The Effect of Phosphorylated Tau and Cognitive Impairment after Exposure to Aluminum Nanoparticles

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Abstract
Aluminum (Al) is an environmental neurotoxin to which humans are widely exposed and which is associated with motor and cognitive impairment and is most commonly associated with neurodegenerative diseases; it can cause abnormal phosphorylation of the tau protein and cognitive impairment. Al has been implicated in the etiology of Alzheimer’s Disease (AD) for many years in the so-called “Al in AD hypothesis” and several studies have described how Al exposure plays a role in the onset, aggressiveness and progression of AD and can cause abnormal phosphorylation of the tau protein. The toxicity of Al is related to its pro-oxidant activity, which acts through the formation of an Al superoxide radical cation. However, the molecular mechanism of Al toxicity is unclear, and although the role of Al in Alzheimer’s disease is becoming clearer, the mechanism of the predominant toxicity is still not understood. In this mini-review, we examine the effect of phosphorylated tau and cognitive impairment after exposure to Al nanoparticles.

Introduction
The Central Nervous System (CNS) disorders and neurobehavioral complications caused by oxidative stress and neuroinflammation following exposure to ambient air pollution nanoparticles have been investigated in our previous studies [1-8]. Among these neurobehavioral alterations, can mention anxiety and depression, memory and learning disorders following exposure to air pollution Particulate Matter (PM) [9-13]. Aluminum (Al) is a relatively light metal that is widely used and its use rate is the second highest among metals [14] is present everywhere in the world. According to previous studies, aluminum accumulates in the environment and is absorbed by the human body through the respiratory tract and gastrointestinal tract. In the workplace, workers are exposed to aluminum mainly by inhaling very small particles of aluminum, and its bioavailability is approximately 5-20 times higher than that of aluminum in drinking water [15]. After inhaling very small particles of aluminum in the workplace, aluminum is released from the lungs into the bloodstream, distributed to the bones and brain, and excreted in the urine, and neurotoxicity is an important effect of very small particles [16]. Exposure to Al may cause a variety of adverse effects on human health such as neurological diseases (Alzheimer’s Disease (AD) and Mild Cognitive Impairment (MCI)) [17]. Exposure to aluminum in the workplace is an important source of high levels of aluminum. In a 1985 study, three patients with a progressive neurological disorder who had worked in an aluminum smelter for more than 12 years were evaluated and described [18]. Since then, numerous studies have shown that occupational aluminum exposure has adverse

effects on workers’ cognitive performance, such as cognitive process, memory, concentration, executive performance, and other cognitive domains [19,20]. Another study in 1975 identified a protein that is a member of the family of Microtubule-Related Proteins (MAPs) and plays a major role in the pathology of cognitive and memory disorders in neurodegenerative diseases [21]. Hyperphosphorylated tau is the main component of Neurofibrillary Tangles (NFT) [22]. NFT is a pathological feature of AD.

Further studies have shown stronger relationships between NFTs, which are mainly hyperphosphorylated tau proteins, and cognitive function. Changes in phosphorylated tau have been observed in many neurological disease studies. Phosphorylated tau (P-tau), especially p-tau181 and p-tau231 are signs of cognitive decline and aggressive course of the disease [23,24]. Previous studies have shown that Al causes tau accumulation and induces neurofibrillary degeneration. It acts as a cofactor in the formation of NFTs by interacting with PHF tau [25,26]. One study found that exposure to aluminum in the workplace can cause changes in phosphorylated tau, and that phosphorylated tau can be a potential biomarker in the process of cognitive impairment and occupational exposure to aluminum. In fact, exposure to aluminum has caused cognitive impairment and altered phosphorylated tau expression in exposed workers [27]. The aim of this mini-review is to investigate the relationship between the effect of phosphorylated tau and cognitive impairment following exposure to aluminum ultrafine particles.

Aluminum ultrafine particles exposure and cognitive impairment

Al is a relatively abundant metal in the crust of the earth and used widely in modern industries. Allen believed to be an neurotoxic agent that has deleterious effects on human cognitive function. Excessive exposure can easily occur in workplace. It is not easy to evaluate aluminum concentrations in workplace, as values of aluminum concentration in the air samples may vary, so biological monitoring is more reliable [28]. Urine aluminum concentration can reflect recent aluminum exposure [29], while plasma aluminum concentration reflects aluminum body burden and is cultivated with exposure [30]. Findings show that the plasma Al only falls slowly after removal from the exposure, and the prevailing plasma Al appears to reflect both current exposure and exposure in the preceding months [31]. In the retired population, serum Al levels remained 2 times higher even 10 years after the end of the exposure compared to that of the control group [30].

Regardless of whether the worker was a retiree or employee in the occupational Al exposure, the plasma Al concentration as body burden index could be monitored. Occupational exposure to Al in different industries, seems to have various effects of worker’s cognitive function. Multiple epidemiological reports have shown the poor performance on the cognitive tests in various occupationally Al-exposed populations such as Al welders [32,33] smelting workers [34], and potroom workers [17,35]. A data meta-analysis on occupational Al exposure effects on motor performance and cognitive, found urinary Al concentrations below 135 μg/l have an affects cognitive performance [29]. Another study shown a negative relationship between the mental state exam and clock drawing test scores and serum Al levels [30]. Another study reported the existence of a strong positive relationship between compromised neurocognitive functions and the Al quantity in blood [20]. Also have been reported that in Al welders, the reaction time may be the first indicator for the possible neurological changes (plasma Al from 4.45 to 44.5 μg/L, exposure time 5 years) [33].

Exposure to aluminum and altered phosphorylated tau

The mechanism of occupational aluminum exposure causing cognitive impairment is unknown. One study indicated that plasma tau is strongly associated with cognitive function [36]. Tau protein is a microtubule-related protein, the major known physiological this protein functions include tubulin polymerization stimulation, microtubule stabilization, and transport of intracellular organelles by microtubules. When tau protein is hyperphosphorylated, it loses its function in microtubule synthesis and stabilization, leading to increased cytotoxicity and neuronal damage [37]. The findings of a study suggest that cognitive impairments are caused by the accumulation of phosphorylated tau in the hippocampus [38]. Recently, increasing evidence suggests that tau protein in the Cerebrosplinal Fluid (CSF) is associated with cognitive function in AD and MCI patients [39], especially P-tau181 and P-tau231, which are more specifically related to cognitive function in early Alzheimer’s disease [40,41]. Al has been shown to be involved in hyperphosphorylation of tau and promote the aggregation of hyperphosphorylated tau protein [42]. A research results determined that aluminum could induce the hyperphosphorylation of tau in learning and memory related mice’s brain areas [43]. In another study, hippocampal CA1 region cells in aged humans were examined and combined with existing evidence to ascertain the role of Al in the NFTs formation and growth in neurons of the humans with AD [44].

Recent studies have provided new insights into the pathological neurotoxicity of aluminum, including oxidative stress and mitochondrial dysfunctions [45], apoptosis [46], tau hyperphosphorylation [43], alterations of rodent brain neurotransmitter level [47] and interference of Ca2+ metabolism [48].

The number of neurofibrillary tangles is strongly associated with both cognitive function [49]. Recent studies have reached a general consensus that tau is marker of neurofibrillary tangles [50]. Published reports have also correlated aluminum exposure with tau phosphorylation [43]. Therefore, aluminum can cause abnormal phosphorylation of tau, leading to cognitive dysfunction. The mediation analysis indicated that the associations of plasma aluminum with RV score were partly mediated by P-tau231. Also reported a negative relationship between plasma t-tau and amygdala volume, hippocampal volume, volume of the total gray matter, and logical memory cognitive measures, visual reproduction, and the verbal fluency in early AD or MCI [51]. Similarly, both t-tau and Aβ42 are considered potential predictors to monitor progressive cognitive decline in MCI stage of AD [52]. Therefore, Al exposure-associated cognitive impairment may be related to mechanisms of hyperphosphorylated tau induced by Al. In future studies should be used multiple point plasma sample measurements should be used to evaluate the individual long-term phosphorylated tau level and exposure to aluminum.

Conclusion

Exposure to Al fine particulate can induce cognitive disorders and hyperphosphorylated tau. P-231tau may mediate cognitive impairment caused by occupational aluminum exposure. Plasma tau may serve as a window that reveals cognitive decline induced occupational aluminum exposure that more studies are needed to investigate it.
Declaration of interest

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