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The effect of solvents on the conformations of Amyloid β-peptide (1–42) studied by molecular dynamics simulation

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ABSTRACT

Amyloid β-peptide (Aβ) is the major component of plaques found in the brains of Alzheimer's patients. Among its two predominate forms – Aβ(1–40) and Aβ(1–42), the latter possesses stronger aggregation and deposition propensity than the former. To explore the conformational preference of Aβ(1–42) in different solvents, molecular dynamics (MD) simulations are performed to investigate its secondary structures in the following four solvents: hexafluoroisopropanol (HFIP), 2,2,2-trifluoroethanol (TFE), water, and dimethyl sulfoxide (DMSO). Structural analyses demonstrate that there are two stable helix regions of Aβ(1–42) in HFIP and TFE, supporting the idea that they act as helix-promoting solvents. In aqueous solution, α-helix to β-sheet conformational transition is observed in the C-terminal domain of Aβ(1–42). However, in pure DMSO, the unfolding of C-terminal region occurs, but no β-sheet structure is observed. The primary mechanism of conformational behaviors of Aβ(1–42) in the four solvents mentioned above is analyzed and discussed based on the results of MD simulations.

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1. Introduction

The self-assemble of the Amyloid β-peptides (Aβs) into Alzheimer's disease (AD) amyloid is believed to involve a conformational change. Hence conformations of Aβ in solutions are of significant interest. It is well known that the mechanism of Alzheimer's disease is related to gradual deposition of amyloid fibrils to form senile plaques [1,2]. The main component of plaques found in the brains of Alzheimer's patients is a small peptide, β-amyloid, consisting of 39–42 amino acids derived from a larger amyloid precursor protein (APP) by proteolytic cleavage [3]. The two major forms of the Aβ are Aβ (1–40) and Aβ(1–42), which possess identical amino acid sequence although the latter has two additional amino acid residues (Ile and Ala) at the C-terminus. The previous results [4–7] indicate that both peptides have different aggregation and deposition properties. Aβ(1–42) has been known to be more neurotoxic than Aβ(1–40) [6,7] and is observed to be a major component in AD amyloid plaque [8,9].

The aggregation states of the Aβ and its relationship to neuronal cell death in AD have been topics of theoretical and experimental studies [10–23]. The fibril structures of Aβ(1–40) and Aβ(1–42) aggregates have been determined by various experimental techniques such as electron microscopy [10–12], X-ray diffraction [13], electron paramagnetic resonance (EPR) spectroscopy [14], and solid state nuclear magnetic resonance (NMR) spectroscopy [15–16]. All these studies indicate that during these β-peptide aggregation processes, the β-peptide may undergo a conformational rearrangement (a-helix → β-sheet and/or random coil → β-sheet) that promotes toxicity to nerve cells, but the precise conformational changes and molecular reorganization of the β-peptide are still somewhat unclear. In addition, since Aβs do not dissolve in water and tend to aggregate, there are only some NMR investigations on small Aβ fragments in aqueous solution [17,18], most NMR measurements on both Aβ(1–40) and Aβ(1–42) are carried out in micellar solutions [19,20] and mixtures of water and organic solvents, particularly fluorinated alcohols, such as 2,2,2-trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP) [21–23]. Many conformational studies have demonstrated that the conformation of Aβ is strongly influenced by the environment [24–29]. A reversible transition of Aβ(23–35) from random coil to β-sheet under a variety of conditions is found experimentally by circular dichroism spectroscopy [27], and Aβ(34–42) has the ability to form stable β-sheet structure in aqueous media, but this β-sheet structure will disappear when it dissolves in organic media [30]. A more detailed study of the secondary structure of Aβ(1–28) by nuclear magnetic resonance spectroscopy in a mixture of TFE and water suggests that Aβ(1–28) adopts a monomeric random coil structure at pH 1–4 and rapidly precipitates from solution as an oligomeric β-sheet structure at pH 4–7 [29]. The normal Aβs with α-helix conformations are reported to be nontoxic or less toxic, but the neurotoxicity increases with the formation of β-sheet structure.

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The α-helix to β-sheet transformation with concomitant peptide aggregation is a possible mechanism of plaque formation in AD. In fact, stabilizing a helix monomeric conformation may be more significant than inhibiting fibril growth by preventing β-sheet formation [31].

According to previous experimental study, Aβ adopts α-helix conformation without aggregation in the presence of TFE and HFIP, but it is not very clear why HFIP and TFE can act as helix-forming solvent. In this work, in order to explore the effect of solvents on the conformation of Aβ(1–42) and gain more insight into the mechanism of plaque formation by Aβs, we examine the conformation of the full length Aβ(1–42) in four pure solvents (HFIP, TFE, water, and DMSO) by molecular dynamics (MD) simulation. The interesting conformation behaviors of Aβ(1–42) in these solvents are represented. The results of MD simulations are helpful for understanding the mechanism of amyloid formation and designing the compounds for inhibiting the aggregation of Aβ and amyloid fibril formation.

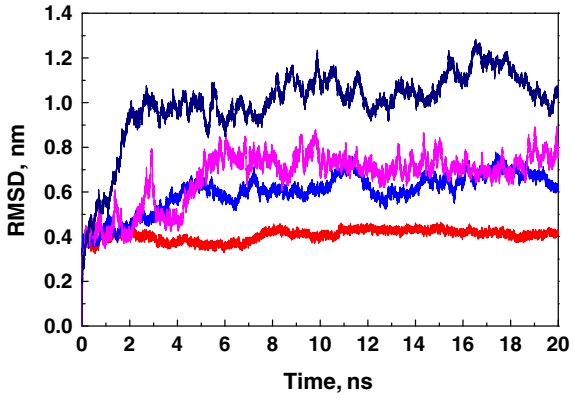

Fig. 1. The RMSD of the all atoms for Aβ(1–42) in four solvents(HFIP (red), TFE (blue), water (magenta), and DMSO (navy)) during simulations compared to the initial conformation (For interpretation of color mentioned in this figure, the reader is referred to the web version of this article.).

2. Computational details

The starting conformation of the Aβ(1–42) monomer is taken from the NMR structure, which is composed of two helices (helix 1(residues 8–25) and helix 2 (residues 28–38)) and a turn region (residues 26–27) linking the helices (PDB-entry: 1IYT) [22]. All MD simulations are performed using GROMACS software package [32,33] with the GROMOS9643A1 force field [34]. The simulations are conducted in the constant-NPT ensemble. The temperature is kept constant during the simulations using a Berendsen thermostat [35] with a coupling time of 0.1 ps. The pressure is maintained by coupling to a reference pressure of 1 bar with a coupling time of 1 ps and an isothermal compressibility of 4.5×10^{-5} bar^{-1}. The linear constraint solver (LINCS) method [36] is adopted to constrain bond lengths. The long-range electrostatic interactions are computed by the particle-mesh ewald (PME) method [37,38]. Two range cut-offs of 0.8 and 1.4 nm are used for the evaluation of the non-bonded interactions. Interactions within the larger cut-off are updated every 10 steps. The motion equations are integrated using the leap-frog algorithm with a time step of 2 fs. The single point charge (SPC) model is used for water molecules. We use a new set of potential parameters for TFE [39] in MD simulations, which can accurately reproduce thermodynamic and structural properties of pure liquid TFE. The potential models of HFIP and DMSO used in our work are proposed by Fioroni [40] and Alekseyev [41], respectively.

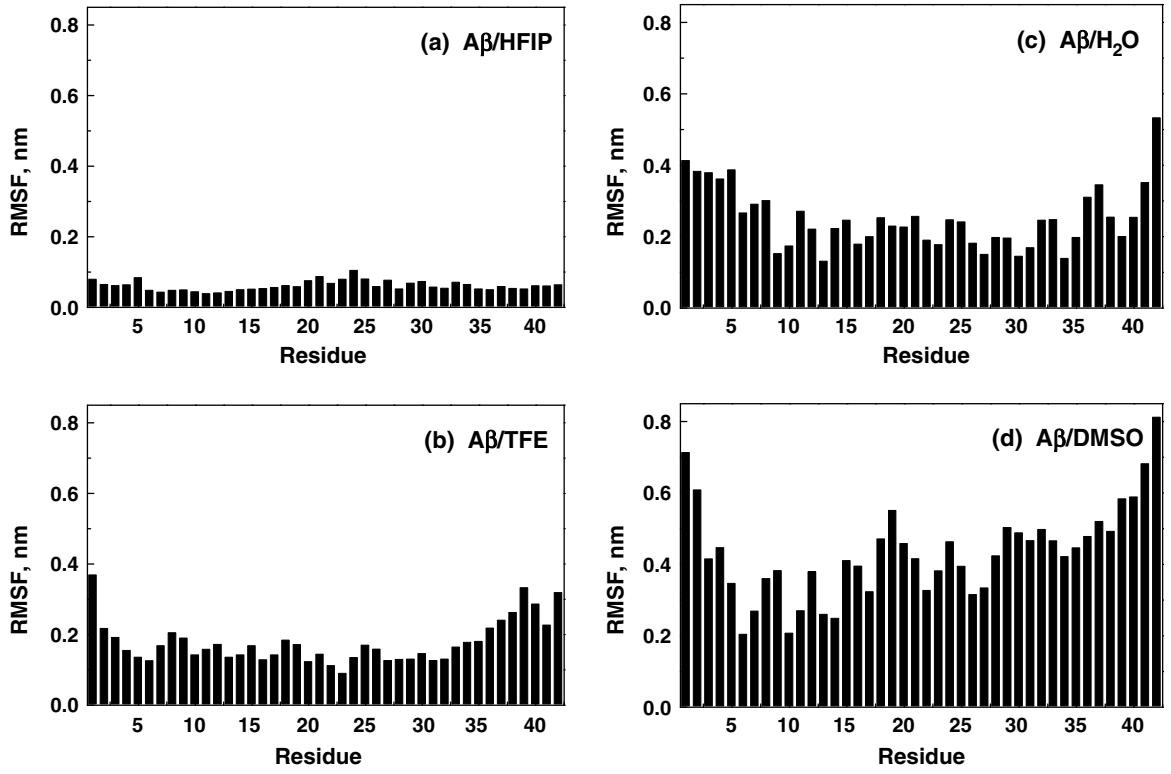

Fig. 2. The RMSF of the all residues of Aβ (1–42) in different solvents. Averages are calculated of based on the Aβ(1–42) conformations during the last 10 ns trajectories. (a) Aβ/HFIP; (b) Aβ/TFE; (c) Aβ/H_2O; and (d) Aβ/DMSO.

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