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Review

ALUMINUM INDUCED OXIDATIVE EVENTS AND ITS RELATION TO INFLAMMATION: A ROLE FOR THE METAL IN ALZHEIMER'S DISEASE

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Abstract - Aluminum (Al) is a simple trivalent cation incapable of redox changes. The toxicity of the metal has been the subject of much controversy in the past few decades. Although it has been generally believed that the metal is 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) although a direct causal role has not been determined. The exact mechanism of Al toxicity is not known. However, there are several lines of evidence that show the metal's capacity to exacerbate oxidative events. The present review is intended to propose a coherent pathway linking Al-induced oxidative events to Alzheimer's disease. The preliminary segment is an introduction to reactive oxygen species and their potential involvement in the pathogenesis of AD and the generation of an inflammatory response. Evidence on the relation between AD and inflammatory processes is also presented. The epidemiological and clinical evidence of Al neurotoxicity is summarized in the second section of the review. Finally, a hypothesis indicating that aluminum can exacerbate AD by activating ROS generation and initiation of an inflammatory cascade is presented.

Key words: Aluminum, inflammation, Alzheimer's disease

RELATION OF REACTIVE OXYGEN SPECIES TO INFLAMMATION

ctive oxygen species in biological systems

mitochondrion utilizes 90% of respired oxygen produce ATP. The active site of most of the ymes of the mitochondrial electron transport ain contain transition metal ions and the capability these metals to transfer single electrons makes em useful for facilitating redox reactions alliwell, 1992). However, electrons can leak from these intermediates and directly react with oxygen. Fridovich (1978) has estimated this leakage to be approximately 5% of the total electron flow. The reaction of one of these single leaked electrons with the oxygen molecule will yield the superoxide radical ($O_2^{\cdot -}$) which is detoxified by superoxide dismutase. The leakage of two electrons will yield hydrogen peroxide (H_2O_2), which is not a free radical because it does not contain any unpaired electrons. However, it is a relatively weak oxidizing agent that can easily traverse cell membranes because of its non-ionic nature and cause injury at sites distal to its formation (Halliwell, 1992).

The most devastating effect of the generation of these two relatively stable free radicals is not from their

Abbreviations: **ACT**: antichymotrypsin; **Al**: aluminum; **AD**: Alzheimer's disease; **BBB**: blood brain barrier; **HNE**: 4-hydroxynonenal; **GFAP**: glial fibrillary acidic protein; **NSAIDs**: non-steroidal anti-inflammatory drugs; **ROS**: reactive oxygen species

direct oxidant effects on the cell. Rather, it is the formation of the highly reactive hydroxyl radical (•OH) that is thought to be the most injurious aspect of oxidative stress. This free radical is formed by the Fenton reaction. The hydroxyl radical is so reactive that it will remove electrons from any molecule in its vicinity. However, it is too short-lived to travel within the cell and thus, depending on where it is formed, it can damage either the DNA or cytosolic and membrane-bound macromolecules. Most of the injury caused by hydrogen peroxide or superoxide results from their conversion to the hydroxyl radical (Cochrane, 1991). Free radicals can also damage the cell membrane by initiating lipid peroxidation. This chain of free radical formation results in changes in the membrane's normal characteristics (Halliwell, 1992). The function of ion channels and receptors can then be compromised.

Excess pro-oxidant events: correlation with, and possible causation of, Alzheimer's disease

Recent studies suggest that oxidative stress may play a role in a wide range of neurological diseases (Bondy, 1998). This includes the neurodegeneration that leads to Alzheimer's disease. 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). 4-hydroxynonenal (HNE) is an advanced end product of lipid peroxidation. There is a significant increase in the level of free HNE in the amygdala, hippocampus and the hippocampal gyrus of AD patients compared to age-matched controls (Markesbery and Lovell, 1997). A 2.5 fold increase in the level of free HNE in the ventricular fluid of patients with AD has also been found (Lovell *et al.*, 1997). When AD brains are treated with antibodies against both 4-hydroxynonenal and neurofibrillary tangles, neurons lacking tangles display HNE-pyrrole immunoreactivity while the age-matched controls only display background immunoreactivity (Sayre *et al.*, 1997). This suggests that oxidative stress is not merely a consequence of pre-existing damage. Rather, it is an already existing condition, which may subsequently lead to neuronal damage. Smith *et al.* (1998) established an association between oxidative stress, τ protein and β-amyloid. This group showed that HNE and the antioxident enzyme heme oxygenase-I, as well as τ-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 by means of this linkage, increase the phosphorylation of the protein while decreasing its dephosphorylation (Mattson *et al.*, 1997).

Neurodegenerative disease and inflammatory events

The brain is largely isolated from surveillance by the systemic immune system. However, intracerebral local immune responses are important in cerebral defense processes. Interleukins, such as IL-1, IL-6 and IL-8, are primarily synthesized by activated microglia and macrophages in response to pathogens and trauma (Dunn, 1991). Their normal function is to recruit more microglia and macrophages to the pathologic site, coordinate the immune response and regulate tissue regrowth and wound healing. These antigen-non-specific 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. Chronic production of these chemotactic factors can result in cytotoxicity because they recruit and activate macrophages that produce high concentrations of ROS (Dunn, 1991).

In the cerebrospinal fluid of AD patients, the level of IL-1 type II receptor is significantly elevated compared to control samples (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 tumor necrosis factor (TNF) (Dunn, 1991). ACT accumulates in neurofibrillary tangles and senile plaques (Gollin *et al.*, 1992). TNF levels are increased in the brain of AD patients and this increase is positively correlated with the concentration of plasma IL-6 (Bruunsgaard *et al.*, 1999; Maes *et al.*, 1999).

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). A review of seventeen separate epidemiologic studies has confirmed that anti-inflammatory drugs may play a protective role against the neurodegeneration (McGeer *et al.*, 1996). It has also been demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs) are able to suppress microglial activation (Mackenzie and Munoz, 1998). Thus, NSAIDs may suppress the inflammation associated with senile plaques and may thus ameliorate the disease process. The NSAID, ibuprofen has been shown to decrease levels of iNOS mRNA in primary cell cultures (Stratman *et al.*, 1997) and dexamethasone 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).

NF-κB: a mediator of inflammatory events

There is a great evolutionary conservation of components of the innate immunity in organisms that diverged over a billion years ago. Studies in *Drosophila* have shown the existence of proteins required for defense against infection. These peptides contain regulatory regions that bind transcription factors with the Rel domain. The NF-κB system in mammals is a homologue of these transcription factors. The induction of the innate immune response requires the presence of signaling modalities involved in the activation pathway. 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 and 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 and Henkel, 1994). This pathway controls the expression of genes that are involved in stress and inflammation (Schreck *et al.*, 1992; Beauparlant and Hiscott, 1996). Table 1 lists some of the genes regulated by the activation of NF-κB.

NF-κB is located in the cytoplasm in an inactive form bound to the inhibitory subunit IκB. The protein is composed of a homodimer or a heterodimer of DNA-binding members of the NF-κB/Rel family. In this trimeric conformation, the transcription factor is unable to translocate to the nucleus. However,

Table 1 *Genes regulated by activation of NF-κB*

NF-κB activating Agents	NF-κB Target Genes
Bacteria and their products *(LPS)*	Major histocompatibility complexes
Viruses and their products *(HIV-1)*	Interleukins
Inflammatory cytokines *(IL-1β)*	Complement factors
Oxidative stress *(H_2O_2)*	NF-κB precursors
Physical stress *(trauma)*	NO-synthase
Acute phase proteins *(TNF)*	IκB subunits
	Superoxide dismutase

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 ubiquitination and proteolytic obliteration of the subunit (Stancovski and 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 level 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 TNF-induced NF-κB activation. This response is very time sensitive and disappears after 40 min. (Schmidt *et al.*, 1995).

Hydrogen peroxide may function as an extracellular messenger since it is uncharged and diffusible. It is also readily degraded by catalase and thus is easily detoxified (Müller *et al.*, 1997). A novel antioxidant L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyl-tridecyl)-2H-1-benzopyran-6-yl hydrogen phosphate] potassium salt (EPC-K1), an amphipathic compound forming a diester linkage between vitamins C and E, has radical scavenging activity and is found to be a strong inhibitor of NF-κB. However, vitamins C and E by themselves cannot inhibit the transcription factor (Hirano *et al.*, 1998).

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 and 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). There is evidence that exposure to TNF causes the diversion of electrons from complex III of the electron chain directly onto oxygen (Baeuerle and Henkel, 1994).The relation is reciprocal since, if the mitochondrial electron transport is inhibited, the activation of NF-κB is blocked (Schmidt *et al.*, 1995).

The relevance of NF-κB to neurodegeneration is suggested by a correlation between the amount of activated transcription factor NF-κB and a key inflammatory enzyme, COX-2, in both aging and AD temporal lobe neocortex (Lukiw and Bazan, 1998).

ROS as regulators of the inflammatory response

Reactive oxygen intermediates have been a threat to organisms ever since the advent of aerobic metabolism. When bacteria are exposed to ROS, they start to synthesize an array of proteins with protective functions (Müller *et al.*, 1997). It is possible that throughout evolution, this response of organisms to reactive oxygen compounds, such as hydrogen peroxide, has led to the ability of cells to use these oxidant molecules in promoting a defensive response to signals relating to pathogenic events.

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). Superoxide and nitric oxide are necessary for the destruction of invasive pathogens through cell-mediated killing. This may explain why ROS formation is only increased in the immunocompetent glioblastoma cells in response to a stressor such as aluminum (Campbell *et al.*, 1999; Campbell and Bondy, submitted). Normally, the cell contains enough antioxidants such as SOD and GSH so that it is able to prevent the harmful effects of such reactive oxygen intermediates. Cells also have the ability to produce more antioxidants in response to oxidative stress and the SOD gene transcription is controlled by NF-κB (Lukiw *et al.*, 1998). Only when the antioxidant capacity of cells are exhausted can these intermediates cause cell damage by initiating lipid peroxidation which can result in the production of 4-hydroxynonenol, which itself is toxic (Blanc *et al.*,

1997; Keller *et al.*, 1997).

When the cell is functioning normally, the production and detoxification of ROS is tightly controlled. Events that chronically exacerbate the natural production of these compounds can lead to a reduction in the natural antioxidant status of the cells and thus 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.

ROLE OF ALUMINUM IN NEURODEGENERATIVE DISEASE AND RELATED PARAMETERS

Aluminum neurotoxicity and its relation to Alzheimer's disease

Aluminum exposure and its relevance to human health has been the subject of much controversy. In 1976, Alfrey *et al.* implicated aluminum as the possible agent responsible for the outbreak of an encephalopathy in uremic patients on chronic hemodialysis who routinely received Al-containing phosphate binding gels. Graphite furnace analysis of the brain of the uremic patients with encephalopathy revealed a significantly higher level of aluminum content in comparison to control values (Alfrey *et al*, 1976). In 1991, a case study further implicated aluminum as the cause of the dialysis encephalopathy syndrome (DES) by showing that the symptoms of the disease completely disappear after cessation of oral aluminum intake (Russo *et al.*, 1991). Aluminum-induced encephalopathy has been reported in patients with renal failure, who have undergone bladder irrigation with 1% alum solutions (Phelps *et al.*, 1999).

Most of the intravenous feeding solutions contain aluminum and impaired neurological development was found in preterm infants subjected to prolonged exposure to these Al-containing intravenous solutions (Bishop *et al.*, 1997). The use of aluminum as a prophylactic agent against silicotic lung disease in mine workers has also been shown to have adverse neurological consequences. Such workers displayed cognitive impairment when compared to workers who were not treated with the aluminum salts. The duration of exposure to the metal correlated strongly with the impaired cognitive function (Rifat *et al.*, 1990). Workers in the aluminum remelting industry also expressed neurobehavioral disturbance although this impairment could also have been related to co-exposure to a variety of other chemicals such as manganese and vinyl chloride monomer (Kilburn, 1998). Residing in areas where aluminum concentrations in the municipal drinking water are 100 µg/l or greater has been reported to increase the risk of developing Alzheimer's disease (McLachlan *et al.*, 1996). This study also revealed a dose-response correlation between increasing concentrations of Al in the drinking water and the risk of developing AD.

One of the first reports linking aluminum to Alzheimer's disease found that there was an elevated level of aluminum in necropsy and biopsy samples of the brains of patients with histopathologically confirmed Alzheimer's disease when compared to necropsy samples of normal brains (Crapper *et al.*, 1973). In contrast, a study by McDermott *et al.* (1979) found no significant changes in the brain aluminum concentration of patients with AD compared to normal age-matched controls. However, they did find that the region with the highest aluminum content is the hippocampus, which is the most critical site for brain lesions in AD. They also found an increase in aluminum concentration with increasing age. A more recent study reported that the level of aluminum is not elevated in the frontal cortex, temporal cortex, liver or the head of femur of patients with AD (Bjertness *et al.*, 1996).

Because of these conflicting results, the issue of whether aluminum plays a role in the etiology of AD has not as yet been resolved. It has been proposed that the root of this discrepancy is in the methodology used to measure the metal. If there is an elevated level of aluminum in the brain of patients with senile dementia, it would be localized only in small areas which are most effected. This increase may be

masked if bulk brain tissue is analyzed (Savory *et al.*, 1997). Indeed, direct analysis of the Al content in neurofibrillary tangles shows an increase in the concentration of the metal (Perl and Brody, 1980).

Role of aluminum in ROS promotion

In isolated systems aluminum can potentiate the oxidative stress produced by iron. Iron, which is present in most cell compartments, is known to be a pro-oxidant metal and aluminum potentiates the capability of Fe to produce oxidative stress (Bondy and Kirstein, 1996). It has been hypothesized that metals without redox capacity such as aluminum can increase iron-induced lipid peroxidation by making fatty acids more available to the attack of free radicals and thus facilitate the propagation of lipid peroxidation (Oteiza *et al.*, 1993). Aluminum acetylacetonate, but not chromium acetylacetonate, is able to significantly increase Fe-induced peroxidation (Ohyashiki *et al.*, 1998). This effect was completely abolished if the membranes were treated with 1% triton, indicating that the intact membrane is necessary for Al potentiation of Fe-induced increase in lipid peroxidation.

Exposure of rat glioma cells to aluminum sulfate for 48 hrs. caused an increase in the generation of ROS. However, the salts did not elicit a similar response in the rodent neuroblastoma cells (Campbell *et al.*, 1999). This effect was reproduced in human cell lines exposed to different concentrations of aluminum (Campbell and Bondy, submitted). Therefore, reactive oxygen intermediates may not simply be undesired products of oxidizing reactions but may be important stress-induced messenger molecules.

In the presence of aluminum, iron is capable of enhanced ROS formation in protein-free liposomes with a negative charge on their outer surface. Thus, the electrostatic attraction of cations to the surface negative charge plays a role in metal-induced potentiation of ROS (Bondy *et al.*, 1998a). *In vivo* studies have also 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 and Gill, 1996). Similarly, the temporal cortex of AD patients showed a significant decrease in SOD and catalase activity, while no change was detected in the level of glutathione peroxidase activity (Marcus *et al.*, 1998)

Aluminum-induced peripheral inflammation

The outcome of inflammation, the innate response of organisms to immunogenic foreign antigens, is determined by the nature of the substance eliciting the reaction. If the agent is soluble, it will be digested by phagocytes and the inflammation will resolve itself. If the agent is indigestible, it will persist and result in a state of chronic inflammation (Dunn, 1991). Since aluminum salts are known to form colloidal species in solution, it is possible that aluminum-induced increase in ROS generation is due to an innate immune response of the cells to the extracellular aluminum particles.

Although there is no direct evidence of Al-induced inflammatory events in the central nervous system, several studies have found that the metal can cause peripheral inflammation. 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 alpha 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 and 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).

In an occupational health study of workers exposed to metals and aluminum, there was a correlation between the total concentration of Al deposited with fibrosis and focal lung inflammation. 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 years old woman with end stage renal failure showed 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 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 local vicinity of the injection site and induced an increase in the number of leukocytes while aluminum lactate caused an increase in the infiltration of inflammatory cells as well as hemorrhage and edema. Al lactate also caused an increase in the production of eicosanoids (Chary-Valckenaere *et al.*, 1994). In both AD and control brains, reactive astrocytes which produce GFAP were associated with both senile plaques and cerebral microvessels (Cullen, 1997). GFAP is also increased in the temporal cortex of AD patients (Anter *et al.*, 1985). Extended aluminum lactate treatment of rabbits also increased GFAP concentrations in the frontal cortex (Yokel and O'Callaghan, 1997). Further evidence for a primary role of glia following aluminum intoxication is that Al salts can increase the expression of activated NF-κB in human glioblastoma cells (Campbell and Bondy, submitted).

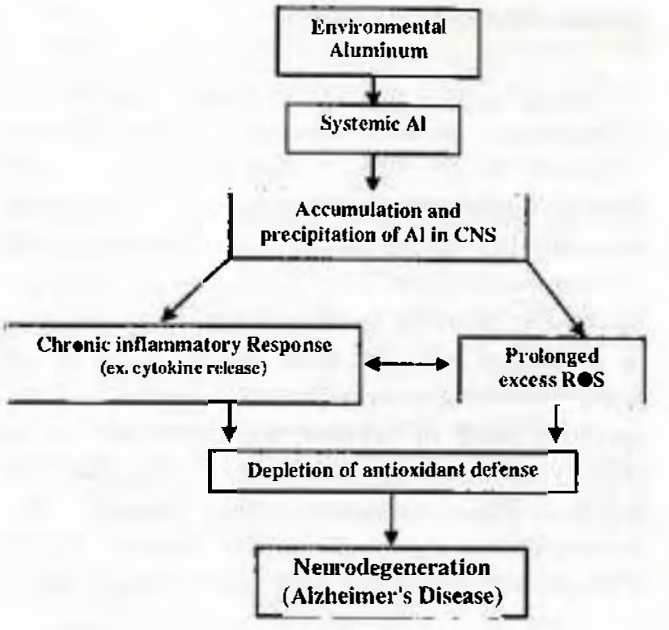

Fig. 1 *The potential link of aluminium exposure to Alzheimer's disease.* Accumulation of extracellular aluminium in the CNS leads to an innate immune response comprising of increased inflammatory and oxidative events. The persistence of insoluble aluminium particles leads to unresolved inflammation and consequent continuation of the production of harmful reactive oxygen species which overwhelm the antioxidant defenses of the cells and subsequently lead to cell death and neurodegeneration.

CONCLUSION

There is continuing controversy as to whether aluminum may play a role in the etiology of Alzheimer's disease. While elevated levels of the metal is found in neurofibrillary tangles (Perl and Brody, 1980), other groups have failed to find any difference between the levels of Al in the AD brain compared to age-matched control (Bjertness *et al.*, 1996). During aging, the cerebral microvasculature becomes more prone to damage and this may result in the compromise of the blood brain barrier (BBB) (Kemper, 1984). Since 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 (McDermott *et al.*, 1979). Once inside the brain, the metal can activate glial cells and cause a chronic inflammatory response, which can then lead to the formation of senile

plaques (Müller *et al.*, 1997).

Primary glial cells are more vulnerable than neurons to long term exposure to aluminum chloride (Suárez-Fernández *et al.*, 1999). While primary cerebellar neurons, containing only 1% glial cells, do not exhibit susceptibility to aluminum chloride, neuroglial cultures consisting of 10% glial cells show a marked decrease in neuronal viability. Aluminum is found to be associated with the cells and the level of this association is higher in the mixed cultures. Al induces 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.

SUMMARY

A clear link exists between several types of chronic age-related neurological disorder and excess production of reactive oxygen species. In parallel, a relation between focal inflammatory events at brain sites pathologically altered by the disease process has frequently been described. While these links are often correlative rather than causal, there are a growing number of reports of amelioration of the disease processes by administration of antioxidant or anti-inflammatory agents.

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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