Effects of an amyloid-inhibiting D-peptide on the structural propensities of the Alzheimer's peptide

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Abstract:

Abnormal protein folding and aggregation are causative mechanisms underlying many different disease conditions. In the case of Alzheimer's disease abnormal aggregation of the 39 to 42-residue long amyloid beta peptides (Aβ) into neurotoxic oligomeric units has been identified as a major cause of the disease. Thus aggregation inhibitors hold a promising prospect to provide a new therapeutic approach for the management of Alzheimer's disease. A 12-residue D-enantiomeric peptide, the so-called D3 peptide, was recently demonstrated to possess inhibitory activity against Aβ1-42 oligomerisation in in vitro and in vivo experiments. In the current study we employed global optimisation and molecular dynamics approaches for gaining atomistic insight into the mode of interaction of D3 with the Aβ1-42 peptide. It was found that negatively charged residues in the N-terminal half of Aβ1-42 are the most important for mediating the demonstrated strong binding with electrostatic attraction being the principal driving force. Effects on the secondary structure of the Aβ1-42 peptide include a reduction in β-sheet and helical contents. In the second phase of the study we examined the interaction of D3 with a pentameric β-sheet assembly of the amyloid peptide employing global optimisation and Brownian dynamics methods, followed by atomic-detail conformational search using MD simulations. Insight from these studies provide us with important information about the principal driving forces of the interaction between Aβ1-42 and D3, and will help us in designing better anti-amyloid structural scaffolds.

[1] T. van Groen, *et al*, *ChemMedChem* , **2008**, *3*, 1848-1852.