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Aluminium Neurotoxicity and Neuroprotection

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ABSTRACT

Aluminium is considered to be the most widely distributed metal in nature and industry and is extensively used in products and processes associated with human activity. Contamination may occur by air, water, food, additives, medicaments, vaccines, cosmetics, agrochemicals, etc. Aluminium is recognized as a highly neurotoxic element in animals and humans connected with several diseases such as Alzheimer's and Parkinson's disease, neurodegenerative motor disorders, encephalopathy, dementia, amyotrophic lateral sclerosis, multiple sclerosis, and autism. There are many animal models in rats developed to investigate aluminium neurotoxicity. Nevertheless, molecular mechanisms of its action are not yet resolved, and mechanisms of damage and safety concentrations are still much discussed. The brain is the most susceptible system to damages provoked by aluminium exposure, such as oxidative stress, iron dyshomeostasis, changes in neurotransmission, immunologic alteration and pro-inflammation, genotoxicity, transformation and peptide denaturation, changes in enzyme activity, membrane perturbation, apoptosis, necrosis, and dysplasia. A novel investigation of aluminium neurotoxicity includes the assessment of neuroprotection and the identification of new substances as potential drugs.

Keywords: Aluminium; Brain; Cognitive and Motor Diseases.

INTRODUCTION

Aluminium (Al) is a lightweight silvery white metal of main Group 13 (IIIa, or boron group) of the periodic table. It is the most widespread metal on Earth, making up more than 8% of the Earth's core mass, and also the third most common chemical element on our planet after oxygen and silicon. Al accumulates into the body through different routes, induces various neurotoxic effects, represents a risk factor in many neurodegenerative diseases, and its side effects may be mitigated by the use of some neuroprotective agents (**Figure 1**).

Aluminium as a Toxic Element

Al is widely spread in nature as a trivalent ion (Al+3) in silicates, oxides, and hydroxides, as well as in combination with chlorine, sulfur, fluorine, or organic matter [1]. Intake of Al is by air, water, food, additives, medicaments, vaccines, cosmetics, agrochemicals, etc. It is in extensive human use in different products such as Al chloride, Al hydroxide, Al nitrate, Al phosphate, Al sulfate, and Al silicate [2]. Al ion has no physiological part in metabolic processes, but it accumulates in mammalian tissue and has toxic and pathologic effects [3,4]. Absorbed through the skin, intestinal and alveolar mucosa, Al enters the brain across the blood brain barrier (BBB), the choroid plexuses, and the nasal cavity and remains for a long time since its removal from the brain tissue is slow [5-8]. The distribution of Al in the brain is about 1% of the total body, in all regions with maximum accumulation in the hippocampus [9-11].

Al has multiple effects on cellular homeostasis and exhibits a pro-oxidant activity that results in oxidative stress, free radical attack, and oxidation of proteins and lipids [7]. It also induces pro-inflammatory and pro-apoptotic gene expression, and affects enzyme activity, and adenosine triphosphate (ATP) energy metabolism. [12-14].

Aluminium Induced Oxidative Stress, Apoptosis and Inflammation

Oxidative stress and changes in energy metabolism and mito-

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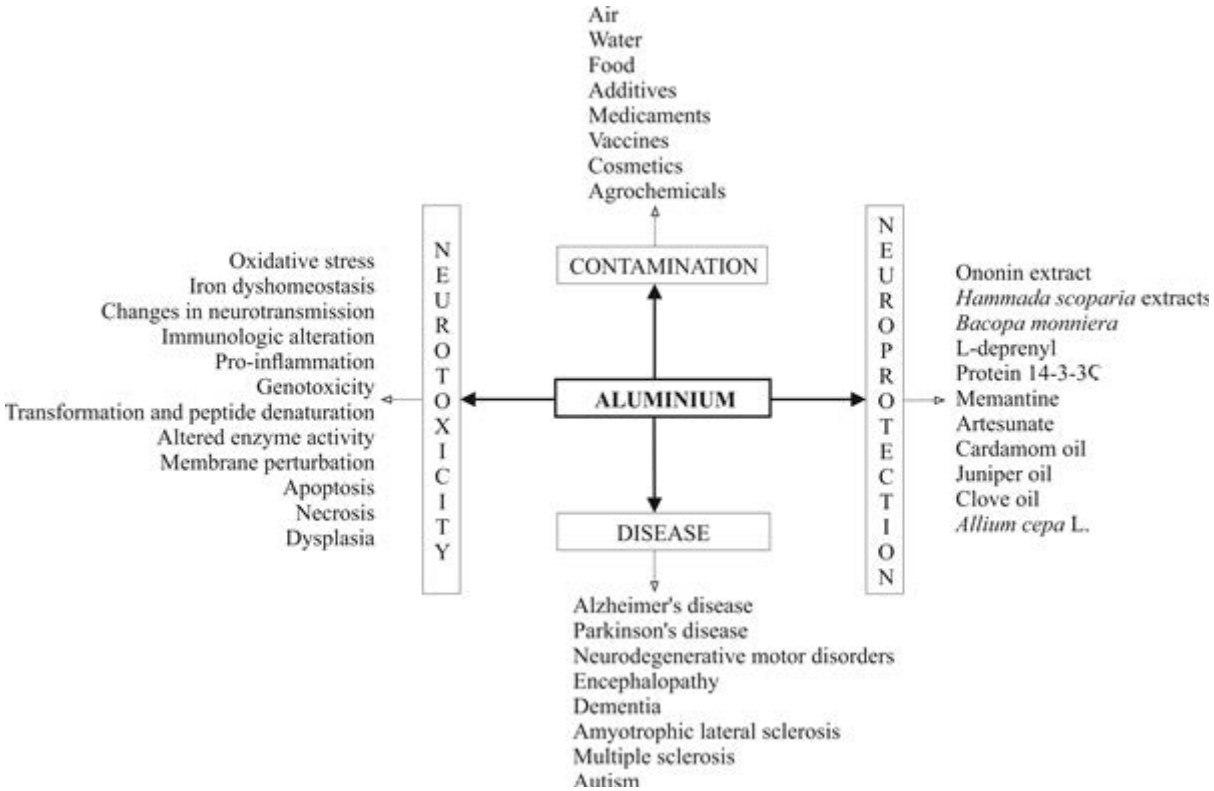
chondrial function are the first events that make the brain sensitive to Al accumulation [15]. In Al-loaded cells is observed loss of christie, chromatin condensation, and decreased number of mitochondria [16]. Oxidative stress is associated with a significant reduction in antioxidant enzyme activity: superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and glutathione-S-transferase with enhanced activity of nitric oxide (NO) levels in some parts of the brain [17]. Induction of apoptosis in cells exposed to Al includes several mechanisms: mitochondrial pathway, p53, Bax, and caspase activation [18-20].

Figure 1. Schematic representation of the Al contamination routes, Al neurotoxicity and neuro protection, and Al-related diseases.



Different Al contractions affect the apoptosis of astrocytes (induce or block selectively the process). On the one side, there is a change in cell cycle distribution and increased intracellular Ca2+ at a dose of 400 μM of Al, whereas the dose of 200 μM of Al blocks the apoptotic process [21]. As a result of these activities, oxidative injury occurs and triggers neuroinflammation and microglial activation. At the place of oxidative injury, the expression of pro-inflammatory cytokines IL-1β, IL-6, TNF-α, and MIP-1a is increased; while the expression of brain derived neurotrophic factor is significantly reduced [22,23]. Microglia activates the secretion of IL-1β and other substances typical for microgliosis inducing memory and learning dysfunction through modulation of prostaglandin E2 synthase-prostaglandin E2-prostaglandins receptors (PGES-PGE2-EPs) signaling pathway [24,25]. Particularly, oxidative stress dependent glial activation in the rat brain is also observed after Al exposure [26].

Al induces endoplasmic reticulum stress, which alters Ca2+ homeostasis [27]. Given the role of the endoplasmic reticulum in Ca2+ handling, altered intracellular Ca2+ levels may be indicative of its dysfunction [28]. Due to toxic events, synaptic plasticity and transmission are reduced, as well as neurotrophin production. Synaptic dysfunction is a consequence of the inhibition of synaptic Na+/K+-ATPase activity and a decrease in nerve growth factor and brain derived neurotrophic factor expression [29, 30]. Axonal transport and perikaryal aggregation are altered in the cytoskeleton, which may lead to neurofibrillary degeneration [31].

DISCUSSION

Aluminium-Induced Changes in Neurotansmission

The central nervous system is the most susceptible to Al toxicity and absorption and accumulation of Al in different brain regions have an impact on glutamatergic, GABAergic, serotonergic, cholinergic, and dopaminergic neurotransmission [32, 33]. It has been shown that Al reduces N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA) expression, glutamate receptors playing an important role in learning and memory, and fast excitatory glutamatergic neurotransmission, respectively [34-36]. It also increases glutamate levels in the cerebrum, thalamus, hippocampus, and cerebellum, while as a response to the increased glutamatergic transmission, GABAergic inhibitory effect is stimulated [37]. Under conditions of Al exposure, the cholinergic system shows a marked reduction in acetylcholinesterase (AChE) activity, muscarinic receptor binding, and nicotinic acetylcholine receptors activity and gene expression [38, 39]. Finally, Al exposure significantly inhibits dopaminergic transmission and affects serotonin levels differently due to a complex network of serotonin receptor subtypes [40, 41].

Animal Models of Aluminium Neurotoxicity

Al is a neurotoxic element implicated in several neurochemical, neuropathological, electrophysiological, and behavioral changes

associated with cognitive impairment [42]. For investigation of Al neurotoxicity, different animal models are used. The most representative is the animal model in rats, which mimics some diseases occurring due to Al exposure. The neurotoxic properties of Al exposure depend on several factors including dose, duration and route of exposure, chemical forms, metabolism, accumulation, detoxification and distribution, and elimination. Al application is followed by differences in tissue distribution between the blood and the target site [43]. Parenteral administration of Al exhibits higher toxicity than oral application [44]. Also, young pups are more sensitive than adults to Al exposure [45]. Cognitive decline can be behaviorally tested on sensory, motor, and learning abilities. The behavioral tests in animals include visual, motor, sensorimotor, gross motor, and fine motor performances and reflexes, coordination and locomotion [46].

According to our previous studies, spectral and fractal analysis of the electrical activity in the brain has proven to be a reliable tool for qualitative and quantitative assessment of changes in the central nervous system in an animal model of intoxication with Al [45, 47-50]. So, a higher presence of power spectra in the delta range of parietal electrocortical activity, a lower presence in the theta range, and increased values of the parameter DT as the ratio of delta to theta range were observed in pups indirectly exposed to Al (whose mothers were drinking a 0.5% water solution of Al chloride during the gestation and lactation periods), compared to controls [45]. In adult male rats, the average fractal dimension of electrocortical activity in chronically Al-treated animals was lower than in the control rats, at cerebral but not at cerebellar level [45-47].

Aluminium Related Diseases

Acute exposure to Al can cause clinical neurotoxicity. Encephalopathy occurs among workers in the Al industry, and the main symptoms are cognitive deficit, in-coordination, tremor, and spinocerebellar degeneration [51]. Al in vaccines can cause neuroinflammation, cell loss, and memory deficit [52]. Sporadic cases include a seizure disorder, ataxia, and dysarthria. Al levels in the brain are increasing with age, which may lead to neurodegenerative diseases [53]. Alzheimer's and Parkinson's disease are the most common Al-related diseases. Alzheimer's disease develops in the areas where the Al concentration in drinking water is higher, and the main symptoms are dementia, development of amyloid plaques consisting of aggregated β-amyloid proteins and neurofibrillary tangles consisting of aggregated tau proteins, production of reactive oxygen species, reactive microglia, and the production of pro-inflammatory cytokines and macrophage activity [54]. Al exposure may induce the disorder in dopamine related brain regions, mostly the striatum, and together with inflammation and microglial activation lead to Parkinson's disease [55, 56]. In rat spinal cord, Al treatment causes severe motor neuron damage resembling amyotrophic lateral sclerosis [57]. Acting as a pro-oxidant or as adjuvant inducing autoimmunity, [7] Al may be involved in myelin loss and axonal degeneration that occurs in multiple sclerosis [58]. The presence of Al in inflammatory cells in the meninges, vasculature, grey, and white matter could implicate Al in the etiology of autism [59].

Neuroprotection against Aluminium Toxicity

A novel investigation is focused on the mechanisms of neuro protection and many substances have been tested on animal models of diseases but potential drugs have not yet been found. Shortly we report some of these studies [60]. It is known that Alzheimer's disease in the initial phase is characterized by changes in mood and behavior, aggression, confusion, avoidance of social connections, and memory loss, while oxidative stress, inflammation, and apoptosis are dysregulated and implicated in the progression of the disease [61]. Ononin extract in an animal model of Alzheimer's disease suppresses oxidative stress and neuroinflammation, activates apoptosis, prevents Al accumulation in the brain, and stimulates cognitive impairment [62]. Hammada scoparia extracts can be used for the treatment of Al neurotoxicity due to the inhibitory effect on AChE activity and recovery from oxidative damage induced by free radicals [63]. Bacopa monniera and L-deprenyl also show neuroprotective efficiency through the prevention of Al-induced oxidative damage and oxidative stress [64]. Protein 14-3-3ζ combing with tau can prevent over phosphorylation of tau, so it has a neuroprotective effect, which has been experimentally proved in the hippocampus of rats [65]. Another study in rats examined the protective effects of memantine and artesunate in Al chloride-induced toxicity [66]. Both substances reduce the cerebral level of TNF-α and IL-1β. Memantine, as an NMDA receptor antagonist, reduces AChE activity, while artesunate improves cognition, has an anti-inflammatory effect, and attenuates oxidative stress. Cardamom oil has been reported to have AChE inhibitory, antioxidant, and anti-anxiety effects [67]. Also, similar activity has juniper oil and clove oil [68]. Allium cepa L. has neuroprotective effects on Al chloride-induced neurotoxicity by improving muscle coordination and memory deficits [69]. It reduces oxidative stress, AChE activity, and Al deposition in the brain.

CONCLUSION

This work is focused on the consequences of contamination with Al, as a highly neurotoxic element, on the central nervous system and provides insight into the main damages caused by Al in the brain, cognitive and motor diseases associated with exposure to Al, and possible mechanisms of neuroprotective action of various agents in conditions of Al intoxication. It summarizes the current state of knowledge on the topic and represents a basis for future research and predictions of Al neurotoxicity and neuroprotection.

AUTHORS CONTRIBUTIONS

All authors participated in the writing of the manuscript; LM conceptualized and wrote the original draft of the manuscript, JP, BP, and GS reviewed and edited the manuscript.

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DECLARATION OF CONFLICTING INTERESTS

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