Aluminium and Alzheimer's Disease
The Science that Describes the Link
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CHAPTER 16

Oxidative and Inflammatory Properties of Aluminum: Possible Relevance in Alzheimer's Disease

Stephen C. Bondy * and Arezoo Campbell

Department of Community and Environmental Medicine, Center for Occupational and Environmental Health, University of California Irvine, Irvine, California 92697-1820, USA

* Corresponding author, email: scbondy@uci.edu

Abbreviations: Al – aluminum; AD – Alzheimer's disease; ROS – reactive oxygen species; NFT – neurofibrillary tangles; HNE – 4-hydroxynonenal; SOD – superoxide dismutase; TNF – tumor necrosis factor; IL – interleukin; ACT – antichymotrypsin; NSAIDs – nonsteroidal anti-inflammatory drugs; iNOS – inducible nitric oxide synthetase; CNS – central nervous system; GFAP – glial fibrillary acidic protein

Summary

Both inflammation and the production of reactive oxygen species may be beneficial short-term response to extracellular stressors, and kill pathogens that have accessed nervous tissue. These factors, however, when active over an extended period following an ineffectual response to a persistent stimulus, can become harmful. Colloidal Al could constitute such irresolvable foci that cannot be cleared by activated microglia. This can lead to chronic inflammatory responses that eventually overwhelm neurons and impair their function.

Historical Perspective

The toxicity of aluminum (Al) has been the subject of much research in the past few decades. Although it has been believed that environmental levels of the metal are generally innocuous to human health, a causal role for Al has been established in dialysis dementia (Alfrey et al., 1976), osteomalacia (Bushinsky et al., 1995) and microcytic anemia without iron deficiency (Touam et al., 1983). Aluminum has also been implicated in Alzheimer's disease (AD) by epidemiological reports and studies describing elevated levels of Al in AD brains although this remains a controversial issue. Other clues come from disorders related to AD. In Down's Syndrome, which leads to early onset of AD (Schupf et al., 1998), aluminum has been reported to be absorbed from the gastrointestinal tract to a greater extent than normal (Moore et al., 1997). The transgenic TS65Dn mouse model for

this disorder which bears a trisomic segment of murine chromosome 16 homologous to human chromosome 22, has a significantly higher brain Al content than the corresponding diploid control (Berg et al., 2000). The exact mechanism of Al toxicity is not known but there is considerable evidence that show the metal's capacity to exacerbate the generation of reactive oxygen species (ROS) despite the fact that Al is a trivalent cation incapable of redox changes.

Correlation with, and Possible Causation of, Alzheimer's Disease with Excess Generation of Free Radicals

Recent studies suggest that oxidative stress may play a role in a wide range of neurological diseases including AD (Bondy, 1998). The frontal cortex of AD patients shows a significantly higher ability to produce ROS compared to control brains (Zhou et al., 1995). Carbonyl modifications are increased in the AD brain, especially in neurofibrillary tangles (NFT), and this oxidative marker may provide a clue for the mechanism by which the cytoskeletal abnormality forms and leads to the pathological lesions (Smith et al., 1996).

A significant increase in lipid peroxidation has been found in the temporal cortex of AD patients when compared to age-matched control brains (Marcus et al., 1998). Levels of 4-hydroxynonenal (HNE) an advanced end product of lipid peroxidation, are elevated in the amygdala, hippocampus and the hippocampal gyrus of AD patients (Markesbery & Lovell, 1997). A parallel increase in the level of free HNE in the ventricular fluid of patients with AD has also been reported (Lovell et al., 1997). When AD brains are treated with antibodies against both 4-hydroxynonenal and neurofibrillary tangles, those neurons lacking tangles also display HNE-pyrrole immunoreactivity (Sayre et al., 1997). This implies that oxidative stress is not merely a consequence of tissue damage but may be a pre-existing state, which may subsequently lead to neuronal damage. Smith et al. (1998) showed that HNE and the antioxidant enzyme heme oxygenase-I, as well as tau-reactive dystrophic neurites, are all located at the periphery of amyloid plaques. HNE is capable of modulating the tau protein by covalently binding to it and this may lead to increased phosphorylation of tau protein (Mattson et al., 1997).

Role of Aluminum on ROS Promotion

Iron is a pro-oxidant metal present in most cell compartments, and aluminum potentiates the capability of Fe to promote oxidative stress and lipid peroxidation in isolated biological preparations (Gutteridge et al., 1985, Oteiza et al., 1993, Ohyashiki et al., 1998, Bondy and Kirstein, 1996). It has been proposed that metals without redox capacity such as aluminum can make fatty acids more available to attack by free radicals, thus facilitating the propagation of lipid peroxidation (Oteiza et al., 1993, Ohyakishi et al., 1998). Aluminum is capable of enhancing iron-based oxidant events in protein-free liposomes with a negative charge on their outer surface suggesting that the electrostatic attraction of cations to the surface negative charge plays a role in metal-induced potentiation of

ROS (Bondy et al., 1998a). Since the potentiation of iron-based ROS production by aluminum can occur in liposomes containing no protein, altered membrane configuration or competition for iron-binding sites on proteins cannot be invoked in order to account for this phenomenon.

Both aluminum and β-amyloid peptides are not intrinsically pro-oxidant but there is a strong resemblance between their ability to stabilize iron in the ferrous form and thus enhance the Fenton reaction (Yang et al., 1999). This may provide a mechanism by which these materials can promote free radical generation by iron and also suggests parallels between the toxicity of amyloid peptides and Al salts.

In vivo studies have demonstrated that aluminum plays a role in ROS generation. Intraperitoneal injection of aluminum gluconate, over a 21-day period, increases the rate of ROS formation in cortical tissue (Bondy et al., 1998b). The brain of rats treated with aluminum lactate for 4 weeks showed an increase in lipid peroxidation and a significant decrease in the antioxidants, superoxide dismutase (SOD), catalase, and glutathione peroxidase (Julka & Gill, 1996). This is paralleled by the finding that SOD and catalase levels were depressed in the temporal cortex of AD patients (Marcus et al., 1998).

Reactive oxygen intermediates have been a threat to organisms ever since the advent of aerobic metabolism. When bacteria are exposed to ROS, they initiate the synthesis of an array of proteins with protective functions (Müller et al., 1997). It is likely that throughout evolution, this response of organisms to reactive oxygen compounds, has led to the ability of cells to utilize these oxidant molecules in promoting a defensive reaction to signals associated with pathogenic events. Exposure of rat glioma cells to aluminum sulfate for 48 h caused an increase in the generation of ROS. However, the salts did not elicit a similar response in rodent neuroblastoma cells (Campbell et al., 1999). This effect was reproduced in human cell lines exposed to different concentrations of aluminum (Campbell and Bondy, 2000). This substantiates the concept that short-term production of reactive oxygen intermediates may not simply be undesired products of oxidizing reactions but may be important stress-induced messenger molecules. Indeed, hydrogen peroxide has been shown to mediate important events in the initiation of innate immunity by controlling the activation of the transcription factor NF-κB, which is involved in inflammation and the immune response (Schmidt et al., 1995).

There is a great evolutionary conservation of components of the innate immune response in organisms that diverged over a billion years ago. The existence of proteins required for defense against infection has been found in *Drosophila*. The NF-κB system in mammals is a homologue of these transcription factors. The protein domains of these activators of the host defense system have been highly conserved in organisms as divergent as plants, *Drosophila*, and mammals (Medzhitov & Janeway, 1998).

NF-κB is activated by an array of different pathogenic conditions. Viral and bacterial products, eukaryotic parasites, inflammatory cytokines, physical and oxidative stress, as well as some drugs such as phorbol esters, all activate NF-κB (Baeuerle & Henkel, 1994). This pathway controls the expression of genes involved in stress and inflammation (Schreck et al., 1992; Beauparlant & Hiscott, 1996). NF- κB is present in the cytoplasm as an inactive complex bound to the inhibitory subunit IκB. In this conformation, the transcription factor is unable to translocate to the nucleus. However, extracellular stress factors can result in the phosphorylation and subsequent release of the inhibitory subunit

(Schreck et al., 1992). Degradation of the IκB depends on phosphorylation of the subunit by a kinase complex that is activated by cytokines. This leads to the ubiquitinylation and proteolytic obliteration of the inhibitory subunit (Stancovski & Baltimore, 1997). Once the dimer is free, it can then enter the nucleus and bind to the promoter region of a variety of genes involved in the stress response and immunity.

The common factor responsible for the release of IκB appears to be the cell's redox status, which is determined by the levels of reactive oxygen intermediates. Very low amounts of hydrogen peroxide, but not superoxide, has been shown to activate NF-κB. In cells, which over express hydrogen peroxide or superoxide dismutase (an enzyme that converts superoxide to hydrogen peroxide), there is an increase in tumor necrosis factor (TNF)-induced NF-κB activation. (Schmidt et al., 1995). Hydrogen peroxide may function as an extracellular messenger since it is relatively stable, uncharged and thus diffusible. It is also readily degraded by catalase and thus is easily detoxified (Müller et al., 1997).

Macrophages and microglial cells produce H_2O_2 at inflammatory sites and several other factors, which activate the transcription factor, also increase ROS production. Factors leading to such activation include UV radiation, LPS, TNF, and IL-1 (Baeuerle & Henkel, 1994). In the case of TNF-induced activation of NF-κB, alteration in mitochondrial electron flow has been shown to underlie the increased production of ROS (Schmidt et al., 1995). The relevance of NF-κB to neurodegeneration is further suggested by a correlation between the amount of activated NF-κB and a key inflammatory enzyme, COX-2, in both aging and AD temporal lobe neocortex (Lukiw & Bazan, 1998).

The Role of Inflammation in Alzheimer's Disease

In the cerebrospinal fluid of AD patients, the level of interleukin-1 (IL-1) type II receptor is elevated (Garlind et al., 1999). IL-1β is a very strong inducer of IL-6 and this stimulation is dependent on transcription and protein synthesis (Cadman et al., 1994). Both cytokines induce the synthesis of acute-phase proteins such as antichymotrypsin (ACT) and TNF, (Dunn, 1991).

Microglia appear to play an active role in neurodegeneration by becoming activated following irresolvable neuroinflammation, and secreting complement proteins, oxygen radicals, cytokines, prostaglandins and adhesion molecules that can be toxic to healthy neurons. This process which may be consequent to a futile attack upon indigestible amyloid aggregates, may ultimately lead to dementia (Bondy and Campbell, 2000). Since the pathological lesions of the AD brain contain activated microglia and astrocytes associated with elevated levels of cytokines, complement proteins and acute phase proteins, it may be that progression of the disease involves chronic neuroinflammation.

The prevalence of AD in rheumatoid arthritis patients, who consume anti-inflammatory drugs over an extended period, is lower than in the normal population (McGeer et al., 1990). Seventeen separate epidemiologic studies all suggest that anti-inflammatory drugs may play a protective role against AD (McGeer et al., 1996). Nonsteroidal anti-inflammatory drugs (NSAIDs) are able to suppress microglial activation (Mackenzie et al., 1998). By this means, NSAIDs may reduce the inflammation associated with senile

plaques and thus slow down the disease process. Ibuprofen, a cycloxygenase-inhibiting NSAID, has been shown to decrease levels of inducible nitric oxide synthetase (iNOS) mRNA in primary glial cell cultures (Stratman et al. 1997) and the glucocorticoid dexamethasone dose-dependently reduces the release of IL-6 from human astrocytoma cell lines (Blom et al., 1997).

Lipopolysaccharide-induced chronic inflammation can cause extensive astrogliosis in the temporal lobe regions of the rat brain. The activation of the astroglial cells is associated with an increase in the production of IL-1β, hippocampal cell loss, and impairment of spatial memory, all of which mirror changes seen in the AD brain (Wegrzyniak et al., 1998).

Aluminum-Induced Inflammation

Several studies have found that Al can cause inflammation in a variety of non-nervous tissues. Low doses of aluminum, present in parenteral nutrition formula, can produce marked portal inflammation correlating with the duration of exposure and the amount of Al accumulated in the liver (Demircan et al., 1998). Rats exposed to oral doses of aluminum chloride and aluminum lactate expressed an increase in plasma α 1 globulins, consequent to inflammation (Cherroret et al., 1995). Alum precipitate, which is composed of a suspension of aluminum hydroxide, is used as an adjuvant in vaccines used to inoculate humans. The effectiveness of the adjuvant is attributed to the irritant effect of alum, which increases macrophage processing of the antigen (Benjamini & Leskowitz, 1991). Aluminum sensitization can develop in some children vaccinated for diphtheria, tetanus and pertussis, using vaccines, which contain aluminum hydroxide as an adjuvant. Al-induced inflammatory nodules are sometimes formed in adults revaccinated for hepatitis B (Cosnes et al., 1990).

There was a correlation between the total concentration of Al deposited with fibrosis and focal lung inflammation in an occupational health study of workers exposed to metals and aluminum. Workers with the mildest histological findings also had the lowest concentration of Al particles analyzed from transbronchial biopsies (Schwarz et al., 1998). A case study of a 72 year old woman with end stage renal failure reported elevated serum Al content as well as amyloid deposits in her joints. The synovial region contained an amorphous material surrounded by chronic inflammatory cells. The mineralization front of her bones stained positive for aluminum and she showed signs of osteomalacia (Isaacs et al., 1992). To determine whether aluminum is responsible for the articular toxicity often found in chronic renal failure patients on hemodialysis, rats were injected in the knee with either Al hydroxide or Al lactate. The aluminum hydroxide remained in the vicinity of the injection site for an extended period and induced an increase in the number of leukocytes. Aluminum lactate caused an increase in the infiltration of inflammatory cells and also caused an increase in the production of eicosanoids (Chary-Valckenaere et al., 1994).

Primary glial cells are more vulnerable than neurons to long term exposure to aluminum chloride. While primary cerebellar neurons, containing only 1% glial cells, did not exhibit susceptibility to aluminum chloride, neuronal–glial mixed cultures consisting of 10% glial cells showed a marked decrease in neuronal viability. This suggests the

activation of glia by Al salts leading to harmful effects on neurons. Aluminum was found to be associated with the cells and the level of the association of aluminum with cells was higher in the mixed cultures than in the primary neurons, suggesting a basis for the responsivity of glial cells to Al (Suárez-Fernández et al., 1999). We have also reported that, following incubation with Al salts, cells of glial origin are associated with aluminum to a greater extent than those of neural origin (Campbell et al., 1999). Finally, Al induced apoptosis only in primary astrocytes and not in primary neuronal cultures (Suárez-Fernández et al., 1999). This supports the concept that neurodegeneration may initially be due to the compromised state of the astroglial cells leading to the secondary loss of viability and function of neuronal cells. Aluminum exposure may activate glial cells and enhance oxidant processes occurring within them, thus indirectly jeopardizing the integrity of neuronal cells.

Informed Opinion

Cytokines in Nervous Tissue

The central nervous system is largely but not completely isolated from surveillance by the systemic immune system by the blood brain barrier (Brightman et al., 1995). However, local immune responses are important in cerebral defense processes. As a result of the presence of pathogens or the occurrence of trauma, a range of interleukins, such as IL-1, IL-6 and IL-8, can be synthesized, by activated microglia and macrophages (Dunn, 1991). Their normal function is to recruit more of these cell types to the pathologic site and thus coordinate the immune response. Their integrated action can effect wound healing, destruction of pathogens and the regulation of tissue regrowth and wound healing. These antigen-nonspecific soluble factors are not stored within cells but are synthesized and secreted as needed. They typically have a short half-life but can damage the CNS when their presence is prolonged. Extended production of these chemotactic factors can lead to cytotoxicity due to the recruitment and activation of cells producing high concentrations of ROS (Dunn, 1991).

Superoxide and nitric oxide are necessary for the destruction of invasive pathogens through cell-mediated killing. This may explain why ROS formation in response to a stressor such as aluminum, is only increased in the immunocompetent cells derived from glia and not in cells of neuronal origin (Campbell et al., 1999; Campbell and Bondy, 2000). The cell generally has enough antioxidant reserve so that it is protected against the harmful effects of reactive oxygen intermediates. Cells also have the capacity to react to oxidative stress by production of increased amounts of antioxidant enzymes. Only when the antioxidant capacity of cells are overwhelmed can these intermediates cause cell damage (Keller et al., 1997; Blanc et al., 1997).

When the cell is functioning normally, the production and detoxification of ROS is tightly controlled. However, chronic exacerbation of levels of ROS can ultimately compromise cell integrity. Thus, controlled free radical formation in conjunction with an acute inflammatory event may serve a benign regulatory function, but if these processes occur chronically, they can eventually be harmful.

The outcome of the cellular immune response at the cell level to foreign antigens is determined by the nature of the substance eliciting the reaction. Soluble materials will be digested by phagocytes and the inflammation will resolve itself. Bacteria can be phagocytosed and also dispersed by proteolytic processes. However, if the agent is indigestible, it can persist and result in a state of chronic inflammation (Dunn, 1991). Since aluminum salts form colloidal species in solution, the aluminum-induced increases in ROS generation observed in intact cells may result from an innate immune response to extracellular aluminum particles.

There is limited direct evidence of Al-induced inflammatory events in the diseased central nervous system. Extended aluminum lactate treatment of rabbits increased glial fibrillary acidic protein (GFAP) concentrations in the frontal cortex (Yokel & O'Callaghan, 1997). Reactive astrocytes, which produce GFAP, are associated with both senile plaques and cerebral microvessels (Cullen et al., 1997) and GFAP is increased in the temporal cortex of AD patients (Panter et al., 1985). The finding that Al salts can increase the expression of activated NF-κB in isolated human glioblastoma cells constitutes further evidence for a primary inflammatory role of glia following aluminum intoxication (Campbell & Bondy, 2000).

The cerebral microvasculature becomes more prone to damage during aging and this may result in the compromise of the blood brain barrier (BBB) (Kemper, 1984). Since

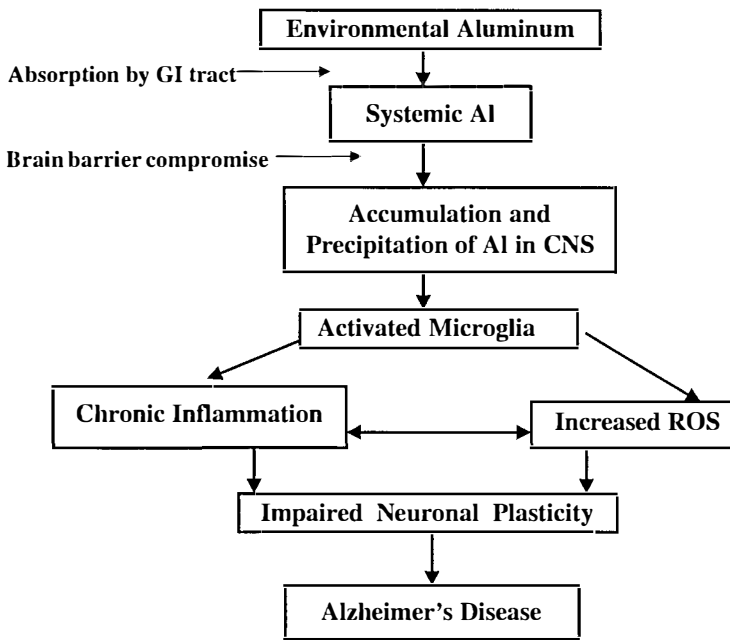

Fig. 1. The potential link of aluminum exposure to Alzheimer's disease. Accumulation of extracellular aluminum in the CNS leads to an innate immune response comprising of increased inflammatory and oxidative events. The persistence of insoluble aluminum particles leads to unresolved microglial inflammation and consequent continuation of the production of harmful reactive oxygen species, which lead to neuronal malfunction.

this barrier is the major mechanism by which the brain keeps out foreign antigens, jeopardizing the BBB could lead to compounds such as aluminum, which are generally confined to the systemic circulation, to enter the brain. Cerebral levels of aluminum have in fact been found to increase with age (Shimizu et al., 1994; McDermott et al. 1979). Once inside the brain, the metal may activate glial cells and cause a chronic inflammatory response, which can then lead to the formation of senile plaques (Müller et al., 1997).

Aluminum has clearly been shown to be capable of inducing both inflammation and excess ROS. While the issue of aluminum as a contributor to AD, remains controversial, much evidence comes from both animal studies and human clinical reports. Furthermore, the mechanistic basis of both the pro-oxidant and glial-activating properties of aluminum is increasingly becoming evident. Immunological failure to disperse xenobiotic inclusions, such as colloidal aluminum particles, within the CNS can lead to chronic inflammatory responses that ultimately involve neurons and impair their function (Fig. 1).

While the relation between Alzheimer's disease and aluminum exposure has yet to be unequivocally demonstrated in clinical and epidemiological settings, a firm mechanistic basis which could subserve such a relation is emerging. The feasibility of this outline of how aluminum may promote extended and interactive oxidant and inflammatory events will be enhanced by new mechanistic and clinical information.

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The Science that Describes the Link

Edited by

Christopher Exley
Birchall Centre for Inorganic Chemistry and Materials Science,
School of Chemistry and Physics,
Keele University,
Staffordshire, ST5 5BG, UK

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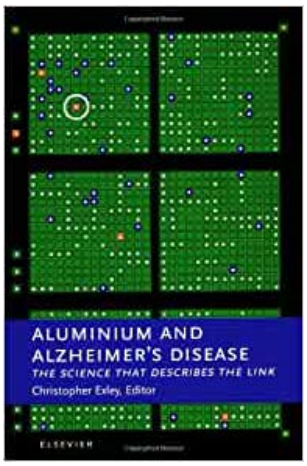

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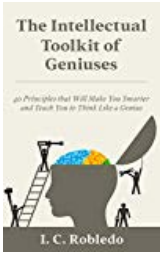

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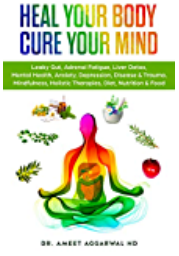

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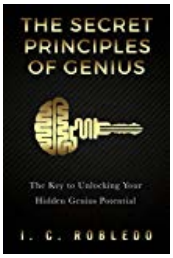

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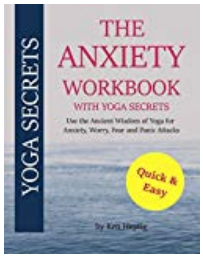

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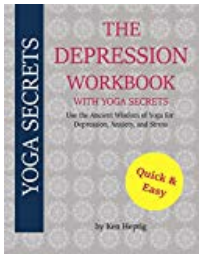

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Editorial Reviews

Review

Mark A. Lovell, University of Kentucky, USA
A review of current research that describes an association between aluminium (Al) and Alzheimer's disease (AD). A "historical perspective" that provides a comprehensive review of research in the area followed by an "informed opinion" that advances what remains to be learned about the association of Al and AD. The inclusion of a table of the main epidemiological studies of the last two decades along with design structure, diagnosis and association is particularly useful. This is a well written and, for the most part, balanced monograph describing current and past studies relating Al to the pathophysiology of AD. Attractively typeset and up-to-date this book would be a useful tool for researchers interested in chemistry and biochemistry of Al not only as it relates to neuron degeneration in AD but in other diseases as well.
Journal of Alzheimer's Disease
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