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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 isabsorbed 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

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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

ALisa relatively abundant metal in the crust of the earth and used widely in modern industries. Alis believed to be an eurotoxic agent that has deleterious effects on t h e cognitive function. Excessive Alexposure 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 reflect aluminum body burden and cultivate 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 occupationalAl 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 mini-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 Cerebrospinal 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 combinedwith 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 Ca^{2+} 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 RVR score were partly mediated by P-tau231. Also reported a negative relationship between plasma t-tau and amygdale 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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References

1. Ehsanifar M, et al. Mold and Mycotoxin Exposure and Brain Disorders. Journal of Integrative Neuroscience, 2023. 22(6): p. 137.
2. Ehsanifar M, Banihashemian S, Ehsanifar M. Exposure to Air Pollution Nanoparticles: Oxidative Stress and Neuroinfl ammation. J Biomed Res Environ Sci. 2021; 2: 964-976.
3. Ehsanifar M, Montazeri Z, Rafati M. Neurotoxicity related exposure to ambient nanoparticles. 2022.
4. Ehsanifar M. Exposure To urban air pollution nanoparticles and CNS disease. On. J. Neur. & Br. Disord. 2021; 5: 520-526.
5. Ehsanifar M, Yavari Z, Rafati M. Exposure to urban air pollution particulate matter: Neurobehavioral alteration and hippocampal inflammation. Environmental Science and Pollution Research. 2022; 1-11.
6. Ehsanifar M, Rafati M, Wang J. Neurological complications related to COVID-19 infections following exposure to airborne aerosol particles. Clinical Research and Clinical Trials. 2022; 5.
7. Ehsanifar M, Montazeri Z. Parkinson's Disease-Like Neuropathology and Phenotype Following Induction of Oxidative Stress and Infl ammation in the Brain. Journal ISSN. 2022; 2766: 2276.
8. Ehsanifar M, Montazeri Z. CNS Demyelination Diseases Following Exposure to Urban Air Pollution. Journal ISSN. 2022; 2766: 2276.
9. Ehsanifar M. Anxiety and Depression Following Diesel Exhaust Nano-Particles Exposure in Male and Female Mice. J Neurophysiol Neurol Disord. 2020; 8: 1-8.
10. Ehsanifar M, et al. Learning and memory disorders related to hippocampal inflammation following exposure to air pollution. Journal of Environmental Health Science and Engineering. 2021.
11. Ehsanifar M, et al. Hippocampal inflammation and oxidative stress following exposure to Diesel exhaust nanoparticles in male and female mice. Neurochemistry International. 2021: 104989.
12. Ehsanifar M, et al. Exposure to nanoscale diesel exhaust particles: Oxidative stress, neuroinflammation, anxiety and depression on adult male mice. Ecotoxicology and Environmental Safety. 2019; 168: 338-347.
13. Ehsanifar M, et al. Prenatal exposure to diesel exhaust particles causes anxiety, spatial memory disorders with alters expression of hippocampal pro-inflammatory cytokines and NMDA receptor subunits in adult male mice offspring. Ecotoxicology and Environmental Safety. 2019; 176: 34-41.
14. Niu Q. Overview of the relationship between aluminum exposure and health of human being. Neurotoxicity of Aluminum. 2018; 1-31.
15. Krewski D, et al. Human health risk assessment for aluminium, aluminium oxide, and aluminium hydroxide. Journal of Toxicology and Environmental Health, Part B, 2007; 10: 1-269.
16. Riihimäki V, Aitio A. Occupational exposure to aluminum and its biomonitoring in perspective. Critical reviews in toxicology. 2012; 42: 827-853.
17. Yang X, et al. The relationship between cognitive impairment and global DNA methylation decrease among aluminum potroom workers. Journal of occupational and environmental medicine. 2015; 57: 713-717.
18. Longstreth W, Rosenstock L, Heyer NJ. Potroom palsy?: neurologic disorder in three aluminum smelter workers. Archives of internal medicine. 1985; 145: 1972-1975.
19. Wang S, et al. The relationship between plasma Al levels and multi-domain cognitive performance among in-service aluminum-exposed workers at the SH aluminum factory in China: a cross-sectional study. Neurotoxicology. 2020; 76: 144-152.
20. Giorgianni CM, et al. Neurocognitive effects in welders exposed to aluminium. Toxicology and industrial health. 2014; 30: 347-356.
21. Wang JZ, Wang ZH. Senescence may mediate conversion of tau phosphorylation-induced apoptotic escape to neurodegeneration. Experimental gerontology. 2015; 68: 82-86.
22. Grundke-Iqbal I, et al. Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. Proceedings of the National Academy of Sciences. 1986; 83: 4913-4917.
23. Gunnarsson MD, et al. High tau levels in cerebrospinal fluid predict rapid decline and increased dementia mortality in Alzheimer's disease. Dementia and geriatric cognitive disorders. 2014; 37: 196-206.
24. Sperling R, Johnson K. Biomarkers of Alzheimer disease: Current and future applications to diagnostic criteria. CONTINUUM: Lifelong learning in neurology. 2013; 19: 325-338.
25. Shin RW. Interaction of aluminum with paired helical filament tau is involved in neurofibrillary pathology of Alzheimer's disease. Gerontology. 1997; 43: 16-23.
26. Ehsanifar M, Montazeri Z, Rafati M. Alzheimer's Disease-Like Neuropathology Following Exposure to Ambient Noise. 2021.
27. Lu X, et al. Cognitive disorders and tau-protein expression among retired aluminum smelting workers. Journal of occupational and environmental medicine. 2014; 56: 155-160.
28. Sjögren B, et al. Effects on the nervous system among welders exposed to aluminium and manganese. Occupational and environmental medicine. 1996; 53: 32-40.
29. Meyer-Baron M, et al. Occupational aluminum exposure: Evidence in support of its neurobehavioral impact. Neurotoxicology. 2007; 28: 1068-1078.
30. Polizzi S, et al. Neurotoxic effects of aluminium among foundry workers and Alzheimer's disease. Neurotoxicology. 2002; 23: 761-774.
31. Bergdahl IA, Skerfving S. Biomonitoring of lead exposure—alternatives to blood. Journal of Toxicology and Environmental Health, Part A. 2008; 71: 1235-1243.
32. Akila R, Stollery BT, Riihimäki V. Decrements in cognitive performance in metal inert gas welders exposed to aluminium. Occupational and environmental medicine. 1999; 56: 632-639.

33. Buchta M, et al. Longitudinal study examining the neurotoxicity of occupational exposure to aluminium-containing welding fumes. International archives of occupational and environmental health. 2003; 76: 539-548.

34. Zawilla N, et al. Occupational exposure to aluminum and its amyloidogenic link with cognitive functions. Journal of inorganic biochemistry. 2014; 139: 57-64.

35. He S, Qiao N, Sheng W. Neurobehavioral, autonomic nervous function and lymphocyte subsets among aluminum electrolytic workers. International Journal of Immunopathology and Pharmacology. 2003; 16: 139-144.

36. Dage JL, et al. Levels of tau protein in plasma are associated with neurodegeneration and cognitive function in a population-based elderly cohort. Alzheimer's & Dementia. 2016; 12: 1226-1234.

37. Reddy PH. Abnormal tau, mitochondrial dysfunction, impaired axonal transport of mitochondria, and synaptic deprivation in Alzheimer's disease. Brain research. 2011; 1415: 136-148.

38. Kandimalla R, et al. Hippocampal phosphorylated tau induced cognitive decline, dendritic spine loss and mitochondrial abnormalities in a mouse model of Alzheimer's disease. Human molecular genetics. 2018; 27: 30-40.

39. Nathan PJ, et al. Association between CSF biomarkers, hippocampal volume and cognitive function in patients with amnestic Mild Cognitive Impairment (MCI). Neurobiology of Aging. 2017; 53: 1-10.

40. Seppälä TT, et al. Longitudinal changes of CSF biomarkers in Alzheimer's disease. Journal of Alzheimer's Disease. 2011; 25: 583-594.

41. Thomann PA, et al. Association of total tau and phosphorylated tau 181 protein levels in cerebrospinal fluid with cerebral atrophy in mild cognitive impairment and Alzheimer disease. Journal of Psychiatry and Neuroscience. 2009; 34: 136-142.

42. Crapper D, Krishnan S, Dalton A. Brain aluminum distribution in Alzheimer's disease and experimental neurofibrillary degeneration. Science. 1973; 180: 511-513.

43. Zhao Hh, et al. Involvement of GSK3 and PP2A in ginsenoside Rb1's attenuation of aluminum-induced tau hyperphosphorylation. Behavioural brain research. 2013; 241: 228-234.

44. Walton J. Evidence for participation of aluminum in neurofibrillary tangle formation and growth in Alzheimer's disease. Journal of Alzheimer's Disease. 2010; 22: 65-72.

45. Kumar V, Gill KD. Oxidative stress and mitochondrial dysfunction in aluminium neurotoxicity and its amelioration: A review. Neurotoxicology. 2014; 41: 154-166.

46. Guo M, Fang Y, Zhu J, Chen C, Zhang Z, Tian X, et al. Investigation of metabolic kinetics in different brain regions of awake rats using the [1H-13C]-NMR technique. Journal of Pharmaceutical and Biomedical Analysis. 2021; 204: 114240.

47. Ehsanifar M, Montazeri Z, Zavareh MS, Rafati M, Wang J. Cognitive impairment, depressive-like behaviors and hippocampal microglia activation following exposure to air pollution nanoparticles. Environmental Science and Pollution Research. 2023 Feb; 30: 23527-37.

48. Walton J. Aluminum disruption of calcium homeostasis and signal transduction resembles change that occurs in aging and Alzheimer's disease. Journal of Alzheimer's Disease. 2012; 29: 255-273.

49. Giannakopoulos P, et al. Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease. Neurology. 2003; 60: 1495-1500.

50. Fagan AM, Perrin RJ. Upcoming candidate cerebrospinal fluid biomarkers of Alzheimer's disease. Biomarkers in medicine. 2012; 6: 455-476.

51. Chiu MJ, et al. Plasma tau as a window to the brain—negative associations with brain volume and memory function in mild cognitive impairment and early alzheimer's disease. Human brain mapping. 2014; 35: 3132-3142.

52. Chen TB, et al. Plasma Aβ42 and total tau predict cognitive decline in amnestic mild cognitive impairment. Scientific Reports. 2019; 9: 1-10.