In silico and *in vitro* study of binding affinity of tripeptides to amyloid beta fibrils: Implications for Alzheimer's disease

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Abstract

Aggregation of amyloid beta (Aβ) peptides has been proposed as the main cause of Alzheimer's disease (AD). Presently, there is no cure for AD, but there are evidences that reversion of amyloid deposits is beneficial. In this paper all 8000 tripeptides were studied for their ability

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to destroy Aβ fibrils. The docking method and the more sophisticated molecular mechanics-Poisson-Boltzmann surface area (MM-PBSA) method were used to calculate the binding affinity and mode of tripeptides to Aβ fibrils. The ability of these peptides to depolymerize Aβ fibrils was also investigated experimentally using ThT fluorescence assay and atomic force microscopy. It was shown that tripeptides prefer to bind to hydrophobic regions of 6Aβ_{9-40} fibrils. Tripeptides WWW, WWP, WPW and PWW were found to be the most potent binders. *In vitro* experiments showed that tight-binding tripeptides have significant depolymerizing activities and their DC_{50} values determined from dose-response curves were in micromolar range. The ability of non-binding (GAM, AAM) and weak-binding (IVL and VLA) tripeptides to destroy Aβ fibrils was negligible. *In vitro* data of tripeptide depolymerizing activities support the predictions obtained by molecular docking and all-atom simulation methods. Our results suggest that presence of multiple complexes of heterocycles forming by Tryptophan and Proline residues in tripeptides is crucial for their tight binding to Aβ fibrils as well as for extensive fibril depolymerization. We recommend PWW for further studies as it has the lowest experimental binding constant.