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ALUMINIUM NEUROTOXICITY: NEUROBEHAVIOURAL AND OXIDATIVE FUNCTION

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Abstract

Aluminium is light weight metal present on earth which has gained considerable attention due to its neurotoxic effects. The widespread use of products made from or containing aluminium is ensuring its presence in our body. Aluminium (Al) inhibits more than 200 biologically important functions. Behavioural, neuropathological, and neurochemical changes are associated with chronic exposure to aluminium. Deficits of learning and behavioural functions are most evident amongthem.

The purpose of this review is to provide the animal or human evidence linking aluminium (Al) toxicity to antioxidant imbalance. Aluminium may impair mitochondrial bioenergetics due to the production of reactive oxygen species and may lead to the generation of oxidative stress. The generation of oxidative stress may be responsible to its toxic consequences in animals and humans. The oxidative stress has been implicated in pathogenesis of various neurodegenerative conditions including Alzheimer's disease and Parkinson'sdisease.

In this review, we have discussed the oxidative stress and mitochondrial dysfunctions occurring in Al neurotoxicity.

Key Words: Aluminium, Neurotoxicity, Oxidative stress

Introduction

Aluminium (Al) is the 3rd most abundant element therein, after oxygen and silicon. The human body gets Al access via gastrointestinal and respiratory tracts [1] from many sources as it is present naturally in food and water and it is added to drinking water, processed foods, cosmetics, toothpaste, antiperspirants and adjuvants in various parenteral preparations and pharmaceuticals agents[2,3].

Aluminium (Al) has been attributed no role by nature in living process, but it disrupts the pro-oxidant/antioxidant balance of tissues leading to various biochemical, physiological, and mental dysfunctions [4]. It is implicated in several neurodegenerative disorders including Alzheimer's disease [5], Parkinson's disease and dementia [6]. Exposure to high levels of Al leads to neurofibrillary degeneration and the concentration of Al has been found to be augmented in degenerating neurons [7]. The brain is a target of Al toxicity which can alter Blood-Brain Barrier (BBB), mediating its transport to the brain [8] and gets deposited in the cortex [9] by altering the physiological ligands present at these barriers [10]. The Al ion has no physiological role in metabolic processes, but it can become a metallic toxicant to human [11].

Absorption

Absorption of aluminium appears to be primarily in the distal intestine of the gastrointestinal tract (GI). There is evidence supporting several mechanisms of intestinal aluminium absorption, including sodium transport processes, an interaction with calcium uptake, and paracellular diffusion. Aluminium penetration of the skin is very shallow. Aluminium may be able to enter the brain, from the nasal cavity by a direct route, bypassing the systemic circulation, but convincing evidence is lacking. Aluminium absorption is significant and may eventually be complete when aluminium hydroxide and aluminium phosphate adjuvants are injected intramuscularly (i.m.). As the age increases, tissue aluminium concentration increases.

Gastrointestinal absorption, after ingestion, is the main route through which Al is systemically accumulated in animals and humans, and absorption occurs largely in the duodenum. The uptake of Al through gastrointestinal pathway is complex and is influenced by various factors including individual differences, age, pH, stomach contents and type of Al compound [12]. Absorption of aluminium from food (about 0.1%) is lesser than from water intake (about 0.3%) [13-15]. This was attributed to organic ligands in foods such as phytates and polyphenols that were suggested to form complexes with Al ion and inhibit its absorption [16]. Absorption of Al via the gastrointestinal tract can be enhanced in the presence of citrate, maltol, lactate and fluoride in water or food, and during chronic renal diseases [14,17,18]. However, there is complete Al uptake from parenteral fluids and vaccines with subsequent distribution to various parts of the body[19].

Distribution

The volume of distribution (Vd) of aluminium is consistent with the blood volume initially and then increases with time. Whole blood aluminium concentrations are ~ equal to the steady state serum. Greater than 90% of serum aluminium is bound to Transfer factor. Aluminium has been reported in many intracellular compartments, while the concentrations were often greater in the nucleus. Ferritin can incorporatealuminium.

Following i.v. injection, ~ 0.001 to 0.01% of the aluminium dose enters each gram of brain and ~ 100-fold more each gram of bone. Aluminium uptake may be mediated by Tf- receptor mediated endocytosis (TfR-ME) to enter the brain across the blood-brain barrier (BBB) and a Tf-independent mechanism that may transport aluminium citrate. The aluminium effluxes from the brain into blood by a transporter[64].

About 90% of the Al circulating in the blood is transported bound to transferrin (iron- transporter protein), while the rest of Al binds to albumin and citrate in the blood [20-23]. Cellular uptake of Al in tissues is relatively slow and is presumed to be mediated by endocytosis and intracellular transfer of the Al bound to transferrin [22,24]. The total body burden of Al in healthy humans has been reported to be approximately 30–50 mg/kg body weight and normal levels of Al in serum are approximately 1–3μg/L [25]. About one-half of the total body Al is in the skeleton, and the levels in human bone tissue range from 5 to 10 mg/kg [26].

Al has also been found in human skin, lower gastrointestinal tract, lymph nodes, adrenals, parathyroid glands, and in most soft tissue organs. In rats, accumulation of Al after

oral exposure was higher in the spleen, liver, bone, and kidneys than in the brain, muscle, heart, or lungs. It has also been reported that Al can reach the placenta and foetus and to some extent distribute to the milk of lactating mothers [18]. Al levels increase with age in tissues and organs (bone, muscle, lung, liver, and kidney) of experimental animals [27]. Moreover, Al has been shown to rapidly enter the brain, extracellular fluid, and the cerebrospinal fluid, with smaller concentrations in these organs than in the blood [27,28]. The iron status is negatively correlated with Al accumulation in tissues and animal experiments have shown that calcium and magnesium deficiency may contribute to accumulation of Al in the brain and bone[29].

Excretion

Aluminium is eliminated by the kidney about more than 95%, probably by glomerular filtration presumably as Al citrate and lesser than 2% of aluminium appears in bile.

Tissue accumulation of Al is reduced by citrates and fluorides through renal excretion when the transferrin-Al binding capacity of the blood is exceeded [18]. Al is also excreted in the milk, feces, sweat, hairs, nails, sebum, and semen [30,31]. Urinary excretion of Al is enhanced by chemical chelators such as deferoxamine and malic, malonic, citric, oxalic, and succinic acids, as reviewed in the later section on treatment of Al in this document. Overall, it is noted that Al accumulation, which is responsible for Al toxicosis, is enhanced by exposure to Al and its continuous intake, as well as increased intestinal absorption and decreased excretion of themetal.

Neurotoxicity of Aluminium

Aluminium (Al) concentration in the body is sufficient to modify the activity levels of several key enzymes and second messenger pathways. Plasma concentrations of Al^{3+}, as high as 0.4 μM, have been reported in humans [32] and orally ingested aluminium salts have been shown to lead to the deposition of Al compounds in the brain [33]. Aluminium levels in brain increase with age. The possibility of Al^{3+} being a causative agent in neurodegenerative diseases was originally raised by several findings suggesting that the metal is not innocuous in a physiological milieu. The occurrence of aluminium-induced dialysis encephalopathy in manfollowinghaemodialysis,isaccompaniedbyelevatedlevelsof aluminiuminthebrain

[34] and recovery is facilitated by application of an Al chelator [35]. Aluminium-induced encephalopathy has also been found in renal failure patients, who have undergone bladder irrigation with 1% alum [36]. These findings suggest that prolonged exposure to the metal can have adverse consequences to humanhealth.

The development of an encephalopathy, characterized by cognitive deficits, in- coordination, tremor, and spinocerebellar degeneration, among workers in the aluminium industry [37] also indicates that exposure to the metal can be profoundly deleterious. Abnormal neurological symptoms have been observed in several patients receiving intramuscular injections of Al-containing vaccines and the WHO Vaccine Safety Advisory Committee has recognized that there may be a subset of predisposed individuals who may be sensitive to Al-containing adjuvant[38].

Alzheimer's disease and other neurodegenerative disease are thought to be related with aluminium. Aluminium have been utilised widely in many fields including human's daily life and industries, as metals, chemical compounds, powders, additives, adjuvants,and nanoparticles in recent decades and their potential adverse effect on health drew great concern. Aluminium can be translocated into blood stream and immune system to induce immunotoxicity, and into central nervous system to induced neurotoxicity when ingested, inhaled, or even injected into human body in the forms of ions, chemical compounds, fine particulate matters. Pneumocytes apoptosis may be induced by aluminium by triggering the oxidative stress and inhibit or activate the activity of cytokines. Higher than that of large aluminium particles, the aluminium ions and fine aluminium particulate matters induce immunotoxicity and neurotoxicityrelatively.

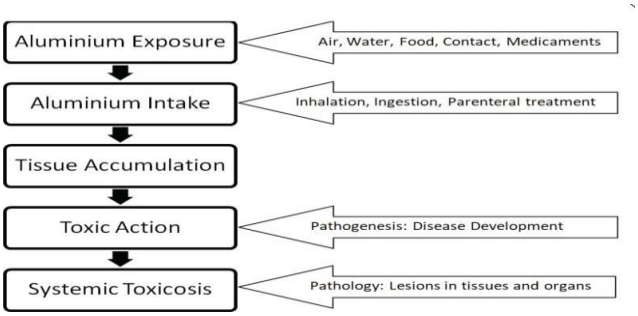
Although the aluminium can damage the blood brain barrier through blood compartment, it may also enter the central nervous system through olfactory nerve. Aluminium impairs behavioural performance of model organisms androdents.

The mechanisms of Al-induced immune and neurotoxicity may be due to neural cell death by triggering oxidative stress, apoptosis, necroptosis, and autophagy through complicated cell signal transmission pathways, which can promote Ab

deposit, promote tau hyperphosphorylation, and together induce neurodegeneration, promote cytokine release, trigger inflammation and immune reactions, and damage DNA and induce epigenetic changes [39].

Al is the most common neurotoxicant and the evidence about its implication in developing Alzheimer's disease are getting increased. It was also found that trivalent cation can participate as a factor in the development of neural tube defects in human. Many studies have showed that there were neuropathological, neurobehavioral, neurophysical and neurochemical changes after Al exposure. The brain is the most vulnerable to the toxic manifestation of Al, and it is particularly sensitive to oxidative stress due to increased levels of free radicals and decreased levels of antioxidants following toxicity. Oxidative events have frequently been linked to neurodegenerative disorders such as Alzheimer's disease.

Pathogenesis of Toxicity



Behavioral Changes

The importance of neurobehavioral studies in risk assessment lies in the fact that behavior can be regarded as the net output of the sensory, motor, and cognitive functions occurring in the nervous system and can serve as potentially sensitive end points of chemical induced neurotoxicity. Many behavioral disorders memory and motor dysfunctions are thought to be associated with impairments of specific neurotransmitters. The cholinergic dysfunction is caused due to acute and sub-acute exposure to aluminum [40]. The relationship between the cholinergic dysfunction and behavior has a longhistory.

The involvement of brain cholinergic system in the mechanisms of learning and memory [41] and the damage caused to them in neurodegenerative diseases [42] are well known.Memorylossisoneoftheinitialandmostconsistentsympto msofencephalopathy

[43] and has been associated with the pathological changes occurring to be seen in the hippocampus [44] a brain region rich in cholinergic neurons. On acute exposure to aluminium, the symptoms in adults, include mainly agitation, confusion, myoclonic jerk, coma or may be death. Aluminium has also been considered as a possible causal factor for the senile dementia, which is characterized by progressive cognitive decline with onset after age65.

Oxidative Stress in Aluminium Toxicity

Aluminium (Al) as a non-redox active metal has been shown to cause oxidative damage to neurons through Fe^{2+}, which stabilizes ferrous (Fe^{2+}) ion by reducing its rate of oxidation. Fe^{2+} is potent in promoting the generation of oxidative species as it catalyzes the Fenton reaction which leads to the formation of OH, OH- and Fe^{3+} from the non-enzymatic reaction of Fe^{2+} with H_2O_2. Because Al is an activator of superoxide dismutase (SOD) and an inhibitor of catalase (CAT), superoxide radical is readily converted to H_2O_2, and the breakdown of H_2O_2 to H_2O and $O_2$by catalase is sloweddown.

Excess accumulation of H_2O_2 further leads to the production of OH radicals which in turn damage various proteins, DNA, and membrane lipids. Al^{3+} ions enhance membrane oxidative damage by accelerating peroxidation of membrane lipids in the presence of Fe^{2+}. the long-term administration of aluminium is associated with oxidative stress, indicated by sharp increase in the MDA levels and depletion of endogenous antioxidant enzymes (CAT andGSH).

Lipid peroxidation is one of the main consequences associated with oxidative stress. Aluminium, a metal without redox capacity in biological systems, in the micromolar range, has the potential to stimulate lipid peroxidation induced by Fe^{2+} in brain homogenates. IncreasedlevelsofMDAreflectthestimulatoryeffectsofaluminiu monlipidperoxidation.

Aluminium has been shown to drastically lower neuronal reduced glutathione levels, and astrocytes are the major source of glutathione for neurons [45]. Increased levels of glutamate may inhibit glutathione production intracellularly by inhibiting thecystine/glutamate antiporter [46]. The depletion of CAT and GSH enzymes were observed which is taken as marker of oxidativestress.

Oxidative Stress and Dsyfunction in Aluminium Induced Neurotoxicity

Al exposure is associated with ROS generation and induction of oxidative stress. The increased generation of ROS may subsequently attack almost all cell components including membrane lipids thus producing LPO. In relation to this, several studies have correlated chronic Al exposure with the oxidative damage in brain followed by increasing lipid peroxide products and functional alterations in antioxidant enzymes. Al mediated oxidative damage in brain might cause damage to various macromolecules including DNA, a phenomenon leading to apoptosis and celldeath.

Aluminium has no redox capacity in biological systems, but it is known that this metal can act as a pro-oxidant in both in vitro and in vivo situations [47,48]. The exact mechanism for its pro-oxidant activity is still the subject of investigation. Studies have revealed that Al accumulation in the brain causes disturbances in both cholinergic and glutamatergic systems [49-52]. Aluminium has been reported to cause alterations in uptake and release of calcium in synaptic vesicles and has been suggested to impair intracellular signal transduction pathways[53-56].

As aluminium is known to bind to transferrin (an iron-binding protein in blood) and able to cross the blood–brain barrier

(BBB), it exerts influence over other trace elements and results in enhanced lipid peroxidation, lysosomalfragility and alters the mitochondrial activity [57-59]. The binding of aluminium to transferrin releases iron, leads to alterations in neuronal free radical homeostasis, and thereby results in oxidative stress within the brain [60,61]. The resultant oxidative insult causes imbalance in the ratio of antioxidants to oxidants in neurons, and this imbalance is one of the factors responsible for the progression of Al-induced neurodegeneration[47,57,61].

Mitochondrial oxidative stress and dysfunction in Al neurotoxicity

Mitochondria is an important organelle involved in maintaining cell functions and represent a primary site of cellular energy generation and oxygen consumption. Mitochondria continuously generate ROS which may compromise the long-term survival of cells. The changes in mitochondrial functions are responsible for generation of oxidative stress, which results in oxidative damage tomDNA.

An accumulating body of evidence implicates that impaired mitochondrial energy production and increased mitochondrial oxidative damage is an early pathological event leading to neurodegeneration [62]. Since Al is involved in ROS generation it is possible that it does execute its effects by impairing mitochondrial functions. The increased production of ROS inside the mitochondria may exacerbate oxidative DNA damage and disruption of oxidative phosphorylation leading to cell damage and death. Many studies have indicated that generation of oxidative stress, release of calcium from intracellular stores or perturbation of mitochondrial function may represent important steps in the mechanisms underlying neuronal cell death induced by Al[63].

Aluminium accumulation is thought to be related to renal impairment, anaemia and other clinical complications. Mitochondria contribute too much of core human metabolism, including oxidative phosphorylation, the tricarboxylic acid (TCA) cycle, fatty acid oxidation, iron sulphurcentre and heme-biosynthesis, and amino acid metabolism. These are inaddition

to the well-established role of the mitochondria in energy metabolism and regulation of cell death. Al induced imbalance in this steady state allows the induction and effects of mitochondrial dysfunction. Since Al induces oxidative damage resulting in an increase of ROS production, it is possible that Al-induced ROS are involved in mitochondrial instability, and release of cytochromeC.

Conclusion

Aluminium is known as major environmental pollutant. These toxic metals are regarded as nonbiodegradable since they cannot be broken down (degraded) by cells. They therefore constitute major global health risk due to their ability to accelerate or contribute to a variety ofdiseases.

Aluminium can induce the production of nitric oxide in the microglia and astrocytes of the brain. The increase in nitric oxide may be a result of the ability of aluminium chloride to accelerate the expression of iNOS. Exposure to aluminium chloride can result in the generation of free radicals, which resulted in the elevation of nitric oxide levels and reduction in the enzymatic and nonenzymatic antioxidantcomponents.

Disruption of the mitochondrial function and energy metabolism by aluminium can be expected to result in a high degree increase in the sensitivity of neuronal cells to excitotoxicity and accelerate neuronal damage within the regions of the brain such as the cerebrum andcerebellum.

Possible mechanisms of aluminium induced neurotoxicity have been related to cell damage via free radical production resulting oxidative stress. Increased lipid peroxidation (LPO) is the major consequence associated with oxidativestress.

Al is reported as a potent neurotoxin and has been associated with AD since it exacerbates brain oxidative injury, causes neuronal inflammation, and induces Aβ deposition, which leads to impairment in working memory. It accelerates LPO and induces increased free radical generation, thereby causing oxidative stress, which results in severe neurotoxicity.

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