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Binding of Aβ peptide creates lipid density depression in DMPC bilayer

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ABSTRACT

Using isobaric–isothermal replica exchange molecular dynamics and all-atom explicit water model we study the impact of Aβ monomer binding on the equilibrium properties of DMPC bilayer. We found that partial insertion of Aβ peptide into the bilayer reduces the density of lipids in the binding "footprint" and indents the bilayer thus creating a lipid density depression. Our simulations also reveal thinning of the bilayer and a decrease in the area per lipid in the proximity of Aβ. Although structural analysis of lipid hydrophobic core detects disordering in the orientations of lipid tails, it also shows surprisingly minor structural perturbations in the tail conformations. Finally, partial insertion of Aβ monomer does not enhance water permeation through the DMPC bilayer and even causes considerable dehydration of the lipid–water interface. Therefore, we conclude that Aβ monomer bound to the DMPC bilayer fails to perturb the bilayer structure in both leaflets. Limited scope of structural perturbations in the DMPC bilayer caused by Aβ monomer may constitute the molecular basis of its low cytotoxicity.

1. Introduction

The onset of Alzheimer's disease (AD) is linked to Aβ peptides, which are the products of normal cellular proteolysis [1]. Depending on the specific location where Aβ is cleaved from the amyloid precursor protein, two main Aβ alloforms, Aβ1-40 and Aβ1-42, are identified, of which the former represents about 90% of all Aβ species in cerebrospinal fluid [2]. Experimental data demonstrate that Aβ peptides, particularly in oligomeric forms, exert cytotoxic effects on neuron cells [3,4]. Yet, from the molecular perspective it is still unclear how Aβ peptides induce damage to cells causing their death. It is reasonable to suggest that Aβ oligomers may disrupt cellular membranes and increase their permeability to ions, particularly Ca^{2+} [5]. Along these lines of thought, theoretical models propose that Aβ aggregates inside the lipid bilayers form stable pores, which lead to uncontrollable ion traffic [6,7]. Independent of specific mode of membrane perturbation, the interactions of Aβ peptides with membranes are likely to destabilize cellular ion homeostasis.

Numerous experimental studies have probed Aβ interactions with lipid bilayers [8–15]. It appears that at low Aβ concentrations (≲150 nM) Aβ peptides bind to lipid bilayers as monomers [13], but at higher peptide concentrations Aβ oligomeric species interact with the bilayers [12]. Furthermore, Aβ oligomers display strongest binding affinity compared to large aggregates [16] and Aβ binding affinity to anionic lipid bilayers is larger than for zwitterionic ones [17]. Aβ peptides not only bind but also penetrate into the core of lipid bilayers. This conclusion follows from the analysis of electron density profiles, which indicates that Aβ1-40 interacts with bilayer hydrophobic cores [9]. Binding of Aβ peptides to the lipid bilayers and penetration into their cores compromise the integrity of bilayers. In the extreme case Aβ peptides can completely destabilize DMPC bilayers transforming lamellar phase into micelles [18]. However, more typically the impact of Aβ peptides is limited to perturbation of bilayer structure and increased permeability of ions [14]. Importantly, deep penetration of Aβ into the bilayer causes more profound disruption of its structure compared to surface binding [8,15]. In support of theoretical models, application of atomic force microscopy and circular dichroism suggests that Aβ peptides can form stable structures resembling ion channels in the bilayers [12].

All-atom explicit water molecular dynamics (MD) is a useful, complementary to experiments, tool offering unparalleled opportunities to probe Aβ-bilayer interactions in atomic detail. Constant temperature MD simulations have investigated the lipid bilayers with preinserted Aβ peptides and performed the analysis of Aβ impact on the bilayer structure [19–21]. These studies have showed that Aβ peptides, even in monomeric form, significantly disorder lipid structure and packing. Although Aβ monomers generally remained embedded in the zwitterionic DPPC or POPC lipid bilayers for the duration of simulations (several hundreds of ns), they also revealed a tendency to move closer to the bilayer surface [19]. One published report has even observed expulsion of Aβ peptide from the lipid bilayer and its readsorption on the surface [22]. Recent MD study utilizing umbrella sampling has revealed that Aβ peptides bound to the bilayer stabilize the formation of pores [23]. Furthermore, MD simulations have probed Aβ aggregation in the lipid bilayers showing that Aβ monomers can form mobile small oligomers,

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which then assemble into larger, channel-forming aggregates [24]. It appears that in general Aβ interactions with the lipid bilayer do not noticeably facilitate water permeation through the membrane [21,23].

Although the studies cited above provide important insights into the mechanism of Aβ-bilayer interactions, it is important to verify their conclusions using simulated tempering methods, such as replica exchange molecular dynamics (REMD). Two very recent studies have applied REMD to the problem of peptide–membrane interactions. Sugita and coworkers have used surface-tension (NPγT) REMD to study the structure of POPC bilayer and its interactions with WALP23 peptide [25]. They showed that NPγT REMD significantly enriches conformational sampling of lipids and peptide. In our previous study we have applied isobaric–isothermal (NPT) REMD to probe the interactions of Aβ10-40 monomer with zwitterionic DMPC bilayer [26]. We found that Aβ monomer binding to the DMPC bilayer causes dramatic structural transition in the peptide resulting in appearance of stable helix structure in the C-terminal. We have also determined that the central hydrophobic cluster and the C-terminal in Aβ not only govern binding to the bilayer, but also penetrate into the bilayer core. In contrast, the polar N-terminal and turn region form interactions mainly with the bilayer surface. Thus, in our previous study [26] we focused exclusively on the conformational changes in the binding Aβ peptide. However, based on the studies performed by other groups [19–21] we expect that binding and penetration of Aβ peptide into the bilayer may also perturb its structure. This specific issue, which was beyond the scope of our previous study [26], is addressed in this article.

Specifically, using NPT-REMD and all-atom explicit water model we study the structural changes in DMPC lipid bilayer caused by binding of Aβ monomer. As a control we use the MD simulations of Aβ-free DMPC bilayer. Our main results are as follows. First, Aβ peptide, which is bound and partially inserted in the bilayer, reduces the density of lipids in the binding "footprint" and indents the bilayer, thus creating a lipid density depression. Second, our simulations reveal thinning of the bilayer and a decrease in the area per lipid in the proximity of Aβ. Third, although the analysis of lipid hydrophobic core detects disordering in the orientation of lipid tails, it also shows surprisingly minor structural perturbations in the tail conformations. We explain these observations by shallow insertion of Aβ, which weakly affects the density of fatty acid tails beneath Aβ binding "footprint". Our fourth result suggests that partial insertion of Aβ monomer does not enhance water permeation through the DMPC bilayer and even causes significant dehydration of the lipid–water interface. We conclude the paper by comparing our results with previous studies and discussing their possible implications for Aβ cytotoxic mechanism.

2. Methods

2.1. All-atom explicit solvent model

We have performed two sets of simulations of the dimyristoylphosphatidylcholine (DMPC) lipid bilayer in explicit water, one with Aβ monomers interacting with the bilayer and another with the pure bilayer without peptides. We have selected DMPC lipids, because they are ubiquitous in cell membranes, small in size, and their structural and physicochemical properties are well known (Fig. 1a) [27]. In our simulations CHARMM22 protein force field with CMAP corrections [28] and the CHARMM36 lipid force field [29] were used. CMAP corrections are necessary to improve the agreement between experimental and in silico protein structures in the disordered regions [28]. To remain consistent with our previous studies [26,30,31], we used the amino-truncated Aβ10-40 peptide. It is important to note that the truncation of polar amino terminal increases the overall hydrophobicity of Aβ peptide that in turn may enhance its affinity with respect to binding to lipid bilayers.

Because the full description of Aβ + bilayer system can be found in our previous study [26], we provide only its brief summary below. We considered two Aβ10-40 monomers interacting with the bilayer formed by 98 DMPC lipids (Fig. 1b). Each bilayer leaflet was composed of 49 lipids arranged in a 7 × 7 square shape. Aβ peptides were placed

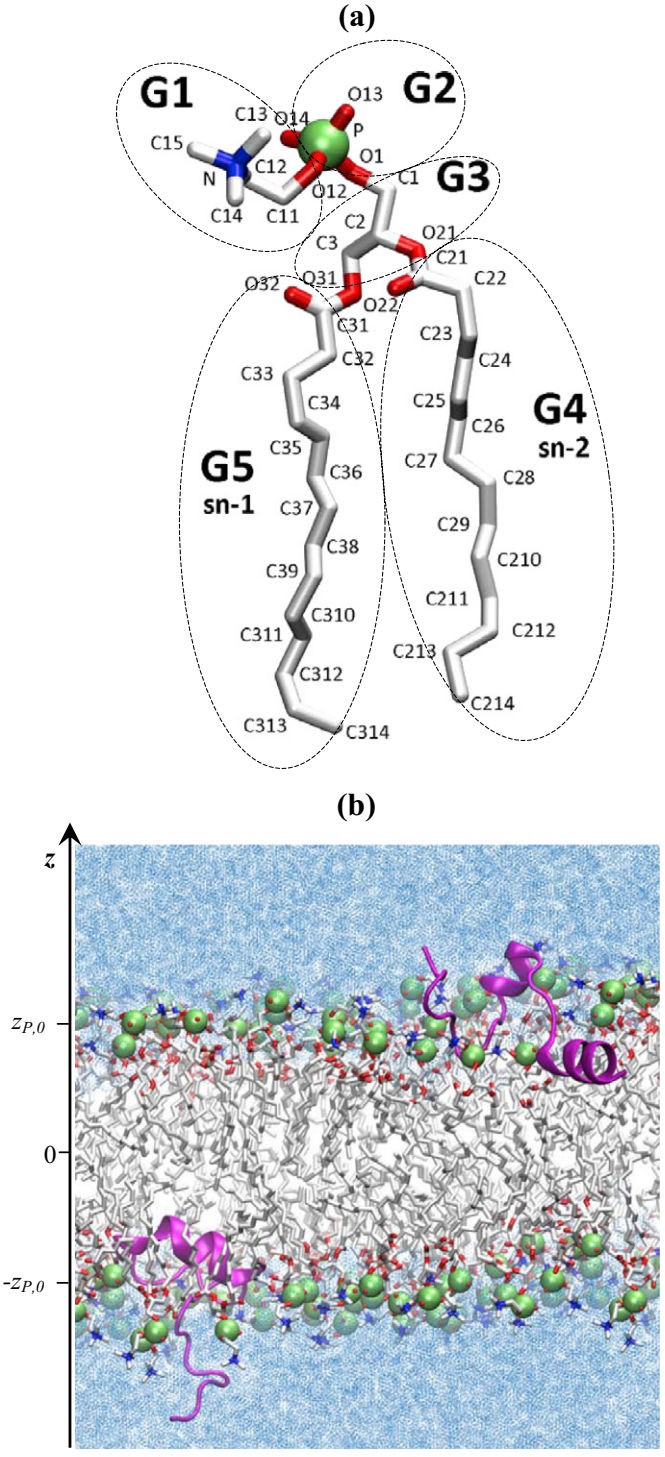

Fig. 1. (a) Chemical structure of DMPC lipid. Atom numbering follows that used in CHARMM36 force field. DMPC lipid is divided as marked into five groups: choline (G1), phosphate (G2), glycerol (G3), and two fatty acid tails (G4 and G5). Fatty acid chains sn-1 and sn-2 are also identified. (b) REMD simulation snapshot at 330 K illustrating binding of Aβ monomers to DMPC bilayer consisting of 98 lipids. The simulation system includes two Aβ monomers, which bind independently to the opposite leaflets of the bilayer. Lipid phosphorus atoms are in green, whereas Aβ peptides are shown in cartoon representation in purple. Water molecules are given by thin blue lines. The centers of mass of phosphorus atoms in each leaflet fluctuate around the positions ± $z_{P,0}$ along the *z*-axis.