Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 9[3] February 2020 : 63-71

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD
Global Impact Factor 0.876
Universal Impact Factor 0.9804
NAAS Rating 4.95

REVIEW ARTICLE **OPEN ACCESS**

Aluminium induced Neurotoxicity: A Review

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ABSTRACT
Aluminium has been reported to be a major neurotoxin but its role in inducing neurodegenerative changes is still not clear. The purpose of this review is to give a comprehensive report of experimental data of last ten years on aluminium induced brain toxicity in different animal models. An attempt has been made to present the findings of various researchers indicating the role of aluminium in inducing oxidative stress, behavioural changes and histological alterations in brain. Along with that the mechanism of aluminium induced apoptosis in brain has also been explained. The present analysis indicated that continued exposure to Al leads to neurotoxicity affecting various oxidative stress parameters and disrupting behavioral activities finally leading to apoptosis, thus confirming its role in neurodegeneration.
Keywords: *Aluminium; oxidative stress; neurodegeneration; apoptosis, behavioural changes.*

Received 25.12.2019 Revised 19.01.2020 Accepted 04.02.2020

INTRODUCTION

Metals are naturally occurring elements that have a high atomic weight and a density at least 5 times greater than that of water. Their multiple industrial, domestic, agricultural, medical and technological applications have led to their wide distribution in the environment; raising concerns over their potential effects on human health and the environment. Their toxicity depends on several factors including the dose, route of exposure, and chemical species, as well as the age, gender, genetics, and nutritional status of exposed individuals [1]. In biological systems most metals have been reported to affect cellular organelles and components such as cell membrane, mitochondrial, lysosome, endoplasmic reticulum, nuclei, and some enzymes involved in metabolism, detoxification, and damage repair [2]. Metal ions have been found to interact with cell components such as DNA and nuclear proteins, causing DNA damage and conformational changes that may lead to cell cycle modulation, carcinogenesis or apoptosis [3,4].

ALUMINIUM AND ITS SOURCES

Aluminium is the third most abundant metal on earth [5] and reports have revealed that it is a major neurotoxin and disrupter of neurological function [6]. Aluminium is the most widely distributed metal on the planet and it's used in the production of many every-day products. Cookware, soda cans and food wrapping foils have aluminium as one of its components. Aluminium is also present in antacids, aspirin, vaccines, and even flour. Unlike vitamins, minerals, and trace elements, the body does not need aluminium. Exposure to aluminium, unfortunately, is common with some occupations like mining, factory work, and welding [7]. Pesticides exposure through pesticides containing aluminium like aluminium phosphide have also caused serious problems in farmers [8]

Aluminium as Neurotoxin

Half life of aluminium elimination in the brain is estimated at >100 days which is a reason for the neurodegeneration caused by aluminium [9]. The elimination of aluminium from the body is very slow. The half life for total body aluminium has been estimated at 7 years in humans and reflects redistribution from bone stores [10]. Aluminum accumulates in the kidneys, brain, lungs, liver and thyroid where it competes with calcium for absorption and can affect skeletal mineralization [7]. Since aluminium has such a long persistence in human body it is supposed to induce toxicity. Most metals generate their toxic effects by generation of ROS which act against the antioxidant defence system. Damage due to free

radicals caused by ROS leads to several damaging effects as they can attack lipids, protein/ enzymes, carbohydrates, and DNA in cells and tissues. They induce undesirable oxidation, causing membrane damage, protein modification, DNA damage, and cell death induced by DNA fragmentation and lipid peroxidation [11]. The oxidative-stress state has an important role in the development of many degenerative diseases, such as autoimmune disease, cancer, cardiac disease, and diabetes, but it also has a crucial role in the neurodegenerative diseases, such as Alzheimer's [12] and Parkinson's [13]. Researchers have reported that aluminium also follow the oxidative stress pathway to induce its toxicity in brain.

Entry of aluminium in brain

The barrier properties of Blood Brain Barrier (BBB) are due to the presence of tight junctions between opposing cell membranes of endothelial cells that surround microvessels that perfuse brain. These endothelial cells have total absence of fenestrations, fluid phase endocytosis (pinocytosis) and receptor mediated endocytosis. Inspite of having so many barrier properties, brain has been exposed to different metals whose toxic effects have been reported. Most of the metals are absorbed from G I tract , across lungs and through skin which then enter the systemic circulation and reach the central nervous system from blood crossing the blood brain barrier or from blood after crossing choroid plexus into cerebrospinal fluid from where it can diffuse into central nervous system [14].

Most metals enter brain after crossing cell membranes through diffusion or carrier mediated transport. Most of the studies suggest that aluminium enters brain through blood brain barrier rather than choroid plexus-cerebrospinal fluid system (CP-CSF)[15,16,17,18].

Two mechanism have been reported by [19] by which aluminium is transported across BBB:

1)Transferrin(TfR-ME) mediated : Transferrins are iron-binding blood plasma glycoproteins that control the level of free iron in biological fluids [20] . Transferrin has been postulated to play a significant role in transporting Ti(4+), VO(2+) (V(4+)), Cr(3+), Ru(3+), and Bi(3+), all metal ions of potential therapeutic significance. Transferrin may possess a physiological role in the transport of manganese, as the trivalent ion. However, the protein may also play a role in carrying potentially toxic Al(3+) and actinide ions, including Pu(4+), to the tissues. [21] and

2) By a Metal Transporter that transfer aluminium citrate. [22,23,24]. Aluminium is transported across cell membranes or cell epi-/endothelia through five major routes: (1) paracellular; (2) transcellular; (3) active transport; (4) channels; (5) adsorptive or receptor-mediated endocytosis [25].

Brain and oxidative stress:

Oxygen is necessary for life but its metabolism produces ROS which induce oxidative stress in cells. Oxidative stress is a state where balance between antioxidants and ROS is lost generating free radicals. Free radicals are highly reactive molecules capable of independent existence and accepting electrons from reduced substrates. Out of the major organs of the human body, brain has been reported to be more prone to oxidative stress due to presence of high levels of polyunsaturated fatty acids, relatively low antioxidant capacity, presence of redox metal ions like iron and copper and high oxygen [26]. Neurons and astrocytes are the two major cells of brain are responsible for most of the consumptions of oxygen and glucose resulting in brain consuming more than 20% of total oxygen of body [27]. Brain cells are more prone to oxidative stress due to the following reasons: i) They consume more oxygen ii) Have non dividing cells like neurons and iii) Have nitric oxide which may result in production of reactive nitrogen species like peroxynitrite [28]. ROS producers in brain as reported by [28] include:

1) NADPH Oxidase : it forms a complex with cytochrome-b 558. This complex transfer proton across membrane and forms superoxide as a end product [29].

2) Xanthine Oxidase: hypoxia induces rise in levels of intracellular calcium which activates a protease that converts Xanthine dihydrogenase into Xanthine Oxidase.

3) Mitochondria: it has oxidative pathways that are packed with redox carriers and centres that can leak electrons to oxygen and convert into superoxide anion, a progenitor to ROS.

4) Monoamine Oxidase: it breaks monoamines using FAD and produce aldehydes. The FAD-$FADH_2$ cycle generates hydrogen peroxide.

Toxicity induced by aluminium on various Oxidative stress parameters:

Author	Animal model and dose	Area	Observation	Inference
[30]	Rat (injected 5 mg aluminium / kg bw/day, five times per week for 3 weeks.)	Brain	MDA and SOD increased non significantly and GSH decreased non significantly.	aluminium actsas an antioxidant at low concentration and pro-oxidant at high concentration suggesting that aluminium might facilitate membrane peroxidation by increasing their susceptibility to free radical induced damage.
[31]	Rabbits(20 mg/l via drinking water for 3 months)	Brain	Increase in MDA and 4-HAD and decrease in SOD .	Aluminium induces oxidative stress in brain.
[32]	Mice(0.1mMol/kg/day 5 days per week for 12 weeks)	Hypothalamus	decrease in AChE activity	Toxic effect of aluminium on AChE activity may be due to a direct neurotoxic effect of the metal or perhaps a disarrangement of the plasmatic membrane caused by increased lipid peroxidation.
		Striatum	Increase in AChE activity	
		Hippocampus	LPO levels were elevated	
		Cerebral cortex	LPO levels were elevated	
[33]	Female rats (40mg/kg b.w./day for 8 weeks)	Hypothalamus	decrease in the activities of SOD and catalase and an increase in LPO in all 4 regions	Aluminium induces oxidative stress in different regions of brain.
		Cerebrum		
		Cerebellum		
		Medulla oblongata		
[34,35]	female rats to aluminium chloride at a dose of 345 mg/(kg day) oral from days 0 to 16 of gestation and 0 to 16 of post-partum (P.P.)	brain of pregnant mothers, fetuses and sucklings	decrease was recorded in reduced glutathione, glutathione reductase (GR), glutathione peroxidase (GPx), catalase (CAT), superoxide dismutase (SOD), acetyl cholinesterase (AChE) and increase was observed in TBARS and glutathione-S-transferase (GST) .	Aluminium induces maternal toxicity leading to oxidative stress in brain.
[36]	Female rats(100 mg/kg b.w. for 8 weeks)	Neuronal and glial cell-enriched fractions obtained from rat cerebral cortex	Significant Increase in TBARS levels in neurons as compared to glial cells which showed a significant decrease in SOD and catalase activity. Increase in Glutathione reducatase and glutathione-s-transferase in glia cells.	glial and neurons show a varied pattern of important antioxidant enzymes and glial cells are more capable of handling the oxidative stress conditions.
[37]	Male wister rats(10 mg/kg/b.wt, intragastrically for 12 weeks)	Brain	Decrease in MnSOD and aconitase	decrease in MnSOD activity in turn might be responsible for the increased protein oxidation which may cause increased oxidative damage to mitochondrial proteins
[38]	Male albino mice (Aluminium acetate at a dose of 3.5 mg/kg bw for 6 weeks, 5 times a week)	Brain	decrease in SOD,catalase,glutathione reductase , GSH, GPx and GST and increase in MDA formation .	Aluminium induces oxidative stress in brain through generating free radicals.
[39]	Mice(aluminium lactate ata dose of 1 mg Al/g diet).	Hippocampus	Increase in the mRNA levels of the antioxidant enzymes SOD, CAT, and Glutathione reductase.	Al acts as a pro-oxidant agent.
[40]	ICR mice(10, 50 or 300 mg/kg b.wt/day through diet for 100 days)	Hippocampus and cerebral cortex	increased MDA levels accompanied by decreased activities of SOD	Aluminium induces oxidative stressmediated neurodegeneration in brain cells.
[41]	Postnatal day 3 ratpups received intraperitoneal injection of aluminium chloride ($AlCl_3$),at dosages of 0, 7, and 35 mg/kg body wt	hippocampus, diencephalon, cerebellum, and brain stem	increase in LPO (TBARs), catalase activity and glutathione peroxidase activity and decrease in SOD	Aluminium overload increases oxidative stress (H_2O_2) in the hippocampus, diencephalon, cerebellum, and brain stem in neonatal rats.

[42]	Male rat ($AlCl_3$ at a dose of 4.2mg/kg/day for 4 weeks)	cerebral cortex, cerebellum and hippocampus	Significant decrease the level of GSH and the activities of SOD, CAT, GPx, Na+/K+ ATPase, Ca2+ ATPase and Mg2+ ATPase and increased the level of LPO and the activities of ALP, ACP, ALT and AST and increase in DNA fragmentation in all the brain regions.	Aluminium induces oxidative stress in brain regions . decrease in the activity of some antioxidant enzymes involved in the detoxification of ROS confirms the prooxidant effect of Al.
[43]	Rat($AlCl_3$ at a dose of 7mg/kg body weight)		Increases in LPO and acetylcholinesterase activity as well as decrease in GSH and SOD.	Decreased activity antioxidant enzymes might have resulted from the oxidative modification of genes that control these enzymes.
[44]	Male Rats[100 mg $AlCl_3$ (by gavage) for 90 days]	Medulla oblongata, pons and brainstem	Increased rate of LPO in hindbrain. maximum LPO was found in medulla oblongata and least in pons. Reduced activity of SOD ,Catalase and GSH in brainstem	Lipid profiles may be the markers of Al neurotoxicity and mid brain and medulla is more affected area of the brainstem.
[45]	Mice (single oral dose of 500 mg/kg of Al_2O_3 for 21 days)	Cerebral cortex	Enhanced levels of Reactive Oxygen Species (ROS) and altered antioxidant enzymes activities. A significant increase in dopamineand norepinephrine levels	Exposure to these nano metallic particles produced a significant oxidative stress in brain
[46]	Mice (100 mg/kg bw 6 weeks daily)	Cerebral tissue	Rise in LPO and decrease in SOD and GPx.	Al induced toxicity by reducing MDA production in cerebral tissue
[47]	Male wistar rats ($Alcl_3$ at a dose of 84 mg/ kg bw for four consecutive weeks)	Cerebrum	Reduced brain total antioxidant status (TAS) with significant enhancement of lipid peroxidation (MDA). Enhanced tumour necrosis factor alpha (TNF-α) and caspase 3) levels, and significantly suppressed brain-derived neurotrophic factor (BDNF) (and serotonin (5-HT)	Al significantly reduces brain total antioxidant status

Behavioural Modifications:

Most metals are reported to be toxic only at certain threshold doses beyond which body is not able to eliminate them leading to their accumulation in body. Similarly Aluminium is reported to be toxic only at higher doses as reported by [48] who treated 40-day old Sprague-Dawley (SD) rats with aluminium chloride by intraperitoneal injection at increasing doses of Aluminium i.e. 0 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg and observed that short time and low dose of Al might not change the ability of learning and memory in juvenile rats, however the permeability and ultrastructures of the Blood Brain Barrier might be significantly changed at higher doses and long duration of treatment. Continous exposure to aluminium at higher doses induces neurobehavioural problems leading to loss of memory. The potential toxicity of aluminium oxide (alumina) nanoparticles in ICR strained mice and found that nano-alumina impaired neurobehavioral functions, including lengthened escape latency, shorter time spent in the target quadrant and reductions in the number of platform crossing [49]. When rats were exposed to aluminium chloride (100 mg/kg/day i.p.) for 60 days caused significant reductions in spontaneous locomotor and exploratory activities in open field test and significant impairments in learning and memory in Morris water maze, radial arm maze and passive avoidance tests [50]. Similar results were also reported by [51, 52]. In addition to this [53] found that when rats were administered oral $AlCl_3$ (100mg/kg) daily for 15days showed degenerative changes characterised by significant weight loss, reduced exploratory/working memory, frontal-dependent motor deficits, cognitive decline, memory dysfunction and anxiety . The reasons behind aluminium causing memory loss were explained by many findings such as that intragastric treatment of mice with aluminium cause a decrease in brain acetylcholine (ACh) level and in activities of choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) which are important neurotransmitters and play important roles in signal transmission between neurons [54]. The role of oxidative stress is highlighted by [53, 55] in inducing memory impairment. Their findings suggested that oxidative impairment-indicated by depleted superoxide dismutase and lipid peroxidation (related to

glutathione-S-transferase activity) along with cholinergic deficits seen by increased neural acetylcholinesterase (AChE) expression and elevated lactate dehydrogenase was the reason behind behavioural alterations.

Chronic aluminium exposure (12.0 and 120.0 mg/kg) decreases expression of brain-derived nerve growth factor (BDNF) which may be one of the mechanisms of learning and memory deficits induced by aluminium [56]. Neurodegenration was also regarded a major reason of memory impairments by [49] who reported that cell necrosis and apoptosis, which were mediated by the reduction of matrix metalloproteins(MMP) and ROS, and the induction of the caspase-3 gene leads to neuronal degeneration . Aluminium chloride when administrated by water at the doses of 0.2%, 0.4% (m/v) for 12 weeks decreases the expression of Bcl-2 protein and increases expression of Fas protein in hippocampus which causes a decline in learning abilities of rats [57]. Aluminium causes neuroinflammation, alter density of dendritic spine, which, in turn, influence cognition function in Rats. Oral administration of rats with $Alcl_3$ at 50, 150 and 450 mg/kg for 90days resulted in increased mRNA levels of IL-1β, IL-6, TNF-α and MCH II, decreased mRNA levels of CX3CL1 and BDNF, decreased density of dendritic spine causing impaired learning and memory in developing rat [58].

Apoptosis:

Apoptosis has been reported to be the final step in the pathway of toxicity induced by aluminium leading to neurodegenration. Various apoptotic markers have been reported to be expressed after aluminium exposure indicating programmed cell death. Intracisternal administration of aluminium into rabbit brain induces cytochrome c release, decreases levels of the anti-apoptotic proteins Bcl-2 and Bcl-X(L), increases levels of the pro-apoptotic Bax, activates caspase-3, and causes DNA fragmentation [59]. Similar findings were also reported by [60] in hippocampus cells. In animals treated intra cisternally with the neurotoxin aluminium-maltolate, that pro-caspase-3 was distributed mainly in the cytoplasm but active caspase 3 i.e. p17 levels were higher in the endoplasmic reticulum suggesting that this organelle is an important site in the caspase-3 mediated apoptosis cascade [61]. Adding to these findings [62] also confirmed that aluminium has the ability to enter into the brain and induce apoptosis in human neuroblastoma SH-SY5Y cells, along with down regulation of miR-19a/miR-19b, upregulation of miR-19-targeted PTEN, and alterations of its downstream apoptosis related proteins including AKT, p53, Bax, and Bcl-2. Increased caspase activation confirmed that Aluminium dose-dependently induces apoptosis in rat brain. Accumulation of active caspase3 due to aluminium toxicity in brain cell extracts [63]. Similarly [64] reported that chronic aluminium exposure (10 mg/kg/b.wt, intragastrically for 12 weeks) resulted in increased formation of 8-hydoxydeoxyguanosine in the mitochondrial DNA isolated from different regions of rat brain. Aluminium induces DNA fragmentation and increased expression of p53 and cyclin D1 indicating that aluminium induced oxidative damage to DNA may be involved in the neurodegeneration via increase in p53 expression and activation of cell cycle.

Like most other metals aluminium also follow oxidative stress mediated pathway of DNA damage and apoptosis. When AlCl(3) was administered through diet for 100 days result in increased MDA levels accompanied by decreased activities of SOD in the the cells from hippocampus or cortex .This oxidative stress induces DNA damage in a dose-dependent manner depicted by highly increased formation of 8-hydroxy 2-deoxyguanosine (8-OHdG) in the mtDNA [65].Similar findings that aluminium dose dependently induces apoptosis and increased malondialdehyde (MDA) and catalase activity in PC12 cells [66]. Intraperitoneal injections of $AlCl_3$ (100mg/kg., b.w.) for 60 days enhanced the learning and memory deficits, levels of TBARS and diminished the levels of reduced glutathione and activities of enzymatic antioxidants .Toxicity of $AlCl_3$ is also accompanied by the enhanced expressions of Bax, caspases-3,-9, cytosolic cytochrome c (cyto c), and pTau along with diminished expressions of Bcl-2, mitochondrial cyto c, pGSK-3β and pAkt [67].

Histological Changes

Some authors regard Al as the root cause of Alzheimer's disease, while others believe that the cause lies elsewhere, and that Al is an opportunistic bystander .Histopathological lesions observed due to aluminium toxicity are similar to those observed during neurodegenerative disorders especially Alzheimer's disease. Aluminium in drinking water has been reported to cause amyloid plaque formation as observed in Alzheimer's disease [68, 69,70].

Intraperitoneally injected adult rats three times a week for 6 months with ecological doses of Al gluconate (0.85 mg/kg) and observed numerous ghost-like neurons with cytoplasmic and nuclear vacuolations in rat brain .The hippocampus contained extracellular accumulations of Al and amyloid surrounded by nuclei of degenerating cells, which were interpreted as neuritic plaques similar to as observed in AD [52]. A dose dependent increase in degeneration and cell distortion in cerebrum and hippocampus similar to AD. Acute aluminium exposure results in appearance of few neurofibrillary tangles in cerebrum and hippocampus, extensive neuronal vacuolation and necrosis of cerebral cortex indicating loss of nissl

substances [71]. In addition to this $AlCl_3$ histopathology also includes appearance of vacuolar spaces around cells as well as cellular degeneration ,appearance of cytoplasmic fragmentation, ghostly appearance of cells as well as absence of basement membrane was also reported by [72, 73]. Exposure to aluminium may cause marked histophathological alterations in the brain tissue which were represented by focal as well as diffuse gliosis on in cerebral cortex, odema and inflammatory cell infiltration and pericellular odema in cerebral cortex with neuronal degeneration. Aluminium induction caused an increased DNA damage and fragmentation. These histopathological observations indicate cellular apoptosis [42]. Aluminium induces atrophy and apoptosis of the neurons in cerebral cortex and hippocampus which was associated with neurofibrillary degeneration, argyrophilic inclusion, Schwan cell degeneration and nerve fiber demylination [31]. Al also causes the accumulation of tau protein and amyloid-beta protein and induces neuronal apoptosis *invivo* as well as in vitro [74]. Accumulation of ß-amyloid was time-dependent as Aß deposition were present even after 2 months of treatment, but that the highest level of accumulation was detected after exposure over 12 months [42]. The formation of senile plaque (SP)-like and neurofibrillary tangle (NFT)-like structures was also observed in brain after aluminium exposure [75].

ALUMINIUM TOXICITY ON DIFFERENT CELL LINES

Aluminium toxicity has also been evaluated on different neural cell lines. Exposure to aluminium (1 mM) for longer period of time leads to its accumulation and finally apoptosis in cultured astrocytes and neurons. After 8-12 days exposure, aluminium caused strong changes in the morphology of astrocytes including shrinkage of cell bodies and retraction of processes. Exposures over 15-18 days reduced astrocytes viability by 50%. Aluminium-induced degeneration of astrocytes involved the DNA fragmentation characteristic of apoptosis. Aluminium was also found to be neurotoxic, causing first (4-6 days) abnormal clustering and aggregation, and later (8-12 days) neuronal death [76]. Similar results were also reported by [77] who found that aluminium induce and block selectively the apoptosis of astrocytes, which depend upon the concentrations of aluminium .Exposure to aluminium at low levels (100 and 200 microM) for up to 6 days did not result in the apoptosis of astrocytes but blockage of apoptotic cells was found at 200 mM aluminium. However, at 400 microM, aluminium induced apoptosis of astrocytes, which was associated with a significant change in cell cycle distribution characterized by increase of G2/M phase cells (128%). In primary cultured rat hippocampal neurons [78] and in 0-3 day rats neurons, neuroglia cells and co-cultured neurocytes [79] reported similar results that aluminium induces apoptosis of different brain cells in a time- and dose-dependent manner. In addition to this [80] also concluded that both apoptosis and necrosis are the prominent cause of cell death in primary cultured neurons, even at a concentration lower than 2 mM. While working on human embryonic cerebral neurocytes explained the reason behind neurotoxicity of Al and concluded that it may be caused by lipid peroxidation and the damage of cell membrane [81]. Primary cultured neurons obtained from newborn SD rats that were exposed to various concentrations of $AlCl_3$ and found that when the concentration of AlCl3 increased, the death rate increased, mitochondria enzyme activity decreased, ROS increased indicating that Al exposure could cause mitochondria oxidative function injury in the primarily cultured rats, which may be the one of the possible mechanism of Al toxicity [82].

CONCLUSION

The present review analysis provides evidence for the neurotoxic action of Al in different experimental animal models brain. Various chemical forms of aluminium at different doses induce oxidative stress and histological changes in different regions of brain. Aluminium toxicity also leads to neurobehavioural impairments and memory dysfunction thus indicating the role of aluminium in causing neurodegenration. This review also provides a insight into the pathway of neurodegenration followed by aluminium which finally leads to apoptosis. Both *in vitro* and *in vivo* studies confirm the ability of aluminium to cause apoptosis.

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CITATION OF THIS ARTICLE

Lata Shahani, Nisha Rathore , Trishna Patel. Aluminium induced Neurotoxicity: A Review. Bull. Env. Pharmacol. Life Sci., Vol 9[3] February 2020 :63-71