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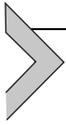
1. Introduction

Aluminum (Al) is considered as the most abundant metal in the Earth's crust, being the third most abundant chemical element after oxygen and silicon. Intensive development of the Al industry (Brough and Jouhara, 2020) due to a wide use of the metal has resulted in a significant increase in environmental Al levels (Crisponi et al., 2012).

The sources of human Al exposure may include diet (Tietz et al., 2019), being responsible for 95% of total body Al (Goullé and Grangeot-Keros, 2020), drinking water (Krupińska, 2020), air (Exley, 2013), as well as cosmetics (Crisponi et al., 2012) and medicinal drugs, namely antacids (Klotz et al., 2017). Involvement in Al processing industry may also result in occupational Al exposure (Skalny et al., 2018). Earlier studies demonstrated that vaccination could be considered as a source of Al exposure due to the presence of aluminium adjuvants

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1

that are currently not widely used thus reducing the risk of vaccine-associated Al exposure (Goullé and Grangeot-Keros, 2020).

Being a non-essential element, Al was shown to be toxic for humans (Exley, 2013), resulting in adverse health effects (Crisponi et al., 2011) including bone pathology (Klein, 2019) and breast cancer (Darbre et al., 2013). Our data also demonstrated the association between obesity (Tinkov et al., 2019), laboratory markers of metabolic syndrome and Al exposure markers (Skalnaya et al., 2018). However, the existing data on adverse effects of Al exposure are limited (Krewski et al., 2007).

Recent studies have demonstrated that the brain may be considered as the target for Al toxicity, resulting in neurodegenerative (Exley, 2013; Shaw et al., 2014) and neurodevelopmental disorders (Blaylock, 2012). Recent detailed studies by Exley and the coauthors have highlighted the association between brain Al accumulation and neurological disorders including Alzheimer's disease, multiple sclerosis and autism spectrum disorder (Exley and Clarkson, 2020; Mirza et al., 2017; Mold et al., 2018). Speciation analysis using hyphenated techniques demonstrated that Al exposure induces a specific bioligand response in Al-exposed neuronal cells (Połeć-Pawlak et al., 2004). However, the particular mechanisms of Al neurotoxicity and their role in Al-associated neurological disorders are still debatable (Morris et al., 2017). This chapter will provide an update on the particular mechanisms of Al neurotoxicity that may be used as targets for development of therapeutic strategies.

Generally, the neurotoxic effect of Al exposure is mediated by its common toxic properties including prooxidant, proinflammatory, proapoptotic activity that are reported for a variety of cell lines and tissues, as well as more specific "neurotropic" effects namely interference with neurotransmitter metabolism and neuronal cytoskeleton.
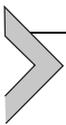
2. Oxidative stress

Oxidative stress along with mitochondrial dysfunction (see next section) are involved in development of a variety of adverse effects of Al including neurotoxicity (Kumar and Gill, 2014). The observed increase in brain lipid peroxidation under Al exposure (Ghorbel et al., 2016; Nehru and Anand, 2005; Yuan et al., 2012) was shown to be associ-

ated with a significant reduction in antioxidant enzyme activity, namely superoxide dismutase (Nehru and Anand, 2005), catalase (Nehru and Anand, 2005), glutathione peroxidase (Sánchez-Iglesias et al., 2009), glutathione reductase (Nehru and Bhalla, 2006), as well as glutathione-S-transferase (Bhalla and Dhawan, 2009). Alteration of glutathione system is also characterized by Al-induced decline in cerebral and cerebellar total, reduced, and oxidized glutathione levels (Anand and Nehru, 2006). In contrast to glutathione, data on involvement of thioredoxin system to Al-induced redox perturbations are insufficient, although recent study revealed a significant decrease in mitochondrial thioredoxin in aluminum chlorohydrate treated SH-SY5Y neuroblastoma cells (Tsialtas et al., 2020).

Al exposure was also shown to reduce mitochondrial Mn-SOD activity thus contributing to mitochondrial dysfunction (Kumar et al., 2009a,b). At the same time, certain studies demonstrated Al-induced increase in SOD activity and gene expression (Ali et al., 2014) that may also contribute to oxidative stress through overproduction of hydrogen peroxide, especially at low catalase and GPx activity. Inhibitory effect of Al on antioxidant system are likely mediated by Al-induced down-regulation of Nrf2/Keap1 signaling pathway (Yu et al., 2019a,b), whereas prevention of this inhibitory effect ameliorated prooxidant activity of the metal (Wang et al., 2017).

In parallel with inhibition of antioxidant system, the role of Al in development of cerebral oxidative stress may be mediated by its impact on prooxidant systems. Particularly, exposure to Al was shown to increase cerebral level of inducible (Bondy et al., 1998) and endothelial NOS (Mokhemer et al., 2020) with a concomitant elevation of brain NO levels (Al-Olayan et al., 2015). The use of the NOS inhibitor *N*-nitro-L-arginine methyl ester (L-NAME) significantly reduced Al-induced oxidative damage in brain, indicating a critical role of NOS induction in the prooxidant activity of Al (Stevanović et al., 2009). Al-induced alteration of vascular reactivity was shown to be associated with increased superoxide production from activated NADPH-oxidase (Schmidt et al., 2016) due to up-regulation of NAD(P)H oxidase 1 and 2 mRNA expression (Martinez et al., 2017). Stimulatory effect of Al was observed in another enzymatic source of superoxide anion, xanthine oxidase, in liver (Moumen et al., 2001) as well as various brain regions (Sushma et al., 2006).

In addition to enzymatic prooxidants, Al was capable of potentiating prooxidant effect of iron in neuronal cultures (Xie et al., 1996). This effect may also underlie a shift to ferroptosis in PC12 cells exposed to aluminium (Cheng et al., 2020). It is also notable that co-exposure to Al and 6-hydroxydopamine enhanced 6-hydroxydopamine autooxidation-induced oxidative stress in brain mitochondrial preparations (Sánchez-Iglesias et al., 2009). Moreover, Al is directly involved in the formation of highly reactive Al superoxide semi-reduced radical ion ($AlO_2^{2+\cdot}$) (Exley, 2012).

Taken together, increased production of reactive oxygen species due to activation of enzymatic and non-enzymatic prooxidant systems and reduced antioxidant capacity of the cells (Fig. 1) result in Al-induced oxidative stress affecting neuronal protein structure and inducing redox-sensitive pathways.
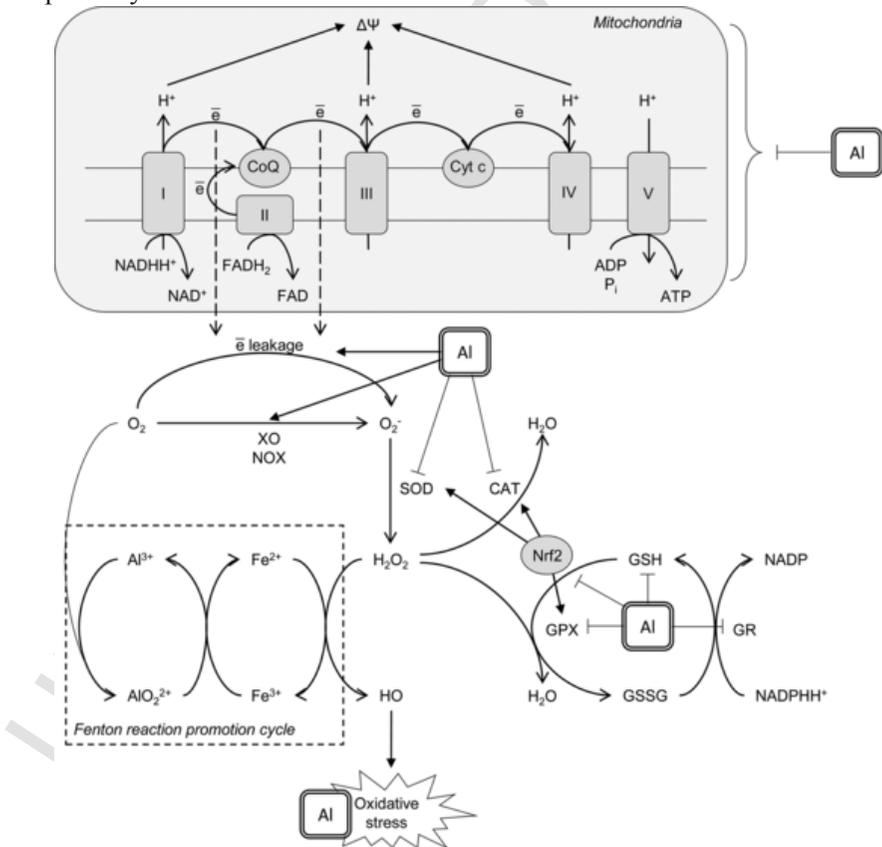
Fig. 1 Mechanisms underlying prooxidant effect of aluminium (Al^{3+}). Al^{3+} was shown to affect mitochondrial electron transport chain thus increasing electron leakage from Complex I and III with subsequent formation of superoxide anion radical (O_2^-). Another mechanism contributing to superoxide production involves Al-dependent increase in xanthine oxidase (XO) and NADPH-oxidase (NOX) activity. Al^{3+} cation is directly involved in the formation of highly reactive Al superoxide semi-reduced radical ion (AlO_2^{2+}) that was shown to promote prooxidant activity of Fe^{2+} in Fenton reaction with generation of hydroxyl radical (HO·). Prooxidant activity of Al is also aggravated by its inhibitory effect on enzymatic antioxidants including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), and glutathione reductase (GR). The latter results in reduced glutathione (GSH) depletion. Moreover, Al was shown to down-regulate nuclear factor erythroid 2–related factor 2 (Nrf2), being the key regulator of the antioxidant system. Taken together, these mechanisms result in development of oxidative stress with increased oxidative modification of lipids, proteins and nucleic acids observed in brain/neuronal cell lines under Al exposure.

3. Mitochondrial dysfunction

Mitochondrial dysfunction is considered as one of the first pathological responses to Al exposure in the cell, resulting in altered energy metabolism, oxidative stress, and apoptosis. Particularly, Al was shown to decrease mitochondrial electron transport chain through inhibition of complex I (NADH dehydrogenase), complex II (succinate dehydrogenase), and complex IV (cytochrome oxidase) in rat cortex and midbrain, as well as cerebellum (Sood et al., 2011). A reduction in cytochrome oxidase activity was also accompanied by significant Al-induced changes in enzyme Arrhenius plot (Dua and Gill, 2004). Complex III activity was found to be significantly inhibited by Al nanoparticles that also induced a sharp decrease in mitochondrial membrane potential and cytochrome c leakage in isolated brain mitochondria (Arab-Nozari et al., 2019). Reduced activity of electron transport chain complexes from Al-treated rats was accompanied by reduction in particular cytochromes cyt a, cyt b, and cyt c, as well as altered mitochondrial ultrastructure in hippocampus and striatum (Kumar et al., 2008). Complex V (ATP-synthase) was also down-regulated along with other fragments of electron

transport chain upon Al exposure (Sharma et al., 2013a,b). Correspondingly, analysis of mitochondrial ultrastructure in Al-exposed neurons revealed mitochondrial swelling, cavitation, altered inner mitochondrial membrane and cristae structure (Niu et al., 2005), as well as loss of cristae, chromatin condensation and decreased number of mitochondria (Sharma et al., 2013a,b). The latter is indicative of Al-induced decrease in mitochondrial biogenesis through down-regulation of peroxisome proliferator activated receptor gamma co-activator 1α (PGC-1α) and the downstream genes including Nrf1, Nrf2, and mitochondrial transcription factor A (Tfam) (Sharma et al., 2013a,b). Taken together, these Al-induced changes result in alteration of mitochondrial transmembrane potential and impaired oxidative phosphorylation that may contribute to increased generation of reactive oxygen species (Iglesias-González et al., 2017). However, results from another study indicate that oxidative stress precedes mitochondrial dysfunction in brain of Al-exposed gerbils (Vučetić-Arsić et al., 2013).

4. Apoptosis

Induction of apoptosis in Al-exposed cells represents one of the mechanisms of direct Al-induced cell damage. Specifically, Al was capable of inducing apoptosis in neuronal (SH-SY5Y), glial (U373MG), and retinal epithelial cells (RPE D407) (Toimela and Tähti, 2004). Exposure of co-cultured neurons and astrocytes to Al resulted in significant metal accumulation on both cell lines, whereas Al-induced apoptosis was revealed only in astrocytes (Suárez-Fernández et al., 1999). In agreement, intensified neuronal apoptosis was observed in a number of *in vivo* studies (Çabuş et al., 2015; Keshava et al., 2019).

As stated earlier, mitochondrial dysfunction causes cytochrome c leakage that binds Apaf-1 with subsequent formation of apoptosome and procaspase 9 activation underlying Al-induced apoptotic neuronal death (Savory et al., 2003), thus indicative of mitochondrial pathway of apoptosis (Fig. 2). Another study demonstrated that prooxidant effect of AlCl$_3$ was associated with a significant increase in cerebral levels of caspase-3 and Bax, whereas antiapoptotic Bcl2 was found to be down-regulated by Al treatment (Mesole et al., 2020). Cortical and hippocampal proapoptotic p53, p21, Bax, caspase 3, and pJNK levels were increased in response to oral Al treatment along with a two- to threefold increase in

Fas levels, being indicative of involvement of Fas/FasL-mediated apoptosis (Keshava et al., 2019). The role of Fas/FasL apoptotic pathway has also been confirmed by the observation of Al-induced caspase-8 (Qin et al., 2020) and DAXX up-regulation (Kumar et al., 2009a,b; Lukiw et al., 2005), which is known to be p53-independent (Wasylishen et al., 2018). Taken together with the earlier demonstrated increase in p53-associated proapoptotic signaling under Al exposure (Johnson et al., 2005), these findings indicate that Al-induced apoptosis may involve both p53-dependent and -independent pathways.
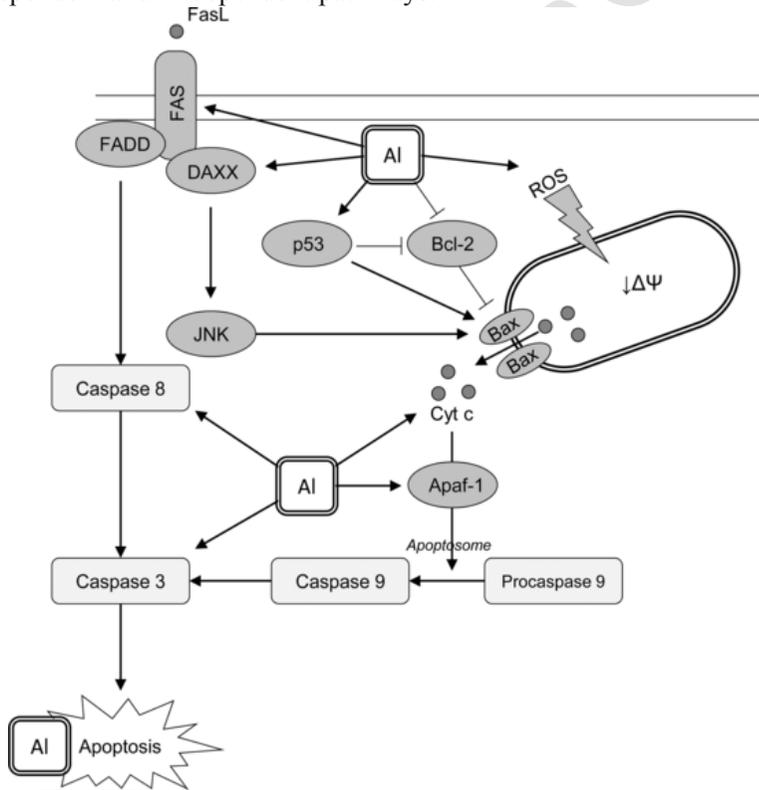
Fig. 2 The proposed model of aluminium-induced neuronal apoptosis. Al was shown to induce apoptosis in neuronal cells through distinct pathways. Mitochondrial pathway is directly related to Al-induced mitochondrial dysfunction and subsequent Bax-mediated cytochrome c release. The latter is also stimulated due to positive and negative regulation of p53 and Bcl-2 expression, respectively. Al was shown to increase the rate of cytochrome c binding to Apaf-1 with subsequent formation of apoptosome and caspase 9 activation with subsequent caspase 3 cleavage

and activation promoting apoptosis. Another pathway of Al proapoptotic effect involves Fas/FasL signaling with activation of caspase 3 following caspase 8 stimulation. In addition, Al^{3+}-induced up-regulation of DAXX results in JNK signaling that also possesses a stimulatory effect on Bax. Prooxidant activity of Al^{3+} is also expected to underlie proapoptotic effect of the metal through increased oxidative modification of biomolecules and particularly nucleic acids.

The use of necrostatin 1 and Z-VAD-FMK, a pan-caspase inhibitor, demonstrated that Al-induced neuronal cell death may involve activation of both necrosis and apoptosis (Hao et al., 2019). This observation corresponds to the proposed role of necroptosis in Al neurotoxicity (Zhang, 2018a,b). The latter was observed at high doses (450 mg/kg AlCl$_3$), whereas lower doses more likely induced apoptosis through IL-1β/JNK signaling pathway (Zhang et al., 2020). Another study also demonstrated that Al-induced apoptosis and necrosis differentially involved ERK and p38 MAPK/ERK signaling pathways in SH-SY5Y cells, respectively (Jia et al., 2014).

As Al is capable of inducing apoptosis in brain cells, it clearly modulates cell cycle in brain cells. A recent study by Reichert et al. (2019) demonstrated that Al^{3+} inhibited proliferation of neural progenitor cells during neural differentiation and induced apoptosis along with modulation of cell cycle by increasing sub-G1 phase and reducing G2/M phase (Reichert et al., 2019). At the same time, in cultured astrocytes Al-induced apoptosis was associated with a shift from S phase to G2/M phase (Guo and Liang, 2001). Al exposure also increases neuronal expression of cyclin-dependent kinase 5 (Cdk5) (Bihaqi et al., 2009), playing an essential role in regulation of neuronal differentiation (Cicero and Herrup, 2005). Several studies demonstrated that a significant increase in cyclin D1 expression in Al-exposed rat brains (Kumar et al., 2009a,b). In contrast, exposure of PC12 cells to Al nanoparticle significantly increased p21 and decreased cyclin D1 expression ultimately resulting in G1 cell cycle arrest (Liu et al., 2020).

5. Neuroinflammation and microglial activation

Existing data demonstrate proinflammatory effects of Al (Lukiw et al., 2005). Specifically, Al exposure was shown to increase expression of proinflammatory cytokines IL-1b, IL-6, TNF-a, and MIP-1a whereas

expression of brain derived neurotrophic factor (BDNF) was significantly reduced (Cao et al., 2016; Kasbe et al., 2015; Prema et al., 2017). Increased expression of proinflammatory cytokines may be associated with up-regulation of nuclear factor-kappa beta (NF-κB) expression (Sood et al., 2012; Zhao et al., 2020), being the key regulator of inflammation (Shih et al., 2015). Particularly, a significant down-regulation of NF-κB inhibitor gene was observed in brains of mice subcutaneously exposed to Al (Li et al., 2017). It is also notable that co-exposure of Al and mercury (as sulfates) significantly potentiated neurotoxic effect of each of these metals alone via NF-κB induction and subsequent proinflammatory signaling, as noted in human neuronal and glial cells co-culture (Alexandrov et al., 2018). Therefore, NF-κB may be considered as a link between Al-induced neuroinflammation and amyloidogenesis (Alawdi et al., 2017). Together with 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP), a dopaminergic neurotoxicant, Al exposure is capable of inducing hippocampal expression of AP-1 (Li et al., 2007), another redox sensitive transcription factor involved in regulation of inflammatory response.

Proinflammatory effect of Al hydroxide was shown to be associated with inflammasome activation and subsequent IL-1β secretion by microglia (Gustin et al., 2015). The results obtained in another study demonstrated that apurinic/apyrimidinic endonuclease 1 may be also considered as negative regulator of Al neuroinflammation (Zaky et al., 2013). It is also notable that induction of systemic inflammation characterized by elevated proinflammatory cytokine (IL-6, TNF-a) and microRNA (miRNA-9, miRNA-125b and miRNA-146a) levels may also contribute to Al-induced inflammatory neurodegeneration (Pogue et al., 2017)
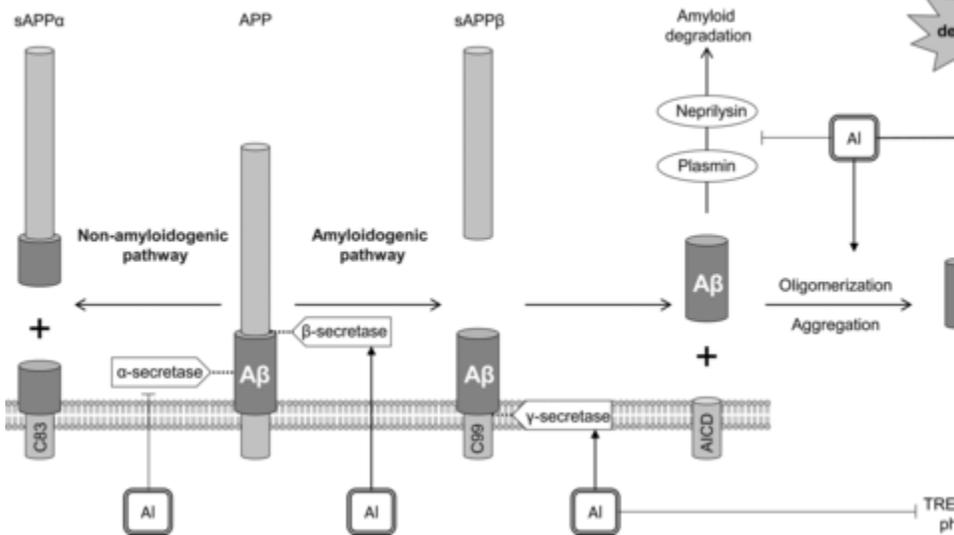
Fig. 3 The role of Al in amyloid β generation. Al exposure promotes amyloidogenic pathway through activation of β- (BACE1) and γ-secretase (presenilin-1), as well as down-regulating non-amyloidogenic pathway due to inhibition of α-secretase. Along with promotion of amyloid oligomerization and aggregation, Al^{3+} also inhibits neprilysin and plasmin that are known to be involved in amyloid degradation. In addition, Al exposure was shown to impair TREM2-mediated phagocytosis of amyloid proteins by microglia. Taken together, these effects of Al exposure result in accumulation of amyloid plaques and Alzheimer disease-like neurodegeneration.

In addition to overproduction of proinflammatory cytokines, Al exposure was also shown to increase both COX-1 and COX-2 activity in cortex and/or hippocampus (Syed et al., 2015). In agreement, Al-induced COX-downstream signaling involving increased prostaglandin synthase and receptor expression, as well as prostaglandin levels in hippocampus (Wang et al., 2015). It is also notable that the use of synthetic prostaglandin E1 (PGE1) analogue, misoprostol, ameliorated Al-induced memory and learning dysfunction through modulation of PGES-PGE2-EP signaling pathway and decreasing PGE2, mPGES-1, EP2, and EP4 expression (Guo et al., 2016). $AlCl_3$-exposed mice treated with COX inhibitor ibuprofen also demonstrated that Al toxicity is associated with hippocampal overexpression of neuronal pentraxin 1 (NP1) (Jamil et al.,

2016) that is considered one of the key factors of Aβ-induced neurite loss and synaptic dysfunction (Abad et al., 2006).

Al -induced (micro)gliosis is considered as the key component of neuroinflammation (Blaylock, 2012). Particularly, exposure to Al was shown to induce oxidative stress-dependent glial activation in rat brain (Akinrinade et al., 2015a,b), being especially observed in striatum and thalamus (Platt et al., 2001). Nanoscaled silica was also shown to induce glial activation in rat brain cortex and hippocampus as assessed by increased number of ED1, GFAP, and nestin-positive cells (Li et al., 2009). Moreover, Campbell et al. (2002) demonstrated that Al sulfate was shown to increase proliferation of glioblastoma cells with the effect comparable to that for LPS (Campbell et al., 2002). It was also demonstrated that glial cells accumulate significantly more Al and iron, although being less sensitive to metal-induced oxidative stress when compared to neurons (Oshiro et al., 2000). These findings also correspond to a recent observation of increased Al deposition in microglia, as well as other inflammatory cells in a patient with cerebral amyloid angiopathy (Mold et al., 2019).
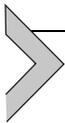
6. Endoplasmic reticulum stress (ERS) and altered Ca^{2+} homeostasis

It has been demonstrated that Al glycinate exposure down-regulates mRNA expression of molecular chaperone BiP/Grp78, as well as certain Ca-handling proteins (e.g., calnexin, calreticulin, stanniocalcin 2), thus inhibiting adaptive response and predisposing astrocytes to ERS (Aremu et al., 2011). Al-induced ERS characterized by an increase in CHOP and caspase 12 expression was shown to induce p53-independent cell death in SH-SY5Y neuroblastoma cells along with development of oxidative stress and Aβ1-40 accumulation (Rizvi et al., 2014). Similarly, development of ERS characterized by increased GADD153 translocation was accompanied by NF-κB induction and Bcl-2 down-regulation (Ghribi et al., 2001). A later study also demonstrated up-regulation of ERS pathway-associated proteins including PERK, EIF2α, and CHOP as a component of Al-induced neurotoxic effect (Bharathi et al., 2019). It is proposed that Al-dependent induction of PERK-EIF2α signaling with subsequent unfolded protein response may induce inflammation in human neuroblastoma SH-SY5Y cells (Rizvi et al., 2016).

Given the role of ER in Ca2 + handling, altered intracellular Ca levels may be also indicative of ER dysfunction (Rizvi et al., 2014). The role of altered Ca2 + homeostasis as the mechanism of Al neurotoxicity was proposed by Julka and Gill (1996). Chronic Al exposure was shown to increase synaptosomal Ca levels through reduction of Ca2 +-ATPase activity (Kaur and Gill, 2005). Taken together with increased Ca2 + release from mitochondria these changes result in increased intracellular Ca2 + levels (Gandolfi et al., 1998). In addition, Al-Aβ conjugate was shown to affect neuronal Ca2 + homeostasis (Drago et al., 2008). Microarray analysis of 35,129 genes in Al-exposed SH-SY5Y cells demonstrated that alteration of Ca2 + homeostasis is the key mechanism mediating neuronal and/or synaptic dysfunction (Gatta et al., 2011). Thus, due to its role in increasing intracellular Ca2 + concentrations, Al can be considered excitotoxic (Exley, 2013).
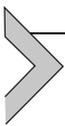
7. Reduced synaptic plasticity and neurotrophin production

Impairment of synaptic plasticity and transmission is known to underlie multiple adverse neurological effects of Al (Zhang, 2018a,b) affecting both presynaptic and postsynaptic mechanisms (Chen et al., 2002). Correspondingly, laboratory studies demonstrated a significant negative effect of Al on synaptic plasticity (Wang et al., 2002), being strongly dependent on the ontogenetic period with the most prominent effect observed in adulthood (Wang et al., 2002b). Al exposure resulted in a significant decrease of field excitatory postsynaptic potentials after high-frequency stimulation, being indicative of synaptic dysfunction (Qin et al., 2020). Al-induced alteration of synapse ultrastructure are characterized by decreased postsynaptic density thickness, increased synaptic cleft width, high frequency of flat synapses, and reduced number of perforated synapse (Jing et al., 2004). Increased rigidity of synaptosomes under Al exposure due to redox-dependent modulation of membrane fluidity and membrane lipid composition (Ahmed et al., 2020a) may reduce the release of synaptic vesicles into synaptic cleft (Ahmed et al., 2020b). Al was also shown to inhibit synaptic (Na +/K +)ATPase activity and contributing to synaptic dysfunction (Silva and Gonçalves, 2003). Al-maltol exposure resulted in a significant alteration of synaptic structure characterized by decreased number of axon

branches and dendritic spines along with neuronal atrophy, being associated with mGluR up-regulation and down-regulation of PKC and the NMDAR subunits (Pan et al., 2020a,b). Another study proposed Al-induced modulation of the PI3K-Akt-mTOR pathway, could result in alterations in synaptic plasticity (Li et al., 2020a,b).

Adverse effects of Al exposure on synaptic plasticity and neurite growth may be mediated by negative regulation of neurotrophic factor production. Al-maltol induced a significant decrease in nerve growth factor (NGF) and BDNF expression in brain cell cultures (Johnson and Sharma, 2003). The decrease in synaptic long-term potentiation in Al-exposed rats was associated with a significant reduction of BDNF expression through modulation of Histone H3K9 demethylation (H3K9me2) demethylase and plant homeodomain finger protein 8 (PHF8) (Li et al., 2020a,b). Other epigenetic mechanisms involving H3K4me3, H3K27me3 and H3K9me2 may also underlie altered BDNF and early growth response protein 1(EGR1) under occupational Al exposure (Pan et al., 2020a,b). Correspondingly, hippocampal expression of activity-regulated cytoskeleton-associated protein (ARC) gene, known to play a significant role in synaptic plasticity (Korb and Finkbeiner, 2011), was also found to be reduced following in utero Al exposure (Inohana et al., 2018). The underlying mechanism was shown to involve a decrease in BDNF-induced Arc expression through alteration of ERK signaling (Chen et al., 2011). Other mechanisms involved in altered synaptic plasticity upon Al exposure may include deregulation of SIRT1, TORC1 and pCREB levels (Yan et al., 2017) and cAMP-PKA-CREB pathway (Zhang et al., 2014).
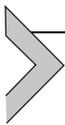
8. Cytoskeletal pathology

Cytoskeleton and microtubules in particular were considered as the potential targets for Al toxicity (Walton, 2014), resulting in altered axonal transport and perikaryal aggregation (Kushkuley et al., 2010). Particularly, Al exposure resulted in a significant aggregation and disruption of cytoskeletal proteins in cerebral cortex, corpus striatum and hippocampus (Kaur et al., 2006). After prolonged exposure Al -rich pyramidal cells are characterized by microtubule depletion with neurite damage and loss of synapse density (Walton, 2009). Particularly, Al is capable of inhibiting neurofilament assembly to axonal cytoskeleton, translo-

cation and degradation of neurofilaments in axonal neurites (Shea et al., 1997). Generally, these observations corroborate earlier data on sharp reduction in neurofilament and tubulin genes in spinal cord motor neurons (Muma et al., 1988) contributing to neuro-fibrillary degeneration (Katsetos et al., 1990). A recent study demonstrated that Al(III) affects microtubule assembly far more effectively than iron (Shevtsov et al., 2016). Al-induced alterations in cytoskeleton may also involve modulatory effects on amyloid β and α-synuclein accumulation.

8.1 Amyloid β

Modulation of amyloid generation and accumulation is considered as the potential pathway of Al-induced neurodegeneration in Alzheimer's disease (Exley, 2005)(Fig. 3). Generally, this suggestion is based on the observation of cooccurrence between Al and amyloid deposits in neurodegenerative diseases (Mirza et al., 2017; Mold et al., 2019).

Al-maltolate exposure was shown to increase Aβ1–42 expression in rat brain through up-regulation of APP, β- (BACE1), and γ-secretase (presenilin-1) mRNA transcription and protein expression in rat brain regions (Liang et al., 2013; Thenmozhi et al., 2015). These changes are also associated with a significant decrease of α-secretase proteins (ADAM9, ADAM10, ADAM17) (Wang et al., 2014). In vitro studies in cell lines also demonstrate a significant impact of Al on proteins of amyloidogenic pathway. Al exposure was shown to increase BACE1 (LI) and BACE2 levels (Castorina et al., 2010), although a significant decrease in both enzyme expression could be observed at long-term exposure (Castorina et al., 2010). Certain studies also demonstrate that along with increasing Aβ production, Al exposure may negatively affect its degradation by decreasing neprilysin expression (Luo et al., 2009). Inhibition of plasmin cascade by Al (Korchazhkina et al., 2002) may be also responsible for both APP α-cleavage and Aβ degradation (Zhao and Pei, 2008). Al is also capable of inhibiting microglial phagocytosis of Aβ42 peptides (Zhao et al., 2014) due to TREM2 down-regulation (Alexandrov et al., 2013).

Promotion of amyloid β oligomerization under Al exposure may also play a crucial role in Al-associated Alzheimer's disease. Pioneer studies by Exley et al. (1993) and Kawahara et al. (1994) demonstrated direct interaction between Al and amyloid β with increasing aggregation of the latter. Later studies have unraveled the particular features of Al-amyloid

β interaction and its effects on the protein structure (Narayan et al., 2013; Turner et al., 2019). Particularly, Al(III) is capable of inducing β-sheet formation and subsequent aggregation of Aβ40 (Zhang et al., 2019). Similar effect was observed for Aβ42 with Al(III) and Fe(II)/Fe(III) being more active promoters of Aβ42 aggregation than Cu(II) and Zn(II) (House et al., 2004).

In addition to modulation of Aβ production and aggregation, Al was also shown to be involved in induction of tau hyperphosphorylation (El-Sebae et al., 1993). Correspondingly, D-galactose and Al chloride treatment were shown to increase phosphorylated tau deposition in brain regions (Chiroma et al., 2018). Al oxide nanoparticles directly interact with the hydrophilic residues of tau protein resulting in cytotoxicity in in SH-SY5Y cells (Kermani et al., 2018). Neurotoxic effect of Al and D-galactose were also shown to be dependent on GSK-3β activity (Chiroma et al., 2019), that is known to play a significant role in tau hyperphosphorylation in AD and cerebral ischemia (Culbreth and Aschner, 2018). In turn, reducing GSK-3β activity may be involved in decreasing Aβ production and tau phosphorylation in Al-exposed PC12 cells (Huang et al., 2017).

However, certain negative findings indicate a lack of Al(III) impact on amyloid β and tau accumulation in AβPP and AβPP/tau transgenic mice (Akiyama et al., 2012). Although being somewhat contradictory to other studies, these observations may be indicative of complex mechanisms of Al neurotoxicity involving a wide variety of mechanisms.

8.2 α-Synuclein

The earlier demonstrated association between Al exposure and PD may be at least partially mediated by the interplay between Al(III) and α-synuclein. Particularly, Al treatment was shown to increase α-synuclein fibril formation more effectively than Cu(II), Fe(III), Co(III), and Mn(III) (Uversky et al., 2001). Correspondingly, knockdown of α-synuclein expression in PC12 cells was shown to ameliorate Al-maltolate toxicity, being indicative of the essential role of α-synuclein in Al neurotoxicity (Saberzadeh et al., 2016). In addition, Al(III) was shown to possess synergistic effect on tau oligomer formation with GSK-3β, as well as to promote tau coaggregation with α-synuclein (Nübling et al., 2012).
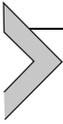
9. Altered neurotransmitter metabolism

Adverse neurological effects of Al exposure are at least partially mediated by interference of Al with neurotransmitter metabolism and signal transduction. Although the particular mechanisms are still unknown, the existing data clearly demonstrate that Al exposure has a significant impact on glutamatergic, gabaergic, cholinergic, serotoninergic and dopaminergic neurotransmission (Gonçalves and Silva, 2007).

9.1 Glutamatergic-gabaergic systems

The majority of the existing studies were devoted to investigation of the impact of Al on glutamatergic mechanisms. Al exposure was shown to reduce NMDA, AMPA, and glutamate-mediated currents in hippocampal neurons (Platt et al., 1994). Al exposure was shown to reduce hippocampal expression of AMPA receptor subunits GluR-1 and GluR-2 (Song et al., 2013) that may be at least partially mediated by modulation of Akt/GSK-3β Pathway (Zhang et al., 2016a,b,c). A dose-dependent hippocampal NMDA receptor (NMDAR) expression was observed in orally exposed rats (Jin et al., 2010) with NMDAR 1A and NMDAR 2A/B subunits affected (Yuan et al., 2011). Altered NMDAR expression was also associated with reduced PLC expression (Jin et al., 2010). Al was also shown to aggravate diabetes-associated alteration of neuroblast differentiation and NMDAR signaling (Nam et al., 2019). At the same time, the use of NMDAR antagonist partially reversed adverse effects of Al in primary neural cultures, indicative of excitotoxic component in Al toxicity (Atterwill et al., 1996). It is also proposed that Al exposure may alter ability of astrocytes to protect neurons from excitotoxic effect of high glutamate levels (Sass et al., 1993).

Al also induced an increase in hippocampal and cortical glutamine levels through increase in glutamine-synthetase (Struys-Ponsar et al., 2002) and reduced glutaminase activity in astrocytes (Zielke et al., 1993), whereas glutamate accumulation was reduced (Struys-Ponsar et al., 2000). Metabolomic study involving HT-29 cells also revealed a significant Al-induced decrease in intracellular glutamate levels (Yu et al., 2019a,b). In agreement, down-regulation of glutamate-NO-cGMP pathway in neurons under Al treatment was observed both *in vitro* and *in vivo* (Canales et al., 2001).

At the same time, i.p. Al administration resulted in a significant increase in glutamate levels in thalamus, hippocampus, and cerebellum along with elevation of glutamate alpha-decarboxylase activity, whereas GABA transaminase was found to be reduced (Nayak and Chatterjee, 2001). Aluminum was shown to have a biphasic effect on GABA-evoked currents by potentiation observed at lower levels (< 100 μM) and reduction at higher concentration (≥ 300 μM) (Trombley, 1998). Modulatory effect of Al on GABA transport may be mediated through Ca2 +/ calmodulin/calcineurin pathway (Cordeiro et al., 2003).

9.2 Cholinergic system

Cholinergic system was shown to be highly vulnerable in response to Al exposure (Yellamma et al., 2010). Al exposure was shown to reduce cerebral acetylcholinesterase (AChE) activity (Sharma et al., 2013a,b) with a biphasic response characterized by an increase in enzyme activity at shorter periods of exposure following by a subsequent depression (Kumar, 1998). Perinatal Al exposure resulted in a significant decrease in cerebellar AChE activity in the offspring (Ghorbel et al., 2016). Expression of choline acetyltransferase and the subsequent acetylcholine synthesis was also found to be reduced in response to Al exposure even despite substrate availability (Farhat et al., 2017). At the same time, certain studies revealed an Al-induced increase in brain AChE activity (Khan et al., 2013). Applying whole-cell patch clamp technique to isolated rat trigeminal ganglion neurons, Hu et al. (2007) observed that Al^{3+} potentiated nicotine-evoked inward currents in a concentration-dependent manner. The authors concluded that the enhanced function of nAChR induced by Al might underlie the neurological alteration induced by Al (Hu et al., 2007).

Moreover, Al exposure is also known to be associated with reduced binding activity of M1 muscarinic acetylcholine receptors (M1AChR) (Harkany et al., 1996) as well as nicotinic acetylcholine receptor (α7, α4 and β2 nAChR) gene expression (Farhat et al., 2019). Importantly, this reduction in nicotinic receptor gene expression is associated with severen neurodegeneration and impaired hippocampus dependent learning in mice (Farhat et al., 2019).

Cholinergic dysfunction may also occur from Al-dependent oxidative stress-induced increase in choline synaptic uptake (Amador et al., 2001). Correspondingly, the use of NOS inhibitors demonstrated that al-

tered cholinergic neurotransmission under Al exposure may be at least partially mediated by disturbances in NO generation (Stevanović et al., 2010).

9.3 Dopaminergic system

Dopaminergic neurotransmission was found to be significantly inhibited by Al exposure (Laabbar et al., 2019). Correspondingly, cerebral dopamine levels were found to be significantly reduced in Al-exposed animals (Bhalla et al., 2010a,b; Singla and Dhawan, 2017). Dopamine synthesis in striatal synaptosomes was also found to be reduced under Al exposure (Pavandi et al., 2014). In addition, Al reduced dopamine D1-like and D2-like receptor expression predominantly in brain cortex and rostral striatum (Kim et al., 2007). Despite these interactions of Al with the dopaminergic system, results of a 36-year multicenter study suggest that aluminum's main toxicity is associated with Alzheimer's disease, Down's syndrome and dialysis dementia syndrome, but not Parkinson's disease or other neurological disorders (Lukiw et al., 2019)

9.4 Serotoninergic system

Certain studies demonstrated that Al exposure may differentially affect serotonin levels (Kumar, 2002; Ravi et al., 2000; Said and Abd Rabo, 2017) and 5-HT2C receptor reactivity (Brus et al., 1997) in brain regions. Exposure to Al was also shown to reduce circulating serotonin levels (Zhang et al., 2016a,b,c). Interestingly, however, a recent study concludes that Al-induced depressive-like behavior in rats is due to activation of hippocampal IL-1β/JNK signaling pathway, resulting in neuronal death in this region (Zhang et al., 2020).
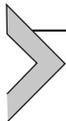
10. Treatment strategies

Due to the revealed high potential of Al as neurotoxic agent as well as its role in development of neurodegenerative and neurodevelopmental disorders, multiple studies aimed at investigation of the potential protective strategies. Due to the role of oxidative stress, mitochondrial dysfunction, inflammation, apoptosis and endoplasmic reticulum stress in Al neurotoxicity, the majority of protective substances are expected to mediate their effect through antioxidant and anti-inflammatory activity. How-

ever, other more specific mechanisms may also mediate neuroprotective effects. The existing protective agents may be mechanistically divided into the following groups: (i) chelators; (ii) trace elements; (iii) amino acids; (iv) polyphenols; (v) polyphenol-rich phytoextracts; (vi) drugs and other agents.

10.1 Chelation therapy

Chelation therapy in treatment of Al toxicity aims to reduce metal bioavailability and facilitates its excretion from the organism, thus preventing its toxic effects. The majority of prior studies demonstrate effective chelation of Al using iron chelator desferrioxamine or deferoxamine (DFO) (Kumar and Gill, 2014). Particularly, DFO was shown to prevent Al-induced oxidative damage to brain proteins (Sivakumar et al., 2012). Ethylene diamine tetraacetic acid (EDTA) (Fulgenzi et al., 2015) and *N*(2-hydroxyethyl) ethylenediamine triacetic acid (HEDTA) (Shrivastava, 2012) were also shown to be effective in reducing Al neurotoxicity. At the same time, comparative analysis of efficiency of other existing Al-chelating agents (Crisponi et al., 2012) in treatment of Al neurotoxicity is highly required.

10.2 Essential trace elements

The existing data demonstrate that silicon (Si), selenium (Se), and zinc (Zn) may possess neuroprotective effect against Al toxicity.

Epidemiological studies demonstrated that increased silicon intake may prevent adverse neurological effects of Al (Davenward et al., 2013; Nielsen, 2014) through its direct interaction with Al ion forming aluminosilicate thus reducing Al bioavailability and toxicity (Domingo et al., 2011). Particularly, increased Si intake was shown to reduce brain Al accumulation in mice (Granero et al., 2004).

Being a structural component of selenoproteins including glutathione peroxidase, protective effects of Se against Al neurotoxicity may be mediated by its antioxidant activity. Particularly, Se treatment significantly reversed Al-induced inhibition of catalase and glutathione reductase activity, as well as reduction of GSH levels. These effects were also accompanied by improved brain morphology, muscle strength, locomotion, and acetylcholinesterase activity (Lakshmi et al., 2015). In addition, neuroprotective effects of Se under Al exposure were shown to involve de-

creased inflammatory response and improvement of NO signaling (Cao et al., 2018).

Zinc was shown to ameliorate adverse effects of Al exposure on brain morphology and redox status, dopamine and serotonin levels, as well as acetylcholinesterase activity (Lu et al., 2013). Particularly, zinc significantly increased total and reduced glutathione levels, as well as improved activity of antioxidant enzymes and metallothionein levels along with reversal of Al-induced neurodegeneration (Singla and Dhawan, 2014). Improved redox status was also associated with lower expression of redox-sensitive transcription factor NF-κB (Singla and Dhawan, 2013). The authors also demonstrated antiapoptotic effect of Zn in Al-exposed animals through reduction of proapoptotic protein expression including Bax, Apaf-1, caspases 3, 6,7, 8, 9 and improvement of cerebral Bcl2 levels (Singla and Dhawan, 2015).

Certain other trace elements were shown to be effective against Al neurotoxicity. Specifically, lithium treatment ameliorated adverse effects of Al on brain ultrastructure (Bhalla et al., 2010a), acetylcholinesterase and monoamine oxidase activity, as well as brain dopamine and serotonin levels (Bhalla et al., 2010b). Another study demonstrated preventive effects of boric acid on neuronal ultrastructure under Al exposure (Colak et al., 2011).

10.3 Polyphenols

Polyphenols represent a wide group of phytochemicals possessing antioxidant and anti-inflammatory effects thus being used as the potential agents in treatment of Al neurotoxicity. Particularly, quercetin was shown to increase cerebral antioxidant enzyme gene expression (Ali et al., 2014) and improve brain mitochondrial biogenesis and function in Al-exposed animals (Sharma et al., 2015). In parallel with improvement of redox status mangiferin (Kasbe et al., 2015) and hesperidin (Jangra et al., 2015) ameliorated Al-induced neuroinflammation, whereas fisetin possessed antiapoptotic effect and reduced Aβ aggregation (Prakash and Sudhandiran, 2015). Naringenin (Haider et al., 2020) and curcumin (Kakkar and Kaur, 2011) were capable of restoration of acetylcholinesterase activity affected by Al.

Significant neuroprotective effect under Al toxicity was observed for phenolic acids. Particularly, chlorogenic acid was shown to improve redox status and antioxidant enzyme activity through up-regulation of

Nrf2-ARE signaling pathway in Al-exposed hippocampal neurons (Wang et al., 2018). Adverse effects of Al treatment on cerebral AChE activity were ameliorated by caffeic (Khan et al., 2013) and syringic (Zhao et al., 2020) acids, whereas the latter also reduced neuroinflammation.

Along with antioxidant and anti-inflammatory effect of the phytochemicals, neuroprotective activity may be at least partially attributed to direct interaction with metal ion. Particularly, it has been demonstrated that polyphenols may bind Al(III) thus reducing its bioavailability (Zhang et al., 2016a,b,c). The role of Al chelation in treatment of neurotoxicity was clearly demonstrated for chlorogenic acid where it increased metal excretion and reduced its accumulation in hippocampus (Wang et al., 2018).

10.4 Phytochemical-rich plants and phytoextracts

Due to clearly demonstrated protective effect of particular phytochemicals (polyphenols) against Al neurotoxicity, the potential efficiency of polyphenol-rich plant extracts was also investigated. Specifically, neuroprotective, antioxidant, and anti-inflammatory effects were demonstrated for green (Jelenković et al., 2014) and black tea (Mathiyazahan et al., 2015), Allium cepa (Singh and Goel, 2015), grape (Lakshmi et al., 2014), Ginkgo biloba (Verma et al., 2020), and saffron (Linardaki et al., 2013) to name a few. The growing body of evidence demonstrate the usefulness of ethnobotanical species. However, further studies are required to characterize the particular mechanisms and active agents contributing to neuroprotective effect of phytoextracts under Al exposure.

10.5 Other agents

A variety of agents with different mechanism of action were also shown to be effective against Al neurotoxicity including melatonin (Sadek et al., 2019), anti-inflammatory drugs (e.g., ibuprofen) (Jamil et al., 2016), lipoic acid (Al-Otaibi et al., 2018), *N*-acetylcysteine (Prakash and Kumar, 2009), etc. Combined therapy may be also considered as a perspective approach due to the use of agents with different mechanism of biological activity (Kumar and Gill, 2014).
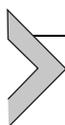
11. Conclusion

The growing body of data demonstrate the potential role of Al exposure and its neurotoxicity as contributors to a wide spectrum of neurodegenerative and neurodevelopmental disorders. The underlying mechanisms of Al(III) neurotoxicity were shown to involve oxidative and endoplasmic reticulum stress, mitochondrial dysfunction, inflammation, cell death, interaction with Aβ and α-synuclein, cytoskeletal abnormalities as well as alteration of synaptic plasticity and signal transduction through interference with neurotransmitter systems. Targeting these mechanisms at different stages may be beneficial for treatment of Al neurotoxicity and associated diseases. However, certain contradictions regarding the mechanisms and the overall effects of Al exposure in vivo and in vitro exist. The latter may at least partially arise from the difference in analytical methodology, whereas development of precise and validated methods including speciation analysis and imaging techniques would significantly contribute to understanding of biological effects of Al. Further studies are required to highlight the intimate mechanisms involved in Al neurotoxicity, as well as its particular contribution to neurological disorders for subsequent development of effective therapeutic strategies.

Acknowledgments

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