

A natural heptameric peptide exhibits multifaceted inhibitory role in the fibrillation pathway of amyloid-beta

Rajanya Bhattacharyya¹, Sayan Bhattacharjee¹, Bani Pathak¹, and JAYATI SENGUPTA¹

¹Indian Institute of Chemical Biology CSIR

May 5, 2020

Abstract

Background and Purpose Alzheimer's disease (AD) pathogenesis involves amyloid- β ($A\beta$) aggregation where the intermediate oligomers are considered the prime toxic species. Here, we aimed to identify an effective peptide sequence from a medicinal plant-derived enzyme having anti-amyloidogenic properties against $A\beta$. Experimental Approach LC-MS/MS followed by computational analysis identified the active peptide (termed here as Pactive). Visualization techniques along with biophysical and biochemical approaches were used to determine the anti-amyloidogenic potency of the purified enzyme and peptides identified from the enzyme. Cytotoxicity was measured on SHSY-5Y cell lines. Interaction studies were done with bio-layer interferometry (BLI) and bio-stability of the peptide was assessed by NMR. Pactive induced conformational alterations of $A\beta$ monomer and oligomers was determined with DSC and NMR. Key Results A small heptameric peptide (Pactive) identified from a medicinal plant-derived fibrinolytic enzyme proved to be a multifunctional inhibitor against $A\beta$ aggregation. The results suggested that Pactive arrests $A\beta$ molecules in non-toxic off-pathway oligomers that can no longer participate in the cytotoxic fibrillation pathway. Mechanistically, Pactive binding induces conformational alterations in the $A\beta$ molecule, thus modulating its hydrophobicity, one of the key players in inducing aggregation. Conclusions and Implications The study identified a natural peptide Pactive (GFLHQQK) that displays potential anti-amyloidogenic properties against $A\beta$ aggregation. The bio-stability of Pactive in human blood serum as well as its non-toxic nature makes it a promising therapeutic candidate against Alzheimer's, for which no disease-modifying treatments are available till date.

Hosted file

Bhattacharyyaetal_BJP_Final18March2020.pdf available at <https://authorea.com/users/304978/articles/435557-a-natural-heptameric-peptide-exhibits-multifaceted-inhibitory-role-in-the-fibrillation-pathway-of-amyloid-beta>

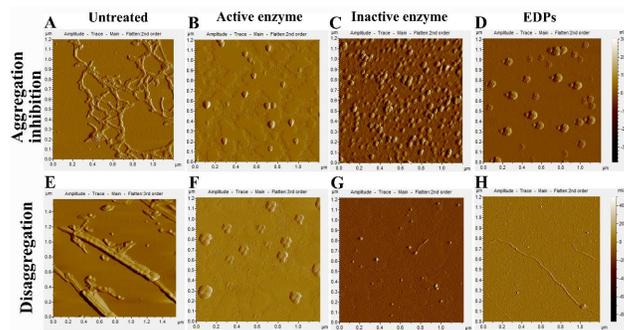


Figure 1