

Commentary

Organosilicon Therapy in Alzheimer's Disease?

Christopher Exley

Birchall Centre for Inorganic Chemistry and Materials Science, Lennard-Jones Laboratories, Keele University, Keele, UK

E-mail: c.exley@chem.keele.ac.uk

I was immediately intrigued by the title of the paper by Friedman and colleagues [7]. A tumult of thoughts ensued as I fought for a basis for linking organosiloxanes with the treatment of neurodegenerative disease! Needless to say, I was surprised at the authors' contention that organosiloxanes might be used therapeutically to prevent or dissolve metal-mediated deposits of brain amyloid though my surprise was tempered by knowledge of an earlier and similar suggestion by Fasman and colleagues that inorganic silicates might be used to the same end [6]. Friedman et al. have acknowledged Fasman et al. as the origin of their idea but were they misled by the earlier publication? According to the abstract and conclusions Fasman et al. demonstrated that an aluminium-induced transition towards β -sheet conformers of $A\beta_{42}$ could be reversed to random coil soluble forms of the peptide by the addition of sodium orthosilicate (Na_4SiO_4) and, crucially, that this effect was attributable to the tight binding of Al^{3+} by SiO_4^{4-} . Unfortunately this conclusion was not supported by their experiments. What they did show was that in a non-aqueous medium of 2,2,2 trifluoroethanol (TFE) the addition of Al (dissolved in TFE) induced a conformational change in $A\beta_{42}$ from predominantly α -helix/random coil to one which included a significant component of β -sheets. When an aqueous solution of Na_4SiO_4 was subsequently added to the mixture of $A\beta_{42}/\text{Al}/\text{TFE}$ a partial reversal of the β -sheet transition was achieved at a SiO_4^{4-} to Al ratio of 1.0. This effect may, as the authors suggested, have been due to the

titration of Al out of $A\beta_{42}$ though none of the required control experiments were carried out to confirm this. For example, we do not know if the observed effect was due to (i) the addition of water (from the addition of aqueous Na_4SiO_4) to the $A\beta_{42}/\text{Al}/\text{TFE}$ mixture; (ii) the increase in pH which would occur when aqueous Na_4SiO_4 (pH > 11.0!!) was added to the mixture; (iii) the rapid formation of metal-greedy polysilicic acids which would have occurred when a 138 mM Na_4SiO_4 was added to an acidic $A\beta_{42}/\text{Al}/\text{TFE}$ mixture or (iv) SiO_4^{4-} binding of Al at 'mixture' pH > 10. Even if the appropriate control experiments had demonstrated that the reversal of the β -sheet transition was due to SiO_4^{4-} titrating Al out of $A\beta_{42}$ what would be the physiological significance of such since under the conditions which could occur in brain fluid the only biologically available form of Si is silicic acid ($\text{Si}(\text{OH})_4$) [2]. My interpretation of Friedman et al., at least in its original form, is that the authors were misled to the extent that they have looked to extend Fasman's earlier studies by appending a notional SiO_4^{4-} functionality to a lipid soluble carrier to improve the accessibility of such a group to a target site in the brain. Once in situ in sufficiently high concentrations the organosilicate would titrate aluminium, and other metals, out of precipitated deposits of $A\beta_{42}$ and prevent any further metal-amyloid induced neuronal damage [9].

Friedman et al. have shown that both aluminium and iron were able to promote the formation of β -sheet conformers of $A\beta_{42}$ and, indeed, that the addi-

tion of organosiloxanes prevented and/or reversed such conformational transitions. The observation of metal-induced formation of β -sheets is not new [1,8] but how might their prevention/reversal using organosiloxanes be explained? No evidence is offered that any of the organosiloxanes bind any metals under any set of conditions. There is no evidence in the scientific literature that any of the organosiloxanes used by Friedman et al. will bind metals and we have shown that neither dimethylsilanediol (DMSD) nor polydimethylsiloxane (PDMS) binds aluminium [5]. Perhaps a more likely explanation of the observed effects may be related to changes in the hydrophobicity of the solvent mixture upon addition of the organosiloxanes? Such differences could act so as to promote conformational changes in $A\beta_{42}$ such that metal-binding sites are either protected (thus preventing metal-induced effects) or rendered unstable/ineffective (acting so as to reverse metal-induced effects).

Even allowing for the proviso that metal-induced aggregation and precipitation of $A\beta_{42}$ has any role to play in the aetiology of Alzheimer's disease [3] I remain unconvinced that organosiloxanes would have any therapeutic value. I worry about how they could be delivered to their target sites at sufficient concentrations to have any effect and I worry about what happens to the metal once it has been purged from its amyloid sink. There is one form of silicon, the biologically available form of silicon known as silicic acid ($\text{Si}(\text{OH})_4$), which binds aluminium, is freely permeable throughout the body and has been shown to facilitate the excretion of aluminium from the body [4]. Friedman et al. seem as

yet unaware of its potential therapeutic value in neurodegenerative disease.

References

- [1] C. Exley, N.C. Price, S.M. Kelly and J.D. Birchall, An interaction of β -amyloid with aluminium *in vitro*, *Febs Lett* **324** (1993), 293–295.
- [2] C. Exley, Silicon in life: A bioinorganic solution to bioorganic essentiality, *J Inorg Biochem* **69** (1998), 139–144.
- [3] C. Exley, Aluminium and iron, but neither copper nor zinc, are key to the precipitation of β -sheets of $A\beta_{42}$ in senile plaque cores in Alzheimer's disease, *J Alzh Dis* **10** (2006), 173–177.
- [4] C. Exley, O. Korchazhkina, D. Job, S. Strekopytov, A. Polwart and P. Crome, Non-invasive therapy to reduce the body burden of aluminium in Alzheimer's disease, *J Alzh Dis* **10** (2006), 17–24.
- [5] C. Exley, The solubility of hydroxyaluminosilicates and the biological availability of aluminium, in: *Thermodynamics, Solubility and Environmental Issues*, T.M. Letcher, ed., Elsevier, In the press, 2007.
- [6] G.D. Fasman, A. Perczel and C.D. Moore, Solubilization of β -amyloid-(1-42)-peptide: Reversing the β -sheet conformation induced by aluminium with silicates, *Proc Natl Acad Sci USA* **92** (1995), 369–371.
- [7] O.M. Friedman, P.J. Matsudaira, A.H. Reis Jr, N. Simister, I. Correia, D. Kew, J.Y. Wei and T. Pochapsky, Substituted organosiloxanes as potential therapeutics for treatment and prevention of neurodegenerative diseases, *J Alzh Dis* In the press.
- [8] E. House, J. Collingwood, A. Khan, O. Korchazhkina, G. Berthon and C. Exley, Aluminium, iron, zinc and copper influence the *in vitro* formation of amyloid fibrils of $A\beta_{42}$ in a manner which may have consequences for metal chelation therapy in Alzheimer's disease, *J Alzh Dis* **6** (2004), 291–301.
- [9] A. Khan, J. Dobson and C. Exley, The redox cycling of iron by $A\beta_{42}$, *Free Rad Biol Med* **40** (2006), 557–569.