What is the risk of aluminium as a neurotoxin?

Christopher Exley

The Birchall Centre, Lennard-Jones Laboratories, Keele University, Staffordshire, UK
Tel.: +44 178 273 4080
c.exley@keele.ac.uk

Aluminium is neurotoxic. Its free ion, $Al^{3+}_{(aq)}$, is highly biologically reactive and uniquely equipped to do damage to essential cellular (neuronal) biochemistry. This unequivocal fact must be the starting point in examining the risk posed by aluminium as a neurotoxin in humans. Aluminium is present in the human brain and it accumulates with age. The most recent research demonstrates that a significant proportion of individuals older than 70 years of age have a potentially pathological accumulation of aluminium somewhere in their brain. What are the symptoms of chronic aluminium intoxication in humans? What if neurodegenerative diseases such as Alzheimer's disease are the manifestation of the risk of aluminium as a neurotoxin? How might such an (outrageous) hypothesis be tested?

Aluminium, the neurotoxin

The neurotoxicity of aluminium has been demonstrated in humans, animal models and in tissue and cell culture [1]. While aluminium's neurotoxicity is incontrovertible, it is much more difficult to understand the risk that this neurotoxin poses to human health. Aluminium is neurotoxic because it possesses an extensive biochemical toolkit and because neurons are predisposed by their longevity toward its intracellular accumulation up to and beyond toxic thresholds [2]. Aluminium is neurotoxic as the establishment of toxicity thresholds can result in neuronal dysfunction, neurodegeneration and ultimately neuronal cell death through a continuum of disruptive events from classical apoptosis through to sudden and violent necrosis [3]. The likely principal antagonist in all such events is $Al^{3+}_{(aq)}$ and its mechanism of action will involve numbers of different agents or intermediates. For example, we know that aluminium is a potent pro-oxidant, its interaction with the superoxide radical anion establishing, fuelling and sustaining redox cycles. The potency of these effects are all the more significant in that the enhanced formation of reactive oxygen species may be accelerated at sites which are distinct and divorced from locations housing the cell's anti-oxidant machinery. For example, aluminium sinks such as the extracellular senile plaques of $A\beta_{42}$ and the intracellular chromatin of neuronal nuclei are both likely targets of aluminium-driven oxidative damage. Aluminium is an excitotoxin and a number of mechanisms have been described, whereby aluminium induces elevated and sustained levels of intracellular Ca^{2+} with significant implications not only for cellular energy metabolism, but also uncontrolled phosphorylation of biomolecules. The presence of biologically reactive aluminium imposes an immediate energy requirement upon a neuron, whether simply because of the need to produce more Ca^{2+}-buffering proteins or because of the requirement to clean-up the consequences of hyperphosphorylation, for example, through autophagosomal activities. Aluminium is a mutagen and the phosphate-rich environment of the nucleus predisposes it to the accumulation of aluminium and subsequent alterations in the expression of genetic materials. The latter may be subtle but sufficient to bring about significant alterations in neuronal physiology over extended time periods. Aluminium is, of course, a powerful immunogen, being the preferred

adjuvant in vaccination and immunotherapy. This activity as an adjuvant, and concomitantly as an antigen, at injection sites in skin or muscle must also be considered for focal accumulations of aluminium within the CNS and such reactivity may underlie aluminium's suggested roles in autoimmunity [3–5].

Aluminium's neurotoxicity

There are simply myriad opportunities for aluminium to exert neurotoxicity and when one considers that Al^{3+} is an effective substituent and, often, potent antagonist for Mg^{2+} then one begins to wonder how neuronal biochemistry persists in the face of an attack by aluminium [6]. The first conclusion has to be that susceptibility and robustness are both serendipitous and that the balance of the two may eventually define whether aluminium exerts toxicity or not. There are circumstances where aluminium is not only biologically reactive, but also neurotoxic and these are situations where the additional presence of aluminium in the brain tips the balance toward toxic effects. Neurodegenerative diseases affecting significant numbers of individuals, such as Alzheimer's disease (AD), Parkinson's disease and multiple sclerosis are likely to be multifactorial in their etiologies and aluminium is a potential contributor to the onset, progression and aggressiveness of these conditions. The difficulty is not in understanding if aluminium is a contributor but when it contributes to disease etiology. For example, in a relatively recent and infamous case the early onset and rapid progression of an aggressive form of congophilic amyloid angiopathy was coincident with extremely high brain aluminium content [7]. Under such circumstances, it is inevitable that aluminium contributes significantly to disease etiology and in this particular case the extremely rare form of congophilic amyloid angiopathy may well have been a direct consequence of high brain aluminium content. Similarly in a recent case of AD in a 66-year-old man occupationally exposed to aluminium, the coincidence of advanced AD pathology and elevated brain aluminium must implicate the latter in the onset and rapid progression of the disease [8]. In neither of these cases is aluminium necessarily the cause of the disease, but to discount its likely role in the etiology of disease is to significantly misunderstand the neurotoxicity of aluminium. It would also be premature to assume that total brain aluminium content is the only determinant of whether aluminium contributes toward neurotoxicity or not. Evidence is burgeoning that once a potentially toxic threshold of aluminium is reached, other factors then come into play as to whether this burden of aluminium is neurotoxic. For example, recent research has highlighted relationships between brain metal content, amyloid pathology and AD such that it was not the absolute brain aluminium content which predicted disease, but the ratio of copper-to-aluminium in the tissue [9]. In individuals demonstrating moderate-to-severe amyloid pathology when the ratio of copper-to-aluminium in brain tissue exceeded 20, the incidence of AD was predicted to be lower. Brain aluminium content must still exceed a toxicity threshold to contribute toward neurotoxicity, though for the non-essential aluminium this burden may be almost

impossible to quantify and may be specific to differences at the level of the individual or even compartment within the CNS. While the potential for aluminium to instigate neurotoxicity may depend upon a particular toxic threshold, there remains a possibility that once aluminium has initiated a toxic cascade it may no longer be required in significant amounts for this toxic effect to be sustained. The potency with which aluminium acts as an adjuvant and additionally as an antigen is testimony to its potential role in autoimmunity and specifically aluminium-related conditions such as multiple sclerosis [10]. Though there is as yet no direct evidence to support it, one should not discount a role for aluminium in the generation of antibodies against essential biomolecules such as myelin basic protein.

Aluminium, an everyday neurotoxin

The case for aluminium the neurotoxin is proven and incontrovertible. The case for aluminium a neurotoxin and a risk to human health will require further examination. What is currently unknown is how our burgeoning exposure to aluminium in everyday life is contributing toward toxic thresholds in individuals and in populations. Aging is a major risk factor for neurodegenerative diseases and it is also a significant risk factor for establishing brain burdens of aluminium [2]. The latter are not expected to achieve levels responsible for overt toxicity, such as were found for dialysis encephalopathy [11], but do they approach or exceed those required for covert toxicity, including exacerbation of an ongoing disease state? Our recent examination of the aluminium content of 60 human brains gave reasons for concern [12]. This was the most comprehensive study of the aluminium content of human brain tissue ever undertaken and involved 12 tissue samples from each brain, three from each of the main lobes, temporal, occipital, frontal and parietal. While the median aluminium content for all tissues (n = 713) was 1.02 μg/g dry wt., a value which might not be considered as unusual, it was noted that 41 of the 60 brains studied included at least one tissue sample where the aluminium content exceeded 3.5 μg/g dry wt., a value which would actually be considered as pathological. This suggested that approximately 70% of the brain donors (aged 70–103) were potentially combating some form of aluminium-related neurodegenerative condition. Since aluminium was not included as a factor in the disease state or death of any of these donors, how do we actually know if aluminium was involved? How do we know if aluminium is ever involved in inducing or accelerating neuronal dysfunction? What are the signs of aluminium acting as a neurotoxin? Are the clinical symptoms of increasingly common neurodegenerative conditions such as AD actually the telltale signs of chronic intoxication by aluminium?

The body burden of aluminium

To understand or even appreciate the risk that aluminium poses as a neurotoxin, we will need to further our understanding of the body burden of aluminium and we will need to implement measures to reduce the body burden to a lowest practical limit. I have recently reformulated the definition of

aluminium's body burden placing it into the context of what I have called aluminium's exposome [13]. We have also been investigating non-invasive ways to reduce the uptake of aluminium into the body and, importantly, to facilitate the excretion of aluminium from the body. We were successful in lowering the body burden of aluminium in individuals with moderate-to-severe AD and concomitantly we were able to demonstrate clinically significant improvements in cognitive performance in some individuals [14]. These experiments offer some hope that the aluminium hypothesis of AD, and indeed other neurodegenerative diseases, might be tested by lowering the body burden of aluminium in affected individuals. Then we might be able to ascertain if AD, for example, is the human manifestation of the risk of aluminium as a known neurotoxin.

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