diminished neurocognitive function (25). Reaction time delays are possible indicators of neurological shifts in Al welders, whose plasma levels range from 4.45 to 44.5 μg/l over 5 years of exposure (20).

Potential neurotoxicity of Al exposure

Al exposure has been linked to disturbances in neurotransmitter levels in the brain. Notably, it results in decreased levels of acetylcholine alongside rising activities of the enzymes acetylcholinesterase and 5-hydroxylase. Additionally, there are lowered quantities of tryptamine and dopamine, which significantly impair mice's cognitive capabilities relevant to learning and memory (26). One research study depicted that the nuclear membranes of cortical neurons in Al-exposed mice appeared less distinct, and the cytoplasm became compacted. Moreover, there

was a decline in both the count and density of cells within the granule and pyramidal layers of the brain, potentially due to oxidative stress triggered by Al (27). Furthermore, electron microscope analyses disclosed post-Al exposure that the nuclear chromatin of rat cortical neurons became tightly packed. Also, mitochondria and endoplasmic reticulum within cells exhibited swelling. In apoptotic cells, cytoplasmic observation revealed nuclear fragments and damaged organelles. Many of these detached nuclear elements formed apoptotic bodies as they were enclosed by intact cell membranes (28). Staining PC12 cells with Al demonstrated noticeable morphological changes—cell bodies became rounded, nuclei reduced in size, synapses shrunk, and interactions among cells diminished. Consequently, this led to reduced cell health and increased levels of cell death (29). The initial evidence of Al's potential neurotoxic effects came to light when individuals exposed to it exhibited brain abnormalities similar to those seen in AD's disease patients (30). This condition further developed into diminished brain function (31). Research indicates that continuous administration of Al to mice, starting from six months of age and continuing throughout their lifespan, leads to elevated levels of amyloid precursor protein in the cortical and hippocampal regions, thus increasing amyloid-beta (Aβ) production (32). When cortical neurons from mice were treated with Al (50 μM over 48 days), Aβ aggregation was observed. Moreover, structural alterations induced by Al in Aβ foster its aggregation by forming fibrillar structures on the external surfaces of neuronal cultures in vitro. Deferoxamine, an Al chelating agent, has been shown to dissolve accumulated Aβ (33, 34). It's also been noted that increased Aβ production in the hippocampus and cortex, used as an animal model for AD, effectively impairs memory. This was achieved through co-treatment involving Al and D-galactose, which heightened BACE1 expression while reducing NEP production (35). Al intake (2 mg/kg diet over 9 months) decreased Aβ degradation by inhibiting cathepsin B activity, suggesting a potential link between enhanced amyloidogenic pathways and reduced Aβ breakdown (36). Additionally, a reduction in LRP1 expression was noted in mice that received D-galactose and Al, indicating a feasible decrease in Aβ clearance (35). In a diet consisting of Al (2 mg/kg over 9 months), transgenic mice (Tg2576) exhibited increased production of Aβ and associated proteins with its synthesis. Consequently, the formation of amyloid plaques was mitigated by the influence of vitamin E, a powerful antioxidant, highlighting the contribution of Al-induced oxidative stress (37).

Mechanism of neuronal cell death induced by Al exposure

Mechanisms of Apoptosis: The activation of intracellular cysteine proteases, specifically the caspase family, is crucial for the transmission of apoptotic signals. Al's impact on neuronal cell death primarily involves the intrinsic mitochondrial pathway of apoptosis activation. Al exposure contributes to neuronal apoptosis by reducing anti-apoptotic Bcl-2 protein levels, augmenting pro-apoptotic Bax protein levels, and resulting in a lower Bcl-2/Bax ratio. This change leads to an increase in apoptotic bodies and the heightened expression of caspases 9 (38) and caspases 3 (39), pivotal initiators and executors in apoptosis signaling responsible for neuronal cell death. Moreover, Al might prompt irregular expression of the Fas ligand (FasL) (40, 41) and caspase-8, further impacting apoptotic processes (42). Continuous exposure to elevated Al levels results in hippocampal damage via both intrinsic and extrinsic apoptotic mechanisms (43). Mitogen-activated protein kinases (MAPKs) are pivotal in converting external cellular signals into internal actions, consequently regulating various bodily functions. In apoptosis mediation via the MAPK pathway, crucial MAPKs, including ERK, JNK, and p38MAPK, are integral in managing cellular reactions to Al, impacting apoptosis modulation (44). Research indicates that nano-Al can trigger caspase-3 activation within the mouse hippocampus by enhancing ERK and p38MAPK phosphorylation, which results in neuronal apoptosis. Notably, JNK expression levels remain unaffected by Al in specific scenarios (45). Nonetheless, studies reveal inconsistent outcomes concerning JNK expression changes following Al exposure. This inconsistency might stem from the diversity of Al compounds, dosage, and exposure durations used in research. For instance, in mouse neuron studies, aluminum chloride boosts JNK activation by facilitating interleukin-1β (IL-1β) binding to its receptor (46). Furthermore, the PI3K/Akt signaling pathway is crucial in determining apoptosis, including a wide array of cellular activities such as survival, differentiation, proliferation, apoptosis, and metabolism. Phosphatidylinositol 3-kinase (PI3K) alongside protein kinase B (PKB/Akt), its downstream component, are vital pathways affecting numerous cellular functions. Al has been demonstrated to influence the expression levels of various signaling molecules through the PI3K/Akt pathway, significantly enhancing neurogenesis (47). In addition, the mammalian target of rapamycin (mTOR), a serine/threonine kinase, exists in two molecular complexes: mTORC1 and mTORC2. mTORC1 predominantly governs cell death processes, including apoptosis, necrosis, and autophagy (48). Studies reveal that Al can heighten neuronal apoptosis by diminishing PI3K, Akt, and mTORC1 expression, impairing zebrafish learning and memory (49). Glycogen synthase kinase 3β (GSK-3β) is crucial in apoptosis. Post-Al exposure, the reduction in Akt activity lessens its inhibitory impact on GSK-3β, thereby increasing GSK-3β activity and pro-apoptotic marker levels (Bad, Bax, caspase-3, and caspase-9). This promotes apoptosis, evident by reduced anti-apoptotic marker levels (Bcl-2 and Bcl-xL), triggering apoptosis in mice's hippocampal and cortical neurons.

Necroptosis, a genetically controlled cell death mechanism, can lead to neuronal demise and significantly influence various neurodegenerative diseases (50).

Upon infection by pathogens or chemicals, cells release damage-associated molecular patterns and pathogen-associated molecular patterns, recognized by surrounding phagocytes, which then induce tumor necrosis. The activation of tumor necrosis factor receptor 1 (TNFR1) or toll-like receptor leads to the activation of receptor-interacting protein 1 (RIP1) and RIP3, which migrate to the cell membrane, causing rupture and forming a complex system (51). Investigations have revealed that exposure to Al increases the levels of TNFR1, RIP3, and MLKL proteins in the hippocampus of rats, indicating that necroptosis, a programmed cell death process, might play a role in neuronal death due to Al. This process may be associated with the IL-1β/JNK signaling pathway (46). The necroptosis inhibitor Necrostatin-1 (Nec-1) is effective in decreasing the activities of RIP1 and RIP3 by interacting with the mTOR signaling pathway. Its application is advantageous in diminishing Al-induced neuronal cell death, notably enhancing cognitive functions, as observed in zebrafish subjected to pollution (52). Autophagy serves as a crucial cellular mechanism where cells decompose and recycle superfluous or harmful components through lysosomal activity. This process involves the sequestration of damaged proteins and organelles by autophagosomes, which are subsequently delivered to lysosomes for breakdown, thus maintaining cellular balance (53). Yet, in situations of stress like nutrient scarcity, absence of insulin, or reduced ATP levels, the kinase complex mTORC1 can become inactive, which in turn triggers an overactive autophagic response that might harm overall health. When mTORC1 is inactive, its ability to phosphorylate autophagy activators like ULK1 and components of the Atg13 complex, which includes elements of the FIP200 protein family and ULK1, diminishes. Enhanced activity of Atg13 and Atg101 subsequently stimulates the downstream PI3K complex comprised of VPS34, VPS15, Beclin-1, and Atg14, culminating in phagocytic vacuole formation. The maturation process results in the development of an autophagosome, a distinct double-membraned lipid vesicle. Autophagosome formation involves 2 primary ubiquitin-like reaction systems: the microtubule-associated protein 3 (LC3) light chain system and the Atg12-Atg5 system. These pathways facilitate the expansion and closure of the autophagosome membrane. Specifically, LC3-I emerges following the protease Atg4-mediated cleavage of LC3, binding with phosphatidylethanolamine to form LC3-II. This protein resides on the surface of mature autophagosomes and serves as a reliable marker for autophagy (54).

Nano-alumina exposure results in both developmental and behavioral issues in zebrafish larvae, likely due to enhanced autophagy-related processes. This is evident from increased protein expression of Beclin-1 and the ratio of LC3-II/LC3-I (55). In mice, Al oxide nanoparticles administered via the carotid artery led to deposition in brain endothelial cells. This triggers a rise in autotrophic gene activity, increases overall autophagy within the brain, reduces tight junction protein expression, and boosts blood-brain barrier permeability, thus exacerbating neurovascular toxicity within the CNS (56). Autophagosomes also engage in selective removal and digestion of specific targets under the guidance of selective autophagy receptors and upstream Atg proteins. This includes the elimination of defective mitochondria, the endoplasmic reticulum, lipid droplets, and pathogens. In a specialized autophagy known as mitophagy, damaged mitochondria are selectively destroyed to sustain energy balance and proper cell function (57, 58). Recent research highlights Al-maltol's effect on mitochondrial dynamics in PC12 cells, disturbing the equilibrium between mitochondrial fusion and fission (29).

Conclusion

Recent years have seen a growing interest from both domestic and international researchers in the neurotoxic impacts of Al exposure. Epidemiological research has linked Al as a potential risk factor for AD. Exposure to Al can occur through various means, such as drinking water, food, hair, skin, cosmetics, and hygiene products. Yet, inhalation of fine particles is considered the primary exposure pathway, highlighting the toxic mechanisms linked to oxidative stress in AD. This involves oxidative stress due to the accumulation of Reactive Oxygen Species (ROS) or the alteration of antioxidant enzymes such as Aβ and tau. These neurotoxins can trigger oxidative stress and modulate several signaling pathways, affecting enzyme activity in ways that lead to the accumulation of harmful substances such as Aβ in AD, damaged proteins, and oxidative byproducts in neuronal cells. This can potentially affect epigenetic or genetic regulation.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Author contributions

All authors contributed to writing—reviewing and editing.

Funding

This review received no external funding and was initiated and funded by Dr. Ehsanifar Research Lab, Tehran, Iran.

Acknowledgment

We thank Dr. Ehsanifar Research Lab. Tehran, Iran.

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