Annals of R.S.C.B., ISSN:1583-6258, Vol. 26, Issue 1, 2022, Pages. 826 - 840
Received 08 November 2021; Accepted 15 December 2021.

Physiological Changes in Cellular and Systemic Activity Due to Aluminum Toxicity

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ABSTRACT

The toxic effects of aluminum (*Al*) are variable and can lead to multifaceted systemic toxicity, which can induce cellular damage that leads to apoptosis and disrupt cellular homeostasis. These negative alterations are leading to systemic toxicity associated with functional and structural cellular and systemic disturbances. Cytotoxic activity of *Al* is attributed mainly due to oxidative stress, free radical scavenging and prooxidant action on the lipids and proteins of the cells. Inflammatory effects have confirmed in different tissues such as pulmonary, hepatic, renal and cardiovascular tissues. This appears due to the oxidative stress of *Al* and formation of free radicals due to *Al*, which increases pro-inflammatory cytokines. There is an increase in levels of IL-1β and TNF-α in addition to MIP-1α as a result of increases of gene expression. Chronic *Al* exposure accumulates in the nervous system and causes severe damage to cellular structures in the hippocampus resulting in thickening and discoloration with edema and severe changes in tissue appearance. Tau phosphorylation is often thought to enhance tau accumulation due to increased hyperphosphorylation and aggregation. Neurobehavioral data are of great significance in risk estimation because behavior could appear as a net consequence of many functions occurred in nervous system. As well as, neurotoxicity of *Al* could be coincided by motor and speech disorders.

Keywords: Toxic effect, Oxidative stress, Pro-inflammatory cytokines, Tau phosphorylation

1. NON-NEUROLOGICAL EFFECTS

1.1. Cellular disruption

The toxic effects of aluminum (*Al*) are variable and can lead to multifaceted systemic toxicity, which can induce cellular damage that leads to apoptosis and disrupt cellular homeostasis (**Xu et al., 2018**). These negative alterations are leading to systemic toxicity associated with functional and structural organ dysfunction. The cytotoxic impacts of *Al* are generally due to oxidative stress, free radical scavenging and prooxidant action on the protein and lipid of the cells (**Igbokwe et al., 2019**).

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1.1.1. *Protein polypeptides*

Protein polypeptide is a structure generated by oxygenated amino acid, protein and side chain and, ultimately resulting in β-amyloid (**Su et al., 2017**). In Alzheimer's patients, exposure to *Al* activates and increases the accumulation and deposition of β-amyloid as a phenomenon that can lead to neuronal deposition, neuronal cell death and the accumulation of dysplasia (**Hernández-Zimbrón et al., 2015**). Fibrillation and accumulation of amylin induces after exposure to *Al* result in formation of β-folded sheet structures that predictive for pancreatic β-cell damage. *Al* also increases amyloid accumulation by inhibiting proteolysis of amyloid peptides (**Khan et al., 2020; Raimundo et al., 2020**). Extracellular surfaces and intracellular ligands can potentially bind *Al* and induce inhibitory or stimulatory effects (**Miyasaka et al., 2016**). In addition, *Al* metabolism and interactions with other enzymes lead to enzyme inhibition or activation as it binds to a group of phosphate nucleotides (**Lehmann et al., 2016; Ramesh et al., 2018**). These metabolic disorders are revealing in a weight loss and reduced productivity (**Park et al., 2015**).

1.1.2. *Iron overload*

Exposure to *Al* can lead to iron overload by altering iron homeostasis (**Nurchi, 2016**). Oxidative stress and iron-induced damage have been described by many studies, in which, High levels of iron could exacerbate cellular damaging, which implicated in degenerative disorders (**Nunomura et al., 2012; Mena et al., 2015**). Excess iron overloads from *Al* have detected to increase peroxidation of lipid, damaging of DNA and induction of apoptosis in red blood cells (erythrocytes), lymphocytes and osteoblasts (**Yu et al., 2019**). Oxidative damages have been shown to activating the c-Jun N-terminal kinases (JNK) apoptosis pathway in this region (**Huo et al., 2017**). In culture, *Al* induce apoptosis of osteoblast through inhibition the apoptosis protein Bcl-2 and increasing of preapoptotic proteins Bax, Bak and Bim (**Cao et al., 2020**). *Al* can inhibit normal transferrin receptor synthesis with ferritin by decreasing ferritin synthesis (**Alu et al., 2020**) and increasing transferrin receptor expression (**Cirovic and Cirovic, 2022**) to produce higher levels of free iron in cells, causing oxidative damage with increased responsiveness of fenton (**Yang et al., 2021**).

1.1.3. *Antioxidant enzymes and lipid peroxidation*

Several studies have demonstrated that the activity of antioxidant enzymes (catalase, glutathione, glutathione peroxidase and superoxide dismutase) were influenced severely post *Al* exposures (**Khadija et al., 2018; El-Hawary et al., 2020; Zhang et al., 2020**).

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Concentrations of malondialdehyde and thiobarbituric acid reagent showed to be abnormally elevates in exposed individuals (**De Leon et al., 2020; Naddafi et al., 2021**).

1.1.4. *Osteoblast proliferation*

Post exposure to *Al*, proliferation and differentiation of osteoblasts have inhibited in the presence of cathodic regulation and signaling pathway inhibition, through inhibiting the BMP-2 signaling pathway (**Huang et al., 2017**). Additionally, osteopontin, osteocalcin, and osteosialoprotein could be inhibited after exposure to *Al* with declining of transforming growth factor β1 expression (**Sun et al., 2016; Leko et al., 2021**). Bone mineralization is affected by reduced calcium uptake due to the role of *Al* in inhibiting of synthesizing of calbindin, osteocalcin and vitamin D (**Song et al., 2017; Zhang et al., 2019; Kim et al., 2021**). Bone macrophage protein-2, transforming growth factor-β1 and cartilage-stimulating growth factors expression might be affected by *Al* through cartilage growth inhibition with destruction the structures of cartilages (**Saberzadeh et al., 2016; Yang et al., 2016; Chien et al., 2020**). These impacts can influence the development of fetal anomalies of teratogenic origin in pregnant women have been demonstrated (**Yassa et al., 2017; Troisi et al., 2019; Ovayolu et al., 2020**).

1.1.5. *Genetic mutation*

Mutations and alterations in gene function due to alterations in transcriptional expression may result from *Al* toxic effects (**Zhang et al., 2019**). In mice, **Francisco et al.** (**2021**) showed that the germinal and somatic genotoxicities are related to aberration and mitotic inhibition in chromosomes. In patients with breast cancer, migratory and reproductive properties of cells were affected significantly when both matrix metalloproteinase (MMP9) and MMP14 increased due to the metalloestrogen action of *Al* on cancerous cells through impacts of metastatic process (**Jurkowska et al., 2019; Francisco et al., 2021**). Therefore, there are unobvious information if *Al* having the capability for initiating and promoting the cancer processes beyond previous intermittent signs of breast cancer (**Anwar et al., 2017; Igbokwe et al., 2019**).

1.2. Systemic disturbances

Inflammatory effects of *Al* have found in different tissues such as pulmonary (**Milnerowicz et al., 2015**), hepatic (**Algandaby et al., 2016**), renal (**Cao et al., 2018**) and cardiovascular (**Vlachogiannis et al., 2021**) tissues. This appears due to the oxidative stress of *Al* and formation of free radicals due to *Al*, which increases inflammatory cytokine (**Milnerowicz et**

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al., 2015). Increases in IL-1β and TNF-α in addition to MIP-1α were reported as a result of increases of gene expression (**Angosto et al., 2018; Jeon et al., 2021**). Genes encoding inflammatory signals are obviously upregulated due to *Al* (**Alexandrov et al., 2018**). The releasing of cytokine may result in recruiting of leukocyte that produce additional inflammatory chemokines and cytokines for promoting of inflammation (**Jangra et al., 2015; Khameneh et al., 2017**). Inflammation can be a type of chronic granuloma and *Al* appeared to form a granuloma (**Haag et al., 2014**). **Pogue et al.** (**2017**) showed that chronic exposures to $Al_2(SO_4)_3$ were resulted in systemic inflammation related to increasing the concentrations of IL-6 and TNFα, CRP, miRNA-9, miRNA-125b, miRNA-146a and inflammatory biomarker over time, indicating that exposed animals undergo an advanced chronic inflammation.

Endocrine disorders or changes in hormones, which related to *Al* accumulation in the endocrine gland can cause damage by the oxidative stress because of reducing the concentration of the hormones secreted into bloodstream leading to hypofunctional endocrine status (**Darbre, 2018**). For example, there are many researchers have demonstrated the ovarian and testicular failure because of inadequate androgen hormone levels (**Al-Eisa and Al-Nahari, 2017**) and decreased androgen receptor function (**Gomes et al., 2019**), bone abnormalities by the parathyroid dysfunction (**Cannata-Andía et al., 2021**). In a report, diabetes and prediabetes were occurred as a result of damaging of pancreatic islets (**Wei et al., 2018**). Functions of parathyroid hormones could be influenced by *Al* ions that reduce Ca receptor receptor expression of the gland (**Bover et al., 2021**). There is additional metabolic effects on concentration of serum T3 and T4 (**Beshir et al., 2021**).

In some cases, *Al* ions stimulate the gland to increase the secretion of a hormone or when the cell membrane receptors are depleted, or receptor expression is reduced (**He et al., 2015; Kida et al., 2016**). In addition, the target organ sometimes becomes resistant or insensitive to the hormone resulting in increased hormone secretion (**Schmidt et al., 2016**). *Al* ions might act as chemical stressors through promotion for releasing of cortisol (**Vasantan and Joshi, 2018**) and norepinephrine (**Zhuang et al., 2016**), which when exist at high concentrations, they elevate the blood pressure (**Goharbari et al., 2018**). Increases of insulin levels have been reported by **Wei et al.** (**2018**) who attributed the results to increasing of insulin resistance and inhibition expression of glucose transporter-4 protein. Pseudohypopara-thyroidism is related to failure of kidneys and osteoarthritis in patients having a hypercalcemia (**Yu et al., 2019**).

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2. NEUROLOGICAL EFFECTS

2.1. Transport of *Al* to brain

Al has considered as a neurotoxin as recently as many studies showed that to *Al* is capable for alteration functions of blood-brain barrier (BBB) that regulating exchange between peripheral circulation and central nervous system (CNS) (**Wang, 2018; Assmann et al., 2021; Ishaq et al., 2021**). *Al* affects certain functions of the BBB membrane as the transmembranes increasing diffusion rate, to enter to CNC without interfering with membrane integrity or altering CNS hemodynamics (**Dadas et al., 2019**). These changes in the brain access to nutrients, hormones, toxins and drugs may underlie CNS dysfunction, and change the functions of BBB (**Sebaiti et al., 2018**). Its appeared that the almost impacts on peripheral tissues and CNS were occurred throughout activity of *Al* as a membrane toxin (**Shaw, 2018; Miller et al., 2019**).

One possible route for *Al* for entering to the brain is through blood sources and ambient air via the nasal passages. In the nasal cavity, its directly enter through olfactory neurons that extend from roof of nasal cavity to olfactory bulbs (**Li et al., 2015**). Blood can enter by BBB to be located into the brain four chambers through choroid plexus as well as subarachnoid space surrounding brain (**Mold et al., 2018**). BBBs act for protecting the brain from sudden alteration in composition of blood, to insulate the brain from any negative effect of any factors that cause a change in the chemistry of the brain, making it a pharmacological sanctuary (**Routy et al., 2022**). Inflammation of endothelial cells, pericardial basement membrane cells and astrocytic processes, low intracellular activity covering 99% of endothelial cell surface (**Pogue et al., 2017**).

The choroid plexus is a capillary network surrounded by tightly connected epithelial cells with specific properties similar to those of BBB. Choroid plexus promotes active transport and proliferative properties (**Johanson and Johanson, 2018**). Substances distributed in the choroid plexus enter the cerebrospinal fluid in the four ventricles of the brain and can be distributed in the brain and the extracellular fluid of brain cells (**Mold and Exley, 2022**). However, the entry of excess fluids from the parenchyma of brain into ventricles can inhibit passage of materials from ventricle into tissues (**Bondarenko and Saarma, 2021**). The endothelial cells make up the BBB adhere strongly to brain tissue and rapidly distributed between the blood and the brain. On the other hand, some brain regions present an inaccessible distances between the CNS and certain cerebral exchange cells (**Nampoothiri et al., 2017**).

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2.2. Mechanism of neurotoxicity

2.2.1. *Accumulation of Al in hippocampus*

Chronic *Al* exposure accumulates in the nervous system and causes severe damage to cellular structures in the hippocampus resulting in thickening and discoloration with edema and severe changes in tissue appearance (**Sharma et al., 2016**). **Wang et al.** (**2018**) showed that *Al* accumulation is mainly localized in DG and CA3 regions of the hippocampus. Studies have shown that CA3 regulatory changes may be important in individual behavioral responses, which may also benefit DG neurogenesis (**Liaquat et al., 2019; Cui *et al.*, 2021**).

2.2.2. *Affinity protein with Al^{3+}*

Several proteins in the body have been identified to possess a high affinity for Al^{3+}, such as 14-3-3γ in rats and CK in porcine hippocampus (**Wang et al., 2018; Chen et al., 2021**). These results will be of great help in future research on the neurotoxic mechanism of *Al*. Seven 14-3-3 isoforms; β, ε, η, δ, ι, ζ, and σ were detected in mammals, which are capable to form the homodimers and heterdimers (**MEZA et al., 2018; Gogl et al., 2021**). Like many interaction partners, 14-3-3 proteins are contributed regulation and upregulation of several cellular activities such as transcriptional regulation of expressed genes and DNA responses, metabolism, apoptosis and cell cycle progression (**Freeman and Morrison, 2011; Munier et al., 2021**). Creatine kinase (CK) is the highest major eukaryotic enzyme in metabolism of energy as well as the role of CK as a much higher peak rate for synthesis of ATP. Also, CK could act critical roles in brain cell energy, suggesting that disruption of this enzyme may accelerate the progression of Alzheimer's disease (**Gürbüz et al., 2021**). **Dogra et al.** (**2019**) demonstrated the changes of CK in brain of Alzheimer's disease patients, leading to loss of activity. **Cheng et al.** (**2014**) found that CK activity in brain was reduced after long exposure to *Al*. Long-term exposure to *Al* can cause progressive decline in mitochondrial function, impaired ATP synthesis and hydrolysis in brain tissue (**Wang et al., 2017**). These changes may account for *Al* cell processing that disrupts the cell structure of the hippocampus and results in cognitive decline (**Hosseini et al., 2020**).

2.2.3. *Aggregation of Tau*

Tau phosphorylation is often thought to enhance tau accumulation due to increased hyperphosphorylation and aggregation (**Chiasseu et al., 2016**). Phosphorylation acts great roles for controlling microtubule stabilization and contraction by regulating the normal function of tau. Microtubule is necessary to maintaining and developing of dendrites and

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axons during the life of neuron, and being susceptible for degradation and organization in any degenerative disease (**Sgrò et al., 2016**).

Throughout any neurodegenerative disease, mass of microtubule is typically decrease; while, polarity and microtubule-mediated modes of transmission are likely to be altered. These side effects can be a major cause of illness or side effects (**Brunden et al., 2014**). In healthy neuron, tau distributes in the axons and acts significant roles in stabilization of microtubule. In addition to modulating microtubule dynamics, tau can modulate axial transport through several mechanisms (**van Beiningen et al., 2015**). During brain diseases, tau is inappropriately phosphorylated to form aggregates in dendritic and bodily nerve processes that accumulate in NFTs and nerve fibers (**Mroczko et al., 2019**).

Tau hyperphosphorylation can lead to a variety of dysfunctional dysregulations, including various intracellular compartments and synaptic dysfunction, due to axial misalignment and dendritic spreading of somatosensory parts (**Kamat et al., 2016**). Additionally, tau having the ability for entering the dendrites and postsynaptic compartments, causing postsynaptic dysfunction in which synapses can be lost or coagulate, resulting in neuronal dysfunction (**Hoover et al., 2010; Tracy and Gan, 2018**).

The importance of neurobehavioral studies in risk assessment is that behavior can be viewed as a net consequence of sensory, motor and cognitive functions occurring in the nervous system and as a potentially sensitive endpoint for the chemically induced neurotoxicity (**Vorhees et al., 2021**). Many studies suggested that behavior is a functional integration of the nervous system and that the capabilities of the nervous system cannot be determined by historical or physiological studies independent of behavioral analysis (**Collins et al., 2009; Keijzer et al., 2013; Sharon et al., 2016**). It has also been suggested that in some cases behavioral changes may be more sensitive to neurochemical changes as indicators of neurotoxicity and can be detected early in exposure (**Zhao et al., 2019**).

The neurotoxicity of *Al* in children is manifested by motor and speech disorders observed at plasma concentrations above 100 g/L. 20 to 50 times higher than normal plasma levels; and many researchers have focused on the possible sensitivity of neuronal function measures to study the negative effects of environmental factors ((**Seidman and Mirsky, 2017; Luby et al., 2020; Homberg and Jagiellowicz, 2021**). Elevated levels of *Al* have been reported in brain samples obtained at autopsy from patients with certain neurological disorders such as Parkinson's disease and amyotrophic lateral sclerosis (**Zeng et al., 2021**). Other study found that higher levels of *Al* were associated with poorer visual memory, lower vocabulary scores

and poorer concentration (**Sebaiti et al., 2018**). The association between *Al* levels and neurocognitive function in dialysis patients was reported also (**Bondy, 2016**).

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