The interrelationship between silicon and aluminium in the biological effects of aluminium

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Abstract. It is well established that aluminium is toxic at the cellular level and that pathological symptoms follow its entry into organisms (plants, fish, humans) when the normal exclusion mechanisms fail or are bypassed, as for example in renal dialysis. The present debate concerns the availability of environmental aluminium and the possible impact of its slow and insidious absorption and accumulation in vulnerable individuals. Silicon is considered an essential element but the mechanisms underlying its essentiality remain unknown and binding of the element (through oxygen) with biomolecules has not been demonstrated. There is, however, a unique affinity between aluminium and silicon, not only in solid state chemistry ([AlO₄]²⁻ and [SiO₄]⁴⁻ are isostructural), but also in aqueous solution chemistry as illustrated by the synthesis of zeolite from aluminate and silicate anions at high pH and under hydrothermal conditions. This affinity exists also in very dilute solution (<10⁻⁵ M) at near-neutral pH when hydroxyalumino-silicate species form. These species mediate the bioavailability and cellular toxicity of aluminium. The observed effects of silicon deficiency can be attributed to consequential aluminium availability. There are important implications for the epidemiology and biochemistry of aluminium-induced disorders and any consideration of one element must include the other.

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There are three threads to the story outlined in this paper. One is the cellular toxicity of aluminium; a second is the ‘essentiality’ of silicon; the third is the question of what determines the bioavailability of aluminium and the cellular response to its presence. With aluminium being so ubiquitous, why, given its cellular toxicity, is there life on the planet? Aluminium is for the most part locked up in the aluminosilicates of rock and soil minerals from which it can be leached by acidity resulting from human activity (‘acid rain’). It is released from its oxide (bauxite) in metallic aluminium production, and many aluminium salts and compounds are used in a wide variety of industries.
In 1982, $4 \times 10^6$ lb of aluminium were used in food additives in the USA (Gregor 1988); the amount of aluminium salts used in water treatment in the UK is of the order of $10^5$ tonnes per year. In a near-neutral aquatic environment the availability of aluminium is limited by the precipitation of gibbsite (the crystalline form of aluminium hydroxide, Al(OH)$_3$), at about pH 6; solubility rises at pH lower than this (the 'acid rain' problem) and at more alkaline pH, owing to the formation of the aluminate anion, Al(OH)$_4^-$ (see this volume: Martin 1992). An important limitation to the bioavailability of aluminium is the interaction of aqueous aluminium species with 'dissolved silica'—silicic acid, Si(OH)$_4$—generating hydroxyaluminosilicates (Birchall & Chappell 1988). These species mediate the bioavailability of aluminium and, early indications suggest, the cellular response to aluminium. Soil scientists (Farmer & Frazer 1982) and ocean chemists (Wiley 1975) have known for some time that the presence of dissolved silica limits the solubility of aluminium. Non-dialysable hydroxyaluminosilicate species form at pH 4 and upwards when silicon concentrations exceed 6 mg SiO$_2$ per litre (Farmer 1986). What has not been recognized is the significance of this control mechanism to biology and its relevance to understanding the epidemiology and biochemistry of aluminium-induced pathology.

Aluminium in biology

When aluminium becomes available to organisms through the acidification of surface waters, it is toxic to plants, affecting root development (Taylor 1988), and to fish, affecting gill function (Driscoll et al. 1980). Its toxicity to humans was first clearly recognized in renal medicine, when the element was identified as the causal agent in the neurological and bone disorders observed in patients dialysed with aluminium-containing water (this volume: Kerr et al 1992). The use of reverse osmosis and de-ionization has removed this problem, although the continued use of oral aluminium hydroxide as a phosphate binder still produces aluminium overload in some patients (Fleming et al 1982).

In dialysis-induced aluminium overload, when plasma aluminium levels can rise from less than 1 µmol/litre to above 5 µmol/litre, aluminium accumulates in many tissues, including kidney, liver, skeletal muscle, heart, brain and bone (Roth et al 1984). It gives rise to encephalopathy, osteomalacia, and an anaemia responsive neither to iron therapy nor to erythropoietin; it may also be responsible for the myocardial dysfunction observed in many dialysis patients (London et al 1989). Symptoms can arise within months. The cellular toxicity of aluminium is undoubted, but the mechanisms of its toxicity are not fully understood. The question of current interest is whether exposure to environmental aluminium in food, water, medication and in other ways is a causal agent in various diseases, in particular Alzheimer's disease. The daily human intake of aluminium is estimated to be about 20 mg (Jones & Bennett 1985) and absorption is influenced *inter alia* by dietary constituents such as citrate.
and maltol. Iron status may influence aluminium absorption (Fernandez Menendez et al 1991). Is a slow and insidious accumulation of aluminium in tissues responsible for disease?

The possible relationship between aluminium and Alzheimer's disease was first suggested by the demonstration of neurofibrillary degeneration in rabbits after direct exposure of the central nervous system to aluminium salts (Klatzo et al 1965). Subsequently, increased aluminium levels were found in the brains of Alzheimer's disease patients; later came the identification of aluminium in tangle-bearing hippocampal neurons (Perl & Brody 1980; this volume: Perl & Good 1992) and at the core of senile plaques (Candy et al 1986; this volume: Edwardson et al 1992).

Silicon in biology

The fact that silicon is present in small concentrations in living organisms has for years prompted questions about a possible functional role. Silicon is considered to be essential for diatoms, not only for the construction of the siliceous frustule, but also for the maintenance of major metabolic processes (Werner 1977). Grasses accumulate silicon, depositing opaline silica as phytoliths in aerial parts, and some plant species (notably rice) are thought to require the element. The experiments that caused silicon to be listed as an essential element in at least some mammalian species were reported in 1972 (Schwarz & Milne 1972, Carlisle 1972). These workers independently showed reduced weight gain and pathological changes to bone and connective tissue in rats and chickens maintained on a silicon-depleted diet—symptoms that could be reversed by silicon (silicate) supplementation. The development of bone was particularly affected, both the formation of the collagenous organic matrix and its mineralization. A role for silicon in osteogenesis had already been suggested by the finding that silicon was uniquely localized at the mineralization front in the bones of young rats and mice (Carlisle 1970). This suggestion was reinforced by the detection of silicon in connective tissue cells and in isolated osteocytes (Carlisle 1982).

There is a striking similarity between the pathological features of bone reported in silicon deficiency and those observed in aluminium-induced osteodystrophy, in which aluminium is localized at the mineralization front (Denton et al 1984) and is found in the osteogenic cells congregated at that front (Schmidt et al 1989). These observations suggested a physiological interaction between these two elements, comparable to their geochemical interaction.

Mechanism underlying the essentiality of silicon

The essentiality of silicon and the possible reasons for it were discussed at an earlier Ciba Foundation Symposium (1986). It was concluded that no Si—C
bonds existed in biology, that the existence of stable Si—O—C bonds had not been demonstrated and, indeed, that there was no convincing evidence for any organic binding of silicon in biological systems, in which the element exists as the neutral silicic acid, Si(OH)$_4$. How then does silicon deficiency produce pathological changes?

At that symposium a relationship with aluminium was first proposed (Birchall & Espie 1986) and the effect of silicic acid on an ‘aluminium-poisoned’ enzyme was demonstrated. It had been suggested that silicon was essential for maximal prolyl hydroxylase activity (Carlisle & Alpenfels 1980), with reduced activity accounting for impaired collagen production in silicon deficiency. It is difficult to envisage any chemical interaction between silicic acid and the known cofactors of this enzyme or the protein itself. The cofactor metal is iron; it was shown that aluminium could act as a weak inhibitor of hydroxyproline production and that this inhibition was eliminated when sufficient silicic acid was present. Although it is almost certainly incorrect to suppose that aluminium will generally interfere with iron-dependent systems, the described effect is reminiscent of the inhibition of hexokinase activity by aluminium and reactivation of the system by citrate, which displaces aluminium from ATP and allows Mg$^{2+}$ to bind (Viola et al 1980). Silicic acid selectively removes aluminium from the aluminium-contaminated prolyl hydroxylase system; preliminary work suggests that a similar effect can be observed in the aluminium-contaminated hexokinase system (C. Exley, personal communication 1991).

The first demonstration that silicic acid prevents a toxic effect of aluminium in an organism was in experiments on Atlantic salmon fry (Salmo salar), which are susceptible to low concentrations (6–7 μmol/l) of aluminium in acidic water. Gill damage was induced, with loss of ionoregulatory and osmoregulatory function (Exley et al 1991). The fish were exposed to water at about pH 5 containing various concentrations of aluminium and silicon (Birchall et al 1989). Figure 1 shows that water containing 6.26 μmol/l Al with only 0.60 μmol/l Si was acutely toxic, whereas water containing 7.15 μmol/l Al and 93 μmol/l Si was innocuous. Furthermore, the average whole-body aluminium content of the fish was >2 μmol/g dry mass in the toxic water, but only 0.40 μmol/g dry mass in the silicon-rich water, 10% less even than that accumulated in the control water (0.85 μmol/l Al, 0.66 μmol/l Si). The water containing 6.26 μmol/l Al and 0.60 μmol/l Si caused extensive gill damage with mucus production and cellular sloughing: gills remained intact in the silicon-rich water and no aluminium was detected at gill surfaces. In the presence of a high level of silicic acid, the adsorption of aluminium onto gill membranes and systemic absorption had both been inhibited.

This effect of silicic acid in promoting the exclusion of aluminium (and manganese) appears also to apply to plants (Foy et al 1978).
Interaction of aqueous aluminium species with silicic acid

The speciation of aluminium in aqueous solution is strongly pH dependent, basic species being produced by the hydrolysis of \([\text{Al(H}_2\text{O)}_6])^{3+}\) above pH 4 (this volume: Martin 1992). The speciation of silicic acid is relatively simple; at pH < 9 and concentrations less than 2 mM, silicic acid exists as the neutral monomer, \(\text{Si(OH)}_4\). This is the physiologically relevant species. At concentrations and pH values found in aquatic environments (< 300 μmol/l) and in biological systems (5–200 μmol/l, say) stable reactions with organic molecules have not been demonstrated. Silicic acid, however, reacts with basic metal ions at a pH just below that at which the hydroxide is precipitated. Thus, at physiological pH there can be no interactions with Ca\(^{2+}\) or Mg\(^{2+}\), but interactions with Fe\(^{3+}\) and Al\(^{3+}\) are possible. Al—O—Si bonds are formed readily at pH 5 and above, whereas Fe—O—Si complexes exist only below pH 2 (Schenk & Weber 1968). Above pH 2, finely divided iron-oxy-hydroxide coated with adsorbed silica is formed. Thus the chemistry suggests that the activity of silicic acid in biology will be restricted to reactions with aluminium.

When dilute (around 10\(^{-4}\) M) acidic (about pH 5) solutions of silicic acid and aluminium are heated, the mineral imogolite is precipitated. This tubiform structure has the ideal composition \((\text{HO})_3\text{Al}_2\text{O}_3\text{SiOH}\) and can be considered as a single gibbsite sheet with inner hydroxyls replaced by orthosilicate.
FIG. 2. The Si:Al ratio of hydroxyaluminosilicate species bound to the functional groups on aminodiphosphonate resin, as a function of pH.

(Farmer & Frazer 1982). Unheated, such solutions remain clear and stable for many weeks, but have been shown to contain hydroxyaluminosilicate species by the infrared examination of solids recovered after freeze-drying solutions (Farmer et al 1979) and by ion-exchange experiments (Birchall & Chappell 1988a, Chappell & Birchall 1988). These species have an Si:Al ratio of 0.25–0.5 and can be regarded as fragments of or precursors to the imogolite structure. Such ‘protoimogolite’ species form above pH 7, even in the presence of citric acid, an aluminium chelator. For example, solutions containing AlCl₃ (0.10 μmol/l) with equimolar citrate and silicic acid (0.5 μmol/l) adjusted to pH 7.4 yield no filterable solids after 12 weeks, yet solutions left for 20 hours can be shown by ion-exchange to contain hydroxyaluminosilicate species with a Si:Al ratio of about 0.5.

These interactions of aluminium with silicic acid are complicated by the presence of phosphate. Solutions containing 0.1 mM aluminium, 0.5 mM silicic acid and 0.5 mM phosphate gave solids in which the Si:Al ratio varied with pH—at pH 7.4 it was 0.44, whereas at pH 6.4 the silicon content was negligible and the Si:Al ratio was 0.02. The switch in the binding of aluminium between phosphate and silicic acid is illustrated in Fig. 2. Solutions with the above composition were passed over an aminodiphosphonate resin and the retained species were analysed. The situation is summarized as follows.
Aluminium phosphate species plus free silicic acid

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<tr>
<th>pH</th>
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<th>PO(_4^{3-} )</th>
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<td>&lt;6.6</td>
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<td>&gt;6.6</td>
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The formation of protoimoglitite species with a Si:Al ratio of 0.5 requires a silicic acid concentration of 100 µmol/l or more. Hydroxyaluminosilicate species with lower Si:Al ratios (0.1–0.5) are generated at lower concentrations.

The formation of hydroxyaluminosilicates clearly reduced the toxicity of aluminium to fish and many of the reported biological effects of silicon can be interpreted in terms of the chemistry outlined above. For example, the beneficial effects of silicic acid on plant growth are likely to be due to its demonstrated abilities to limit the uptake of toxic metals. Above pH 6.6, the ability of silicic acid to prevent aluminium from binding phosphate aids plant (and diatom) growth by maintaining phosphate availability.

**Biological consequences of aluminium–silicic acid interactions**

We need now to consider two possibilities: firstly, the effect of silicic acid on the availability of ingested aluminium and, secondly, the effect of plasma and tissue silicic acid on the cellular response to aluminium.

**Availability of ingested aluminium**

Does the effect of silicic acid observed on fish gills also apply to the mammalian intestine? In normal human subjects, aluminium ingestion is about 20 mg/day. Silicon ingestion has been estimated at 20–50 mg/day, most (60%) of which is derived from cereals. Water and other drinks can provide 19%, presumably in a highly absorbable form (Pennington 1991). The contribution from water will vary geographically; silicon concentrations in water range from 10 µmol/l to 300 µmol/l, being generally high in hard water areas and low in soft water areas (Dobie 1982). Absorbed silicon is rapidly excreted in urine, as is shown by studies of patients taking magnesium trisilicate (Dobie & Smith 1986). Few studies have been reported on the effect of a high silicic acid intake on aluminium absorption in the gastrointestinal tract. Aluminium dietary supplementation increased brain aluminium levels in 28-month-old rats on a low silicon diet, but no such increase was observed in the brains of rats on a silicon-supplemented diet (Carlisle & Curran 1987). A study of aluminium absorption in patients on oral aluminium hydroxide therapy in areas with high or low silicicion levels in water is warranted.

Plasma silicic acid concentrations are normally in the range 5–20 µmol/l, but can rise to above 100 µmol/l in renal disease. An important question is whether a sustained high level of silicon in plasma protects against aluminium-induced
disorders such as osteomalacia and encephalopathy. Experiments to investigate this are planned.

**Cellular response to aluminium and effect of silicic acid on it**

A major cause of aluminium’s toxicity is its ability to displace Mg\(^{2+}\) from key sites at which this metal is catalytic. Aluminium will also bind to phosphate groups, especially when two or more phosphate groups can cooperate. Therefore aluminium is commonly bound to chromatin and to phosphorylated polymers (this volume: Perl & Good 1992). This drew attention to the possible effects of aluminium on the inositol phosphate second messenger system and hence on intracellular Ca\(^{2+}\) homeostasis (Birchall & Chappell 1988b).

In isolated pancreatic cells, acetylcholine provokes an oscillatory increase in cytoplasmic Ca\(^{2+}\) which can be monitored by measuring the Ca\(^{2+}\)-dependent chloride current. Intracellular infusion of an AlCl\(_3\)-containing solution using a fine tube inserted into a patch-clamp pipette eliminated or attenuated the response to acetylcholine (Wakui et al 1990; this volume: Petersen et al 1992). The Ca\(^{2+}\) release channel is activated by micromolar Ca\(^{2+}\), but inhibited at millimolar levels. It is possible that aluminium has a high affinity for this site and blocks Ca\(^{2+}\) release. It is considered that aluminium can successfully compete for Mg\(^{2+}\)-binding sites even in the presence of a 10\(^8\)-fold molar excess of Mg\(^{2+}\). This demonstrated effect on Ca\(^{2+}\) homeostasis supports the perceptive comment made by Kruck & McLachlan (1988) that: ‘aluminium is implicated as an agent involved in disruption of Ca\(^{2+}\) dependent electrophysiologic functions and of intra-cellular Ca\(^{2+}\) regulation’.

Preliminary experiments (this volume: Petersen et al 1992) have shown that the injection of silicic acid (100 \(\mu\)M solution) alone into pancreatic cells stimulates the response to acetylcholine. This might be due to ‘neutralization’ of traces of aluminium introduced during cell isolation (such contamination has been shown in our laboratory to be inevitable). The co-injection of aluminium and silicic acid greatly reduced the inhibitory effect of aluminium. If this latter effect is confirmed, the potential protective effect of elevated levels of plasma/tissue silicic acid will be strongly indicated.

Recent in vitro work (Wiegland 1990) has indicated that silicic acid stimulates the activity of adenylate cyclase in several tissues, including bone, kidney and liver. It has been suggested that this effect may be due to silicic acid binding excess Ca\(^{2+}\) which would otherwise inhibit the enzyme. At physiological pH this is an unlikely explanation. A more plausible mechanism is competition for binding sites between trace aluminium (introduced during tissue manipulation) and Mg\(^{2+}\), followed by removal of aluminium by silicic acid.
Implications of aluminium–silicon interaction

Epidemiological studies relating aluminium in water to the incidence of Alzheimer’s disease (Martyn et al 1989; Martyn 1992: this volume) raise several problems, notably a lack of correlation between dose and effect, and the fact that the intake of aluminium from water is but a fraction of that from food. Water that contains significant amounts of aluminium (soft water and that from upland areas) contains little silicic acid, whereas water high in silicic acid (hard) contains little aluminium. The epidemiological studies therefore suggest an inverse relationship between silicon in water and Alzheimer’s disease, with a high silicic acid intake restricting the absorption of aluminium from food (Birchall & Chappell 1989).

The ingestion of aluminium in food will be relatively constant throughout a population. Superimposed on this will be the dietary silicon intake (mainly from cereals and vegetables), but this silicon may be less available for reaction with ingested aluminium than the monomeric silicic acid in water. The silicon concentration in domestic water can vary from 10 µmol/l to >200 µmol/l and any exclusion of aluminium would be likely only when water contains more than 100 µmol/l silicic acid. Fresh epidemiological studies may reveal such a relationship.

Recent results indicate that a high plasma silicon content may protect against the detrimental effects of absorbed aluminium. Studies of aluminium and silicon excretion in patients after kidney transplantation suggest that the two elements are excreted in tandem (N. Roberts, personal communication 1991). Are they combined together as hydroxyaluminosilicates? It appears that much of the absorbed aluminium is temporarily (and some permanently) stored in tissue, so there is a delay before excretion (Schlatter & Steinegger 1991). Preliminary work (J. P. Belia & N. Roberts, personal communication 1991) suggests that a high silicic acid intake may mobilize aluminium and reduce its tissue storage. There is therefore a puzzle.

Solid silica (for example, phytoliths in cereal foods) will adsorb aluminium and so prevent its gastrointestinal absorption. A high intake of silicic acid may, through the formation of hydroxyaluminosilicates of low molecular mass, increase gastrointestinal availability (to high affinity sites), but compensate by increasing aluminium excretion. Although most (95%) aluminium in plasma is bound to high molecular mass (>5 kDa) components (Day et al 1991), the rest is contained in a low molecular mass form. Citrate (0.1 mM in plasma) is a candidate carrier, but plasma silicic acid may contribute, because hydroxyaluminosilicates form in the presence of citrate above pH 7 and remain of low molecular mass. These would be expected to be rapidly excreted, prompting the mobilization of aluminium.

Finally, the switch in the binding of aluminium from phosphate to silicic acid above about pH 6.6 (Fig. 2, p 55) suggests that intracellular aluminium will be bound to phosphate groups, with binding to silicic acid being possible only
in the extracellular milieu. Intracellular aluminium will cause cell death (by interference with Ca\(^{2+}\) homeostasis—this will have consequences for phosphorylation, for example); after which the export of aluminium (bound to phosphate groups on macromolecules, which would thereby be cross-linked) into the extracellular environment would allow its binding to silicic acid and 'co-deposition' in senile plaques. This is seen as a 'late stage' event, following primary cell damage.

In summary, it is proposed that the role of silicon (silicic acid) is to aid the exclusion of aluminium from organisms, to 'sequester' the metal, so reducing its effect on enzymic and Mg\(^{2+}\)-dependent processes, and to reduce tissue retention, promoting the excretion of aluminium. Much work is required to confirm these ideas, which could have far-reaching implications in renal medicine and in the understanding of (and possibly the control of) aluminium-related disorders, including Alzheimer's disease, if it is shown that aluminium has a role in this condition.

Acknowledgements

I would like to thank colleagues who over the years have contributed to this research, especially Dr A. Espie, Dr J. S. Chappell and Dr C. Exley.

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DISCUSSION

_Garruto_: You referred to the possible ‘co-deposition’ of Al and Si in senile plaques. In 1984 we reported the first chemical mapping (imaging) of the intraneuronal co-deposition of Ca and Al, and two years later Si, in neurofibrillary tangle-bearing hippocampal neurons in patients with amyotrophic lateral sclerosis (ALS) and parkinsonism-dementia (PD) of Guam (Garruto et al 1984, 1986). Our order-of-magnitude estimates for the highest concentrations
of these elements in neurons were 500 p.p.m. for Al, 3000 p.p.m. for Si and 7000 p.p.m. for Ca.

Williams: Can I just clarify that these deposits were inside the cells? How did you make the analysis?

Garruto: Yes, these were intracellular deposits. We used a novel application of computer-controlled X-ray microanalysis and wavelength dispersive spectrometry to produce chemical maps of these intracellular deposits (see p 230).

Williams: So the cells were dead?

Garruto: The studies were conducted using both fixed and frozen autopsy tissue and the elemental deposits were found in neurofibrillary tangle-bearing neurons. The deposits appear to be ‘ghost’ neurons as well as in intact neurons—a point which I shall amplify later (p 230–231).

Birchall: One problem has been that people who have analysed for Si in tissue have seldom analysed for Al, and vice versa. It is important to know if the two elements occur together.

Garruto: I agree.

Candy: Dr Garruto refers to the co-localization of Si and Al in the Guam cases. In contrast, in renal dialysis patients, we find, using SIMS, numerous focal accumulations of Al in the frontal cortex in the absence of any evidence of Si accumulation, even in cases with the highest Si concentrations determined using graphite furnace atomic absorption spectrometry. We find co-localization of Al and Si only in the core of senile plaques. Whether silicic acid actually gets inside neurons is another question.

Birchall: There is a pH-sensitive competition between phosphate and silicic acid binding to aluminium, with Al–phosphate bonds being favoured at acidic pH and Al–silicic acid bonds being favoured at pH values above 6.6 (Birchall & Chappell 1988a) (Fig. 2, p 55). At around pH 6.6, mixed binding is possible (‘silicophosphate’). This pH sensitivity will dictate the intracellular and extracellular binding of aluminium.

Martin: The cross-over in solubilities described by Derek Birchall, with AIPO₄ more insoluble in acidic acid and aluminosilicates more insoluble in basic solutions, is evident from the results in Table 1 of my paper (p 9) (this volume: Martin 1992). At pH 6.6, AIPO₄ exhibits the greater pAl (lower [Al³⁺]), while at pH 7.4, kaolinite shows a greater pAl. The cross-over has also been illustrated graphically (Martin 1990).

Blair: Dr Candy told us earlier (p 43–44) about studies on focal Al deposition in the neonate and newborn. Was there any co-deposition of Si there?

Candy: We didn’t look at Si in those cases; we have only studied Si, using SIMS, in renal dialysis patients, so far.

Perl: We too have probed the brains of the Guam ALS/parkinsonism-dementia complex cases (Perl et al 1986), and in intact tangle-bearing neurons we don’t find these high levels of Si in the tangled neurons that Dr Garruto
and his colleagues found. Whether that's true of cells that have died and have the remaining so-called 'tombstone' tangles is another story. But, as you say, the concept of Al and Si being in an intact cell is difficult to accept.

Birchall: One must be careful to distinguish between finding Al and Si 'co-localized' and the existence of aluminosilicate species. In the former, the two elements may be at the same site but they need not be chemically combined. When phosphate is present, aluminosilicates require a pH above 6.6 to form.

Perl: In the intact neurons that we have probed, we don't find Si accumulating with Al.

Garruto: Theoretically we cannot differentiate whether neurons are intact or not, using X-ray microanalysis.

Williams: It is important to discover whether the living cell is allowing these ions to come in, and if you just do post mortem analysis, of course, you won't know whether the Al is coming in after the death of the cell. This leads on to what could be mechanistically important in the nature of aluminium deposits.

Klinowski: Professor Birchall, you are saying that silicate ions are produced by solubilization of silica, which is measurable, even at room temperature. Aluminosilicate species form when you introduce Al into the system. These are insoluble, but are also difficult to crystallize, and therefore they form a 'subcolloid', which is completely harmless to man or beast, I gather?

Birchall: Certainly, these species are harmless to fish and to plants, because the aluminium in them is unavailable.

Klinowski: This process explains the increased solubility of Al, because you are removing it from the solution by producing the subcolloid. By the law of mass action, you can introduce more and more Al. But in this case, why don't the water companies, having added aluminium sulphate to water, titrate the excess of Al with silicic acid?

Birchall: That is a very good point!

Fawell: This would require making considerable changes in water treatment procedures and water treatment works, and Professor Birchall's suggestions are relatively recent. Also, in the UK, when you look at the northwest–southeast distribution pattern of silica in water, you can also correlate it with a range of other things. I am not denying what Derek Birchall says. We need to look more closely and see how some of these other things (such as hardness) correlate with Al, silica, and the incidence of Alzheimer's disease as well.

Birchall: I agree that this is a complex problem. One of the curious paradoxes is that the areas in the UK which have low Si levels in water happen to be the areas where most often you need to use aluminium salts, in order to clarify the water. Whereas in areas with high Si, you don't need to use Al in water treatment; so everything works against you, in this sense. People living in areas with Al in water will, I suggest, be exposed to Al in water and in food with no 'neutralizing' silicic acid, or too little of it.
Kerr: When Jim Dobbie described the Si levels in tap water and in uraemic patients he showed, as you would expect from your data, higher serum Si levels in London than in Glasgow or Edinburgh (Dobbie & Smith 1986). The levels correspond to the Si concentrations in the dialysis fluid, because in those days we were not treating the tap water by de-ionization or reverse osmosis and Si was readily taken up by the patients in the course of one dialysis. Nowadays most renal units remove all solutes from water used for dialysis, yet you are still finding similar differences in serum Si. Are they therefore traceable to Si in the drinking water?

Birchall: Yes, in most cases. There might be a difference of 20-fold in silicon levels in drinking water from different regions, sufficient to produce quite significant differences in plasma silicon.

Kerr: And you absorb enough Si from drinking water to raise the plasma level substantially?

Birchall: Yes; you absorb almost all the silicon in water.

Martin: Dr Birchall, would you say more about the postulated Al-citrate-silicic acid ternary complex?

Birchall: It used to be said by the soil scientists that hydroxyaluminosilicates, such as imogolite, didn’t form in the presence of citrate. In fact, the truth seems to be that the imogolite solid phase doesn’t form in the presence of citrate, but its precursors seem to form, so that it ‘wants’ to crystallize; there are aluminosilicate units of the crystal in solution which don’t aggregate into a crystal when citrate is present. Imogolite can be considered as a single gibbsite sheet with Si(OH)₄ adsorbed on the surface. We seem to have citrate adsorbed as well, sitting on that plane. This complex can’t grow to form imogolite solid phase, but subcolloidal or solution species exist, containing aluminium, silicic acid and citric acid (Lou & Huang 1989).

Blair: The key to your work seems to be the ratio of Si to Al, not the absolute concentrations of each, in an aqueous phase. How do these ratios conform to the ratios of Al and Si in human plasma?

Birchall: Al in plasma is normally less than 1.0 μM. Silica in normal plasma varies between 5 and 20 μM. It can rise to 100 μM. Hydroxyaluminosilicate species with low Si:Al ratio (0.1) can be detected at silicic acid concentrations as low as 10⁻⁶ M at pH 7.2. The Si:Al ratio of the species rises with silicic acid concentration to that of imogolite precursors (0.5, the ideal composition of imogolite being (HO)₃Al₂O₅SiOH) at 10⁻⁴ M silicic acid. At plasma pH, silicic acid can be a significant ligand for aluminium, its potential for binding rising with concentration, perhaps in cooperation with citrate.

We looked at the effect of silicic acid and citrate on the competitive binding of Fe³⁺ and aluminium by desferrioxamine at pH 7.2 (Birchall & Chappell 1988b). The binding of Fe³⁺ was promoted in the presence of silicic acid/citrate, which cooperate in keeping Fe³⁺ hydroxide of low molecular mass and dispersed. The binding of aluminium was inhibited in the presence of silicic
acid, at least in the early stages of the reaction, due to hydroxyaluminosilicate formation. This suggests that silicic acid could influence the kinetics of ligand exchange of aluminium in vivo. Silicic acid (from magnesium trisilicate, or beer, which can contain > 500 μM Si, etc.) is rapidly absorbed and excreted in urine. A high plasma level resulting from continuous ingestion (as in a hard water area) might be expected to influence not only the availability of ingested aluminium, but also the destination of absorbed aluminium—that is to say, its entry into cells, mobilization, excretion, and so on.

**Day:** In the early days of purifying water for renal dialysis at home, de-ionizers were used; more recently it has become fashionable to use reverse osmosis. There is a big difference in the effect on silicon. The de-ionizer doesn’t remove Si from water; in fact, our experience is that it often increases it, because in most de-ionizers the resins are in fibre-glass containers and the Si concentration rises enormously as the water goes through. Whereas reverse osmosis removes all the solute components, ions or molecules, and Si levels will be very low. So your observations could be very important for the practical treatment of renal patients.

**Birchall:** I am aware of the difference between the early de-ionization, which put silica into water and took cations out, and what is done now, using reverse osmosis. We are looking retrospectively at that, and hoping to find a difference in patients exposed to the two conditions. In other words, in the old days, in high-silicon water areas, one might expect no obvious aluminium toxicity.

We have variable silicon levels in tap water in Liverpool, with an enormous variation of 10–200 μg per litre in different areas. But if it’s right that the effects of Al are neutralized by high plasma levels of Si, that would be extremely important.

**Fawell:** How important do you think high Si levels are in relation to the availability of Al from other environmental sources such as food? And how does that compare to the importance of Si actually being absorbed and providing silica which will combine with Al in the blood plasma, and help to remove the Al? In other words, Si has two roles, stopping Al going in and helping it to come out. Which is more significant?

**Birchall:** A good question! In the fish, the gill is rather a curious organ; on one side of the gill is the lake, and the other side is the fish! It is clearly the case that Si stops Al adsorbing to the gill membranes and to mucus. It equally stops it getting absorbed, so we don’t find Al in the chloride cells of the gill. So Si stops Al getting into the fish itself. Also, Si stops Al getting into root cell membranes in plants. One might think that this happens in the gut too. However, that has yet to be demonstrated. We don’t know enough about the mechanism of aluminium absorption to predict with certainty, and it is difficult to extrapolate from fish gill and plant root cell membranes to intestinal epithelia. I expect absorption to be reduced. There is an argument for increased aluminium absorption in the gut because hydroxyaluminosilicates are subcolloidal (not
precipitates). However, in this case, I would expect rapid clearance by the kidneys and decreased ‘hang up’.

_Edwardson:_ What do you mean by this ‘hang-up’ in the excretion of Al?

_Birchall:_ One recent paper (Rollin et al 1991) suggests that if you absorb Al and measure the amount excreted there is a delay in excretion, and there is retention.

_Edwardson:_ If you are inhaling dust which contains Al into the lungs, and then expectorating and swallowing it and subsequently absorbing Al from the gastrointestinal tract, there will be a delay between exposure and excretion. Similarly, with a large Al exposure, there will be uptake into bone, which acts as a sink, with subsequent slow release and excretion. However, the evidence suggests that most circulating Al is excreted rapidly.

_Birchall:_ We have not got a mass balance; as a simple chemist, I don’t understand anything until I have a mass balance! So we cannot say what happens, but there is strong evidence of Al retention.

_Blair:_ Intestinal absorption represents a dynamic system, consisting not only of flow out of the lumen of the gut into the body, but the flow from the stomach, through the lumen of the small intestine and into the lower colon. According to Professor Birchall, if you have Si and phosphate competing for Al, the pH level is important: phosphate is the dominant species at acidities greater than pH 6.6. Ingested material enters the stomach, where it reaches pH 2, so the Al will all bind to phosphate. It then leaves the stomach, moves into the duodenum, where it goes into pH 6 at the top of the duodenum, fluctuating a bit with the various fluid secretions. Then it passes down the gut and becomes more alkaline, so that Al binds to silicate. What is the rate of change from Al bound to phosphate to Al bound to silicate? Is it a slow rate? If it is (and the passage down the gut will be relatively fast), silicate species will not have any significance. With a fast rate of exchange, my argument doesn’t hold. We need to know the kinetics of the change in Al binding as pH changes.

_Birchall:_ I don’t know the exact kinetics: I think that exchange is fast.

_Blair:_ It would be interesting to know, because it could vitiate your argument. This is the kind of variable we need to think about when we consider intestinal absorption of aluminium. It is a very fine and complicated piece of plumbing!

_Williams:_ We have some evidence, from plants, which supports the type of argument that Derek Birchall is making. There are two types of flowering plant, in terms of leaf structure. The grasses (monocotyledonous plants) take up an enormous amount of silica; they don’t make what you describe as imogolite; they make amorphous silica, with a random distribution of Si, O and OH groups, i.e. $\text{SiO}_2\text{(OH)}_{4-2n}$ where $n$ goes from 0 to 1, in little globules, like opals (phytoliths). These ‘silicates’ in the grasses never contain any Al, to my knowledge.

Most broad-leaved plants do not take up much Si. An example is the tea plant, which does not take up Si, but its leaves are often heavily laden with Al. They
put this Al in combination with phenolate groups for example, in the tannins. But in a certain chemical sense this phenolate OH surface is exactly the same as the surface of SiO(OH)₂, except that it is carbon hydroxyl instead of Si hydroxyl. These hydroxyls have about the same acidity constant (pKₐ). So, higher plants such as the broad-leaved plants (dicotyledonous plants) have devised a trick to get rid of Al, based on phenols, whereas the grasses must have got rid of Al earlier within uptake mechanisms, and can lay down silica later absolutely free of Al. The chemistry nicely matches these different types of plant.

It would be interesting to look further at all these plant systems; obviously they must all be taking some Al across into the roots, but plants that make silica (the grasses) never get it into the leaf. Perhaps Al uptake is prevented because they are taking up so much silica in the root, by deliberately pumping Si in, that they protect themselves from Al, following Birchall’s recipe. And that isn’t the end, because the grass-eating animals then take in the phytoliths, which could well protect sheep and cows from Al in their first digestive system.

Klinowski: In support of what you say, in certain areas of India and China there are bamboo plants, which contain enormous amounts of Si inside the stem: it rattles when it dries. There is not a trace of Al in there. Where does it go? The white product, a hydrated silicic acid known locally as ‘tabasheer’, is purer than a silicon chip from Sinclair Research!

Williams: Some broad-leaved plants can handle silica, for example pears, but it would be interesting to investigate this further, because the plants may be able to help us in resolving the Al–Si story before we need to go to animal experiments.

References

Discussion

