Simulations of peptide inhibitors of Amyloid-β aggregation

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Alzheimer's disease is associated with the abnormal self-assembly of the Alzheimer Amyloid-β (Aβ) peptide into aggregate structures. Both the end-product amyloid fibrils as well as smaller soluble oligomers formed in the initial stages of aggregation appear to be toxic to the cell. An attractive therapeutic approach to combat amyloid diseases lies in the development of strategies to inhibit or reverse aggregation. We consider here the 16-22 fragment of the (Aβ) peptide, the shortest sequence of Alzheimer Aβ peptides capable of forming fibrils. An N-methylated version of this peptide has recently been shown to inhibit fibrillogenesis and disassemble Aβ fibrils. We present molecular dynamics simulations of the interaction of this inhibitor peptide with small oligomers of Aβ peptides, as well as with a model fibril. Our simulations suggest that the inhibitor peptide can act on both prefibrillar and fibrillar forms of Aβ, and that the specific mechanism of inhibition depends on the structural nature of the Aβ aggregate.