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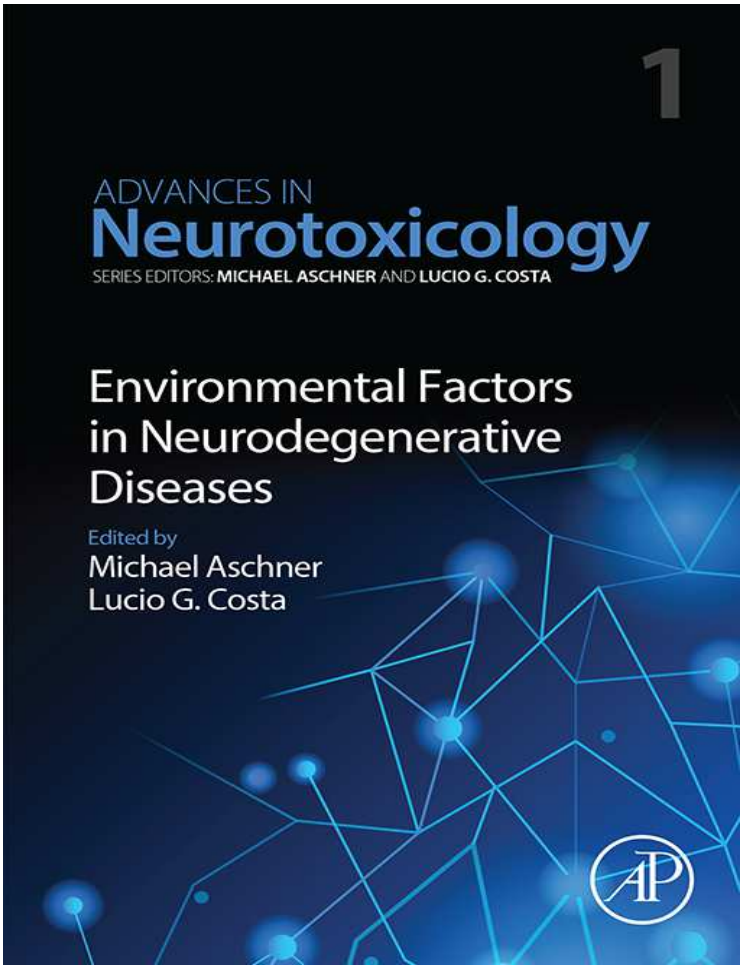

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CHAPTER FIVE

Aluminum and Neurodegenerative Diseases

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1. INTRODUCTION

Aluminum (Al) is a common element found in large amounts in the earth's crust (Priest et al., 1988). Aluminum-containing minerals are present in relatively inert rock types, especially in igneous formations, such as granite

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and quartz. Laterization of various silicate rocks weathering into finer particles results in the formation of sedimentary bauxite, where together with iron, Al is present largely as the oxide. It is as bauxite that Al is generally mined and second only to iron, Al is the most widely used metal (Hetherington, 2007).

Despite its commonality, Al has no known beneficial biological roles and is not an essential element for any organism. Aluminum-containing minerals are rather unreactive, and this is also true for metallic aluminum, as this is quickly oxidized in air and thus coated by a very thin but robust layer of the oxide. This apparent inertness has led to the concept that aluminum may not constitute a health hazard. Consequently a wide range of Al compounds have been added as stabilizers in many processed foods. Alum, which is any trivalent Al-containing salt, is the oldest and most commonly used vaccine adjuvant. Recent findings indicate that the effectiveness of the adjuvant relies on both its immunomodulatory as well as inflammatory properties. Al salts have also found utility in water clarifying processes by effecting precipitation of organic particulate matter. Growing incidence of acidic rain has led to greater solubilization of aluminum salts from their insoluble form in rocks. This has led to an elevated Al content in many water reserves used for residential supply. Thus, human exposure to more soluble forms of Al in water and foodstuffs has grown.

Reports from both biological laboratories and from study of human population health indicate that prolonged aluminum ingestion can result in neurological abnormality. Accumulating indications strongly suggest that Al can further the onset and development of neurodegenerative disorders, principally Alzheimer's disease (AD). There are many reports suggesting that Al can provoke excessive inflammatory events in the brain. Superfluous immune reactivity that is not an obvious response to a trauma such as injury or infection is a distinguishing feature of the elderly brain and appears exacerbated in nervous system abnormalities. Most neurodegenerative diseases have no obvious cause and do not have a clear genetic basis. Thus, it is probable that the origin of such diseases lies in unknown environmental influences that interact with the progression of aging. The nature of most of such factors is unknown, but there is growing evidence, indicating that Al is likely to be one of these environmental factors. In this review, reports that point to the conclusion that aluminum are able to speed up the worsening of brain function with age, and potential mechanisms are discussed. It should be noted that acceleration of this process would inevitably increase

the prevalence of those specific neurological disorders where age is a concomitant risk factor.

2. GROWING BIOAVAILABILITY OF ALUMINUM IN THE ENVIRONMENT

Metallic aluminum was first made by Hans Oersted in 1825 by heating aluminum chloride with elemental potassium (Sigel and Sigel, 1988). Al-containing chemicals have many uses. Mixing aluminum sulfate and lime together in water leads to formation of colloidal aluminum hydroxide, and this can bring about precipitation and removal of waterborne organic material. This method for water clarification is widely used. Al-containing additives are also found in many foodstuffs. They are used as emulsifying agents in preparation of processed cheese, as crisping agents in pickles, in baking powder, and in a variety of food colorings. Aluminum-containing compounds are also found in cosmetics. Commercial preparations of infant formula can contain significant amounts of the metal (Burrell and Exley, 2010; Dabeka et al., 2011).

High concentrations of soluble Al can be found in the juice resulting from boiling of acidic fruit in aluminum cookware (Fimreite et al., 1997). The aluminum content of city water supplies is variable, but on occasion, concentrations as high as 0.4–1 mg/L have been reported in drinking water. Although the health effects of these levels of the metal on humans are uncertain, the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives in 2007 recommended a maximum intake of Al less than 1 mg/kg body weight per week. This corresponds to 63 mg per week for a 140-pound adult. Some commercial pastry products contain Al sulfate and sodium aluminum phosphate levels up to 28 mg in a single serving of muffin or other baked products where baking powder is used (Pennington and Jones, 1989). Alum is a powerful adjuvant in vaccines and performs this role by enhancing the intensity of the immune responses evoked by the vaccine. The interest in determining the mechanism by which Al salts produce adjuvant action has led to the understanding that insoluble aluminum salts activate innate immune responses that lead to a T helper 2 (Th2)-type reaction (Marrack et al., 2009). The metal is also present in most antiperspirants, in buffered aspirin, and in antacids where the Al content can reach 600 mg/tablet.

The most common form of human absorption of Al compounds is by way of the gastrointestinal tract where the degree of uptake can be about

0.2% (Priest et al., 1988). When Al salts are transferred from the stomach to the hepatic portal vein, the metal is largely bound to transferrin (Harris et al., 2003). Al can subsequently reach the brain by means of receptor-mediated endocytosis of this transferrin complex. By this means, around 0.005% of the total aluminum–transferrin complex can cross the blood–brain barrier (Yokel et al., 2001).

Since soluble Al salts are gradually changed into insoluble high-molecular-weight aggregates and the absorption of such Al complexes is limited, environmental Al has often been considered to be harmless. Yet there is evidence that Al-containing materials can be injurious to both plants (Kochian and Jones, 1997) and animals (Sparling and Campbell, 1997). There has been mounting disquiet over the possible toxic effects of Al on humans (LaZerte et al., 1997). While some trepidation about Al harmfulness to humans has been expressed for over 90 years, conventional medical views have generally disregarded such concerns. An example of the dismissive tone used is to be found in an article in JAMA stating, "Propaganda as to possible dangers resulting from the use of aluminum cooking vessels is so persistent that one suspects ulterior motives in its background" (Monier-Williams, 1935). The recent advances in understanding the mechanisms by which adjuvant alum salts lead to cell death and immune activation reopens the concept that aluminum salts may be biologically harmful (Reed et al., 2013).

3. ACUTE EXPOSURE TO HIGH LEVELS OF ALUMINUM CAN LEAD TO ADVERSE NEUROLOGICAL CONSEQUENCES

There is good evidence that relatively high concentrations of Al can be acutely neurotoxic once accumulated. Formerly, hemodialysis of patients suffering from kidney failure often led to toxic levels of Al in the blood. The sources of the metal were from both the tubing used during dialysis, and also the administration of aluminum-containing phosphate binders in patients who already had an impaired ability to excrete Al. This often led to aluminum-induced dialysis encephalopathy, which was attributed to the ability of major amounts of Al to traverse into the brain (Russo et al., 1992). Blood concentrations up to 7 μM Al were found in dialysis patients prior to the onset of obvious dementia (Altmann et al., 1987). This encephalopathy was associated with pathological changes in the brain indicting an inflammatory state. In one case, treatment of a chronic renal failure patient, with phosphate-binding Al gels produced an encephalopathy, which after

9 months, led to death. Postmortem neuropathology showed pronounced proliferation of microglia and astrocytes, indicative of an inflammatory response, in specific brain areas (Shirabe et al., 2002). The clinical status of patients suffering from such encephalopathy has been reported to be improved by administration of deferoxamine, an Al chelator (Erasmus et al., 1995). Encephalopathy due to acute exposure to high levels of Al has also been found in patients suffering from kidney failure, treated by bladder irrigation with 1% alum (Phelps et al., 1999). Neurological derangement involving intellectual deficits, loss of muscle control, tremor, and spinocerebellar degeneration has been described in workers in the aluminum industry (Polizzi et al., 2002).

An abnormal neurological condition has on occasion been found consequent to an intramuscular injection of a vaccine preparation containing alum adjuvant (Couette et al., 2009). The World Health Organization Vaccine Safety Advisory Committee has determined that there is likely to be a subset of individuals who respond undesirably to Al-containing vaccines (Authier et al., 2001).

In the past, inhalation of Al oxide powder was used as a means of protecting against silicotic lung disease in miners (Crombie et al., 1944). This approach was reported to have utility in an animal model of silicosis (Dubois et al., 1988). This inhalation procedure was continued for some years despite the fact that miners suffering from silicosis did not report any benefit from this treatment (Kennedy, 1956). Injurious effects of this procedure upon brain function were ultimately clearly recognized (Rifat et al., 1990), and such administration was terminated. A major accidental discharge of Al sulfate into the drinking water supply of the town of Camelford, UK, took place in 1988. After the spill, authorities initially indicated that the water was safe to drink and suggested the addition of fruit juice to conceal any unpleasant taste. Many acidic fruit juices can also enhance the absorption of Al from the gastrointestinal tract. Evidence emerged later on, of harmful neurological consequences to at least some of the exposed population (Altmann et al., 1999). Postmortem pathology of a person, who was exposed to Al at Camelford and later died of an undetermined neurological disorder, revealed evidence of early-onset beta amyloid angiopathy in the cerebral cortical and leptomeningeal blood vessels. The Al content of some brain areas, especially the cortex, was also strikingly elevated (Exley and Esiri, 2006).

Correlative findings by themselves cannot conclusively demonstrate causation, and it has been suggested that excessive penetrance of Al into the

brain is an ancillary event following disruption of the blood–brain barrier and may not in itself effect neurotoxicity. However, in patients suffering from dialysis encephalopathy, chelation therapy using deferoxamine both reduced the Al burden of the brain and improved neurological status. And this suggests a direct causal relation between Al exposure and neurotoxicity (McLachlan et al., 1991). A recent report of the use of chelation with EDTA to effect Al excretion in "Al-intoxicated patients" acknowledges that reduction of levels of other toxic metals by this relatively nonselective chelator might also account for recovery of patients (Fulgenzi et al., 2015). These findings have not been extensively pursued, perhaps in part because these chelators are rather nonspecific and can chelate essential as well as nonessential metals. This can result in many undesirable side effects including muscle pain, nausea, and visual deficits. Another possible hazard of chelation therapy as means of effecting Al removal from the body is that it can mobilize Al from quiescent deposits in bone, and thus lead to high serum levels of Al which can then translocate to the brain. This then may cause emergence of neurological symptoms resembling those found in dialysis dementia (Sherrard et al., 1988).

Other indications of the acute neurotoxicity of Al include a case report where aluminum-containing cement was used in the surgical resection of an acoustic neuroma. Six weeks later the patient suffered from loss of consciousness, myoclonic jerks, and persistent grand mal seizures, clinical symptoms that resembled those of lethal dialysis encephalopathy (Reusche et al., 2001). Overall, there is considerable evidence that acute exposure to large amounts of Al in humans can have harmful effects on cerebral function.

4. BASAL INFLAMMATION WITHIN THE BRAIN INCREASES WITH AGING. MOST NEURODEGENERATIVE DISEASES ARE CHARACTERIZED BY AN EVEN GREATER DEGREE OF INFLAMMATORY ACTIVITY

In order to assemble evidence that ingestion of Al-containing materials can accelerate brain aging, it is necessary to first take into account some of the transformations associated with normal aging of the brain. This is typically attended by evidence of elevated levels of inflammatory activity (David et al., 1997; Sharman et al., 2004). Even in the absence of detectable provocative exogenous immune stimuli, cerebral immune activity becomes

increasingly pronounced during normal aging (Lucin and Wyss-Coray, 2009; Sharman et al., 2008).

Following the systemic injection of mice with an inflammogen such as lipopolysaccharide, levels of inflammatory cytokines rapidly increase in many tissues including serum and liver, but these are restored to basal concentrations within a week. However, the response in the brain to such treatment leads to a much more sustained elevation of inflammatory cytokine content. TNF-α remains at high levels for up to 10 months, before reverting to basal levels. This extended response, which continues over a significant portion of the mouse life span, is attended by evidence of glial activation and extended neuronal death (Qin et al., 2007). Responses to acute inflammatory events such as infections are maintained for a long time in the brain (Bilbo et al., 2005; Galic et al., 2008; Shi et al., 2003). In consequence, the brain progressively accumulates changes reflecting a history of adverse systemic events, leading to a persistent and undesirable degree of inflammatory activity. This may account for the many reports of the excessive extent of inflammation present in the aged brain (Bondy and Sharman, 2010). A continuing state of inflammation is likely to contribute toward the development of age-related neurodegenerative changes (Block et al., 2007; Lucin and Wyss-Coray, 2009).

Several age-related neurological disorders are accompanied by the onset of additional elevations of neuroinflammation greater than that present in normal aging (Bondy, 2010). Neurodegenerative diseases where this has been reported include AD, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). This additional inflammation may underlie some of the characteristic pathological changes associated with each disorder. In AD, evidence of astrocytic and microglial activation is most prominent at the site of amyloid plaques, and such activated glia generate inflammatory cytokines and acute-phase proteins (Cullen, 1997; Mrak et al., 1995; Styren et al., 1998). This can also result in the appearance of inflammatory cytokines in brain and cerebrospinal fluid (Sun et al., 2003; Zhao et al., 2003). Some of these prolonged changes reflect altered expression and activation of inflammatory genes, especially in the hippocampus (Colangelo et al., 2002). Aluminum nanoparticles can also reach the CNS. Following deposition on the nasal epithelium such particles may be taken up by exocytosis and then conveyed into the brain by way of the olfactory nerve. This can result in phosphorylation of various kinases leading to signal transduction and altered gene expression (Kwon et al., 2013).

AD is characterized by amyloid beta (Aβ) deposition as senile plaques. Aluminum salts can promote amyloid peptide aggregation in defined in vitro preparations (Bolognin et al., 2011; Bondy and Truong, 1999; Exley, 1997). Exposure of transgenic mice overexpressing amyloid precursor protein (APP) to Al salts by way of their drinking water has been described as promoting Aβ accretion in plaques and leading to evidence of oxidative stress in the cortex (Pratico et al., 2002). The ability of Al to promote Alzheimer-like changes in animal models of AD has, however, been questioned. Administration of Al salts in drinking water to a double transgenic mouse line overexpressing both APP and Tau protein led to no significant changes in Aβ levels or prooxidant activity (Akiyama et al., 2012). Another study, which tested both wild-type and mutant mice, also found no effect on the extent of amyloid deposition or cerebral Al content (Ribes et al., 2012). Finally an experiment involving normal rats receiving Al in drinking water reported negative results (Poirier et al., 2011). Such conflicting results are hard to explain, but study design variables in terms of varying dosage of Al, duration of exposure, age of animals at the initiation of exposure may all play a substantive role.

5. EPIDEMIOLOGICAL STUDIES SUGGEST A RELATIONSHIP BETWEEN ALUMINUM EXPOSURE AND THE INCIDENCE OF NEURODEGENERATIVE DISEASE

The neurotoxicity of Al was originally reported in patients experiencing comparatively brief exposure to high levels of Al notably in renal dialysis patients. More controversially, harmful effects of prolonged exposure to lower levels of Al have been described. Elevated cerebral Al in brains of AD patients has been found. A greater content of Al has also been reported in brains of less common neurological disorders such as Guamanian Parkinsonian–ALS complex and Hallervorden–Spatz disease (Eidelberg et al., 1987; Garruto et al., 1988). This has led to the question as to whether Al may be a factor in the initiation and development of several neurological disorders (Kawahra and Kato-Negishi, 2011).

Several studies have focused on specific types of worker such as welders, exposed to high levels of Al. In an analysis, no association among welders exposed to Al by inhalation and neurobehavioral functioning was apparent (Kiesswetter et al., 2009). However, behavioral deficits in welders, which showed a dose–response relation in proportion to the degree of Al exposure, have been described (Giorgianni et al., 2014). This latter report highlighted

the fact that the tests most sensitive to Al exposure involved intricate trials reflecting attention and memorial capacity.

5.1 Alzheimer's Disease

The possibility that Al exposure may advance the progression of AD is strengthened by descriptions of excessive levels of Al in analyses of AD brain tissue postmortem. The first report of this (Perl and Brody, 1980) was questioned because of the difficulty of precise quantitation of Al in brain samples (Bjertness et al., 1996). However, a range of more advanced analytical methods, such as laser microprobe mass analysis (Bouras et al., 1997), neutron activation (Andrasi et al., 2005), upgraded graphite furnace atomic absorption methods (Xu et al., 1992), or energy-dispersive X-ray spectroscopy together with transmission electron microscopy (Yumoto et al., 2009), have all substantially confirmed the original report. Laser microprobe mass analysis revealed Al to be primarily concentrated in the neurofibrillary tangles associated with AD (Bouras et al., 1997). High Al content is also present in the cerebral arteries of AD patients (Bhattacharjee et al., 2013a). The possibility that high Al content in AD brains may be a secondary epiphenomenon, consequent to disruption of the blood–brain barrier must therefore be borne in mind (Guerriero et al., 2016).

The suggestion of a causal relation between Al ingestion and neurodegenerative disease is apparent from the number of studies linking the Al content of drinking water and the incidence of AD. An early study reported the AD prevalence was highest in areas where Al concentrations in the drinking water supply were over 100 μg/L and incidence was directly related to the concentration of Al in the drinking water (McLachlan et al., 1996). A similar finding was made in a study of the elderly with AD and Al content of drinking water (Rondeau et al., 2009). A review assembling data from a range of epidemiological reports suggested that generally, there is a significant relation between usage of Al-containing antacids and AD prevalence (Flaten, 2001). A meta-analysis of nine independent studies where urinary Al concentrations were measured determined that cognitive performance was impaired relative to control (Meyer-Baron et al., 2007). The effects of protracted exposure to low levels of Al on AD incidence are difficult to unambiguously identify. Since AD is largely idiopathic and not of genetic origin, many possible confounding environmental factors exist that may influence the incidence. For instance, AD has also been associated with other metal imbalances such as abnormal copper levels, but the establishment of a causal

relation remains unresolved (Akatsu et al., 2012; Exley et al., 2012; Kitazawa et al., 2009).

There are conflicting claims concerning the neurotoxic hazard of the levels of aluminum present in the human environment. These range from claims that "AD is a human form of chronic aluminum neurotoxicity" (Walton, 2014) and "aluminum may be the single most aggravating factor related to AD" (Tomljenovic, 2011), through the more circumspect "exposure to aluminum dust may possibly increase the risk of cardiovascular disease and dementia of the Alzheimer's type" (Peters et al., 2013), to totally dismissive reports of the lack of evidence for any correlation between AD and occupational exposures to aluminum (Santibáñez et al., 2007), with inferences such as "lifetime occupational exposure to Al is not likely to be an important risk factor for AD" (Flaten, 2001). A recent review sums up this view with "consideration of the published research concerning aluminum's role in AD indicates that none of the four Bradford Hill criteria considered necessary to establish causation with respect to Al and neurocognitive disorders has been fulfilled" (Lidsky, 2014).

In an endeavor to resolve this issue, it has been proposed that inconsistent findings may in part be due to a common failure to take silicate levels in drinking water into account. Aluminosilicates do not readily cross the bloodstream from the alimentary tract, and the presence of silicates in water can be protective against the toxic effects of Al (Foglio et al., 2012; Krewski et al., 2007). When the silicate content in drinking water is low, the risk of impairment of brain function by Al is raised (Rondeau et al., 2009), suggesting that silicates may reduce the harmfulness of waterborne Al (Gillette Guyonnet et al., 2007). The use of chelators to enhance Al excretion has been suggested to be beneficial in the treatment of AD (Jansson, 2001; McLachlan et al., 1991). Chelators with a greater selectivity for Al may improve this approach (Shin et al., 2003).

Overall, despite an extensive literature, the issue of the relation between AD and exposure to aluminum remains unresolved. This is partly due to the difficulty in obtaining unambiguous data from epidemiological studies. Furthermore, a clear identification of the molecular basis of Al toxicity is lacking. However, laboratory studies under well-defined conditions, where the number a confounding factors is lower, are generally consonant with epidemiological reports. In this review, a subsequent section summarizes findings from research involving Al-treated animals.

In summary, while mechanisms by which Al acts as a neurotoxicant are unclear, Al exposure has been repeatedly found correlated with

neuropathological changes associated with AD. This association between Al and incidence of AD has been much more frequently described compared to other neurological disorders. This may be at least in part because of the high incidence of the disorder, which expedites epidemiological studies.

5.2 Association Between Al Exposure and Neurological Disorders Other Than AD

Evidence of a link between Al and other neurological disorders is less well established. Aluminum-containing salts that enhance the immune response to vaccines are often used as adjuvant constituent of vaccines (Alvarez-Soria et al., 2011; Chang et al., 2010; Girard, 2005; Schoenfeld and Agmon-Levin, 2011; Sutton et al., 2009). Injection of alum into neonatal mice in quantities parallel to those used in childhood vaccination schedules results in behavioral abnormalities which persist into adulthood (Shaw et al., 2013). Administration of aluminum-containing adjuvants led to induction of granuloma, which persisted for a prolonged period in the injected muscle, and Al was ultimately able to be transferred into the brain from this location (Crépeaux et al., 2015). Injection of alum-containing vaccine intramuscularly induced Al deposition in mouse brain in gradually progressive way (Khan et al., 2013). However, there was no penetrance of Al into the CNS following direct infusion of the vaccine into the vascular system. Entry of Al from vaccines into the brain was facilitated by the lymphatic system and monocyte chemoattractant CCL2 (Khan et al., 2013). Administration of an Al-containing vaccine led to behavioral abnormalities in female mice that was associated with microglial activation in the hippocampus (Inbar et al., 2017). Furthermore, the neurobehavioral effects of Al adjuvant occurred at the lowest but not highest doses tested. Thus, it appears that the neurotoxicity of the metal may follow a nonparametric dose–response relationship. It was also noted that while Al levels in the injected muscle resolved in 6 months, the cerebral levels were selectively increased (Crépeaux et al., 2017).

Peripheral administration of aluminum-containing nanoparticles, 30–60 nm in diameter, for 3 weeks, elevated the Al content of mouse brain and also increased prooxidant events. In this study, hippocampal memory-forming processes were impaired and there was an elevated rate of Aβ formation (Shah et al., 2015). Significant amounts of Al are often present in infant formulae at significant levels, 100–756 μg/L, and it may be that this represents a nontrivial developmental hazard (Chuchu et al., 2013). The use of vaccines has been associated with increased incidence of MS, and urinary

aluminum content is elevated in MS patients (Exley et al., 2006). Chelation therapy leading to reduced levels of circulating Al has been stated to have therapeutic value in the treatment of MS (Fulgenzi et al., 2015). On the other hand, vaccines with Al-containing adjuvants have been described as protecting mice from developing experimental autoimmune encephalomyelitis (Wållberg et al., 2003). Despite these apparently conflicting reports, there is convincing evidence that nanomolar levels of aluminum can increase expression of the inflammatory biomarker C-reactive protein in isolated endothelial cells derived from microvessels (Alexandrov et al., 2015). The consistent findings that Al can increase markers of neuroinflammation, either directly by microglial activation, or indirectly by influencing the microvasculature, may be an important mechanism by which exposure to the metal can enhance and promote neurodegeneration and subsequent behavioral abnormalities.

There are suggestions linking Al and PD. PD is another rather widespread common neurological disease characterized by elevated levels of oxidative and inflammatory events (Selley, 2005). Such an association has been made based on a relation between gastric ulcers and the incidence of PD, which may reflect the high use of Al-containing antacids by those suffering from ulcers (Altschuler, 1999). Other hints of a possible connection between Al and PD lie in the property of Al salts to bring about activation of monoamine oxidase B. This enzyme is elevated with age and further raised in PD (Zatta et al., 1999). Monoamine oxidase B is able to promote aggregation and fibril formation of α-synuclein, which could account for the reported association between several neurotoxic metals and PD (Uversky et al., 2001). Activated microglia and high levels of inflammatory cytokines within nervous tissue are present in PD (Nagatsu and Sawada, 2005). The activation of NF-κB, a transcription factors leading to induction of a series of inflammatory events, can occur in a synergistic way after treatment of experimental animals with both the dopaminergic neurotoxin, MPTP in conjunction with the presence of low levels of Al in drinking water (Li et al., 2008). Nonsteroidal antiinflammatory drugs may delay the onset and progression of the disease (Hald et al., 2007).

Neuropathological and behavioral modifications resembling those found in ALS have been described in animals after administration of Al salts. Injection of Al-containing adjuvants at levels equivalent to those typically administered to humans, resulted in motoneuron death, impairments in motor performance, reduced retention of spatial memory and increased activation of astrocytes, and microglia in mice (Petrik et al., 2007; Shaw and Petrik,

2009). Thus, exposure to Al may promote an array of neurological impairments. The unique epigenetic and genetic profile of diverse individuals, the dose and duration of exposure to Al, as well as combination of other environmental factors such as coexposure to other metals may all determine the specific type of neurological abnormality that is manifested.

6. RESEARCH FROM ANIMAL MODELS AND IN VITRO SYSTEMS IMPLIES THAT HIGH LEVELS OF ALUMINUM CAN FURTHER THE EVOLUTION OF AGE-RELATED COGNITIVE DEFICITS

Clinical reports of aluminum neurotoxicity are matched by similar findings found in several experimental animal models. Administration of Al salts in such models can result in neuropathological changes resembling those found in human brain aging (Bowdler et al., 1979; Miu et al., 2004). However, several of these studies have involved concentrations of Al not commonly met among human populations. Other studies that better mirror human exposures have been performed using more extended treatment using low levels of Al paralleling those found in environmental exposures. It is apparent that immunomodulation, neuroinflammation, and oxidative stress are mechanisms that have consistently been shown to contribute to neurodegenerative diseases. In this section, the role of Al in exacerbating these events will be further delineated (Fig. 1).

6.1 Immunomodulation and Neuroinflammation

Aluminum salts, used as adjuvants in vaccines, cause necrosis and uric acid production which functions as a danger signal to activate the NLRP3 inflammasome (Eisenbarth et al., 2008). The activation of the NLRP3 inflammasome plays a crucial role in amplifying the inflammatory response (Baroja-Mazo et al., 2014). Furthermore, it has been reported that DNA released from alum-exposed dying cells functions as another danger signal (damage-associated molecular pattern) contributing to the immunomodulatory role of aluminum adjuvants (Marichal et al., 2011). These findings all point to the impression that Al salts are not biologically benign and that prolonged environmental exposure to the metal may lead to cellular stress and subsequent potentiation of inflammatory events. Since an enhanced inflammatory state underlies many disease states, including age-related neurodegenerative diseases, the role of Al in exacerbating the pathology of these disorders should be further examined.

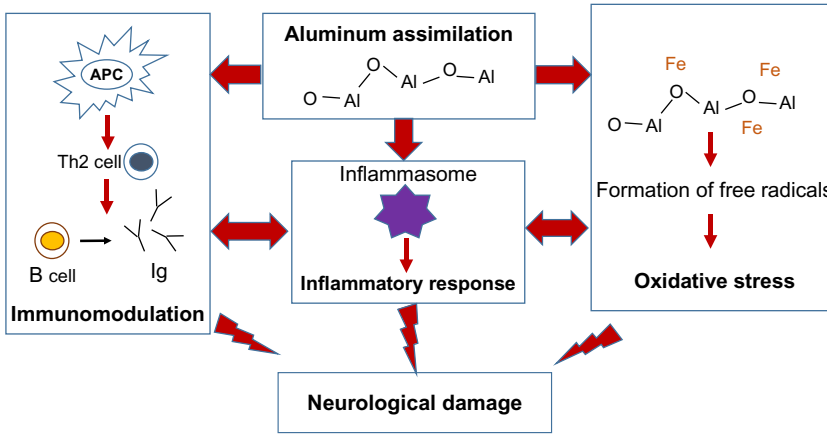

Fig. 1 Mechanisms by which aluminum enhance neurotoxicity. The *left panel* shows how aluminum aggregates cause enhanced activation of antigen-presenting cells (APC) which then provide the signals necessary to promote a T helper 2 (Th2) subset of T cells. Th2 cells are important mediators of B cell activation and antibody (Ig) production. Different isotypes of antibodies cause immunomodulation by their effects on different immune cells. This immunomodulation may result in enhanced neurotoxicity. The *center panel* shows how aluminum aggregates can also activate the NLRP3 inflammasome and by doing so amplify the inflammatory response. Enhanced inflammation has been shown to directly lead to neurotoxicity. The *right panel* shows that aluminum aggregates can function as a platform for redox-active metals such as iron to induce a Fenton reaction. The accelerated formation of free radicals then leads to oxidative stress, another mechanism directly linked to neurotoxicity. Although separate phenomenon, these events may be interrelated and this is indicated in the figure by the two-sided *arrows*.

Low levels of Al in the drinking water of mice led to elevation of indices of inflammation in brain tissue such as increases in levels of inflammatory cytokines and nitric oxide synthase (Campbell et al., 2004). These changes occurred after 3 months of contact with Al salts in the drinking water using concentrations of Al below some of those reported for some residential water reserves. Extended exposure to low levels of Al can also lead to elevated levels of glial fibrillary astrocytic protein an indicator of astrocytic immune activation (Yokel and O'Callaghan, 1998). Other evidence concerning the potential neurotoxicity of Al includes descriptions of cognitive and pathological alterations in aged rats resembling those characteristic of AD, following exposure to Al at levels equivalent to those ingested by some human populations (Walton, 2009a,b, 2012; Walton and Wang, 2009). Exposure to dietary Al also resulted in increased levels of APP in a rodent model (Walton and Wang, 2009). AD-like changes in rats following

aluminum exposure have been attributed to induction of α- and β-secretases, leading to increased formation of Aβ from APP (Wang et al., 2014). The evidence for Al salts to induce Aβ formation and its aggregation has been previously reviewed (Zhao et al., 2014).

Changes in expression of specific genes have been described in a transformed neuronal cell line following exposure to an Aβ–aluminum complex, and several of the genes whose expression was increased are among those also elevated in AD (Gatta et al., 2011). After Al treatment of transgenic mouse models of AD, the profile of micro-RNA-mediated gene expression distinctly resembles changes found in AD (Pogue and Lukiw, 2016). These accounts suggest a genetic or epigenetic basis for many of those changes caused by Al treatment that resemble altered expression associated with AD.

If the extended increase in inflammatory activity that characterizes brain aging was worsened in the presence of low Al, this would resemble the doubly enhanced level of inflammation found in many neurodegenerative diseases. Thus, Al may act initially by accelerating the rate of normal brain aging. This could then form a platform that would further the development of a range of more specific neurodegenerative disorders.

Despite the relative inertness of Al salts, there are several potential pathways by which Al could initiate toxic events (Tomljenovic, 2011). The activation of glia and macrophages by Al-containing chemicals and mineral has been described (Evans et al., 1992; Gorell et al., 1999; Platt et al., 2001). Similar to the alum adjuvant, the activation of the NLRP3 inflammasome and consequent amplification of the inflammatory response may play a role in this glial activation. Since Al salts can produce inflammatory reactions in isolated glia as well as in glia of intact animals, it is probable that a direct action on some glial species is implicated (Campbell et al., 2002).

6.2 Oxidative Stress

Al is not a valence-active element and does not have a significant affinity for sulfhydryl groups, but it has the capacity to enhance the production of oxidant free radicals. This property may be due to the enhancement of the redox activity of trace amounts of iron. The ability of aluminum to increase the prooxidant properties of iron is found even in the absence of tissues or organic material (Bondy et al., 1998). The mechanism by which this catalysis is brought about is likely to be by Al complexes in solution forming colloids, upon whose surfaces iron can be loosely sequestered. This partial complexation enables iron to undergo Fenton dynamics and undergo valence redox

flux thus causing production of reactive oxygen species (Bondy, 2009; Ruipérez et al., 2012). This can then lead to increased expression of genes associated with inflammation (Alexandrov et al., 2005). An analogous enhancement of the prooxidant properties of iron by an inert mineral is known in the case of silica fibers (Napierska et al., 2012). The binding of transition metals on the surfaces of nanoparticles composed of inert core materials can greatly enhance the toxicity of such particles (Bhattacharjee et al., 2013b). This is likely to have applicability to aluminum salts, which generally exist as colloids in aqueous media.

7. THE NEUROTOXICITY OF ALUMINUM IN AMOUNTS ENCOUNTERED IN THE HUMAN ENVIRONMENT CONTINUES TO BE CONTENTIOUS

The question of Al neurotoxicity has a long history, but no consensus has been reached concerning the hazard posed by environmental exposure. As a result the necessity for increased regulatory action is not regarded as critical. Research on animals is limited by the fact that rodent biology does not completely reflect the human condition, especially as regards to brain function. While there is a range of diverse and often opposing opinions, the preponderance of evidence from both laboratory studies and epidemiology suggests that the issue of Al neurotoxicity should not be cavalierly dispelled. In view of the large number of people ingesting various amounts of this element, this risk should not be dismissed but should remain under careful consideration.

The history of lead toxicity can perhaps give clues as to why there has been failure to reach agreement on the importance of hazards posed by Al, and why there is an inclination to regard these as not of critical concern. Lead has been in use in its metallic form and as salts for more than 3000 years and has been intermittently recognized as poisonous since 700 B.C., and its widespread global presence has risen markedly in the last 200 years. However, only in the last two decades has the harmfulness of lead at low levels been widely accepted. In consequence, increasingly severe legislative measures to curtail lead exposure have been instituted and these appear to be generally effective. A long period of controversy preceded the recognition of the neurotoxicity of lead. Before the universal acceptance of the harmfulness of low levels of lead, the lead industry vigorously fought against the regulation of environmental lead and damaged the reputation of researchers in this area. Prominent scientists evaluating the effects of

exposure to low levels of lead on child development were accused of bias and fraud (summarized in Needleman, 2008).

In comparison, Al has only had broad industrial use for a comparatively short time. However, as was the case leading up to recognition of the neurotoxicity of low levels of lead, the harmfulness of low levels of Al is intensely disputed as, once again, major economic forces are involved. Accordingly, no new major efforts to minimize Al levels in food or drinking water are currently being legislatively deliberated. The much shorter history of Al use means that we appear to be at an early stage of concern regarding the dangers posed for human health, than is the case with lead. In common with lead, levels of this metal, once regarded as trivial, are likely to be recognized as potentially hazardous. Also, in common with lead, broad population exposure to ingested Al may cause subtle deficits and vulnerabilities rather than spectacular and specific toxic incidents. It is thus hoped that similar to lead, there will be a growing recognition of the neurotoxicity of environmental aluminum and the introduction of legislation that would protect populations at risk, which are likely to be manifold.

8. SUMMARY

The potential for aluminum ingestion to further the development of neurodegenerative disease is not yet unambiguously accepted. However, several key findings are undisputable. These are as following:

- Al-containing materials have a widespread presence in the environment, and when ingested by humans, some Al salts can reach the brain.
- Brief exposure to high levels of Al can lead to clear evidence of neurological damage.
- The level of basal inflammatory activity in the brain is progressively increased with aging, and this is intensified in several neurodegenerative conditions.
- Administration of amounts of Al to experimental animals in the drinking water that correspond to levels found in some residential water sources can increase inflammatory activity in the brain and are associated with neuropathological changes, resembling those found in AD.

As life expectancy in the United States grows, a greater incidence of slow developing neurodegenerative disorders such as AD, PD, ALS, and MS can be anticipated. These diseases are largely of nongenetic origin and are likely to be initiated by unidentified gene–environmental interactions. As long dormant periods can occur between exposure to an injurious

environmental or occupational agent and the manifestation of explicit clinical symptoms, this makes the identification of specific factors that initially begin the disease trajectory difficult. Aging is a critical feature in permitting occurrence of neurodegenerative syndromes. Hastening of normal changes taking place during brain aging could facilitate the incidence of distinctive neurological disorders. A favorable strategy toward alleviation of slowly developing age-related changes might be the recognition of those environmental factors which hasten changes associated with normal brain senescence, and then developing measures to protect against such harmful factors.

The simplest way of explaining much of the research on Al neurotoxicity is the idea that Al can accelerate the development of the inflammatory changes that characterize the normally aging brain. Colloidal aluminum can also exist in a form that promotes the free radical-producing potential of redox-active metals such as copper and iron. Such enhanced free radical generation may also contribute to the inflammatory cascade. This could be a mechanism underlying the impact of Al ingestion upon the promotion of AD. It could also help to account for more tenuous connection suggested for Al and less prevalent age-related neurological diseases. Thus, if Al is able to amplify the inflammatory aspect of normal brain aging, such a chronic state of excessive and ineffective immune function could form a base for the advent and expansion of more specific neurological age-related disorders.

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