

# **Can the Neurotoxic A $\beta$ Intermediate Be Structurally Similar to the Fibril But More Toxic?**

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$\beta$  amyloid peptide (A $\beta$ ) is believed to play a key role in the mechanism of Alzheimer's disease (AD). A $\beta$  tends to associate and form amyloid fibrillar aggregates rich in  $\beta$ -sheet content. A variety of evidence indicates that A $\beta$  aggregates are toxic in vitro, and the presence of certain A $\beta$  oligomers species appear to be correlated with AD pathology in vivo. An early 'A $\beta$  hypothesis' postulated that AD was the consequence of neuron death induced by insoluble deposits of large A $\beta$  fibrils. Newer findings indicate that the small soluble A $\beta$  oligomers are the neurotoxic species. However, the structure of the toxic A $\beta$  species and the pathway by which it forms are still unknown. Some researchers suggest that the toxic intermediate species is simply a premature fibril, while others reported a structurally distinct spherical intermediate that is associated with toxicity. We are using a variety of tools to examine the structure of toxic A $\beta$  species that are intermediates in the fibril formation pathway.

We describe here an assessment of the hydrophobicity and solvent accessibility of A $\beta$  species upon aggregation and use those experiments to guide development of a model that examines A $\beta$  toxicity. Hydrophobicity specific fluorescence probes were used to detect the exposure of hydrophobic residues of the different A $\beta$  aggregation species. Hydrogen exchange mass spectrometry was used to examine the solvent accessibility of the backbone of different A $\beta$  aggregation species. The results reveal that the transition between the monomer to the mature fibril is smooth, and that the intermediate aggregate does not seem to have unique structural features. Moreover, it seems that the intermediate has lower level characteristics of the mature fibril, implying that the intermediate is a smaller fibril and is not structurally different. This result may imply that the intermediate appears more toxic than the fibril due to its higher mobility and higher concentration, and not due to differences in structure specific interactions of the different aggregated species. We estimated the rate of reaction between A $\beta$  aggregates and neurons, assuming that the reaction was diffusion-limited reaction. Using this simple model and information about the geometry of the fibrils and oligomers, we can explain the difference in biological activity of these different A $\beta$  aggregates.

In the light of our hypothesis that the toxic intermediate and fibril share the same molecular level structure, we are currently using atomic-level docking to predict the interaction of A $\beta$  fibril and aggregate species with other small molecules and proteins. With these results, we hope to be able to infer differences in interaction associated with self assembly and those associated with toxicity.