Ab initio molecular simulations for proposing potent inhibitors of amyloid-β aggregation

Akisumi Okamoto [1], Kazuya Nomura [1], Atsushi Yano [1], Shin'ichi Higai [2] and Noriyuki Kurita [1,*]

[1] *Department of Computer Science and Engineering, Toyohashi University of Technology*

[2] *Analysis Center, Murata Manufacturing Corporation*

1. Introduction

Aggregation of the Alzheimer's peptide amyloid-β (Aβ) is believed to play a key role in pathogenesis of Alzheimer's disease (AD). Inhibitors for this aggregation attract much attention as therapeutic agents for the prevention and treatment of AD, and numerous compounds have been synthesized. It was found [1] that a triazine derivative AA3E2 has anti-amyloidogenic ability, while a triazine derivative AA3D2 having a different substituent has no inhibitory effect. In the present study, we obtained stable structures of the solvated complex with Aβ and AA3E2/AA3D2 by using classical molecular mechanics (MM) method and investigated the specific interactions between Aβ and AA3E2/AA3D2 by *ab initio* fragment molecular orbital (FMO) calculations. Based on the results obtained, we attempted to propose new potent inhibitors for Aβ aggregation.

2. Details of molecular simulations

We considered two types of Aβ structures with α-helix or β-sheet conformation, and their three-dimensional structures were obtained from PDB. Structures of AA3E2 and AA3D2 were optimized by MP2/6-31G(d,p) calculation, and they were docked to Aβ by using a protein-ligand docking program, in which a thousand of candidate structures for the complex were produced. Their representative structures were optimized in water by using the MM method based on AMBER force field. Finally, the most stable structure was determined by the *ab initio* FMO method, and the specific interactions were investigated to elucidate which amino acid residues of Aβ and which parts of the AA3E2 and AA3D2 are important for the binding between Aβ and inhibitors.

3. Results and discussion

The most stable structure of α-helix Aβ + AA3E2 complex determined by the *ab initio* FMO method is shown Fig. 1. AA3E2 binds specifically to around the amino acid residues of Phe19 and Phe20 in α-helix Aβ. AA3D2 binds to α-helix Aβ in a similar way. The calculated binding energies between α-helix Aβ and inhibitors are 31.7 (AA3E2) and 13.4 kcal/mol (AA3D2), respectively. Accordingly, our calculated results can explain the inhibitory effect of AA3E2/AA3D2 on Aβ aggregation obtained by the experiment [1, 2].

The results on the specific interactions between the amino acids of α-helix Aβ and inhibitors and the results for β-sheet Aβ will be shown at the conference.

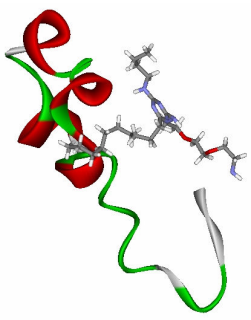

Fig. 1 Most stable structure of α-helix Aβ + AA3E2 complex

---

* Corresponding author: Tel. +81-532-44-6875, e-mail: kurita@cs.tut.ac.jp

[1] W. Kim, *et al.*, *ACS Chem. Biol.*, 1 (**2006**) 461.

[2] H. Shaykhalishahi, *et al.*, *Chem. Biol. Interact.*, 186 (**2010**) 16.