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REVIEW

Aluminium in the human brain

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Abstract An inevitable consequence of humans living in the Aluminium Age is the presence of aluminium in the brain. This non-essential, neurotoxic metal gains entry to the brain throughout all stages of human development, from the foetus through to old age. Human exposure to myriad forms of this ubiquitous and omnipresent metal makes its presence in the brain inevitable, while the structure and physiology of the brain makes it particularly susceptible to the accumulation of aluminium with age. In spite of aluminium's complete lack of biological essentiality, it actually participates avidly in brain biochemistry and substitutes for essential metals in critical biochemical processes. The degree to which such substitutions are disruptive and are manifested as biological effects will depend upon the biological availability of aluminium in any particular physical or chemical compartment, and will under all circumstances be exerting an energy load on the brain. In short, the brain must expend energy in its 'unconscious' response to an exposure to biologically available aluminium. There are many examples where 'biological effect' has resulted in aluminium-induced neurotoxicity and most potently in conditions that have resulted in an aluminium-associated encephalopathy. However, since aluminium is non-essential and not required by the brain, its biological availability will only rarely achieve such levels of acuity, and it is more pertinent to consider and investigate the brain's response to much lower though sustained levels of biologically reactive aluminium. This is the level of exposure that defines the putative role of aluminium in chronic neurodegenerative disease and, though thoroughly investigated in numerous animal models, the chronic toxicity of aluminium has yet to be addressed experimentally in humans. A feasible test of the 'aluminium hypothesis', whereby aluminium in the human brain is implicated in chronic neurodegenerative disease, would be to reduce the brain's aluminium load to the lowest possible level by non-invasive means. The simplest way that this aim can be fulfilled in a significant and relevant population is by facilitating the urinary excretion of aluminium through the regular drinking of a silicic acid-rich mineral water over an extended time period. This will lower the body and brain burden of aluminium, and by doing so will test whether brain aluminium contributes significantly to chronic neurodegenerative diseases such as Alzheimer's and Parkinson's.

Keywords Metal · Neurodegenerative disease · Neuropathology · Neurotoxicity · Alzheimer's disease · Parkinson's disease

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Aluminium is present in the human brain

While aluminium is present throughout human brain tissue, it is a point of debate as to what level of brain aluminium constitutes a 'normal' amount. Since aluminium is non-essential and is not known to be beneficial [1], then its presence in brain tissue, at any level, could be construed as abnormal. There are no 'normal' levels of brain aluminium, only levels that equate with an individual's age, their state of health and, perhaps, the presence of certain diseases. Quantitative values of brain aluminium in tissue homogenates have been determined using a range of analytical techniques and have been expressed numerically in a number of different ways [2–29]. It is not always

straightforward to decide which of such a range of measurements should be interpreted as absolute values and which would be better understood as relative determinations. Of paramount importance to the confidence that is placed in absolute measurements are their provenance, a complete record of their natural history from sampling through to their analysis and statistical significance. The data must be supported by quality assurance programmes that have taken account of issues with tissue sampling and their contamination from extraneous sources and that also demonstrate the precision and sensitivity of the chosen analytical method. Finally, the analysis and interpretation of high quality data of tissue aluminium levels must take into account that aluminium is unlikely to be distributed homogeneously in brain tissue, and so computations of mean or median values either should be avoided or should be based upon as many replicates as is practical. Despite the problems associated with accurate and reproducible measurements of brain aluminium in tissue homogenates, the scientific literature has over several decades consistently recorded values for 'normal' brains as being in the range 0.1–4.5 μg Al/g tissue (dry wt) with the higher values (>2.0) being measured in brains taken from the non-demented elderly. There is a clear trend for an increase in brain aluminium content with age [23]. Brain aluminium is also increased in a number of disease states including: Alzheimer's disease (up to 11.5 μg/g dry wt); dialysis encephalopathy (up to 14.1 μg/g dry wt); congophilic amyloid angiopathy (up to 23.0 μg/g dry wt); and various aluminium-related encephalopathies (up to 47.4 μg/g dry wt). Semi-quantitative evidence has also demonstrated elevated levels of aluminium in: neurones and neurofibrillary tangles in Alzheimer's disease [30–33] and dementia pugilistica [34]; Lewy bodies in Parkinson's disease [35]; lipofuscin in Alzheimer's disease and aged brains [36]; senile plaques in Alzheimer's disease [37]; pathological lesions in Fahr's and Behcet's disease [38, 39]; myelin in progressive leukoencephalopathy [40]; and neurones, glia and the choroid epithelium in aluminium-induced encephalopathies [41, 42]. Aluminium can also be identified in brain tissue using histochemistry and light microscopy (Fig. 1).

Where is aluminium in the brain?

The quantitative data of the presence and content of aluminium in human brain tissue are complemented by detailed studies of its multifarious locations. There are probably five or six major sinks or compartments for aluminium, and their aluminium loads are likely to be in some form of equilibrium (fast, slow, etc.) with one another. For example, the major compartments and their likely constituent sinks/sources for aluminium would include: (1) the blood-brain barrier including endothelia, choroid epithelia, cerebrospinal fluid, pericytes and the basal laminas; (2) the brain interstitial fluid including, proteins (transferrin, albumin); neurotransmitters (glutamate, gamma amino butyric acid, acetylcholine, dopamine); nucleotides (ATP, ADP, AMP); amino acids (aspartate, serine, tyrosine); small organic anions (citrate, lactate); (3) non-neuronal cells (astrocytes, oligodendrocytes, microglia, mononuclear migratory cells); (4) neurones; and (5) pathological features (senile plaques, neurofibrillary tangles, Lewy bodies, lipofuscin). Subcellular compartments for aluminium would include nuclei, mitochondria, liposomes, ferritin, cytosolic pools of citrate and ATP, and neuronal stores of neurotransmitters such as glutamate (Fig. 2). The experimental evidence for the distribution of aluminium in the brain supports a higher content of aluminium in gray (e.g. 0.40 μg/g dry wt) as opposed to white (e.g. 0.34 μg/g dry wt) matter [4, 16, 23], and especially so in brains affected by an aluminium-induced encephalopathy (e.g. 8.72 and 0.75 μg/g dry wt for gray and white matter, respectively [24]). The preferential accumulation of aluminium in gray matter is supported by many studies that have demonstrated high levels of aluminium in neuronal bodies and often specifically neuronal nuclei [9, 12, 13, 19, 20, 24, 30, 32, 33, 42]. High levels of aluminium have also been identified in glia, again specifically in liposomes and in nuclei [20, 24, 35, 42]. The choroid epithelia and adjacent supporting structures of the blood-brain barrier as well as the oligodendrocytes that constitute the myelin sheath of axons are all sites of significant focal accumulations of aluminium [20, 24, 38, 42]. The strong association of aluminium with the blood-brain barrier (up to ca. 50 μg/g dry wt) most probably reflects this structure's role as aluminium's main point of both entry into and exit out of the brain, whereas that with myelin is indicative of a significant chemical affinity between it and aluminium [43]. There are also good chemical reasons for the co-localisation of aluminium with the neuropathological features, senile plaques, neurofibrillary tangles, Lewy bodies and lipofuscin as each of these have significant component parts (beta amyloid [44], tau [45], alpha synclein [46] and lipofuscin [36], respectively) with strong affinities for binding aluminium. It remains to be determined whether the presence of aluminium in these structures is also indicative of a role in their formation, as has been suggested recently for both neurofibrillary tangles [47] and senile plaques [48]. The cerebrospinal fluid and brain interstitial fluid will act as reservoirs of aluminium that are in continuous exchange with all other compartments. The 'normal' concentration of aluminium in the brain interstitial fluid is probably less than 5.0 μg/dm^3, though it has been measured at levels as high as 190 μg/

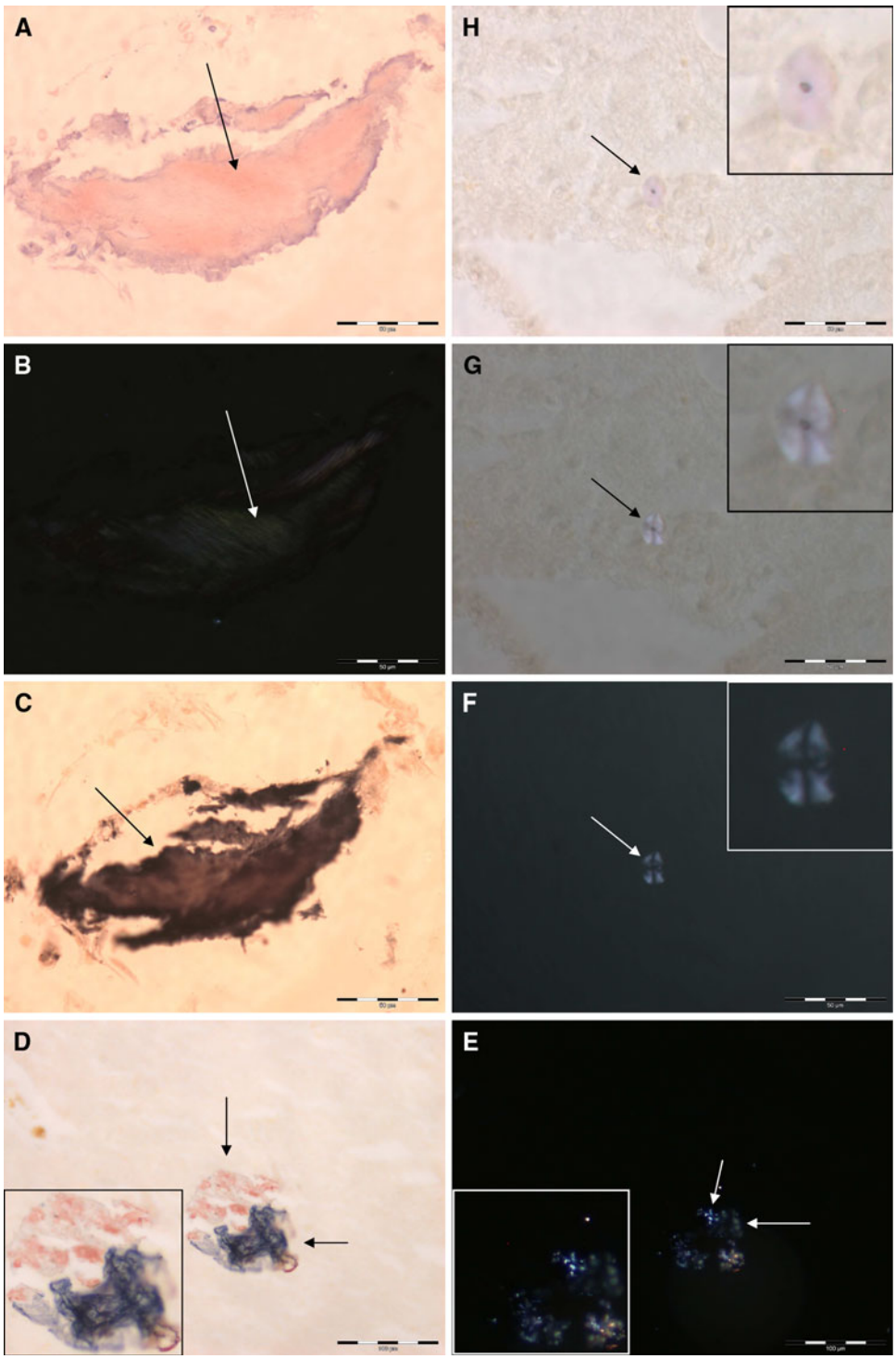

Fig. 1 The identification of aluminium in human brain tissue using histochemical methods and light microscopy. **a** Section of temporal lobe: *arrow* shows a senile plaque-like structure stained for amyloid using Congo red. **b** The same section under polarised light showing (*arrow*) apple-green birefringence characteristic of β-sheets of amyloid. **c** The same section stained for aluminium (*arrow*) using modified haematoxylin. The *scale bar* for **a**–**c** is 50 µm. **d** Section of temporal lobe showing a senile plaque-like structure that has been stained for both amyloid and aluminium (indicated by *arrows* and *inset*). **e** The same section under polarised light showing apple-green birefringence and spherulites (*arrows* and *inset*) [69]. The *scale bar* for **d**, **e** is 100 µm. **h** Section of temporal lobe stained using modified haematoxylin and showing an amyloid spherulite positively stained for aluminium (*arrow* and *inset*). The same section under partial (**g**) and full (**f**) crossed polarisers shows (*arrows* and *insets*) the spherulitic signature of a Maltese cross pattern of light extinction and that the core of the spherulite stains positively for aluminium. The *scale bar* for **f**, **g** is 50 µm

dm^3 in acute aluminium intoxication [24, 42]. The major ligand for aluminium in brain interstitial fluid is probably citrate at ca. 250 µM [49], whereas other competitive ligands would include transferrin (ca. 1 µM) [49], glutamate (ca. 10 µM), pyroglutamate (ca. 180 µM) [50], and the nucleotides ATP, ADP and AMP (ca. 5 µM) [51]. All of these ligands along with insoluble phases involving hydroxide, phosphate and possibly silicic acid will participate in competitive equilibria that under kinetic control will drive and determine the fate of the brain interstitial fluid aluminium load. The neuronal microenvironment and the various cell types it supports are together potentially awash with aluminium that has gained entry to the brain either across the blood-brain barrier or via the olfactory

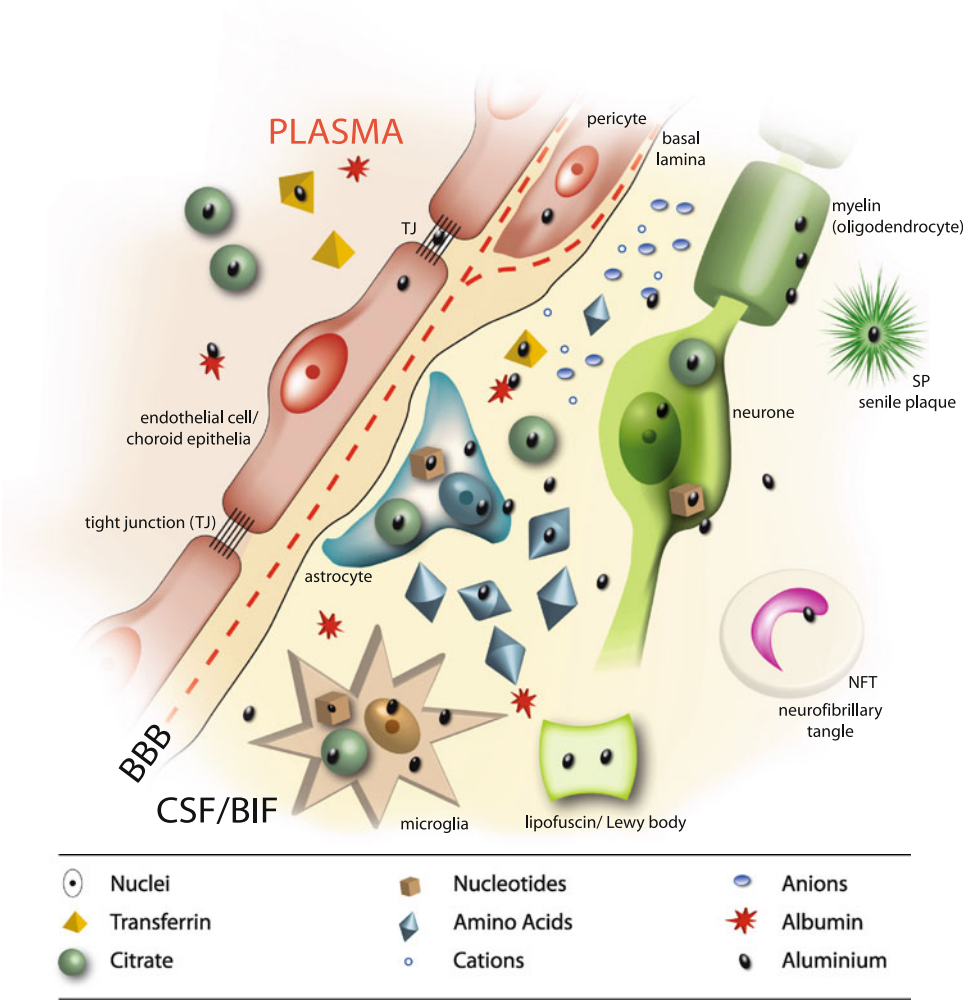

Fig. 2 A schematic of the possible distribution of aluminium in plasma, the blood-brain barrier (BBB), the cerebrospinal fluid (CSF), the brain interstitial fluid (BIF), and the cellular and pathological compartments of the human brain

route [52]. The known persistence of aluminium within the brain probably reflects the longevity of neurones, which are significant sinks for aluminium, while the increased permeability with age of epithelial barriers such as those of the gut, lung, olfactory system and the blood-brain barrier must contribute towards its accumulation over lifetimes. However, neither presence nor location of aluminium necessarily infers biological effect or neurotoxicity.

The neurotoxicity of aluminium

Since aluminium is not known to participate in any essential brain biochemistry, its neurotoxicity might simply be defined in terms of its biological availability. Since biological availability infers a biological response, then aluminium could be considered neurotoxic whenever its presence results in an aluminium-induced change in brain biochemistry. Quite simply, all biologically available aluminium in the brain is neurotoxic, and it is only the degree to which the toxicity is manifested as an unwanted biochemical change that defines the acuity and 'phenotype' of its neurotoxicity. Most, if not all, of the toxicity of aluminium is through the biochemical reactivity of $Al^{3+}_{(aq)}$, which is bound avidly by oxygen (and fluoride)-based ligands and functional groups [1]. It is often the rate of delivery of $Al^{3+}_{(aq)}$ to target ligands that determines the extent of its toxicity in any given system. Indeed, once aluminium has entered the brain its rate of delivery of $Al^{3+}_{(aq)}$ to target groups is the only limit upon its neurotoxicity, and so the identification of sinks/sources of biologically available aluminium is critically important in predicting its neurotoxicity. Numerous animal models have demonstrated the neurotoxicity of aluminium when the delivery of $Al^{3+}_{(aq)}$ is potentiated [53]. Similar degrees of potency are also observed in fatal aluminium-induced encephalopathies in humans, though such are probably the only examples of confirmed aluminium neurotoxicity in humans. Aluminium-induced encephalopathies are acute events in which an accelerated neuronal loss is accompanied by a miscellany of additional aberrant processes including alterations in the processing of tau protein [15]

and the deposition of aluminium in neurones, glia and the choroid epithelium [12, 17, 19, 20, 24, 27, 41, 42]. In these acute episodes in which high concentrations of toxin are delivered to the brain from the blood, the disturbance of the selectivity of the blood-brain barrier [54] is probably an early event in a rapidly progressing cascade of deleterious events that culminate in neuronal necrosis. In these acute events the constancy of the neuronal microenvironment is lost and brain biochemistry is overwhelmed both directly and indirectly by the aluminium challenge. While aluminium-induced encephalopathies serve to demonstrate the acute neurotoxicity of aluminium, they are unlikely models of lower levels of exposure to brain aluminium. Under conditions of chronic exposure to aluminium, the selectivity of the blood-brain barrier may not be seriously compromised, and aluminium will gain entry to the brain by piggy-backing upon normal transport mechanisms as well as through more indirect processes such as residual leakiness and fluid phase endocytosis. Immediately upon entry $Al^{3+}_{(aq)}$ will be continuously shuttled between chemical and physical compartments, leading to both its removal from the brain back across the blood-brain barrier and its retention in the brain through associations with extracellular and intracellular sinks. It is important to emphasise that the fate of brain aluminium is not under any form of homeostatic control; the analogy is with a game of bagatelle or pinball with aluminium accumulating slowly where its persistence will be supported by the local chemistry [55]. Similarly it is this same chemistry that will also dictate how a sink might also act as a source of biologically available $Al^{3+}_{(aq)}$. For example, extracellular and intracellular pools of citrate will accommodate significant concentrations of $Al^{3+}_{(aq)}$, as soluble complexes, and they will also act as sources of biologically reactive $Al^{3+}_{(aq)}$, promoting, for example, the pro-oxidant activity of aluminium through formation of the putative aluminium superoxide semi-reduced radical ion, $AlO^{\cdot 2+}_{2(aq)}$ [56]. The remarkable propensity for aluminium to promote oxidative events makes such highly likely throughout the brain, with membrane lipids, nucleic acids and free radical-mediated signalling as prime targets for oxidative damage. However, the high likelihood of aluminium-induced oxidative damage must, in the main, be countered by the brain's sophisticated mechanisms of antioxidant protection. These have evolved alongside oxidative metabolism, and though they might be expected to protect against aluminium-induced oxidative damage, their upregulation will add to cellular energy requirements and hence, eventually, deficits. In addition, the protection afforded by antioxidants may be focally as opposed to universally distributed throughout the brain and so free radical damage initiated by, for example, the co-deposition of iron, aluminium and amyloid in senile plaques [57] may not be so easily countered. In summary, under conditions of chronic (everyday) exposure to aluminium, we would expect the brain to be subject to aluminium-induced oxidative stress, though probably without sustaining any short-term damage.

Extracellular and intracellular citrate pools are likely sources of $Al^{3+}_{(aq)}$ to many biochemical targets in the brain. The establishment of micromolar concentrations of aluminium within such pools will allow $Al^{3+}_{(aq)}$ to compete effectively with millimolar concentrations of competitive cations such as Mg^{2+} and Ca^{2+} and displace such essential metals from coordination sites in enzymes, signalling molecules, receptors, transporters, channels, nucleic acids and many other biochemical ligands [1]. While each of such target systems would be influenced by aluminium under the finite conditions of in vitro preparations, the inherently robust and flexible nature of in vivo physiology must dictate that only when the number of displacements reaches a particular threshold will the functioning of the system be disrupted and neurotoxicity manifested. These 'thresholds' may be reached over decades of chronic exposure, though in the interim each displacement of an essential metal by aluminium will use up some of the energy currency of the brain.

While the majority of the neurotoxicity of aluminium is predicted to emanate from the action of $Al^{3+}_{(aq)}$ at a target site, the accumulation of aluminium within the cytosolic pool of ATP might also result in neurotoxicity following the secretion of ATP into the brain interstitial fluid and the action of Al-ATP at extracellular purinergic receptors [58]. ATP is arguably the single most important extracellular signalling molecule in the brain [59], and upon being bound by specific P2X and P2Y receptors acts like a gain control on many other receptor-based signalling systems, such as the NMDA receptor complex. When Al-ATP substitutes for Mg-ATP at ATP receptors, the likely result is that the dissociation of the agonist-receptor complex will be delayed due to the enhanced stability of the Al-nucleotide complex. This will have the effect of extending the overall stimulus and hence signalling event beyond its normal lifetime. In the case of the NMDA receptor complex, this could result in a transient elevation in cytosolic $[Ca^{2+}]$ for which the cell has to expend additional energy to bind and/or remove it from the cell cytosol [58]. The net effect of such a persistent affect of biologically available aluminium would be an underlying excitotoxicity that in time would deplete neuronal energy reserves and instigate neuronal cell death by apoptosis.

The consistent observation of aluminium in the brain associated with neuronal and glial nuclei [9, 19, 24, 30–32] must highlight nucleic acids as additional sinks for $Al^{3+}_{(aq)}$, not only in cell nuclei but also in the cytosol and in mitochondria. The phosphate-rich nuclear compartment is

an obvious site for aluminium to bind and accumulate over time. Indeed, the persistent occurrence of aluminium in all cell nuclei has recently prompted speculation that aluminium through its compaction of chromatin may actually serve a biological purpose in silencing the expression of genetic information [60]. Aluminium is a powerful cross-linking agent, a property that is used in many industrial processes, including leather tanning, and its potential longevity in neuronal nuclei is envisaged to prevent or at least slow down the unravelling of DNA. Whether such a process could be under any sort of homeostatic control remains to be investigated. Certainly biologically reactive aluminium is bound by nucleic acids [61], and through such interactions could influence and modify many aspects of a neurone's genetic machinery.

The majority of the potential neurotoxicity of aluminium outlined thus far is assumed to result from the binding of $Al^{3+}_{(aq)}$ by myriad oxygen (and possibly fluoride)-based ligands. However, there is a burgeoning interest in the putative neurotoxicity of nanoparticulates, many of which are aluminium-based [62]. There is evidence that nanoparticulates of aluminium are found in the brain and that they either form in situ or that they enter the brain across the blood-brain barrier or via the olfactory system. There is currently very little understanding about the mechanisms of toxicity of aluminium-based nanoparticulates and almost no understanding of their putative neurotoxicity. However, there are well-defined precedents for the toxicity of such forms of aluminium, and in particular from data that purport to describe the activity, one could say immunotoxicity, of aluminium-based adjuvants [63]. Unfortunately there is, as yet, no consensus on whether the immunobiology of aluminium-based adjuvants is mediated through their particulate or dissolved forms. Certainly aluminium either directly as a particulate or indirectly following the dissolution of nanoparticulates could induce an inflammatory action in the human brain, and this has been demonstrated in animal models [64]. The immunopotency of aluminium-based adjuvants outside their role as adjuvants in vaccine and allergy therapies seems to have been largely ignored as a potential mechanism of aluminium toxicity throughout the body [65] and especially in the nervous system [66]. The consistent observation of significant accumulations of aluminium in the brain should at least be a warning of the potential for such to participate in neuroinflammatory toxicity.

The brain is an obvious target for aluminium toxicity. Neurotoxicity is evident under acute conditions such as encephalopathies, and it is predicted but not necessarily recognised as such under chronic or everyday exposures to environmental aluminium. The mechanisms of neurotoxicity are potentially myriad, while their manifestations as biochemical changes are probably quite subtle for all but the most vulnerable groups. While the latter must include the foetus and neonate, there are few indications as to the identities of others who are susceptible to the neurotoxicity of aluminium. Since the advent of the Hall-Héroult process (and thereafter Bayer process) towards the end of the nineteenth century and our ability to extract aluminium from its inert ores on an industrial scale, we have all been living in the Aluminium Age [67]. Now, in the twenty-first century, we can no longer completely avoid environmental exposure to aluminium. Since there is as yet no proven requirement for aluminium in any living organism, never mind in humans, it would be prudent to reduce our everyday exposure to avoid aluminium entering the body and persisting in the human brain [68]. We have begun to show that this can be achieved by using nature's own way of avoiding biologically available aluminium. We have shown that regular consumption of silicon-rich mineral waters both reduce our gastrointestinal uptake of aluminium and, importantly, facilitate our urinary excretion of systemic aluminium [48]. Life on Earth evolved in spite of a crust of aluminosilicate [1]. However, the Hall-Héroult process and the subsequent arrival of an Aluminium Age have let the aluminium genie out of the bottle. Our final wish should be that the unique inorganic chemistry of aluminium and silicic acid will help to put the genie back where it can be used effectively but, most importantly, safely.

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