Classical Molecular Dynamics Simulation to Understand Role of a Zinc Ion for Aggregation of Amyloid-β Peptides

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Metal ions such as those of copper and zinc are considered to accelerate initial formation of amyloid fibril of amyloid-β (Aβ) peptides. In this study, the role of a zinc ion for Aβ peptide aggregation was investigated by the classical molecular dynamics (MD) simulations. The MD results indicated that the negatively-charged residues gained large stabilization in the existence of a zinc ion. On the other hand, histidine and tyrosine which were reported as making a bond with a metal ion were slightly stabled. Therefore, a zinc ion is thought of as combining with histidine or tyrosine after being attracted by negatively-charged residues, because these residues exist near negatively-charged residues. These results indicate that the metal-containing system needs to be treated by quantum-mechanical techniques.

Keywords: Amyloid-β aggregation, Molecular dynamics, Metal-containing biomolecules

1 Introduction

An amyloid fibril of amyloid-β (Aβ) peptides is well known as the cause of Alzheimer's disease. A part of the Aβ, Aβ(1–16) fragment which has an amino acid sequence DAEFRHDSGYEVHHQK, is considered to be important for the initial formation of the amyloid fibrils. Furthermore, some experimental researches indicate that the Aβ aggregation is accelerated under existence of metal ions [1–4]. For example, Miura et al. proposed the metal binding structures which were determined by Raman spectroscopy [1]. Curtain et al. also investigated the binding structure using NMR and EPR [2]. These results indicated that His6, Tyr10, His13, and His14 of Aβ peptides are combined with a zinc ion and that one or two Aβ peptides are involved for the binding structure.

Based on the experimental results, computational approaches have been also carried out [5–9]. Furlan and La Penna studied the binding between an Aβ(1–16) peptide and a zinc ion using the Car-Parrinello quantum mechanics and molecular mechanics- (QM/MM-) MD technique [5]. Pan and Patterson simulated Zn(Aβ) and Zn(Aβ)2 using MM-MD with constraints between a zinc ion and specific residues [7]. However, in these approaches, numerical models that were designed to reproduce experimental data were used.

In this study, to consider the aggregation of Aβ peptides under existence of a metal ion, the stabilization energy between a metal ion and Aβ residues is investigated by using a more general model. Therefore, a system consisting of two Aβ(1–16) peptides and a zinc ion is simulated by classical MD techniques.

2 Computational details

We performed classical MD simulations to investigate the role of a zinc ion for Aβ(1–16) peptides in explicit water solvent. The Generalized-Ensemble Molecular Biophysics (GEMB) program, which has been applied to several biomolecules [10–13], was used to perform the MD simulations. The system consisted of two Aβ(1–16) peptides, a zinc ion, and 12,954 water molecules. The N-terminus of the Aβ(1–16) peptide was un-
capped while the C-terminus was capped by N-methyl amine. The Aβ(1–16) peptide has −1 charge, and the zinc ion has +2 charge. The total charge of the system is zero. Initial conformations were made by aligning two Aβ(1–16) peptides and putting a zinc ion between them at seven different positions as shown in Figure 1. Seven conformations were prepared in this way, because the positions of the zinc ion may affect simulation results. The AMBER parm99SB force field \[14,15\] was used for the Aβ(1–16) peptides and the zinc ion, and the TIP3P rigid-body model \[16\] was used for the water molecules. The temperature was controlled at 300 K using the Nosé-Hoover thermostat \[17–19\]. This system was put in a cubic unit cell with a side length of 74.57 Å under periodic boundary conditions. The cut-off distance for the Lennard-Jones potential energy was 12.0 Å. The electrostatic potential energy was calculated by the particle mesh Ewald method \[20\]. The multiple-time-step method \[21\] was also applied to the simulations. The time step was taken to be 0.5 fs for the protein atoms and 4.0 fs for the zinc ion and water molecules. Because the symplectic rigid-body algorithm \[22\] was used for the water molecules here, the time step can be taken as 4.0 fs \[23\]. The simulations were performed for 100 ns including an equilibration period of 20 ns. The total simulation time was 700 ns ( = 100 ns × 7 initial conformation). All calculations are performed using the Fujitsu PRIMEHPC FX10 at Information Technology Center, the University of Tokyo.

3 Results and discussions

First, we investigated the behavior of the zinc ion and two Aβ(1–16) peptides. Figure 2 shows the time series of (1) the minimum distance between the zinc ion and the main chain of one Aβ(1–16) peptide, (2) that between the zinc ion and the main chain of the other Aβ(1–16) peptide, and (3) that between two main chains of the Aβ(1–16) peptides in one simulation run.

![Figure 2. Time series of (1) minimum distance between the zinc ion and the main chain of one Aβ(1–16) peptide, (2) that between the zinc ion and the main chain of the other Aβ(1–16) peptide, and (3) that between two main chains of the Aβ(1–16) peptides in one simulation run.](image)

Figure 1. Initial conformation of two amyloid-β peptides and a zinc ion. Seven locations of a zinc ion are also shown.

![Figure 1. Initial conformation of two amyloid-β peptides and a zinc ion. Seven locations of a zinc ion are also shown.](image)
tion. This tendency was also observed in other MD runs. These results indicate that the zinc ion attracts negatively-charged residues of the two Aβ(1–16) peptides by electrostatic interaction only at the initial stage of the aggregation.

Next, we estimated the stabilization between the zinc ion and each Aβ residue. The stabilization energy was evaluated by \(-k_B T \ln P(r)/4\pi r^2\), where \(k_B\), \(T\), and \(r\) are Boltzmann constant, simulation temperature, and minimum distance between the zinc ion and an atom in the residue, respectively. The probability \(P(r)\) was obtained by counting the number of snapshots in which the minimum distance between the zinc ion and an atom in the residue was \(r\) and taking an average over the seven MD simulations. The same residues in two Aβ peptides were not distinguished. The results are shown in Figure 5. These results indicate that the negatively-charged residues are more stable. This result was reproduced in six MD simulation runs out of seven runs. Therefore, we can interpret that this phenomena is occurred regardless of the initial positions of the zinc ion. On the other hand, His and Tyr, which are reported to combine with the zinc ion, gain only slight stabilization. Therefore, the present classical MD simulations did not reproduce the experimental results. To treat these phenomena, the QM techniques are needed. However, from these results we can deduce that the zinc ion is attracted by the negatively-charged residues such as Asp and Glu, then the His or Tyr make a bond with a zinc ion, because these residues exist around the negatively-charged residues, for example, His6-Asp7 and Tyr10-Glu11.

4 Concluding remarks

In this study, the behavior of a zinc ion for Aβ peptides aggregation was investigated using classical MD simulations. The system consisted of a zinc ion and two Aβ(1–16) peptides, which is the part of the Aβ, in explicit water solvent. These results indicated that the zinc ion is important for the first aggregation of the Aβ(1–16) peptide. Thereafter, two Aβ(1–16) peptides were kept aggregated by electrostatic interaction regardless of the existence of the zinc ion. Furthermore, the stabilization energy was also obtained. The results indicated the
negatively-charged residues, Asp or Glu, were most stable by existence of the zinc ion. Although His or Tyr gained slight stabilization, these residues exist near the negatively-charged residues. Therefore, we can deduce that the zinc ion attracts negatively-charged residues, then makes a bond with His and/or Tyr. However, because the classical MD method cannot reproduce the chemical bond, we did not obtain the results of acceleration of Aβ(1–16) peptide aggregation in this simulation. The QM- and/or QM/MM-MD techniques are necessary to investigate the correct behavior of the zinc ion. The MD results using the QM techniques will be seen elsewhere.

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