Journal of Alzheimer's Disease 11 (2007) 303–304
IOS Press

Commentary

Authors' Reply to "Organosilicon Therapy in Alzheimer's Disease?"

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Professor Exley raises a number of interesting points in his commentary, and we thank him for opening the discussion. First, we wish to point out that, although the present work was indeed inspired by Dr. Fasman's original publication, we are not trying to defend that work nor are we attempting to explain Fasman's observations. Our paper reports a series of phenomenological observations on the interaction of certain organosiloxane compounds with metallated Aβ_{42}. We think these will be of interest in their own right to the AD community. We are careful not to draw any conclusions concerning the mechanism of action of these compounds, which, as Prof. Exley notes, is not addressed by our experiments. Clearly, questions regarding the interaction between organosiloxanes and metal ions should be a primary focus of future research.

A number of issues raised in the Commentary specifically relate to our paper [1]. First, it is reported that dimethylsilanediol (which is structurally related to the some of the organosiloxanes under discussion) does not interact with aluminium [2], but the context of that measurement is not clear: Is this in aqueous solution, in a biphasic mixture or under non-polar conditions? One might expect that interaction to be very context-dependent. Another issue raised is whether changes in the polarity of the medium (trifluoroethanol with maximum 5% water) due to siloxane addition might be causing the observed reversal of the metal-induced helix-coil transition. While we cannot rule this out, the nominal concentrations of siloxanes being added are quite low (quasi-stoichiometric with metal ($\sim$200 μM) and peptide ($\sim$20 μM)), and would require a fairly strong interaction of some sort between Aβ_{42} and the organosiloxane to increase local concentration sufficiently to perturb the peptide's environment.

As to the potential applicability of organosilicon compounds to the treatment or prevention of AD, we are obviously somewhat more optimistic than Prof. Exley. Still, as any pharmaceutical researcher knows, there is a long road between compounds that show interesting behaviour *in vitro* and a usable treatment. In the case of the compounds under discussion, a number of obvious problems (some beyond our small company's capability to deal with) must be solved. For one thing, these are not compounds that one normally puts into an aqueous environment, since all of the title compounds are more or less prone to polymerization in aqueous media, and solutions must be freshly prepared and clarified for each test. Even so, inevitable loss of material due to precipitation, polymerization or poor initial dispersion means (as stated in the paper)

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ISSN 1387-2877/07/$17.00

that reported concentrations are nominal. Furthermore, we do not expect that the compounds described here are necessarily the best or even first choice for further testing. These were simply the best behaved of those silanes that could be obtained commercially. We do see trends (e.g., the benefit of nitrile substitution on the alkyl moiety, reminiscent of acetonitrile, or avoidance of large hydrophobic substituents, which appear to encourage aggregation/polymerization in aqueous environments) that a careful synthetic program could use to identify compounds with better dispersibility/solubility or transport characteristics.

Finally, we observe that, while any number of objections can be raised to the described organosiloxanes as potential therapeutics/prophylactics in AD, they are chemically simple, inexpensive and offer a fresh perspective on a massive public health problem. It is helpful to remember the value of "outside-the-box" ideas. For example, although heavy metals are not usually associated with medicine other than as toxins, *cis*-platin remains one of the most useful clinical weapons against cancer. In this light, the potential of unusual approaches to therapy in AD should not be overlooked.

References

[1] 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).

[2] C. Exley, The solubility of hydroxyaluminosilicates and the biological availability of aluminium, in: *Thermodynamics, Solubility and Environmental Issues*, T.M. Letcher, ed., Elsevier, in press.