Review Article

Molecular mechanisms of aluminium neurotoxicity in animal models of Alzheimer’s disease

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ABSTRACT
Alzheimer’s disease (AD) is the most common cause of dementia that affects one patient every seven seconds. With over 35 million people currently affected worldwide, it has been projected that the disease will affect about 115 million people by 2050. The disease is characterized by dysfunctional cellular and molecular networks and/or genomic and epigenomic interactions that affect the normal function of brain cells, leading to a defective cellular communication and function, and ultimately neurodegeneration. Aluminium (Al3+) is the third most abundant ubiquitous element in the earth crust which has gained easy access to humans and extensively used in daily life. It is an essential component of many materials used in households, such as clays, glasses, and alum. An increasing body of evidence implicates Al3+ in the progression of events that lead to neurodegenerative diseases, some of which remains controversial, but it is widely accepted that Al3+ is a recognised neurotoxin that could cause neurodegenerative diseases such as AD. The pathophysiological changes induced in Al3+ neurotoxicity leading to AD result in critical impairments of the central nervous system functions, which are essential for healthy brain ageing. These changes include; axonal transport, neurotransmitter synthesis and synaptic transmission, disruption of calcium homeostasis, alteration of energy metabolism, phosphorylation/dephosphorylation of proteins, protein degradation, gene expression, formation of reactive oxygen species and inflammatory responses, inhibition of DNA repair system, activation of glial cells, reduction of activities of antioxidant enzymes, alterations of pathways of NF-κB and JNK, binding DNA, cell death, motor and cognitive decline. These multi-faceted pathways provide a link between Al neurotoxicity and AD by modulating both tau and amyloid beta hypotheses of AD.

INTRODUCTION
Alzheimer’s disease (AD) is the most common cause of dementia that affects one patient every seven seconds, with over 35 million people currently affected worldwide (Mohandas et al. 2009; Prince et al. 2013). It has been projected that the disease will affect about 115 million people by 2050 (Prince et al. 2013). First described over 100 years ago (Stelzma et al. 1995), AD is thought to be caused by both genetic and environmental factors (Gatz et al. 2006). The common signs associated with the disease firstly described by Alois Alzheimer in 1906 include severe cognitive impairment and hallucinations, microscopically visible cortical atrophy without macroscopic focal degeneration; disintegrated neurones, presence of extracellular foci (now called neuritic/senile plaques) and intracellular neurofibrillary tangles (Stelzmann et al. 1995). Alzheimer’s disease affects predominantly people aged 60 and above (American Health Assistant Foundation, 2000-2012). Indeed, it forms the most frequent form of dementia found in the elderly with an estimated prevalence of 25-50% in people over the age...
of 85, making it one of the most important medical problems in the elderly (Hong-Qi et al. 2012). The prevalence of dementia is expected to further increase in the forthcoming decades, as a consequence of the steady growth of the ageing population in both developed and developing countries (Aprahamian et al. 2013).

Alzheimer’s disease was believed to be mainly due to the accumulation of free radicals that trigger the membrane peroxidation and protein oxidation in brain tissue (Balgoon et al. 2019). It is characterized by dysfunctional cellular and molecular networks and/or genomic and epigenomic interactions that affect the normal function of brain cells, leading to a defective cellular communication and function, and ultimately leading to neurodegeneration. The principal histological hallmarks of the disease are the presence of aggregated amyloid-beta (Aβ)-laden plaques and hyperphosphorylated tau-laden neurofibrillary tangles (NFTs) (Selkoe 2001). The abundance of Aβ – a product of the sequential cleavage of amyloid precursor protein (APP) by β and α-secretase in plaques, and microtubule-associated protein tau, in tangles, coupled with their toxic nature (both in vitro and in vivo) provided strong evidence to their involvement in the pathogenesis of AD (Benilova et al. 2012; Aprahamian et al. 2013). However, the neurodegeneration that occurs in AD has been proposed to arise not only from the accumulation of Aβ and/or aberrant modification of tau, but from a number of other factors that include oxidative stress, inflammation, vascular disease, accumulation of metals, such as zinc and aluminium (Al3+) (Mohandas et al. 2009; Armstrong 2011; Craddock et al. 2012). These factors induce cell membrane leakage, damage to organelles, such as the mitochondria and the nucleus, that cumulate to cause defects in various systems, including the acetyl cholinesterase system, which is essential for learning and memory (Contestabile 2011; Benilova et al. 2012; Sours et al. 2012).

The majority of AD cases are sporadic, having a non-Mendelian contribution, and some cases have an environmental contribution (Gatz et al. 2006), such as exposure to Al3+ (Kurland 1988). Environmental stimuli such as physical exercise, pollutants, lifestyle, chemicals, pesticides, nutrition, physical stress, behavioural stress and exposure to metals such as Al3+ affects the normally inherited methylome throughout the lifespan of an organism, leading to either healthy or diseased ageing (Nicolia et al. 2015). The negative impacts of some of these stressors such as Al3+ toxicity may lead to diseased ageing by altering cellular and molecular mechanisms through gene activation and silencing. These may eventually lead to the manifestation of various aged related disorders such as AD. Indeed, the human brain is a target and a sink to Al3+, making its link to the pathogenesis of AD highly attractive (Exley 2014). Interestingly, Al3+ is an important component of many materials used in households, such as clays, glasses, and alum (Rui & Yongjian 2010; Kawahara & Kato-Negishi 2011). The accumulation of Al3+ in the brain has been linked to the pathophysiology of some neurodegenerative disorders, including AD, amyotrophic lateral sclerosis and Guam-Parkinson’s dementia (Kurland 1988). It has also been linked to the cause of some neurological symptoms and biochemical responses, associated with severe learning disabilities in children (Zafar et al. 2004). As such, many experimental models have unveiled numerous pathways, thus, provided novel insights into the cellular and molecular mechanisms of Al3+-induced neurotoxicity, especially in AD.

Aluminium
Aluminium is the third most abundant ubiquitous element in the earth crust which has gained easy access to humans and extensively used in daily life (Kawahara and Kato-negishi, 2011; Rui and Yongjian, 2010). First isolated in 1827, it exists in three oxidation states of (+1, +2 and +3) but commonly exist in the (+3) oxidation state, and does not undergo oxidation-reduction reactions (Kumar & Gill 2014). It has an affinity for negatively charged, oxygen-donor ligands and forms strong bond with inorganic and organic phosphates, carboxylate, and deprotonated hydroxyl groups. It react with other metals in the environment to form various complexes. Compounds containing Al3+ such as clays, glasses, and alum have been used in manufacturing for centuries (Kumar & Gill 2009). Aluminium has widespread and important use in industrial applications and consumer products due to its beneficial characteristics such as lightweight, malleable, ductile and non-magnetic. It is also used in cooking utensils and pharmacological agents, including antacids and antiperspirants (Kawahara & Kato-negishi 2011).

Sources of aluminium
Aluminium is an essential component of many materials used in households, such as clays, glasses, and alum (Rui & Yongjian 2010). The daily intake, absorption or accumulation of Al3+ in humans is estimated to be around 3–20 mg, which occurs via diet, antacids, cosmetics, cooking utensils, parenteral fluids, inhaled fumes and particles from occupational exposures, industrial cement waste and drinking water (Yokel 2000). This is influenced by pH, organic acids, such as citrate and lactate (Kumar & Gill 2014). Aluminium has been shown to accumulate in various mammalian tissues such as brain, bone, liver and kidney and does not appear to have any role in animal and human biology but its increased biological availability has been linked to both acute and chronic diseases in humans (Sahin et al. 1994; Yokel 2000; Exley 2005).
Aluminium neurotoxicity

In 1921, the first association between Al\(^{3+}\) poisoning and memory disorder in humans was reported and Al\(^{3+}\) was later shown to induce epilepsy in experimental animals (Spofforth et al. 1921). Aluminium was shown to cause various dialysis-related disorders, including osteomalacia, microcytic anaemia, \(\beta2\)-microglobulin-associated amyloidosis and dialysis encephalopathy in hemodialysis patients (Alfrey et al. 1976; Wills & Savory 1989). A number of symptoms related to cerebral impairments (e.g. loss of concentration and short-term memory) was revealed in people from Camel ford (Cornwall, UK) who accidently became exposed to large quantity of Al\(^{3+}\) due to contamination in their drinking water in in 1988 (Altmann et al. 1999). Few years later, a considerable number of studies in different part of the world provided evidence supporting an association between AD and Al\(^{3+}\) in drinking water, hence suggesting the adverse effects of Al\(^{3+}\) on human memories when it enters the brain (Flaten 2001; Rondeau et al. 2009; Azib et al. 2019).

The adverse effects of Al\(^{3+}\) on the central nervous system include crucial reactions for brain development such as the axonal transport, neurotransmitter synthesis and synaptic transmission, phosphorylation/dephosphorylation of proteins, protein degradation, gene expression, and inflammatory responses (Bizzi & Gambetti 1986; Rao and Stein 2003; Lukiw et al. 2005; Huh et al. 2005; Maya et al. 2016; Rather et al. 2019). Aluminium binds to the phosphate groups of DNA and RNA, affecting DNA topology and influencing the expression of various genes essential for brain functions (Rao and Stein 2003). It also binds to the phosphate groups of nucleoside di- and triphosphates, such as ATP thereby influencing energy metabolism (Kumar et al. 2008; Lemire et al. 2009). Furthermore, Al\(^{3+}\) inhibits the functions of various protein kinases and phosphatases (Soccorro et al. 2000).

Aluminium has strong positive charges and a relatively small ionic radius in comparison to other metal ions such as Ca\(^{2+}\), Zn\(^{2+}\), and Na\(^{+}\). This gives it a high affinity to firmly binds to metal-binding amino acids such as histidine, tyrosine, arginine or phosphorylated amino acids and acts as a cross-linker making it useful as a leather tanning agent (Cornwall, UK) who accidently became exposed to large quantity of Al\(^{3+}\) due to contamination in their drinking water in in 1988 (Altmann et al. 1999). Few years later, a considerable number of studies in different part of the world provided evidence supporting an association between AD and Al\(^{3+}\) in drinking water, hence suggesting the adverse effects of Al\(^{3+}\) on human memories when it enters the brain (Flaten 2001; Rondeau et al. 2009; Azib et al. 2019).

Consequently, Al\(^{3+}\) causes apoptotic death of neurons and glial cells through activation of SAPK/JNK (stress-activated protein kinase or c-jun N-terminal kinase) signal transduction pathway (Fu et al. 2003; Savory & Herman, 2003). Chronic administration of Al\(^{3+}\) was also reported to impair long term potentiation (Ribes et al. 2008). Aluminium also inhibits voltage-gated Ca\(^{2+}\) channels, neurotransmitter receptors, and impairs synaptic transmission (Meiri et al. 1993). It causes spatial memory deficit, influences emotional reactivity, and impairs various brain functions related to learning and memory in transgenic mice model of AD (Ribes et al. 2008; (Mathiyazahan et al. 2015).

Link between aluminium and alzheimer’s disease: cellular and molecular mechanisms

The hypothesis that Al\(^{3+}\) is an environmental contributor to the pathogenesis of AD, termed the “Aluminium hypothesis”, was proposed in the 1960s based on various neurotoxicological, analytical, and epidemiological findings (Klatzo et al. 1965; Martin et al. 1989). Despite debates over the past decades, Al\(^{3+}\) and other metals such Zn\(^{2+}\), Cu\(^{2+}\), and Fe\(^{3+}\) have consistently been linked to the “amyloid cascade hypothesis”, as influencing the oligomerization and conformational changes of A\(\beta\) peptides as cross-linkers, and, therefore, implicating them in the pathogenesis of Alzheimer’s disease (Kawahara and Kato-Negishi 2011). Despite supporting evidence, the Al\(^{3+}\) hypothesis has been extensively debated in the past few decades. It has been argued that neurofibrillary changes in Al\(^{3+}\) intoxicated animals (Al-NFTs) are different from those in AD patients (AD-NFTs) and there is no significant difference in Al\(^{3+}\) levels of AD patients and age-matched controls (Wisniewski and Wen 1992). However, most recent investigations reveal the link between Al\(^{3+}\) and AD pathogenesis through various mechanisms ranging from oxidative stress to neuroinflammation, leading to oligomerization of amyloid beta protein and hyperphosphorylation of Tau protein (Mathiyazahan et al. 2015; Al-Amin et al. 2016; Cao et al. 2016; Balgoon et al. 2019; Rather et al. 2019). Evidence of aluminium intoxication in amyloid beta protein hypothesis

Amyloid \(\beta\) Peptide is a small peptide of 39–43 amino acid residues, secreted by cleavage of the amyloid precursor protein (APP) N-terminus by \(\beta\)-APP cleaving enzyme (BACE) and intra-membrane cleavage of its C-terminus by \(\gamma\)-secreatinase. According to ‘amyloid cascade hypothesis’, the accumulation of A\(\beta\) peptide and its neurotoxicity due to abnormal expression of APP play a
central role in the pathogenesis of AD (Hardy and Sekoe 2002; Wirths et al. 2004). Multiple research have shown that trace elements including Al$^{3+}$ are potential acceleratory factors that play important roles in the accumulation of Aβ peptides in the human and rodents brain leading to pathogenesis of AD (Campbell et al. 2000; Bharathi et al. 2019). Aluminium was also found to induce AD pathology and increased Aβ42 content, by the down-regulation of the expression of ApoER2 and LRP1 proteins (Zhang et al. 2019).

Aluminium has been shown to cause elevated expression of APP in experimental animals and stimulates Fe-induced membrane lipid peroxidation indirectly, causing oxidative damage in vitro and in vivo (Lin et al. 2008; Walton et al. 2009; Akinrade et al. 2015). Together with other metals such as Zn$^{2+}$, Fe$^{3+}$, and Cu$^{2+}$, Al$^{3+}$ also causes oligomerization of Aβ peptide making it resistant to proteases; thus enhancing its accumulation in the brain and eventually leading to AD (Kawahara and Kato 2011). Furthermore, the secreted Aβ peptide is usually degraded by various proteases such as neprilysin within a short period. Aluminium down regulate neprilysin which results in further accumulation of Aβ peptide and its neurotoxicity (Luo et al. 2009).

Role for aluminium in TAU hypothesis
A role for Al$^{3+}$ has been suggested in the formation of hyperphosphorylated tau-laden NFT through impairment of calcium homeostasis. The Aβ peptide oligomers formed from the amyloid cascade are incorporated into cell membranes and results in the formation of ion channels (Kawahara 2010). A subsequent influx of Ca$^{2+}$ through these amyloid channels lead to the phosphorylation of tau, depletion of neurotrophic factors, and the formation of free radicals, which consequently results in neuronal death (Johnson and Sharma 2003; Gracia et al. 2010). Aluminium blocks various Ca$^{2+}$ channels and influences Ca$^{2+}$ homeostasis (Moya et al. 2016). It also inhibits the increase in Ca$^{2+}$ levels induced by the brain-derived neurotrophic factor (Ghribi et al. 2001). Aluminium binds to iron regulatory protein (IRP) and thus influences the expression of Fe-binding proteins with iron response elements (IREs) in their mRNA causing an elevated Fe concentration (Yamanaka et al. 1999; Crichton et al. 2002). This causes disruption of Fe homeostasis leading to membrane lipid peroxidation, free radical formation and oxidative stress, tau protein phosphorylation, neurofibrillary tangles formation, neuronal death and consequently Alzheimer’s disease. Aluminium chloride also induces AD-like pathology demonstrated by significant reduction in spatial memory performance, anxiety, and motor dysfunction, diminished expression of cyclin-dependent kinase 5 (CDK 5-enzyme implicated in the phosphorylation of tau proteins), pTau, oxidative stress, and apoptosis, effects of which could be attenuated by activation Akt/GSK3β pathway (Rather et al. 2019). It also increases the levels of protein phosphatase 2 (PP2A), increased the expression of mRNA of Bcl-2 in CA3, and decreased the levels of glycogen synthase kinase-3 beta (GSK-3β) in experimental rats (Chiroma et al. 2019), thus implicating the role of Al$^{3+}$ in the tau pathology leading to AD.

Animal models used for aluminium neurotoxicity
Although a lot of research has focused on the association between Al$^{3+}$ exposure and development of neurodegenerative disorders like AD, the molecular mechanisms behind the Al$^{3+}$ transport in neurones and subsequent neuron damage is yet to be unravelled. In order to achieve this, numerous animal models of Al$^{3+}$-induced AD have been developed but the most commonly used models are discussed below.

Mechanisms of aluminium-induced neurotoxicity in nematode worm (Caenorhabditis elegans model)
Caenorhabditis elegans has been used as a research tool to understand the mechanisms underlying numerous neurodegenerative diseases. It has approximately 60–80% of human genes and contains genes involved in metal homeostasis and transport. This makes it a good model for studying the mechanism of metal-induced degeneration such as Al$^{3+}$ (Maya et al. 2016). The small size, transparent nature, low culture cost, fast life-cycle, complete nervous system with four functional categories of neurons based on their circuitry: motor, sensory, inter and polymodal neurons makes it easy to investigate neurological function in C. elegans (Maya et al. 2016). C. elegans has 302 neurons and about 5000 synapses and shares similar neurotransmitters with humans, including dopamine (DA), acetylcholine (ACh), serotonin (5-HT), γ-aminobutyric acid (GABA), glutamate, and others (White et al. 1986; Aschner et al. 2013). Locomotive behaviours are the most commonly used indices for analysis and determination of neurodegeneration in C. elegans. Aluminium exposure decreases mitochondrial membrane potential and cellular ATP levels, and confers DA neuron degeneration in the genetically tractable C. elegans due to a reduction in the gene expression of the vertebrate apoptotic caspase homologue Apaf1 and ced-4 (VanDuyn et al. 2013).

Mechanisms of aluminium-induced neurotoxicity in fruit fly (Drosophila melanogaster)
Drosophila melanogaster is one of the cheapest and well-understood models of neurodegenerative disorders having a life-span range of 40–50 days in optimal
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temperature but can extend to about 120 days depending on diet and stress conditions (Lenz et al. 2013). This gives it an advantage over other models in biomedical research, especially in the field of neurodegenerative diseases. The Drosophila genes are so close to human genes, including disease genes which can be matched with equivalent genes in the fly (Hime 2013). The fly’s behavioural pattern used to phenotype AD ranges from simple avoidance to learning and memory, and typical neurodegenerative phenotypes like reduced life span, locomotor deficits, olfactory learning abnormalities and vacuolisation of the brain were observed after feeding Drosophila with excess amount of Al3+ (McGuire et al 2005; Wu et al. 2012). Changes in other markers observed include a large amount of iron, reactive oxygen species, and elevated SOD2 activity. These changes were however, shown to be independent of β-amyloid and tau-associated toxicity (Wu et al. 2012). Other studies show that Al3+ significantly decreases the life span of Drosophila by significantly reducing the Na content of the flies, increases the rigidity of the cell membrane and alters the locomotor activity (Deleers et al. 1986; Kijak et al. 2014). It also decreases the activity of ATPase and binds to calmodulin leading to conformation changes in the protein in Drosophila (Siegel and Haug 1983). Overall, in vivo studies using Drosophila as a model could provide a potent lead that may help in drug development in neurodegenerative diseases (Prübbing et al. 2013).

Evidence for Aluminium-induced neurotoxicity in rats (Rattus norvigicus)

Rat is one of the most widely used organism in medical research serving as the best model for cognitive and memory studies due to the extensive studies carried on their physiological systems involved in learning and memory. Studies in rats exposed to Al3+ has revealed changes in the level of 5-hydroxytryptamine and its metabolite 5-hydroxyindole acetic acid in different regions of the rat’s brain (Kumar 2002). Numerous studies have revealed the pro-oxidant properties of Al1+ in the rat brain by inhibiting the enzymes superoxide dismutase (SOD) and catalase (CAT). It also decreases the level of Glutathione, Mg2+ATPase and increases the level of lipid peroxidation and the activities of alkaline phosphatase, acid phosphatase, alanine transaminase and aspartate transaminase in all brain regions of rat brain (Stevanovic et al. 2009; Majumdar et al. 2014; Sumathith et al. 2015). These established a link between Al exposure and AD-like neurodegenerative changes in rat. Aluminium administration alters the Bcl-xl, bcl-2 and Caspase-3 protein and mRNA expressions of hippocampus and cerebral cortex of rats leading to changes in behaviour and long term memory in the animals due to aggregation of A-beta protein and acetylcholinesterase activity, consequently leading to neurotoxicity and cerebral damage in rat brain (Kuroda et al. 1994; Thirunavukkarasu et al. 2013; Lin et al. 2015; Chiroma et al. 2019). Finally, long-term Al3+ exposure may lead to electrophysiological, cognitive and biological modifications in the whole brain of rats that may lead to neurodegeneration, hence making Al3+ a potent rat model for studying the links between Al3+ and AD (Sethi et al. 2008).

Evidence for Aluminium-induced neurotoxicity in mouse (Mus musculus)

Mice are one of the most commonly used models for neurodegenerative research like AD. Investigation revealed that Al3+ exposure alters the major chemical constituents, such as lipids, proteins and nucleic acids of mice brain (Sivakumar et al. 2012). Chronic Al3+ administration results in significant motor incoordination and memory deficits associated with increased oxidative stress and elevated acetylcholinesterase activity followed by decreased pyramidal cells in the hippocampal area of mice brain (Singh and Goel 2015). Numerous studies reported a decrease in the activity of the antioxidant enzymes such as SOD, CAT, Glutathione peroxidase (GSH-Px) in Al3+ treated mice and increase in lipid peroxidation, thus establishing a link between oxidative stress and Al3+ induced neurodegeneration (Shati et al. 2011). These consequently result in deposition and accumulation of amyloid beta, one of the hallmarks of AD (Rodella et al. 2008).

Mechanisms of aluminium-induced neurotoxicity in rabbits (Oryctolagus cuniculus)

Studies revealed that Rabbits have proven to be sensitive to Al3+ exposure, with intracerebral and intravenous infusions reproducing some of the pathological features consistent with AD (Savory et al. 2006). Aluminium exposure has been shown to induce neuro-cytoskeletal changes in the fetal rabbit midbrain in matrix culture and induced neurofibrillary tangle formation in rabbit midbrain (Hewitt et al. 1991). Aluminium also induces mitochondrial and endoplasmic reticulum stress in the rabbit brain by mediating apoptotic cascade thereby paving a way to one of the major pathways in the neurodegenerative diseases (Savory et al. 2003). Changes in haemato-biochemical parameters, lipid peroxidation and activities of antioxidant enzymes in rabbit brain plasma, liver, kidney and testes were also reported due to Al3+ administration (Savory et al. 2003; Yousef 2004). These make rabbit a viable tool for Al3+-induced AD study.

SUMMARY

An increasing body of evidence implicates Al3+ in the progression of events that lead to neurodegenerative diseases, some of which remains controversial, but it is
widely accepted that Al$^{3+}$ is a recognised neurotoxin that could cause neurodegenerative diseases such as AD. The pathophysiological changes induced in aluminium neurotoxicity leading to AD result in critical impairments of the central nervous system functions, which are essential for healthy brain ageing. These changes include: axonal transport, neurotransmitter synthesis and synaptic transmission, disruption of calcium homeostasis, alteration of energy metabolism, phosphorylation/dephosphorylation of proteins, protein degradation, gene expression, formation of reactive oxygen species and inflammatory responses, inhibition of DNA repair system, activation of glial cells, reduction of activities of antioxidant enzymes, alternations of pathways of NF-κB and JNK, binding DNA, cell death, motor and cognitive decline. These multi-faceted pathways provide a link between Al$^{3+}$ neurotoxicity and AD by modulating both tau and amyloid beta hypotheses of AD.

CONCLUDING REMARKS
Reverse pathophysiological processes/interventions that decrease synthesis of Aβ-laden plaques and hyperphosphorylated tau-laden NFTs play important role in the links between cellular and molecular mechanisms underlying aluminium neurotoxicity. Measures aimed at modulating various neuropathophysiological processes induced by Al$^{3+}$ neurotoxicity in AD may be of potential therapeutic and prophylactic benefits. Agents that mitigate the potentiation of deleterious redox activity and disruption of intracellular calcium signalling may reduce aluminium-induced neurotoxicity and associated disease conditions.

REFERENCES


Aluminium neurotoxicity in Alzheimer’s disease


arises from increased iron accumulation and reactive oxygen species (ROS) production. Neurobiology of aging, 33(1), pp.199-e1.