J. Afr. Ass. Physiol. Sci. 7 (2): 70-79, December 2019

Journal of African Association of Physiological Sciences

Official Publication of the African Association of Physiological Sciences
http://www.jaaps.aapsnet.org

Review Article

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

M.S. Muhammad[1,2*], J.O Ayo[3], N.M. Danjuma[4], A. AbdulWahab[2], A.S. Isa[2] and M.B. Maina[5].

Departments of Human Physiology, [1]College of Medical Sciences, Gombe State University, Nigeria, [2]Faculty of Basic Medical Sciences, Ahmadu Bello University Zaria, Nigeria, [3]Veterinary Physiology, Faculty of veterinary Medicine, Ahmadu Bello, University Zaria, Nigeria, [4]Pharmacology and Therapeutics, Faculty of Pharmaceutical Sciences, Ahmadu Bello University Zaria, Nigeria and [5]Neuroscience Centre, School of Life Sciences, University of Sussex, Brighton, United Kingdom

Keywords:
Alzheimer's disease, Aluminium chloride, Amyloid beta, Tau, Animal models

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 (Al^{3+}) 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 Al^{3+} 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 Al^{3+} 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-kB 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

*Address for correspondence:
Email: mshehu84@gmail.com
Tel: +2347032527295

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 forth-coming 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 (Al^{3+}) (Mohandas et al. 2009; Amstrong 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; Benilove et al. 2012; Soura 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 Al^{3+} (Kurland 1988). Environmental stimuli such as physical exercise, pollutants, lifestyle, chemicals, pesticides, nutrition, physical stress, behavioural stress and exposure to metals such as Al^{3+} 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 Al^{3+} 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 Al^{3+}, making its link to the pathogenesis of AD highly attractive (Exley 2014). Interestingly, Al^{3+} 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 Al^{3+} 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 Al^{3+}-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 Al^{3+} 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 Al^{3+} 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, β2-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 (Socorro 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 (Kawahara & Kato-Negishi 2011). By binding to various proteins, Al^{3+} causes the oligomerisation of proteins, inducing conformational changes that can inhibit their degradation by proteases. Strong binding of Al^{3+} to phosphorylated amino acids promotes the self-aggregation and accumulation of highly phosphorylated cytoskeleton proteins, including neurofilaments and microtubule-associated proteins (Diaz-Nido & Avila 1990).

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 Aβ 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 β Peptide is a small peptide of 39–43 amino acid residues, secreted by cleavage of the amyloid precursor protein (APP) N-terminus by β-APP cleaving enzyme (BACE) and intra-membrane cleavage of its C-terminus by γ-secretase. According to 'amyloid cascade hypothesis', the accumulation of Aβ 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-Negishi 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), ɣ-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

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 Al^{3+} (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 Al^{3+} 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 (Prüßing 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 Al^{3+} 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 Al^{3+} in the rat brain by inhibiting the enzymes superoxide dismutase (SOD) and catalase (CAT). It also decreases the level of Glutathione, Mg^{2+}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; Sumathi 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 Al^{3+} exposure may lead to electrophysiological, cognitive and biological modifications in the whole brain of rats that may lead to neurodegeneration, hence making Al^{3+} a potent rat model for studying the links between $Al^{3+}$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 Al^{3+} exposure alters the major chemical constituents, such as lipids, proteins and nucleic acids of mice brain (Sivakumar et al. 2012). Chronic Al^{3+} administration results in significant motor in-coordination 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 Al^{3+} treated mice and increase in lipid peroxidation, thus establishing a link between oxidative stress and Al^{3+} 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 Al^{3+} 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 Al^{3+} administration (Savory et al. 2003; Yousef 2004). These make rabbit a viable tool for Al^{3+}-induced AD study.

SUMMARY

An increasing body of evidence implicates Al^{3+} 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, alterations of pathways of NF-kB 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

Akinrinade, I.D., Memudu, A.E., Ogundele, O.M. and Ajetunmobi, O.I., 2015. Interplay of glia activation and oxidative stress formation in fluoride and aluminium exposure. *Pathophysiology*, *22*(1), pp.39-48.

Al-Amin, M.M., Reza, H.M., Saadi, H.M., Mahmud, W., Ibrahim, A.A., Alam, M.M., Kabir, N., Saifullah, A.R.M., Tropa, S.T. and Quddus, A.R., 2016. Astaxanthin ameliorates aluminum chloride-induced spatial memory impairment and neuronal oxidative stress in mice. *European journal of pharmacology*, *777*, pp.60-69.

Alfrey, A.C., LeGendre, G.R. and Kaehny, W.D., 1976. The dialysis encephalopathy syndrome: Possible aluminum intoxication. *New England Journal of Medicine*, *294*(4), pp.184-188.

Altmann, P., Cunningham, J., Dhanesha, U., Ballard, M., Thompson, J. and Marsh, F., 1999. Disturbance of cerebral function in people exposed to drinking water contaminated with aluminium sulphate: retrospective study of the Camelford water incident. *Bmj*, *319*(7213), pp.807-811.

American Health Assistance Foundation (2000-2012). www.AHAF.com/alzheimers. [online] (Retrieved, 10/06/2012).

Aprahamian, I., Stella, F. and Forlenza, O.V., 2013. New treatment strategies for Alzheimer's disease: is there a hope?. *The Indian journal of medical research*, *138*(4), p.449.

Armstrong, R.A., 2011. The pathogenesis of Alzheimer's disease: a reevaluation of the "amyloid cascade hypothesis". *International journal of Alzheimer's disease*, *2011*.

Aschner, M., Chen, P., Martinez-Finley, E.J., Bornhorst, J. and Chakraborty, S., 2013. Metal-induced neurodegeneration in C. elegans. *Frontiers in aging neuroscience*, *5*, p.18.

Azib, L., Debbache-Benaida, N., Da Costa, G., Atmani-Kilani, D., Saidene, N., Ayouni, K., Richard, T. and Atmani, D., 2019. Pistacia lentiscus L. leaves extract and its major phenolic compounds reverse aluminium-induced neurotoxicity in mice. *Industrial Crops and Products*, *137*, pp.576-584.

Balgoon, M.J., Ahmed, G.A.R., Qusti, S.Y. and Shaker, S., 2019. Transit phases of β-amyloid and tau proteins formation and re-solubilisation in AD rat hippocampus tissue as probed by ATR-IR spectroscopy. *Neurology, Psychiatry and Brain Research*, *31*, pp.1-8.

Benilova, I., Karran, E. and De Strooper, B., 2012. The toxic Aβ oligomer and Alzheimer's disease: an emperor in need of clothes. *Nature neuroscience*, *15*(3), p.349.

Bharathi, M.D., Justin-Thenmozhi, A., Manivasagam, T., Rather, M.A., Babu, C.S., Essa, M.M. and Guillemin, G.J., 2019. Amelioration of aluminum maltolate-induced inflammation and endoplasmic reticulum stress-mediated apoptosis by tannoid principles of emblica officinalis in neuronal cellular model. *Neurotoxicity research*, *35*(2), pp.318-330.

Bizzi, A. and Gambetti, P., 1986. Phosphorylation of neurofilaments is altered in aluminium intoxication. *Acta neuropathologica*, *71*(1-2), pp.154-158.

Campbell, A., Kumar, A., Rosa, F.L., Prasad, K.N. and Bondy, S.C., 2000. Aluminum Increases Levels of β-Amyloid and Ubiquitin in Neuroblastoma But Not in Glioma Cells (44507). *Proceedings of the Society for Experimental Biology and Medicine*, *223*(4), pp.397-402.

Cao, Z., Yang, X., Zhang, H., Wang, H., Huang, W., Xu, F., Zhuang, C., Wang, X. and Li, Y., 2016. Aluminum chloride induces neuroinflammation, loss of neuronal

dendritic spine and cognition impairment in developing rat. *Chemosphere*, *151*, pp.289-295.

Chiroma, S.M., Baharuldin, M.T.H., Taib, M., Norma, C., Amom, Z., Jagadeesan, S., Ilham Adenan, M., Mahdi, O. and Moklas, M.A.M., 2019. Centella asiatica Protects d-Galactose/AlCl3 Mediated Alzheimer's Disease-Like Rats via PP2A/GSK-3β Signaling Pathway in Their Hippocampus. *International journal of molecular sciences*, *20*(8), p.1871.

Contestabile, A., 2011. The history of the cholinergic hypothesis. *Behavioural brain research*, *221*(2), pp.334-340.

Craddock, T.J., Tuszynski, J.A., Chopra, D., Casey, N., Goldstein, L.E., Hameroff, S.R. and Tanzi, R.E., 2012. The zinc dyshomeostasis hypothesis of Alzheimer's disease. *PloS one*, *7*(3), p.e33552.

Crichton, R.R., Wilmet, S., Legssyer, R. and Ward, R.J., 2002. Molecular and cellular mechanisms of iron homeostasis and toxicity in mammalian cells. *Journal of inorganic biochemistry*, *91*(1), pp.9-18.

Deleers, M., Servais, J.P. and Wülfert, E., 1986. Neurotoxic cations induce membrane rigidification and membrane fusion at micromolar concentrations. *Biochimica et Biophysica Acta (BBA)-Biomembranes*, *855*(2), pp.271-276.

Diaz-Nido, J. and Avila, J., 1990. Aluminum induces the in vitro aggregation of bovine brain cytoskeletal proteins. *Neuroscience letters*, *110*(1-2), pp.221-226.

Exley, C., 2005. The aluminium-amyloid cascade hypothesis and Alzheimer's disease. In *Alzheimer's Disease* (pp. 225-234). Springer, Boston, MA.

Exley, C., 2014. Why industry propaganda and political interference cannot disguise the inevitable role played by human exposure to aluminum in neurodegenerative diseases, including Alzheimer's disease. *Frontiers in neurology*, *5*, p.212.

Flaten, T.P., 2001. Aluminium as a risk factor in Alzheimer's disease, with emphasis on drinking water. *Brain research bulletin*, *55*(2), pp.187-196.

Fu, H.J., Hu, Q.S., Lin, Z.N., Ren, T.L., Song, H., Cai, C.K. and Dong, S.Z., 2003. Aluminum-induced apoptosis in cultured cortical neurons and its effect on SAPK/JNK signal transduction pathway. *Brain research*, *980*(1), pp.11-23.

Gatz, M., Reynolds, C.A., Fratiglioni, L., Johansson, B., Mortimer, J.A., Berg, S., Fiske, A. and Pedersen, N.L., 2006. Role of genes and environments for explaining Alzheimer disease. *Archives of general psychiatry*, *63*(2), pp.168-174.

Ghribi, O., Herman, M.M., Forbes, M.S., DeWitt, D.A. and Savory, J., 2001. GDNF protects against aluminum-induced apoptosis in rabbits by upregulating Bcl-2 and Bcl-XL and inhibiting mitochondrial Bax translocation. *Neurobiology of disease*, *8*(5), pp.764-773.

Hardy, J. and Selkoe, D.J., 2002. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *science*, *297*(5580), pp.353-356.

Hewitt, C.D., Herman, M.M., LOPESM, M., Savory, J. and Wills, M.R., 1991. Aluminium maltol–induced neurocytoskeletal changes in fetal rabbit midbrain in matrix culture. *Neuropathology and applied neurobiology*, *17*(1), pp.47-60.

Hime, G. 2016. Animals in research: Drosophila (the fruit fly), 2013. http:// theconversation.com/animals-in-research-drosophila-the-fruit-fly-13571 (accessed 30.10.16).

Hong-Qi, Y., Zhi-Kun, S. and Sheng-Di, C., 2012. Current advances in the treatment of Alzheimer's disease: focused on considerations targeting Aβ and tau. Translational neurodegeneration, 1(1), p.21.

Huh, J.W., Choi, M.M., Lee, J.H., Yang, S.J., Kim, M.J., Choi, J., Lee, K.H., Lee, J.E. and Cho, S.W., 2005. Activation of monoamine oxidase isotypes by prolonged intake of aluminum in rat brain. Journal of inorganic biochemistry, 99(10), pp.2088-2091.

Johnson, V.J. and Sharma, R.P., 2003. Aluminum disrupts the pro-inflammatory cytokine/neurotrophin balance in primary brain rotation-mediated aggregate cultures: possible role in neurodegeneration. Neurotoxicology, 24(2), pp.261-268.

Kawahara, M. and Kato-Negishi, M., 2011. Link between aluminum and the pathogenesis of Alzheimer's disease: the integration of the aluminum and amyloid cascade hypotheses. International journal of Alzheimer's disease, 2011.

Kawahara, M., 2010. Neurotoxicity of β-amyloid protein: oligomerization, channel formation and calcium dyshomeostasis. Current pharmaceutical design, 16(25), pp.2779-2789.

Kijak, E., Rosato, E., Knapczyk, K. and Pyza, E., 2014. Drosophila melanogaster as a model system of aluminum toxicity and aging. Insect science, 21(2), pp.189-202.

Klatzo, I., WISNIEWSKI, H. and Streicher, E., 1965. Experimental production of neurofibrillary degeneration: 1. Light microscopic observations. Journal of neuropathology and experimental neurology, 24(2), pp.187-199.

Kumar, S., 2002. Aluminium-induced changes in the rat brain serotonin system. Food and chemical toxicology, 40(12), pp.1875-1880.

Kumar, V. and Gill, K.D., 2009. Aluminium neurotoxicity: neurobehavioural and oxidative aspects. Archives of toxicology, 83(11), pp.965-978.

Kumar, V. and Gill, K.D., 2014. Oxidative stress and mitochondrial dysfunction in aluminium neurotoxicity and its amelioration: a review. Neurotoxicology, 41, pp.154-166.

Kumar, V., Bal, A. and Gill, K.D., 2008. Impairment of mitochondrial energy metabolism in different regions of rat brain following chronic exposure to aluminium. Brain research, 1232, pp.94-103.

Kurland, L.T., 1988. Amyotrophic lateral sclerosis and Parkinson's disease complex on Guam linked to an environmental neurotoxin. Trends in neurosciences, 11(2), pp.51-54.

KURODA, Y. and KAWAHARA, M., 1994. Aggregation of amyloid β-protein and its neurotoxicity: enhancement by aluminum and other metals. The Tohoku journal of experimental medicine, 174(3), pp.263-268.

Lemire, J., Mailloux, R., Puiseux-Dao, S. and Appanna, V.D., 2009. Aluminum-induced defective mitochondrial metabolism perturbs cytoskeletal dynamics in human astrocytoma cells. Journal of Neuroscience research, 87(6), pp.1474-1483.

Lenz, S., Karsten, P., Schulz, J.B. and Voigt, A., 2013. Drosophila as a screening tool to study human neurodegenerative diseases. Journal of neurochemistry, 127(4), pp.453-460.

Lin, R., Chen, X., Li, W., Han, Y., Liu, P. and Pi, R., 2008. Exposure to metal ions regulates mRNA levels of APP and BACE1 in PC12 cells: blockage by curcumin. Neuroscience letters, 440(3), pp.344-347.

Lin, W.T., Chen, R.C., Lu, W.W., Liu, S.H. and Yang, F.Y., 2015. Protective effects of low-intensity pulsed ultrasound on aluminum-induced cerebral damage in Alzheimer's disease rat model. Scientific reports, 5, p.9671.

Lukiw, W.J., Percy, M.E. and Kruck, T.P., 2005. Nanomolar aluminum induces pro-inflammatory and pro-apoptotic gene expression in human brain cells in primary culture. Journal of inorganic biochemistry, 99(9), pp.1895-1898.

Luo, Y., Niu, F., Sun, Z., Cao, W., Zhang, X., Guan, D., Lv, Z. and Xu, Y., 2009. Altered expression of Aβ metabolism-associated molecules from d-galactose/AlCl3 induced mouse brain. Mechanisms of ageing and development, 130(4), pp.248-252.

Majumdar, A.S., Nirwane, A. and Kamble, R., 2014. Coenzyme Q10 abrogated the 28 days aluminium chloride induced oxidative changes in rat cerebral cortex. Toxicology international, 21(2), p.214.

Mathiyazahan, D.B., Thenmozhi, A.J. and Manivasagam, T., 2015. Protective effect of black tea extract against aluminium chloride-induced Alzheimer's disease in rats: A behavioural, biochemical and molecular approach. Journal of Functional Foods, 16, pp.423-435.

Maya, S., Prakash, T., Madhu, K.D. and Goli, D., 2016. Multifaceted effects of aluminium in neurodegenerative diseases: a review. Biomedicine & Pharmacotherapy, 83, pp.746-754.

McGuire, S.E., Deshazer, M. and Davis, R.L., 2005. Thirty years of olfactory learning and memory research in Drosophila melanogaster. Progress in neurobiology, 76(5), pp.328-347.

Meiri, H., Banin, E., Roll, M. and Rousseau, A., 1993. Toxic effects of aluminium on nerve cells and synaptic transmission. Progress in Neurobiology, 40(1), pp.89-121.

Mohandas, E., Rajmohan, V. and Raghunath, B., 2009. Neurobiology of Alzheimer's disease. Indian journal of psychiatry, 51(1), p.55.

Nicolia, V., Lucarelli, M. and Fuso, A., 2015. Environment, epigenetics and neurodegeneration: Focus on nutrition in Alzheimer's disease. Experimental Gerontology, 68, pp.8-12.

Prince, M., Prina, M. and Guerchet, M., 2013. Journey of Caring: an analysis of long-term care for Dementia. (N/A ed.) London: Alzheimer's Disease International, 2013. 92 pp.

Prüßing, K., Voigt, A. and Schulz, J.B., 2013. Drosophila melanogaster as a model organism for Alzheimer's disease. Molecular neurodegeneration, 8(1), p.35.

Rao, K.S.J. and Stein, R., 2003. First evidence on induced topological changes in supercoiled DNA by an aluminium D-aspartate complex. *JBIC Journal of Biological Inorganic Chemistry*, *8*(8), pp.823-830.

Rather, M.A., Justin-Thenmozhi, A., Manivasagam, T., Saravanababu, C., Guillemin, G.J. and Essa, M.M., 2019. Asiatic Acid Attenuated Aluminum Chloride-Induced Tau Pathology, Oxidative Stress and Apoptosis Via AKT/GSK-3β Signaling Pathway in Wistar Rats. *Neurotoxicity research*, *35*(4), pp.955-968.

Ribes, D., Colomina, M.T., Vicens, P. and Domingo, J.L., 2008. Effects of oral aluminum exposure on behavior and neurogenesis in a transgenic mouse model of Alzheimer's disease. Experimental Neurology, 214(2), pp.293-300.

Rodella, L.F., Ricci, F., Borsani, E., Stacchiotti, A., Foglio, E., Favero, G., Rezzani, R., Mariani, C. and Bianchi, R., 2008. Aluminium exposure induces Alzheimer s disease-like histopathological alterations in mouse brain. Histology and histopathology. 23: 433–439.

Rondeau, V., Jacqmin-Gadda, H., Commenges, D., Helmer, C. and Dartigues, J.F., 2008. Aluminum and silica in drinking water and the risk of Alzheimer's disease or cognitive decline: findings from 15-year follow-up of the PAQUID cohort. American journal of epidemiology, 169(4), pp.489-496.

Rui, D. and Yongjian, Y., 2010. Aluminum chloride induced oxidative damage on cells derived from hippocampus and cortex of ICR mice. Brain research, 1324, pp.96-102.

Şahin, G., Varol, I., Temizer, A., Benli, K., Demirdamar, R. and Duru, S., 1994. Determination of aluminum levels in the kidney, liver, and brain of mice treated with aluminum hydroxide. Biological trace element research, 41(1-2), pp.129-135.

Savory, J., Herman, M.M. and Ghribi, O., 2003. Intracellular mechanisms underlying aluminum-induced apoptosis in rabbit brain. Journal of inorganic biochemistry, 97(1), pp.151-154.

Savory, J., Herman, M.M. and Ghribi, O., 2006. Mechanisms of aluminum-induced neurodegeneration in animals: Implications for Alzheimer's disease 1. Journal of Alzheimer's Disease, 10(2-3), pp.135-144.

Selkoe, D.J., 2001. Alzheimer's disease: genes, proteins, and therapy. Physiological reviews, 81(2), pp.741-766.

Sethi, P., Jyoti, A., Singh, R., Hussain, E. and Sharma, D., 2008. Aluminium-induced electrophysiological, biochemical and cognitive modifications in the hippocampus of aging rats. Neurotoxicology, 29(6), pp.1069-1079.

Shati, A.A., Elsaid, F.G. and Hafez, E.E., 2011. Biochemical and molecular aspects of aluminium chloride-induced neurotoxicity in mice and the protective role of Crocus sativus L. extraction and honey syrup. Neuroscience, 175, pp.66-74.

Siegel, N. and Haug, A., 1983. Aluminum interaction with calmodulin: evidence for altered structure and function from optical and enzymatic studies. Biochimica et Biophysica Acta (BBA)-Protein Structure and Molecular Enzymology, 744(1), pp.36-45.

Singh, T. and Goel, R.K., 2015. Neuroprotective effect of Allium cepa L. in aluminium chloride induced neurotoxicity. Neurotoxicology, 49, pp.1-7.

Sivakumar, S., Sivasubramanian, J. and Raja, B., 2012. Aluminium induced structural, metabolic alterations and protective effects of desferrioxamine in the brain tissue of mice: an FTIR study. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 99, pp.252-258.

Socorro, J.M., Olmo, R., Teijon, C., Blanco, M.D. and Teijon, J.M., 2000. Analysis of Aluminum—Yeast Hexokinase Interaction: Modifications on Protein Structure and Functionality. Journal of protein chemistry, 19(3), pp.199-208.

Soura, V., Stewart-Parker, M., Williams, T.L., Ratnayaka, A., Atherton, J., Gorringe, K., Tuffin, J., Darwent, E., Rambaran, R., Klein, W. and Lacor, P., 2012. Visualization of co-localization in Aβ42-administered neuroblastoma cells reveals lysosome damage and autophagosome accumulation related to cell death. Biochemical Journal, 441(2), pp.579-590.

Spofforth, J., 1921. CASE OF ALUMINIUM POISONING. The Lancet, 197(5103), p.1301.

Stelzmann, R.A., Norman Schnitzlein, H. and Reed Murtagh, F., 1995. An English translation of Alzheimer's 1907 paper,"Über eine eigenartige Erkankung der Hirnrinde". Clinical Anatomy: The Official Journal of the American Association of Clinical Anatomists and the British Association of Clinical Anatomists, 8(6), pp.429-431.

Stevanović, I.D., Jovanović, M.D., Jelenković, A., Ninković, M., Đukić, M., Stojanović, I. and Čolić, M., 2009. The effect of inhibition of nitric oxide synthase on aluminium-induced toxicity in the rat brain. Gen Physiol Biophys, 28, pp.235-42.

Sumathi, T., Shobana, C., Thangarajeswari, M. and Usha, R., 2015. Protective effect of L-theanine against aluminium induced neurotoxicity in cerebral cortex, hippocampus and cerebellum of rat brain–histopathological, and biochemical approach. Drug and chemical toxicology, 38(1), pp.22-31.

Thirunavukkarasu, S.V., Jayanthi, M., Raja, S. and Venkataraman, S., 2013. Effect of Manasamitra Vatakam against aluminium induced learning and memory impairment of apoptosis in rat's hippocampus and cortex. J. Drug Metab. Toxicol, 4, p.154.

VanDuyn, N., Settivari, R., LeVora, J., Zhou, S., Unrine, J. and Nass, R., 2013. The metal transporter SMF-3/DMT-1 mediates aluminum-induced dopamine neuron degeneration. Journal of neurochemistry, 124(1), pp.147-157.

Walton, J.R. and Wang, M.X., 2009. APP expression, distribution and accumulation are altered by aluminum in a rodent model for Alzheimer's disease. Journal of Inorganic Biochemistry, 103(11), pp.1548-1554.

White, J.G., Southgate, E., Thomson, J.N. and Brenner, S., 1986. The structure of the nervous system of the nematode Caenorhabditis elegans. Philos Trans R Soc Lond B Biol Sci, 314(1165), pp.1-340.

Wills, M.R. and Savory, J., 1989. Aluminum and chronic renal failure: sources, absorption, transport, and toxicity. Critical reviews in clinical laboratory sciences, 27(1), pp.59-107.

Wirths, O., Multhaup, G. and Bayer, T.A., 2004. A modified β-amyloid hypothesis: intraneuronal accumulation of the β-amyloid peptide–the first step of a fatal cascade. Journal of neurochemistry, 91(3), pp.513-520.

Wisniewski, H.M. and Wen, G.Y., 1992. Aluminium and Alzheimer's disease. Aluminium Biology Med, 169, p.142.

Wu, Z., Du, Y., Xue, H., Wu, Y. and Zhou, B., 2012. Aluminum induces neurodegeneration and its toxicity

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

Yamanaka, K., Minato, N. and Iwai, K., 1999. Stabilization of iron regulatory protein 2, IRP2, by aluminum. FEBS letters, 462(1-2), pp.216-220.

Yokel, R.A., 2000. The toxicology of aluminum in the brain: a review. Neurotoxicology, 21(5), pp.813-828.

Yousef, M.I., 2004. Aluminium-induced changes in hemato-biochemical parameters, lipid peroxidation and enzyme activities of male rabbits: protective role of ascorbic acid. Toxicology, 199(1), pp.47-57.

Zafar, T.A., Teegarden, D., Ashendel, C., Dunn, M.A. and Weaver, C.M., 2004. Aluminum negatively impacts calcium utilization and bone in calcium-deficient rats. Nutrition Research, 24(3), pp.243-259.

Zhang, T., Wang, S. and Niu, Q., 2019. Effect of Aluminum-Maltolate on the Content of Aβ Protein and the Expression of ApoER2, VLDLRs, and LRP1 in PC12-ApoE4 Cells. *Neurotoxicity research*, *35*(4), pp.931-944.