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Mini Review

Occupational Exposure to Aluminum Particles and Alzheimer's Disease-Like Damage

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Abstract

Cohort studies have indicated that prolonged occupational exposure to aluminum causes cognitive impairment and neurotoxicity. Al is a widespread neurotoxin that can induce Aβ deposition and abnormal tau protein phosphorylation, leading to Alzheimer's disease-like damage, such as reduced learning and memory and neuronal damage. For many years, Al has been implicated in the etiology of AD according to the so-called "Al in AD hypothesis", and researchers have described how it plays a role in the onset, progression, and aggressive nature of AD. The toxicity of Al is related to its prooxidant activity, which occurs through the formation of Al superoxide radical cations. However, although the role of Al in AD has become clearer, the dominant toxic mechanism involved is still not understood. In this mini-review, we investigated the effect of exposure to aluminum particles on phosphorylated tau levels and cognitive impairment.

Keywords: ***Occupational exposure; Aluminum particles; Phosphorylated tau; Alzheimer's disease.***

1. Introduction

Long-term exposure to ambient PM can cause neurobehavioral, neurochemical, and neuropathological alterations in the brain, impairing learning ability. The CNS disorders and neurobehavioral complications caused by oxidative stress and neuroinflammation following exposure to air pollution particles were investigated in our previous studies [1-4]. Among these neurobehavioral alterations are anxiety and depression and memory and learning disorders following exposure to air pollution PM [5-7]. Al is the most abundant metallic element in nature. Due to its excellent properties, Al is widely used in construction, cooking, transportation, vaccine aid and food additive use [8]. With the introduction of very fine Al particles, Al can reach the human body through the digestive system, skin, respiratory system, etc., increasing the body's Al burden and becoming a public health issue that is of concern [9]. Occupational exposure is considered a serious health problem due to the high bioavailability of inhaled fine particles during exposure [10]. Research has shown that Al is one of the most important ambient factors for neurological diseases, especially AD [11]. Research findings have indicated that the incidence of AD in elderly individuals significantly increases after prolonged drinking of water containing excess Al [12]. Exposure to Al can lead to damage to the nervous system and has a significant relationship with the dose of Al, so chronic exposure to Al particles impairs memory, learning and cognitive disorders [3,13]. The mechanism of Al neurotoxicity has been investigated from different perspectives. Al can affect the conduction of nerve impulses by inhibiting acetylcholinesterase [14]. In the brain, Al mainly accumulates in the frontal cortex and hippocampus, regions that are particularly susceptible to AD. Al can cause oxidative stress, damage the mitochondrial membrane, increase ROS, and cause programmed necrosis and neuronal cell apoptosis [15,16]. In animal models orally administered Al, significant accumulation of Aβ and rapid accumulation of tau protein have been observed [17,18]. Al can reduce memory and learning performance in mice by impairing hippocampal synaptic plasticity. However, which pathways are involved in the neurotoxicity of Al have not yet been determined [19,20]. A study showed that exposure to aluminum in the workplace can cause changes in phosphorylated tau and that phosphorylated tau may be a potential biomarker in the process of cognitive impairment and occupational exposure to aluminum. Indeed, exposure to aluminum has been shown to cause cognitive impairment and altered the expression of phosphorylated tau in exposed workers [20]. The aim of this study was to investigate Alzheimer's disease-like damage after occupational exposure to aluminum particles.

2. Cognitive disorders following exposure to Al particles

Today, in addition to being utilized in the electronics, aerospace, medical, and cosmetic industries, Al is widely used in food contact materials and food additives. This widespread use has inevitably led to the widespread release of Al in the ambient environment so that Al can also be detected in PM2.5. As a result, public and occupational exposure to Al has increased significantly. Al particle exposure causes cognitive dysfunction [21]. The urinary aluminum concentration can reflect recent aluminum exposure [22], while the plasma aluminum concentration reflects the aluminum body burden and cultivation exposure [23]. The findings showed that the plasma Al concentration decreased only slowly after removal from the exposure, and the prevailing plasma Al concentration appeared to reflect both the current exposure and the exposure in the preceding months [24]. In the retired population, the serum Al concentration was 2 times greater even 10 years after the end of the exposure than in the control group [23].

The plasma Al concentration can be evaluated as an indicator of body burden regardless of whether the employee or

retired worker was occupationally exposed to Al. Occupational exposure to Al has different effects on the cognitive performance of workers in different industries. Epidemiological studies have shown poor performance on cognitive tests in various occupational populations exposed to Al, such as Al welders [25,26], smelting workers [27], and potroom workers [11,28]. The results of a meta-analysis of the effects of occupational exposure to Al on cognitive and motor performance showed that urinary Al concentrations less than 135 µg/L had an effect on cognitive performance [22]. A negative relationship between serum Al concentrations and mental state test and clock drawing test scores was shown in another study [23]. A review reported a strong positive association between compromised neurocognitive functions and blood Al levels [13]. It has also been reported that reaction time can be the first indicator of possible neurological changes in Al welders (plasma Al from 4.45 to 44.5 µg/L, exposure time 5 years) [26].

3. Altered Phosphorylated Tau following Exposure to Al

The mechanism through which occupational Al exposure causes cognitive impairment is unknown. One study indicated that plasma tau is strongly associated with cognitive function [29]. The tau protein is a microtubule-associated protein, and the main known physiological functions of this protein include the stimulation of tubulin polymerization, microtubule stabilization and intracellular organelle transport by microtubules. When the protein is hyperphosphorylated, it loses its ability to synthesize and stabilize microtubules, leading to increased cytotoxicity and neuronal damage [30]. P-tau and Aβ42 are among the most important biomarkers for AD pathology. Aβ42 fibril accumulation is considered to trigger neuropathology and a series of events, including oxidative stress, inflammation and neurotoxicity. The hippocampal accumulation of phosphorylated tau is responsible for cognitive impairments [31]. Recently, increasing evidence has suggested that tau protein in the CSF is associated with cognitive function in AD and MCI patients [32], especially P-tau181 and P-tau231, which are more specifically related to cognitive function in early AD [33,34]. Al plays a role in the hyperphosphorylation of tau and promotes the aggregation of the hyperphosphorylated tau protein [35]. Research has shown that aluminum can induce the hyperphosphorylation of tau in learning- and memory-related brain areas in mice [36].

Recent studies have provided new insights into the pathological neurotoxicity of Al, including oxidative stress and mitochondrial dysfunctions[37], apoptosis[38], tau hyperphosphorylation [36], alterations in rodent brain neurotransmitter levels [39] and interference with Ca2+ metabolism[40].

The number of neurofibrillary tangles is strongly associated with cognitive function [41]. Recent studies have reached the general consensus that tau is a marker of neurofibrillary tangles [42]. Published reports have also shown that aluminum exposure is correlated with tau phosphorylation [43]. Misfolding of cytoskeletal proteins leads to the formation of Aβ plaques [43] and neurofibrillary tau [44] in the brain. Therefore, aluminum can cause abnormal phosphorylation of tau, leading to cognitive dysfunction. The mediation analysis indicated that the associations between plasma Al concentrations and the RVR were partly mediated by P-tau231. A negative correlation was also reported between plasma t-tau and total gray matter volume, amygdala volume, hippocampal volume and cognitive measures of logical memory, visual reproduction and verbal fluency in individuals with MCI or early AD [45]. Similarly, both t-tau and Aβ42 are potential predictors of progressive cognitive decline in the MCI stage of AD [46]. Therefore, Al exposure-associated cognitive impairment may be related to the mechanism through which Al hyperphosphorylates tau. In future studies, multiple plasma sample measurements should be used to evaluate individual long-term phosphorylated tau levels and exposure to aluminum.

4. Conclusion

There are various sources of exposure to metals, including diet (water or food), occupational exposure, and inhalation of polluted air containing suspended particles. Compared to occupational exposure to other sources, occupational exposure to metals is rarer but greater in dose. Epidemiological findings have identified Al as a risk factor for AD. Exposure to Al may occur through drinking water, food, hair, skin, topically applied cosmetics, and the use of hygiene products; however, inhalation of fine particles is the most relevant route of exposure to Al. Exposure to occupational Al particles can induce cognitive impairment and hyperphosphorylated tau. P-231tau may mediate cognitive impairment caused by occupational aluminum exposure, but additional studies are needed to investigate this phenomenon.

Abbreviation

Al: aluminum
AD: Alzheimer's disease
Aβ: Amyloid beta
CNS: central nervous system
PM: Particulate matter
ROS: reactive oxygen species
P-tau: Phosphorylated tau protein
Aβ42: 1-42 amino acid form of beta-amyloid
CSF: cerebrospinal fluid
MCI: Mild cognitive impairment

5. Declaration of interest

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Authors' contributions

All the authors contributed to writing, reviewing and editing the manuscript.

Competing Interests

The authors declare that they have no competing interests.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Availability of data and materials

Not applicable.

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