MODULATION OF THE CONFORMATIONAL BEHEVIOR OF A β(25-35) BY INTERACTION WITH TWO POTENT β-SHEET BREAKER PEPTIDES

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The major components of neuritic plaques found in Alzheimer disease (AD) are peptides known as amyloid β-peptides (A-β-peptides). The A-β-(1-42) is the most prone to aggregation and is produced in larger quantities.
A-β-(25-35), sequence GSNKGAIIGLM, is a synthetic derivative of amyloid β-peptide, that is highly toxic and forms fibrillar aggregates typical of β-amyloid. Like the A-β-(1-42), A-β-(25-35) undergoes a conformational transition from a soluble, alpha-helical form to aggregated fibrillary β-sheet structures which are neurotoxic (1). Since it retains both the physical and biological properties of A-β-peptides it can be used as a suitable model of full-length peptides, for testing inhibitors of aggregation and toxicity. The design of inhibitors of aggregation is one of the strategies to overcome the Alzheimer disease. Many oligopeptides have beta-breaking activity since they are able to disaggregate the beta fibrils. The pharmacological profile of β-sheet breaker peptides can be improved to produce compounds with drug-like properties that might offer a new promise in the treatment of Alzheimer's disease.
Recently a 5-amino acid β-sheet breaker peptide (iAβ5p), end-protected, was shown to have the ability to induce a dramatic reduction in amyloid deposition in two different transgenic Alzheimer's models (2). Furthermore one peptide analog of iAβ5p containing a methyl group introduced at the nitrogen atom of one amide bond showed increased farmacocinetic and farmacodynamic characteristics (3). The ability of iAβ5p and of its N-methyl- derived analog to affect the conformation of A-β-(25-35) was investigated by Circular Dichroism and NMR spectroscopies.
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References
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