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P. Anand, F. S. Nandel

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# Conformational Study of Amyloid Beta (ABeta) Peptide

Priya Anand and F. S. Nandel

Department of Biophysics,  
Panjab University, Chandigarh-160014, India  
*E-mail: priyaanand\_27@hotmail.com*

ALZHEIMER'S DISEASE is the most common cause of senile dementia. Pathological hallmarks of the disease include senile plaques and neurofibrillary tangles. The plaques result from the transformation of soluble A $\beta$  protein monomer into insoluble aggregates. Determination of the molecular structure of A $\beta$  fibrils by using molecular dynamic simulation softwares provide an insight into the precise arrangement of monomers that would allow targeting the critical steps in fibrilogenesis process. The optimized geometry for the (A $\beta_{15-42}$ ) monomer is a U-like structure.

## 1 Introduction

Alzheimer's disease (AD) is a neurological disorder, affecting approximately 12.5 and 47.2% of the population in the United States over the ages 65 and 85, respectively. Defining features are formation and progressive deposition of insoluble amyloid plaques and presence of neurofibrillary tangles. ABeta-peptide is 39-43 amino acids polypeptide with heterogeneous termini that is generated from the cleavage of a larger amyloid precursor protein (APP), which under appropriate cellular conditions, aggregate as senile plaques, which is a critical step in the neurodegenerative processes associated with AD.

A detailed understanding of the structural properties of amyloid monomer could play a crucial role in the understanding the molecular mechanism of the disease. Despite the limitations of conventional NMR or X-ray in the amyloid fibril structural study, some structural information has emerged from various techniques<sup>1,2</sup> mass spectroscopy, and solid state NMR spectroscopy. However, the structural characterization of the Abeta monomer still remains difficult due to its tendency to aggregate.

Complimentary to the experimental studies, computer simulations can yield valuable information on structure, and stability, of the monomer resulting in the possible fibril formation mechanism of the ABeta protein. We have undertaken molecular dynamics (MD) simulations study on monomer of different short length peptide i.e 1-16 (referred as N-terminal region) and 15-42 residue fragments in aqueous solution to complement, and to add further extend the experimental solution studies of the beta-peptides and to explore the structural stability, hydration and dynamics of peptide fibrils. The N-terminal region of ABeta has been shown to be flexible and accessible within amyloid fibrils and the remaining 29-42 hydrophobic is shown to adopts a beta-sheet conformation. N-terminal constitutes an attractive therapeutic target for active or passive immunization approaches, as illustrated by the ability of monoclonal antibodies directed towards this region to dissociate amyloid fibrils.

## 2 Material and Methods

The peptide  $A\beta$  originally consists of 42 amino-acid residues: [Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ala-Ala], which is usually expressed as  $A\beta_{1-42}$ . The conformational analysis of  $A\beta_{1-42}$  has been first carried out using quantum mechanical methods (QM) PCILO program (Perturbative Configuration Interaction Using Localized Orbitals) on Sun W, Ultra 5-10; sparc was used, for which the  $A\beta_{1-42}$  peptides were fragmented into smaller overlapping fragments with both the N- & C- terminal protected by acetyl and dimethylamine group respectively.

The  $(\phi, \psi)$  values obtained from the quantum mechanical calculations were used as the starting geometry for molecular mechanics and molecular dynamics. Another structure used as the starting geometry for molecular dynamics was a linear extended starting structure, minimized structure obtained after running molecular dynamics in vacuum for 50ns at 300K using AMBER8 molecular dynamics.

For Molecular dynamics simulations  $A\beta_{1-42}$  was fragmented into N-terminal region with 1-16 residues peptide and C-terminal fragment with 15-42; (where no 1,16,15,42 indicates the residue no) peptide utilizing the program the GROMACS 3.3.1.

Energy minimization was carried out using steepest descent followed by conjugate gradient method. All atoms of the system were considered explicitly, and their interactions were computed by using the 43a1 force field with periodic boundary conditions. Peptide was solvated in a box by using SPIC216water molecules. All solute and solvent atoms were treated explicitly. Water molecules were added around the peptide to fill a octahedron box with walls at least 9nm, from any peptide atom. All simulations were performed using periodic boundary conditions to eliminate surface effects. Long-range electrostatic interactions were handled by using the particle mesh Ewald methodology. The solvated peptides were subsequently minimized. Position restraining done using weak coupling to a bath of constant temperature ( $T_0 = 300$  K, coupling time  $T = 0.1$  ps), and the pressure controlled using weak coupling to a bath of constant pressure ( $P_0 = 1$  bar, coupling time  $T = 0.5$  ps). The production runs were done with the same pressure and temperature coupling constants as the restrained runs. From the trajectories obtained we extracted the potential energy, Root mean square deviation, radius of gyration and Surface area properties and number of hydrogen bonds formed during the simulation. For visualization of the structures and the interactions RASMOL, and VMD was used.

## 3 Results and Discussion

Molecular view suggests that optimized geometry for the ( $A\beta_{15-42}$ ) monomer has a U-like structure (Fig A). Phi, psi values indicate that  $A\beta_{15-42}$  peptide does not adopt any regular secondary structure, instead a turn is present between residues 26-32. As displayed in figure, its amphipathic character is not lost i.e the longer arm has hydrophilic and charged amino acid residues while the smaller arm has hydrophobic branched residues exclusively. Side chain of most of the hydrophobic residues are oriented inwards with the exception of Leu 34, Val 36, Val 40 and Ala 42 which project outwards, that may lead to the association of one A with another A through hydrophobic interactions involving the C-terminal stretch. Analysis of the interactions stabilizing the U-like structure of  $A\beta_{15-42}$ , and identification

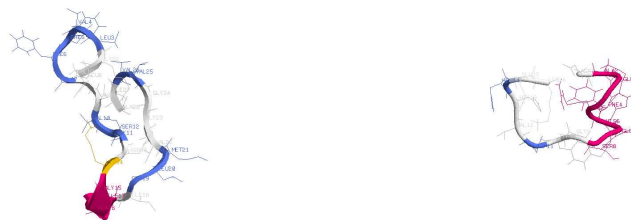


Figure 1. A molecular view of optimized ( $A\beta_{15-42}$ ) and ( $A\beta_{1-16}$ ) peptide fragment in aqueous medium, Fig A and Fig B respectively

of the possible interactive regions in Abeta peptides will be utilized for construction of  $A\beta$  dimers and high-mers.

Molecular view suggests that optimized geometry for the  $A\beta_{1-16}$  monomer is stabilized by hydrogen bonds are formed primarily between the carbonyl oxygen and the amino group of the backbone as displayed in Figure B. At 300 K, the peptide is seen to exist 25% in a helical conformation. The phi, psi values of the various residues indicate the presence of gamma turn around the residue Glutamine 7 and Glycine 9. Though residues with polar side chains are present only a few of them (ARG5, GLU3, ASP1, TYR10 and Glu15) participate in hydrogen bond formation. From the graphical display of the molecule, it is apparent that the carbonyl oxygen of His 6 backbone is near to the OH group of the aromatic ring of TYR 10 as the distance of the oxygen atom of the carbonyl group and OH moiety is 1.8 Å. This may be interpreted as though the carbonyl moiety is involved in pi-pi interaction with the aromatic ring.

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