Stability of full-length amyloid-β (1-42) monomer in water: Replica exchange molecular dynamics and *ab initio* molecular simulations

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1. Introduction

The Alzheimer's peptide amyloid-β (Aβ) plays a key role in pathogenesis of Alzheimer's disease. The previous studies [1, 2] have been performed to characterize the ensemble of the full-length Aβ (1-42) monomer. However, the difference in stability between representative conformations and the interactions between amino acid residues of Aβ have not been elucidated at an electronic level. We here obtained various conformations of the solvated Aβ monomer by replica exchange molecular dynamics (REMD) simulations and determined the most stable conformation by *ab initio* fragment molecular orbital (FMO) calculations. We furthermore investigated the specific interactions between amino acid residues of Aβ.

2. Details of molecular simulations

We first performed REMD simulations at constant volume of Aβ in explicit water molecules to search for stable conformations, starting from the α-helix Aβ structure obtained by experiment. We created 32 replicas, whose temperatures are exponentially spanned in the range of 270.0–363.4 K. REMD simulations were done for 50 ns per replica, i.e., totally 1.6 μs MD simulation time. The representative structures sampled from the trajectories of the nine replicas in the range 288.7–311.7 K were optimized in water by the molecular mechanics (MM) method. For REMD and MM calculations, we used the FF99SB force field in combinations with the TIP4P-Ew water model. Finally, the total energies for the optimized solvated structures were evaluated by the *ab initio* MP2/6-31G method in FMO, and the most stable structure was determined. From the FMO results, the specific interactions between amino acid residues of Aβ were investigated to elucidate which residues of Aβ are important in producing the stable conformation of Aβ monomer.

3. Results and discussion

The most stable structure of solvated Aβ monomer determined by the *ab initio* FMO method is shown in Fig. 1. This structure is at least 147 kcal/mol more stable compared with the other optimized structures. The residues 8-16 (sequence SGYEVHHQK) were found to form an α-helix structure, and this structure was also observed in the other optimized structures. In addition, a brief 3_{10}-helix structure was observed at the residues 3-5 (sequence EFR). These residues are expected to contribute to form specific conformations of Aβ monomer. The specific interactions between the Aβ residues will be shown at the conference.

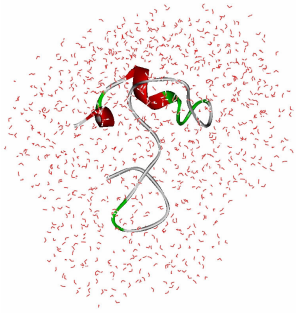

Figure 1 Most stable structure of solvated Aβ monomer

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[1] M. Yang, *et al.*, *J. Mol. Biol.* 384 (**2008**) 450. [2] N. G. Sgourakis, *et al.*, *J. Mol. Biol.* 405 (**2011**) 570.