Inhibition of aggregation of amyloid peptides by beta-sheet breaker peptides and their binding affinity

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Abstract

Effects of beta-sheet breaker peptides KLVFF and LPFFD on oligomerization of amyloid peptides are studied by all-atom simulations. It is shown that LPFFD interferes the aggregation of Aβ_{16-22} peptides to a greater extent than KLVFF. Using the molecular mechanics-Poisson-Boltzmann surface area (MM-PBSA) method we find that the former stronger binds to Aβ_{16-22}. Therefore, by simulations we have disclosed the relationship between aggregation rates and binding affinity that the stronger is ligand binding the slower is oligomerization process. The binding affinity of pentapeptides to full-length peptide Aβ_{1-40} and its mature fibrils has been considered using the Autodock as well as MM-PBSA methods. The hydrophobic interaction between ligands and receptors plays a more important role for association than the hydrogen bonding. The influence of beta-sheet breaker peptides on secondary structures

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of monomer $A\beta_{1-40}$ was studied in detail and it turns out that in their presence the total beta-content may get enhanced. However, the aggregation can be slowed down because the beta-content is reduced in fibril-prone regions. Both pentapeptides strongly bind to monomer $A\beta_{1-40}$ as well as to mature fibrils but KLVFF displays lower binding affinity than LPFFD. Our finding is in accord with earlier experiments that both of them can serve as prominent inhibitors. In addition we predict that LPFFD inhibits/degrades the fibrillogenesis of full-length amyloid peptides better than KLVFF. This is probably related to difference in their total hydrophobicities that the higher is hydrophobicity the lower inhibitory capacity. The Gromos 96 43a1 force field with explicit water and the force field proposed by Morris *et al* (G.M. Morris *et al*, J. Compt. Chem. **1998**, 19, 1639) are employed for all-atom molecular dynamics simulations and Autodock experiments, respectively.