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The potential role of aluminium in Alzheimer's disease

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Abstract
Aluminium is a trivalent cation that does not undergo redox changes. It has, nonetheless, been implicated in a variety of neurological disorders that have been associated with an increase in the formation of reactive oxygen species (ROS). The exact mechanism of aluminium toxicity is not known. However, accumulating evidence suggests that the metal can potentiate oxidative and inflammatory events, leading to tissue damage. A review of the epidemiological and clinical evidence linking aluminium to Alzheimer's disease (AD) is presented. The article discusses the role of aluminium in two mechanisms that have been linked to neurodegenerative disorders, including AD. Studies are summarized that describe how aluminium can potentiate iron-induced oxidative events. Involvement of aluminium in inflammatory responses, mediated by interleukins and other inflammatory cytokines, is also discussed. Although a direct relationship between aluminium and AD has not been clearly demonstrated, a detailed mechanistic basis for the hypothesis that aluminium may exacerbate events associated with AD is clearly emerging. The results discussed here have broad implications for the role played by aluminium and other metals in neurodegenerative diseases, and suggest that long-term exposure to supra-physiological amounts these metals should be avoided.

Keywords: aluminium; Alzheimer's disease; inflammation; reactive oxygen species

Introduction

Aluminium is an abundant metal that has long been used for water treatment and medicinal purposes. Concern over the systemic effects of chronic aluminium exposure, however, has been increasing over the last 25 years. Although it appears that environmental levels of the metal do not pose an immediate health concern, aluminium has been implicated in dialysis dementia [1], osteomalacia and other forms of renal bone disease [2] and microcytic anaemia in the absence of iron deficiency [3].

While a direct causal role for aluminium in Alzheimer's disease (AD) has not yet been demonstrated definitively, epidemiological evidence suggests that elevated levels of aluminium in brain tissue may be linked to the progression of AD. This subject, however, remains controversial. In order to gain better insight into aluminium toxicity, the mechanisms by which aluminium may impact the progression of neurological disorders is discussed. In this review, the oxidative and inflammatory properties of aluminium in the context of AD and other neurodegenerative events are described.

Aluminium-induced neurological deficits

In 1976, Alfrey implicated aluminium as the possible cause of encephalopathy in uraemic patients on chronic haemodialysis who routinely received aluminium-containing phosphate binders [1]. The study measured the aluminium content of muscle, bone and brain in control subjects and in uraemic patients. In uraemic patients, muscle and bone showed high levels of aluminium (14.8 and 98.5 p.p.m., respectively) compared with control subjects (1.2 and 2.4 p.p.m., respectively). Values of aluminium in brain grey matter in a group of uraemic patients on dialysis who died of a neurological syndrome of unknown cause were 25 p.p.m., compared with 6.5 p.p.m. in a group of uraemic patients on dialysis who died of other causes, and 2.2 p.p.m. in control subjects. Symptoms of severe encephalopathy and high brain aluminium concentration were also reported in a uraemic boy who was not undergoing dialysis, but was treated with oral aluminium hydroxide [4]. A more recent case study further implicated aluminium as the cause of the dialysis encephalopathy syndrome by demonstrating that the symptoms completely disappeared after oral

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aluminium intake was stopped [5]. In another study, a patient with advanced obstructive nephropathy displayed symptoms of encephalopathy after continuous bladder irrigation with 1% alum for 2 days, and these symptoms were associated with elevated serum aluminium levels [6].

Studies in other populations also point to aluminium induction of neurological damage. Infants subjected to prolonged feeding with aluminium-containing intravenous solutions exhibited impaired neurological development [7]. The study demonstrated that increasing aluminium exposure was associated with a reduction in the Mental Development Index, with an adjusted loss of one point per day of intravenous feeding for infants receiving the standard solutions [7].

'McIntyre Powder' (finely ground aluminium and aluminium oxide) was used as a prophylactic agent against silicotic lung disease between 1944 and 1979 in miners in northern Ontario. A morbidity prevalence study conducted between 1988 and 1989 showed that miners exposed to aluminium performed less well on cognitive examinations than did unexposed workers. Further, the likelihood of scores in the impaired range increased with duration of exposure [8]. These studies have prompted considerable investigation into the mechanisms by which aluminium may be linked to neurodegenerative events.

Epidemiological evidence for aluminium implication in AD

There have been no reported cases of acute aluminium toxicity in healthy individuals exposed to environmental levels of the metal in food or water. However, some studies indicate that chronic aluminium exposure may have long-term detrimental effects. Animal studies initially suggested a link between administration of aluminium in drinking water and AD [9]. These studies suggested that the development of brain alterations might depend on the aluminium species present and the method of administration. Subsequently, a Canadian study investigated the effects of aluminium exposure through municipal drinking water systems, using a 10-year residential history. The study correlated the relative risk of developing AD with residence in areas where the concentration of aluminium in drinking water was $\geqslant 100$ μg/l [10]. Similar results were obtained in a French study that included >3700 subjects aged 65 and over. The study determined that the adjusted relative risk for dementia was 1.99 and that for AD disease was 2.14 in subjects exposed to aluminium concentrations >0.1 mg/l [11].

Aluminium and oxidative stress

Oxidative stress is a biochemical process typically caused by the formation of reactive oxygen species (ROS), such as hydrogen peroxide (H_2O_2) and the superoxide radical ($O_2^{\bullet -}$). These species are generated by electron leakage from enzymes involved in the mitochondrial electron transport chain, which contain transition metal ions at their active sites [12]. Most of the cell damage caused by ROS is due to their conversion into a relatively short-lived but highly reactive intermediate, the hydroxyl radical ($^{\bullet}OH$), which can damage DNA, and cytosolic and membrane-bound macromolecules.

Current research indicates that oxidative stress may be a factor in various neurological diseases, including AD [13]. Using electron paramagnetic resonance spectroscopy, it was shown that post-mortem frontal cortex tissue samples of AD patients contained 22% higher (and $>50\%$ higher in the presence of ferrous salts) free radical burdens compared with controls [14]. A study using biochemical measurements of lipid peroxidation found a significant increase in the temporal cortex of AD patients when compared with age-matched control samples [15]. Furthermore, the study showed that the level of superoxide dismutase (an enzyme that helps break down the superoxide free radical) was significantly lower in the frontal and temporal cortex of AD brain samples compared with controls [15]. Another measure of lipid peroxidation is 4-hydroxynonenal (HNE). There is a significant increase in HNE in the ventricular fluid of AD patients compared with control subjects, as measured by high-performance liquid chromatography and immunoassays, demonstrating increased lipid peroxidation in AD brain and suggesting a role for HNE in the neurodegenerative process [16].

Since aluminium exists only as a trivalent cation, it is incapable of promoting redox reactions. However, aluminium is capable of enhancing iron-based oxidation *in vitro* and *in vivo*. While aluminium alone did not promote the formation of ROS in cerebral tissues, aluminium and iron promoted the generation of ROS over concentrations ranging from 50 μM to 1 mM [17]. Similar results were observed in a protein-free liposome system [13]. While the exact mechanism for aluminium-enhanced oxidation by iron is not known, it appears to be tissue and cell specific: intraperitoneal injection of aluminium salts in rats over a 3-week period showed a high level of ROS formation in cortical, but not hepatic tissue [18]. Furthermore, in cells of glial origin, aluminium caused an increase in the rate of ROS production, glutathione depletion and mitochondrial dehydrogenase activity, while cells of neuronal origin were not responsive to the same treatment [19].

Aluminium and the inflammatory response

Several studies have described the inflammatory action of aluminium in a variety of tissues. Low doses of aluminium administered in parenteral nutrition formula in rats caused portal inflammation. This inflammation correlated with the duration of exposure and the amount of aluminium accumulated in liver [20].

Some patients revaccinated for hepatitis B with vaccine preparations that contain aluminium-based adjuvants developed inflammatory nodules [21]. A study of workers exposed to heavy metals and aluminium oxide determined a correlation between the total concentration of aluminium deposited with fibrosis and focal lung inflammation [22].

The role of cytokines and NF-κB

The blood–brain barrier largely isolates the brain from surveillance by the systemic immune system [23]. However, localized immune responses within the brain are important in the cerebral defense mechanism. Interleukins, such as IL-1, IL-6 and IL-8, are synthesized by activated microglia and macrophages in response to pathogens or the occurrence of trauma [24]. These interleukins normally recruit more microglia and macrophages to the affected site, thereby coordinating the immune response, regulating tissue regrowth and promoting wound healing. Since interleukins are synthesized and secreted as needed, and are not stored, they typically have a short half-life. However, they can damage the central nervous system (CNS) when they are secreted over a prolonged period, in part because they recruit and activate macrophages that produce high concentrations of ROS [24].

There is limited direct evidence of aluminium-induced inflammatory events in the CNS. Extended treatment of rabbits with aluminium lactate increased the concentrations of glial fibrillary acidic protein (GFAP) in the frontal cortex [25]. The level of tumour necrosis factor-α (TNF-α), another cytokine implicated in neuronal damage, was significantly increased in the cerebrum of mice exposed to aluminium in drinking water, compared with controls [26]. The observed effects were dose-dependent over a range of concentrations from 0 to 125 p.p.m.

The transcription factor NF-κB is activated by a variety of cell signalling events; it is involved in multiple regulatory pathways, including the regulation of interleukin gene expression and other inflammatory cytokines. Activation of NF-κB is mediated by the release of an inhibitory protein, IκB, a process that is largely dependent on the cell's redox status [27,28]. *In vitro* studies have shown that cells expressing catalase, an enzyme that degrades hydrogen peroxide, are unable to activate NF-κB in response to TNF-α; conversely, cells that accumulated large concentrations of hydrogen peroxide potentiated NF-κB activation [28]. Recently, we have reported that aluminium salts can increase the expression of activated NF-κB in isolated human glioblastoma cells (unpublished observations). Our preliminary results provide further evidence that glia play a primary inflammatory role in aluminium toxicity. A relationship between NF-κB and neuroinflammatory events was also established by a study suggesting that increased NF-κB–DNA binding may be fundamental in driving transcription from inflammation-related genes, such as COX-2, that operate in neurodegenerative disorders including AD [29].

Inflammation and AD

Inflammation has been implicated as one of the causes of AD. The association of astrocytes with plaques is a well-established feature of AD and has generally been interpreted as a secondary reaction to amyloid deposition or neuronal degeneration. A study using brain tissue from AD and control patients suggests that plaques form at the site of microvascular aberrations, followed by reactive and degenerative changes in perivascular astrocytes [30]. Others have examined the regional distribution of cytokines in the temporal cortex, and found that these cytokines were co-localized with reactive microglia and astrocytes in affected regions of AD brain [31]. A review of 17 epidemiological studies from nine different countries in which subjects used non-steroidal anti-inflammatory drugs (NSAIDs) determined that the drugs may have a protective effect against AD [32]. It is thought that the mechanism of this protective effect may involve suppression of microglial activation, rather than inhibiting the formation of senile plaques or neurofibrillary tangles [33].

Conclusions

Although there is increasing evidence that implicates aluminium in the progression of events that leads to AD, some of this evidence remains controversial. Early studies found elevated levels of aluminium in the brain of AD patients [34], and later studies using more sensitive detection methods confirmed small, but significant elevations of aluminium in AD hippocampus, inferior parietal lobule and superior and middle temporal gyri, compared with corresponding control tissues [35]. However, other groups have failed to find any difference between the levels of aluminium in AD brain compared with age-matched controls [36,37].

As the blood–brain barrier is compromised with age, metals that are normally confined to the systemic circulation potentially can enter the brain. Cerebral levels of aluminium have been found to increase with age, supporting the hypothesis that the permeability of the blood–brain barrier increases with age [36,38]. Once inside the brain, aluminium can potentiate the formation of ROS, and activate glial cells. Both these mechanisms stimulate a chronic inflammatory response that ultimately may lead to neurodegeneration [39]. A direct link between aluminium and AD is yet to be established definitively. Nonetheless, it is clear that aluminium is capable of inducing both inflammation and the generation of ROS and thus contributes to the progression of the disease process.

Does aluminium induce a specifically triggered innate immune response? *In vivo*, does chronic aluminium treatment cause an increase in oxidative and inflammatory events in the brain? Can the pro-inflammatory

effects of aluminium be modulated by anti-oxidants or NSAIDs? The answers to these questions will undoubtedly present a clearer picture of the precise roles played by aluminium and other metals in the disease process. Meanwhile, the implication of aluminium in neurodegeneration and other serious disorders should serve as a caution against the long-term ingestion of aluminium and other physiologically similar metals that can accumulate in the brain.

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