AMORPHOUS HYDROXYALUMINIUM SILICATES FORMED UNDER PHYSIOLOGICAL SALINE CONDITIONS, AND IN CaCO₃-BUFFERED SOLUTIONS. STABILITY AND SIGNIFICANCE FOR ALZHEIMER PLAQUE PRECIPITATES

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ABSTRACT: In an attempt to determine the nature and conditions of formation of the aluminium silicate precipitates present at the core of senile plaque in the brains of patients with Alzheimer’s disease, aluminosilicate precipitates have been prepared and equilibrated for up to one year in physiological saline conditions at 40°C and a pH near 7-4. The structure and composition of these precipitates, and the associated concentrations of free silicic acid, were similar to those found in systems buffered with CaCO₃ at 20-25°C. Imogolite-like products with Si:Al ratios near 0-5 were obtained at silicic acid concentrations <100 μM, and hydrous feldspathoid products with ratios ≥1-0 became dominant at silicic acid concentrations greater than ~150 μM. These products do not match senile plaque precipitates, which have Si:Al ratios ≥1-0, but form in an environment with <100 μM Si. The relative stability of aluminium hydroxides, proto-imogolite allophane and hydrous feldspathoids are estimated from equilibrated silicic acid concentrations.

Amorphous aluminium silicate precipitates have been identified as a consistent feature of the core of senile plaques in the brains of sufferers from Alzheimer’s disease. Similar precipitates are present in senile plaques in intellectually normal elderly people, but at much lower density (Edwardson et al., 1986). A plausible mechanism for their formation has been advanced by Birchall & Chappell (1988a,b) who proposed that Al is slowly accumulated within neurons, where it becomes bound to functional inositol phosphates and phosphorylated proteins, finally leading to cell death. These aluminium phosphate complexes are stable in the weakly acidic (pH <6-6) intracellular environment, but it is argued that they become unstable relative to aluminium silicate species at the higher pH (7-4) of the extracellular environment to which they are exposed when the neurons disintegrate. In support of this mechanism, Birchall & Chappell (1988a,b) have shown that silicic acid competes successfully with the strong chelating anion, citrate, at pH 7-4. Solutions containing 0-1 mmol Al and 0-5 mmol each of silicic acid and citrate per litre gave no filterable solids, but contained soluble aluminosilicate species with an Si:Al ratio >0-5, which were retained on an ion exchange resin.

Nevertheless, there remain puzzling features about the aluminium silicate present in senile brain. The in vitro experiments of Birchall & Chappell were performed at silicic acid concentrations over twelve times those typically present in blood serum (mean 21 μM, range 14–39 μM: Dobbie & Smith, 1986). At these low concentrations, the amorphous aluminium silicate that precipitates from solution of pH up to at least 7-8 at 20°C has an Si:Al molar
ratio ≤0.5, and has an imogolite-like structure, with 6-coordinated Al incorporated in fragments of gibbositic sheets, and orthosilicic groups (O₃SiOH) replacing hydroxyls on one side of the sheets (Farmer & Fraser, 1982; Farmer et al., 1991). This composition and structure does not match the characteristics of senile plaque precipitates for which a typical molar ratio of Si:Al = 1:1 has been reported, and in which a proportion of the Al is 4-coordinated (Edwardson et al., 1986).

Moreover, citrate at typical serum concentrations (100 µM) has been calculated to maintain some 30 µM Al in solution over gibbsite at pH 7.4 (Ohman, 1988), and the imogolite structure is more soluble than gibbsite at silicic acid concentrations less than ~70 µM. Even in patients suffering from chronic renal failure, serum Al is <4 µM (Stewart, 1989). Thus, the imogolite structure is unlikely to persist in the serum environment.

It seems, therefore, that the precipitates present in senile plaque are more silica rich and more insoluble than those formed in in vitro experiments at 20°C. This difference in composition and stability could arise from the ionic environment and higher temperature (~40°C) at which senile plaque precipitates are formed. To explore this possibility, we have examined the nature of the aluminosilicate precipitates formed under physiological saline conditions at 40°C at a pH near 7.4, and at various silicic acid concentrations.

**EXPERIMENTAL**

Solutions (400 cm³ each) with an ionic composition near blood serum (145 mM NaCl; 1.19 mM CaCl₂; 0.62 mM MgCl₂; 4.5 mM KCl) and a pH of 7.3–7.5 were prepared with Si : Al molar ratios ranging from 1 : 4 to 4 : 1. The Al concentration was 0.75 µM for Si : Al ratios up to 2 : 1, dropping to 0.375 µM at the 4 : 1 ratio. Their pH was adjusted with NaOH to just over 6.0, then with 0.05 µM NaHCO₃ to 7.4. These solutions were incubated at 40°C in an oven with occasional shaking, and the pH checked and readjusted at intervals. The deviation in pH did not exceed 0.2 units. Free silicic acid in the supernatants over the centrifuged precipitates in 5 cm³ aliquots was determined colorimetrically (Farmer et al., 1991) after 2, 6 and 9 weeks, when one set of precipitates was harvested and characterized by infrared (IR) spectroscopy. A further set, with Si : Al ratios ranging from 3 : 8 to 6 : 8, were incubated for one year, with free silicic acid determined at 2, 6 and 52 weeks, when the precipitates were harvested and characterized. The pH was not readjusted after 6 weeks, and drifted to 7.4–7.9 over one year.

For comparison, solutions containing only Al, Si and Ca were incubated in the presence of excess CaCO₃ (pH 7.65–7.75) at 20–25°C for one year. The preparation of these solutions and the products formed after ten weeks have been described (Farmer et al., 1991).

The compositions of the aluminium silicate precipitates were calculated on the basis that they contained all the added Al and the difference between the total and the free silicic acid.

**RESULTS AND INTERPRETATION**

In Fig. 1, the concentrations of free silicic acid are plotted against the calculated composition of the aluminium silicate precipitates for the physiological saline (serum) solutions at 40°C after 2–52 weeks incubation. Points referring to the same solution are joined by thin lines. For the Al-Si-CaCO₃ systems at 20°C, points are plotted only for 6, or 10, and 52 weeks. Data for 2–10 weeks for this system have been reported (Farmer et al., 1991).
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Fig. 1. Concentrations of Si(OH)₄ in supernatants over aluminium silicate precipitates, plotted against the calculated composition of the precipitates for physiological saline solutions at 40°C (open symbols) and CaCO₃-buffered solutions at 20-25°C (filled symbols). The progress of each system with time is indicated by points joined by thin lines. Where symbols would overlap, only the later point is plotted. Starting ratios of Si:Al are indicated for some systems.

The IR spectra of the nine-week products from saline solutions with starting Si:Al molar ratios of 1:2, 1:1, 2:1 and 4:1 are shown in Fig. 2. These are very similar to those previously found for the Al-Si-CaCO₃ system at 20°C (Farmer et al., 1991). The product from the 1:2 system shows the features of the imogolite structure, with maxima at 975, 590, 430 and 350 cm⁻¹, whereas the products from the 1:1, 2:1 and 4:1 systems show the features of hydrous feldspathoid allophanes, with maxima at 1035, 890, 710 and 450 cm⁻¹ which are assignable to a polymeric tetrahedral aluminosilicate network, and a band at 600 cm⁻¹ assignable to 6-coordinated Al (Farmer et al., 1979).

The product from the 1:2 system after nine weeks showed, in addition to the imogolite absorption bands, a shoulder near 1020 cm⁻¹ indicative of a small proportion of the hydrous feldspathoid structure. This feature disappeared in the product incubated for one year, and the bands of the imogolite structure intensified and sharpened. This indicates that the imogolite structure is more stable than the hydrous feldspathoid structure at the equilibrated silicic acid concentration (36 μM) in the one-year supernatant (see Fig. 1). In the one-year products, the absorption bands of hydrous feldspathoids were still only weakly developed when Si in solution reached 100 μM. It became the dominant component when soluble Si exceeded about 150 μM.

A comparison of the curves relating precipitate composition to solution concentration of Si for the saline and CaCO₃-buffered systems (Fig. 1) shows that these are almost identical for starting ratios of Si:Al from 1:2 to 1:1. At starting ratios of 2:1 and 4:1, the products from the saline solutions are more silica rich. This is reflected in their IR spectra by an increase in the intensity of the band at 450 cm⁻¹ (4-coordinated Al + Si) relative to the 600 cm⁻¹ band (6-coordinated Al) in the products from the saline systems, compared with those from the CaCO₃-buffered systems (Farmer et al., 1991).
For Si : Al starting ratios less than 1 : 2, the products from both the saline and CaCO₃-buffered systems contained crystalline aluminium hydroxides as well as imogolite-like material. Bayerite was present in all systems, but nordstrandite was also present in the CaCO₃-buffered systems with starting Si : Al ratios of 1 : 8 and 1 : 4. In the one-year systems, the silicic acid in solution should be approaching the equilibrium concentration for the co-existence of imogolite-structures and crystalline aluminium hydroxides. These concentrations (Fig. 1) are 52 μM for a saline system at 40°C containing bayerite, and 64 μM for two CaCO₃-buffered systems at 20–25°C containing bayerite and nordstrandite. A very low silicic acid concentration (26 μM) was present in the CaCO₃-buffered system with Si : Al starting ratio of 3 : 8, in which only a poorly crystalline bayerite had formed after one year.

DISCUSSION

Relevance to Alzheimer plaque precipitates

The exploratory investigation reported above has failed to reproduce convincingly the type of aluminosilicate precipitate found in senile brain, i.e. with an Si : Al ratio ≥1 and a proportion of tetrahedral Al in its structure. Precipitates of the hydrous feldspathoid type
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have this composition and structure, but they require silicic acid concentrations in excess of \(-150\ \mu M\) for their formation at pH 7.4. Such high concentrations of silicic acid do occur in the serum of individuals suffering from chronic renal failure in areas where tap water is equally high in silicic acid, *e.g.* in London, concentrations of 120–174 \(\mu M\) have been reported, whereas in Glasgow and Edinburgh the range is 45–100 \(\mu M\) (Dobbie & Smith, 1986). Below 100 \(\mu M\) silicic acid, the precipitates formed in physiological saline solutions were identical with those formed in solutions buffered with CaCO\(_3\), and consisted predominantly of imogolite-like materials, with Si : Al atomic ratios of 0.43–0.64, in which Al is 6-coordinated.

In the present study, precipitates of the imogolite type have been found to form in solutions containing as little as 26 \(\mu M\) Si, *i.e.* within the range of serum concentrations of healthy individuals (14–39 \(\mu M\): Dobbie & Smith, 1986), although the imogolite structure is unstable relative to crystalline aluminium hydroxides below 52–65 \(\mu M\) Si. However, given the reported stability of aluminium citrate complexes at pH 7.4 (Ohman, 1988) it is unlikely that the imogolite structure can survive in physiological fluids with citrate concentrations near that of serum and silicic acid concentrations <100 \(\mu M\).

Amorphous aluminium silicates more stable than imogolite or hydrous feldspathoids were found to form in CaCO\(_3\)-buffered solutions kept at 80\(^\circ\)C for eight weeks (Farmer et al., 1991) and in dilute sodium solutions of pH 8.9 at 95–100\(^\circ\)C for seven days (Wada et al., 1988). These have Si : Al ratios approaching unity, and a structure which appears to be close to that of halloysite. Although halloysite itself contains predominantly 6-coordinated Al, ~30% of the Al is 4-coordinated in these more disordered structures (Wada et al., 1988). It may be that the conditions under which Al is released in the senile brain favour the formation of this more stable product. However, no trace of halloysite-like material was detectable in precipitates from physiological saline solutions at 40\(^\circ\)C in the present study even after one year.

The nature and conditions of formation of the aluminium silicate precipitates in senile brain remain an unsolved problem.

**Stability of amorphous aluminosilicates**

The present results provide a check on published estimates of the stability of proto-imogolite allophane and hydrous feldspahoids. In acid solutions with starting ratios of Al:Si>2, in which a mixture of aluminium hydroxides and proto-imogolite allophane should precipitate, Farmer & Fraser (1982) found that silicic acid in solution stabilized rapidly (7–14 days) in the range 33–100 \(\mu M\). They suggested that the higher figure corresponded to equilibrium between gibbsite and imogolite, albeit both in poorly crystalline forms. This concentration of silicic acid is close to that found in streams (70 \(\mu M\)) in terrains where soils containing proto-imogolite allophane suffer acidic leaching (Dahlgren et al., 1989).

In the CaCO\(_3\)-buffered systems, equilibrium is approached much more slowly, and after four weeks the silicic acid in solution amounted to only 4–18 \(\mu M\) for Al:Si starting ratios of 8 : 1 and 4 : 1 (Farmer et al., 1991). However, after one year, silicic acid concentrations reach 64 \(\mu M\) in these systems, associated with fairly well-crystallized bayerite and nordstrandite. The relative stability of gibbsite, bayerite and nordstrandite is still uncertain, but they cannot differ by much. Thus the present best estimate of 64 \(\mu M\) Si in solution for equilibrium
between proto-imogolite allophane and crystalline Al(OH)_3 species is close to the previous estimate of 100 μM.

Bilinski et al. (1990) have derived solubility products for proto-imogolite allophane (their phase VIIb) and hydrous feldspathoids (phases VII and VIII) on the basis of the solid phases and precipitation boundaries characterizing the system H^+-Al^{3+}-oxalic acid-silicic acid-Na^+. From these values, the concentration of silicic acid in equilibrium with gibbsite and proto-imogolite allophane can be calculated to be 0.25 M. This greatly under-estimates the stability of proto-imogolite, probably because the light-scattering method used to detect the formation of solid phases failed to detect the formation of a proto-imogolite sol, whose dimensions are initially less than the diameter of an imogolite tube (2-3 nm; Farmer, 1986).

Partly for the same reason, the solubility products derived by Bilinski et al. (1990) overestimate the stability of the hydrous feldspathoid phases relative to proto-imogolite allophane. Their results predict that, at an Si(OH)_4 concentration of 100 μM, phase VII would be more stable than proto-imogolite allophane above pH 6.1 in the 0.6 M NaCl medium used, or above about pH 7.1 in the 2.5 mM Ca(NO_3)_2 present in the CaCO_3-buffered systems at pH 7.7. The hydrous feldspathoid phase VIII need not be considered as it is unstable relative to phase VII at silicic acid concentrations <1-12 mM.

A recalculation of the solubility product of proto-imogolite allophane in 0.6 M NaCl on the basis that it is in equilibrium with gibbsite (log K_{sp} = 9.6) at a silicic acid concentration of 64 μM, gives

$$2 \log [AI^{3+}] + \log [Si(OH)_4] + 6 \text{ pH} = 15$$

A recalculation of the solubility product of phase VII would not be justified on the basis of the present findings, as the hydrous feldspathoid precipitated in CaCO_3-buffered solutions differs significantly in composition from that postulated by Bilinski et al. (1990) for phase VII. Phase VII is formulated as NaAl(OH)_4·H_2SiO_4, that is, with only tetrahedral Al and a high exchangeable cation content. The IR spectrum of the product from CaCO_3-buffered systems showed a substantial proportion of 6-coordinated Al absorbing at 600 cm⁻¹; semi-quantitative electron microprobe analysis showed only a low content of Ca. Apparently, the negative charge arising from tetrahedral Al is largely compensated by positive charge associated with the 6-coordinated Al.

REFERENCES


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