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Alzheimer Aβ peptide interactions with lipid membranes

Fibrils, oligomers and polymorphic amyloid channels

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Fibrillar aggregates of misfolded amyloid proteins are involved in a variety of diseases such as Alzheimer disease (AD), type 2 diabetes, Parkinson, Huntington and prion-related diseases. In the case of AD amyloid β (Aβ) peptides, the toxicity of amyloid oligomers and larger fibrillar aggregates is related to perturbing the biological function of the adjacent cellular membrane. We used atomistic molecular dynamics (MD) simulations of $Aβ_{9–40}$ fibrillar oligomers modeled as protofilament segments, including lipid bilayers and explicit water molecules, to probe the first steps in the mechanism of Aβ-membrane interactions. Our study identifies the electrostatic interaction between charged peptide residues and the lipid headgroups as the principal driving force that can modulate the further penetration of the C-termini of amyloid fibrils or fibrillar oligomers into the hydrophobic region of lipid membranes. These findings advance our understanding of the detailed molecular mechanisms and the effects related to Aβ-membrane interactions, and suggest a polymorphic structural character of amyloid ion channels embedded in lipid bilayers. While inter-peptide hydrogen bonds leading to the formation of β-strands may still play a stabilizing role in amyloid channel structures, these may also present a significant helical content in peptide regions (e.g., termini) that are subject to direct interactions with lipids rather than with neighboring Aβ peptides.

Keywords: Alzheimer disease, Aβ peptide fibrils, Aβ protofilaments, Aβ fibrillar oligomers, amyloid channels, structural polymorphism of amyloid aggregates

Abbreviations: AD, Alzheimer disease; Aβ, amyloid-β; MD, molecular dynamics; NMR, nuclear magnetic resonance; POPE, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine; POPC, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine; COM, center of mass

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Introduction

Alzheimer disease (AD) is characterized by a strong loss of cognitive functions that is pathologically correlated with the appearance in neural tissue of fibrillar deposits in extracellular plaques and intracellular tangles containing amyloid β (Aβ) peptides and tau proteins, respectively. Two mutually non-exclusive concepts emerged regarding Aβ neurotoxicity, one is that the peptides may be cytotoxic by themselves[1,2] and that their aggregation is required for toxicity,[3,4] and the other is that the amyloid peptides may interfere synergistically with the normal biochemical processes involving other molecules.[5,6]

It has been demonstrated that amyloid plaques can be induced in mice via intracerebral[7] or intra-peritoneal[8] injection of misfolded Aβ-containing brain extract, this behavior of the peptide being similar to that of prions.[9] However, there is no direct evidence that injected Aβ is both necessary and sufficient to trigger cerebral amyloid deposition without cofactors that facilitate its aggregation. Induction of amyloid formation in vivo with synthetic Aβ has been unsuccessful so far, leading to the hypothesis that an amyloid-enhancing factor or a particular peptide conformation is required to trigger its deposition in vivo.[7]

Several studies have supported the idea that the interactions between Aβ peptides and cellular membranes lead to the formation of fibrillar Aβ aggregates and to their subsequent cytotoxicity.[10,11] The presence of intermediate aggregation

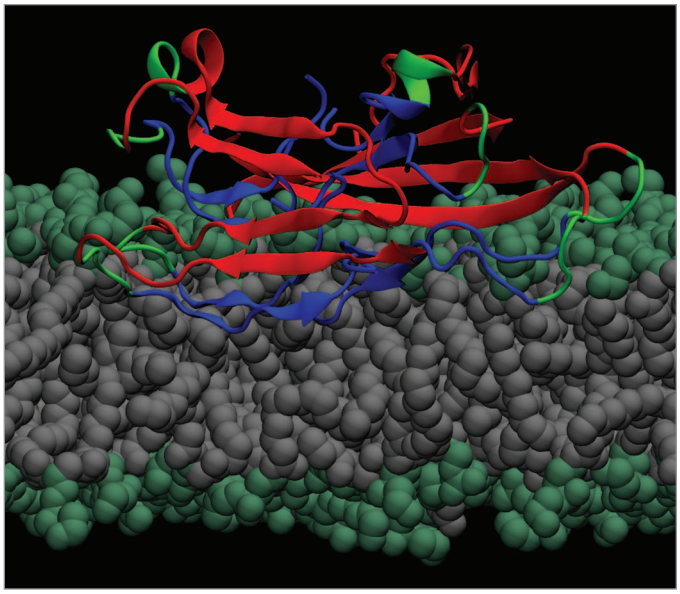

Figure 1. Molecular model of an $A\beta_{40}$ fibrillar octamer interacting with a POPE bilayer membrane (lateral view). The N-terminal β-strands are shown in red, the core C-terminal β-strands are blue, and the turn regions are green. The hydrophilic lipid headgroups (lime) and the lipid tails (gray) are illustrated by spheres.

products (Aβ oligomers) in the extracellular or intracellular environment, rather than that of fully formed fibrils, seems to alter the membrane structure and functions and is related to the dysregulation of cellular ionic homeostasis.[12]

Although the details of the molecular mechanism of membrane permeation are unknown, amyloid oligomers have been shown to interact with lipid membranes and cause nonspecific ion leakage,[13-15] or may transform into annular protofibrils that can form ion channel-like structures.[16-18]

Finding detailed molecular information about the structural organization of amyloid fibrils, fibrillar and pre-fibrillar oligomers and annular amyloid channels remains a major yet challenging goal of both experimental and computational modeling studies of Aβ aggregates. In a recent study,[19] we used molecular modeling in conjunction with atomistic molecular dynamics to investigate in detail the early steps in the mechanisms of interaction between preformed $A\beta_{9-40}$ fibrillar oligomers (generated using protofilament-like structures[20,21]) and a model bilayer membrane consisting of 98 POPE lipids. The initial protofilament structures are built based on experimental and computational studies of Aβ protofilaments formed in solution,[20,22] which have been simulated and studied previously in detail both under physiological conditions[20] and at elevated temperatures.[21] Consistent with previous studies, the first eight residues from the N-terminus of the Aβ peptides are not included in the protofilament models because they were shown to be significantly more disordered than residues in the 9–40 region.[19-21,23-25] The main focus of our new work[19] is on the atomistically detailed analysis of the role of different molecular and structural elements in the stability and conformational dynamics of Aβ protofilaments near lipid bilayers, and on the implications on the mechanism of possible insertion of fibrillar oligomers and protofilaments into the membrane.

Molecular Interactions with POPE Lipids

In reference 19, we used MD simulations to probe with atomistic-level detail the mechanism of interaction between molecular models of protofilaments of $A\beta_{40}$ peptides and a POPE lipid bilayer in explicit water. The POPE lipids were chosen similarly to previous studies,[26,27] and because the smaller headgroups of POPE lipids are expected to promote a more favorable interaction with amyloid peptides. Note however, that we have later used POPC lipids as well (see below) which lead to generally less favorable interactions with inserted peptides, being thus more stringent tests of the stability of amyloid channels. Here, we built protofilament systems consisting of eight Aβ peptides and explicit water molecules, with a total number of 42,000–57,000 atoms, with different initial conformations, and simulated them for 150 ns each in the NPT ensemble (i.e., constant number of molecules, pressure and temperature), using periodic boundary conditions, at a constant pressure of 1 atm and at the temperature of 310 K, close to the physiological values, similar to previous studies.[19-21,28] The simulation range was long enough to observe the first detailed steps of the intermolecular interactions. After the Aβ protofilaments lost their initially ordered β-sheet-rich structures, they reached quasi-equilibrated states, preserving only a fraction of their characteristic β-sheet content. The change of structure near the membrane was significantly greater than the change observed for corresponding simulations in bulk water,[20,21] due to the presence of the specific lipid environment.

Analysis of both the change in the number of peptide-related hydrogen bonds (NHBs) and of the electrostatic interactions between the peptides in the protofilament and the membrane demonstrated that the changes observed in structure of the protofilaments are due to specific interactions with the lipids.[19] We identified the electrostatic attraction between the charged residues and the lipid headgroups acting as the main driving force that leads to a further penetration of the C-termini into the hydrophobic lipid tails region, as illustrated in **Figure 1**. At the same time, we observed perturbations in the membrane as an effect of the proximity of the protofilaments, as the lipid headgroups reposition themselves around the charged residues, as shown in **Figure 2**. This figure shows that, along the MD trajectory there is an area consistently avoided by the center of mass (COM) of the phosphorus atoms, which coincides with the COM positions of the atoms in the C-termini. Also, the tails in the upper membrane leaflet reorient themselves closer to the surface and the C-termini, which leads

to a local membrane-thinning effect.[19] Our study demonstrates that in the proximity of lipid membranes the protofilaments adopt structures that have a lower content of β-sheet compared with the ones formed in bulk water. Although the timescales accessible to MD studies cannot provide us with a full insight into the complete insertion process of aggregated Aβ peptide structures into the membrane, the early interactions observed show that the structure formed in solution cannot be transferred to the membrane environment without a significant loss of β-sheet content. This concept has direct potential implications in the understanding and further modeling of Aβ ion channel-like structures formed in membranes.

In our MD studies, after the initial protofilament association with the lipid bilayer (i.e., at about 45 ns of NPT dynamics), the content of β-sheet structure was stable for the rest of the simulation and we observed little helical structure formation. These results suggest that, if the channels are formed through direct membrane incorporation of β-sheet-rich fibrillar oligomers, these would need to undergo further conformational changes before or after being incorporated into lipid bilayers, and may need to be associated with other similar units in order to form β-turn-β ion channel-like structures.

Note also that experimental studies showed that it is the prefibrillar, globular-like oligomers rather than the fibrillar ones that might associate into annular structures,[28] but their exact secondary structure is still unkown. Another possibility is that the predominantly helical membranar Aβ peptides may be associated with other similarly-structured Aβ monomers before leaving the membrane, as there have been studies[29] supporting the idea of dimerization in the transmembranar domain of APP. On the other hand, experimental studies analyzing the structure of Aβ peptides in membranes, amyloid channels or pore-like structures showed that they contained a high percentage of β-sheet,[30-32] suggesting that, if it the aggregation starts from a helical structure, the N-terminus may adopt β-sheet conformations, while the C-terminus has been shown to have a high percentage of helix when in a lipid environment.[33]

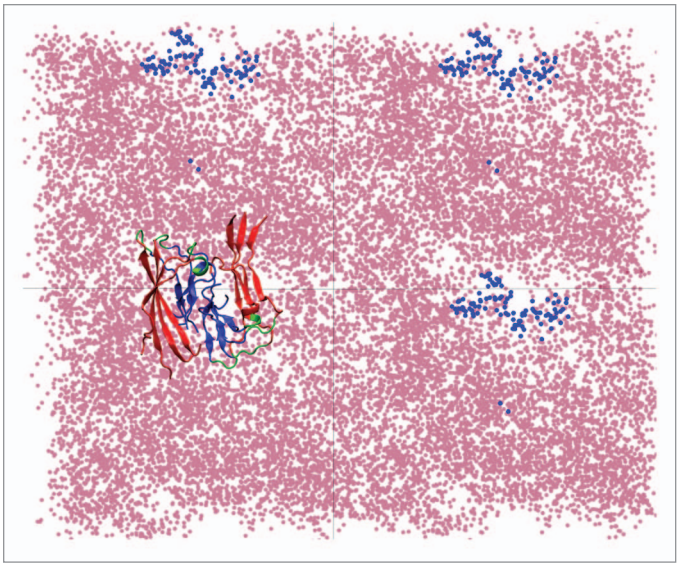

Figure 2. Repositioning of lipid headgroups due to interactions with the $A\beta_{40}$ protofilament segment facilitates the access of the hydrophobic C-terminal β-strands into the lipid tail region (top view; see also **Fig. 1**). Here, four top-view periodic images of the simulation box are shown for a typical trajectory. The dots represent the positions sampled by the center of mass (COM) of the lipid P atoms (pink) and the COM of the C-termini (blue) during the 45–150 ns trajectory segment when the C-termini are associated with the lipid head groups. A representative $A\beta_{9-40}$ octamer structure is shown in only one periodic image.

Polymorphism of Aβ Peptide Channels

The ability of amyloid oligomers to perturb cellular membranes, whether it is by thinning the membrane or through ion channel formation, is related to their cytotoxicity. Our study of $A\beta_{40}$ interacting with a POPE bilayer focused on the mechanism of interaction between fibrillar oligomers and lipid bilayer models. Understanding these interactions opens new questions on the molecular pathways of aggregation of Aβ peptides into annular channel-like membrane structures. Membrane disruption by non-fibrillar (globular) amyloid proteins is followed by an increase in membrane conductance either through specific[18] or non-specific ion leakage.[13] The mechanism of globular oligomers inducing cell dysfunction due to membrane permeabilization has been documented in several studies,[14,34] but their atomistic structure in membrane is still unknown. Experimental evidence (e.g., X-ray fiber diffraction and solid-state NMR) has characterized the Aβ fibrilar aggregates in solution as being definitely β-sheet rich, whereas their conformations in lipid bilayers is largely unclear. Previous studies predicted Aβ ion channel conformations based on the peptide sequence and on how it relates to other patterns observed in different membrane-bound and channel-forming peptides and proteins.[35] More recently, electron microscopy images revealed "pore-like" annular structures for amyloidogenic protofibrils (i.e., mutants of $A\beta_{1-40}$ and of α-synuclein).[17] However, these structures were not formed in membranes and were not associated within bilayers, their atomistic details in lipids being uncertain. Using a series of experimental techniques (AFM, CD, gel electrophoresis and electrophysiological recordings), reference 36 showed that amyloid proteins including $A\beta_{40}$, α-synuclein and amylin can undergo structural conformation changes and associate into ion-channel-like structures comprising typically of a few subunits. It has also been suggested that an α-helical form can be involved in a process of membrane poration.[37,38]

Based on similar experimental studies[39-42] Nussinov et al. pioneered the atomistic modeling of these structures.[43-47] These models comprise of 10–24 $A\beta_{40}$ or $A\beta_{42}$ monomers, each with a β-turn-β structure—the main tertiary structure

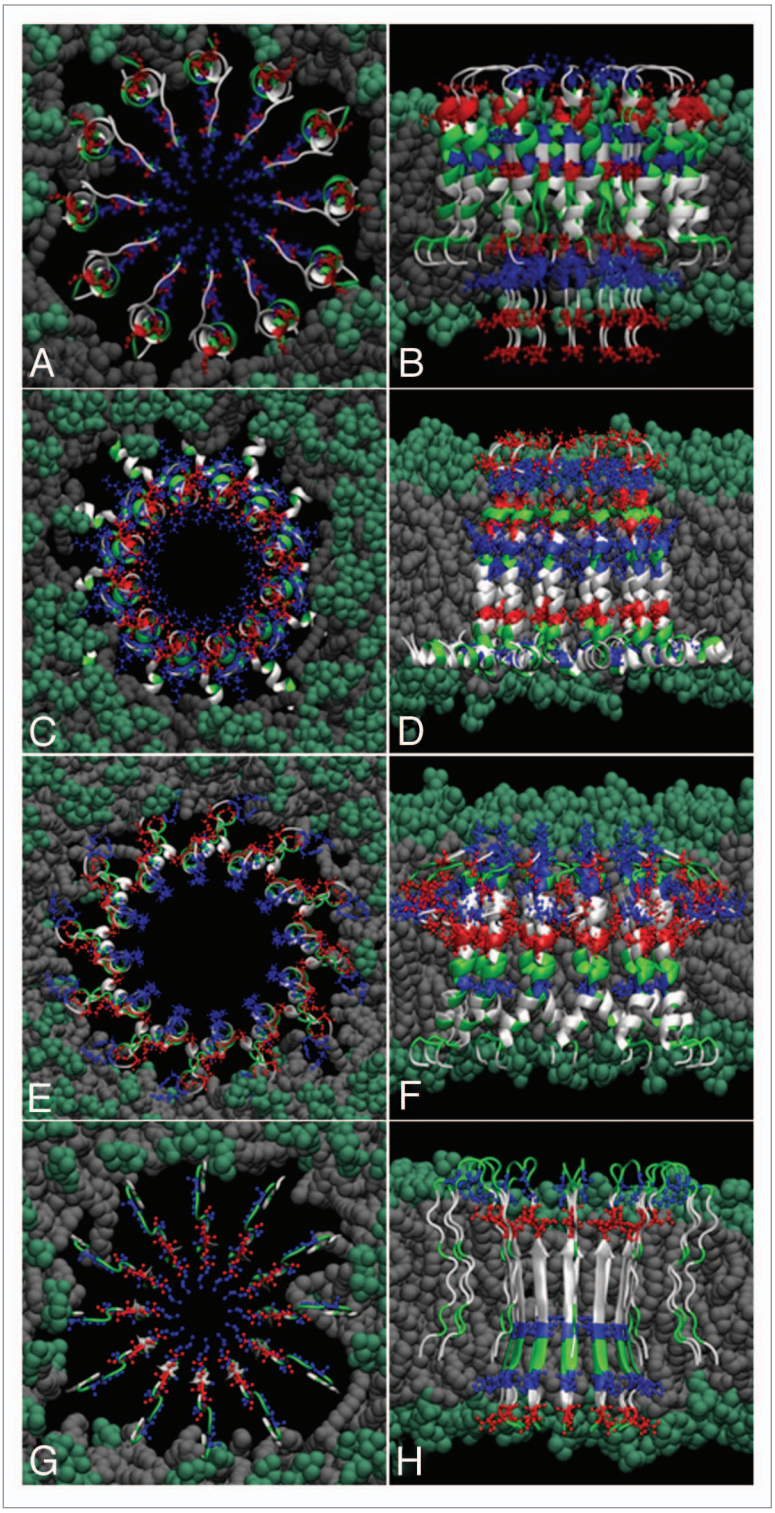

Figure 3. Possible models of Aβ dodecameric ion channels. The 12 peptides are colored by residue type: blue, positively charged; red, negative; green, polar; white, nonpolar. Top (A, C, E and G) and lateral (B, D, F and H) views of several models (see text).

motif that characterizes the peptide as part of mature fibrils in formed in water. MD refinement of these models shows that the initially continuous fibrillar structures break in about the same number of oligomeric subunits as reported by AFM imaging experiments, the final channel-like structure having similar dimensions compared with the AFM images. The Aβ N-termini maintain essentially their initial β-sheet structures, whereas the C-termini become more distorted. These studies, together with others looking at structures that aggregated Aβ peptides can adopt in lipids or different hydrophobic environments (e.g., some that consist of two helical regions of residues 8–25, and 28–38[33,48-51]) led us to infer that the β-turn-β might not be necessarily the only structural motif adopted by Aβ peptides when embedded in lipid bilayers. Some of our recent models shown in **Figure 3** consist of 12 monomers with a combined β-strand in the N-termini region and helical C-termini. Here, 12-mer channels are shown for illustrative purposes, and to keep the size of the overall atomistic model small. However, similar atomistic models may be easily extended to larger (e.g., 16-mer, 20-mer, etc.) amyloid-channel-like structures. Here, we have also modeled two structures containing only α-helices and no significant β-strand content. We note that, while these all-atom models were built using a standard force fields and have been minimized and equilibrated using explicit water molecules (i.e., similarly to the methods described in ref. 19) they have not been yet fully tested and are only suggestions of such possible structures.

For example, to obtain the first model (shown in **Fig. 3A and B**), we merged structures of an Aβ monomer in a two-stranded fibril of Tycko's model[22] (which has thus originally a β-turn-β pattern) with the helical structure of $A\beta_{40}$ suggested in reference 52. The result, represented in **Figure 3A**, is a transmembrane-spanning channel-like structure with the N-termini containing charged residues (D1, E3, R5, H6, D7, E11, H13, H14 and K16) in the interior, as β-strands, and the more hydrophobic C-termini modeled as helices toward the exterior of the channel, interacting with the hydrophobic lipid tails. Note that the charged residues are structurally located such that the first two negatively-charged residues (D1 and E3) would interact with the positively-charged amino groups of the lipid headgroups and thus stabilize (anchor) the protein segments in the lower membrane leaflet. The same kind of rationalization goes for the top part of the channel, with the charged residues E22

and D23 performing the same role. Here, we used POPC lipids, which are found abundantly in the membrane of neuronal cells, have the same tails as POPE,[19] but the ethanolamine is replaced by choline in their headgroups. Our lipid bilayer has a thickness of about 38 Å (i.e., between the planes containing phosphorus atoms in the two membrane leaflets).

In **Figure 3C, E and G** (top views) and **3B, D and F** (lateral views) are shown other possible structural models of transmembrane amyloid channels. In **Figure 3C and D** is shown an $A\beta_{1-42}$ channel modeled as a helical structure, starting from the monomer conformation in aqueous solution of fluorinated alcohols[49] (Protein Data Bank code 1IYT). Each monomer has two helices, one in the region of residues 8–25 and at residues 28–38. Thus the possibility that charged residues D1, E3 and R5 may act as "electrostatic anchors" to keep the peptides in the lipid bilayer.

In **Figure 3E and F** is shown an $A\beta_{1-40}$ channel that is essentially helical, modeled starting from the PDB structure 1BA4.[52] The N-terminus is mainly unstructured, with the C-terminus forming a long helix in the region of residues 20–39. The hydrophobic C-terminus can interact with the lipid tails, and the charged residues can also anchor the structure in the upper membrane leaflet.

Note that these first three cases (i.e., shown in **Fig. 3A–F**) inherit three successive (G-XXX-G) motifs from the transmembrane region of the amyloid precursor protein. This type of motif is known to promote dimerization of polypeptides via C_α-H· · ·O hydrogen bonds between two segments in a membrane environment[29,53]—a phenomenon that might occur when the helical parts of the peptides in the amyloid channel interact inside the lipid membrane. This factor could contribute as a further stabilizing interaction between the channel subunits.

Finally, in **Figure 3G and H** is shown an $A\beta_{9-40}$ pore-like structure comprising of monomers with a β-turn-β structural motif, closely related to the structures that have been pioneered and studied extensively by Nussinov et al.[43-47]

Concluding Remarks and Outlook

Aβ peptides have an amphipathic-like nature and can become associated with neuronal membranes and affect their biological function, resulting in the disruption of ion (e.g., calcium) homeostasis. Presenting only residual secondary structure in solution,[54] Aβ monomers have been shown to undergo a membrane-induced conformational change to either primarily β-sheets or to helical structures, depending, among other factors, on the peptide concentration and model membrane composition.[55,56] Several studies showed that Aβ association to lipid bilayers renders them permeable to ions but it is not established if this is due to the formation of discrete transmembrane ion channels of Aβ peptide aggregates, to larger pores,[57] or to a non-specific perturbation of bilayer integrity by lipid headgroup-associated Aβ peptides. Our MD-based studies do support the former hypothesis, but do not exclude the latter.[19] By using atomistic modeling of the interactions between Aβ protofilament segments and lipid bilayers, we showed that Aβ peptides are first subject to strong electrostatic interactions with the lipid headgroups, which facilitate subsequent hydrophobic interactions between the Aβ C-termini and the lipid tails. This mechanism leads to a significant loss of the rich β-sheet content characteristic to Aβ fibrillar oligomers and protofilaments in water,[20,21] and has further consequences on modeling the molecular structures of membrane-absorbed fibrillar oligomers and amyloid channels. While not dismissing the possibility that in certain conditions membrane-incorporated Aβ aggregates may present a similar β-turn-β structural motif with their fibrillar water-formed counterparts, our studies suggest that this would require a rather special mechanism that would protect the fibrillar structures from disruption upon strong interactions with the lipid headgroups. We thus find it more likely that, just as demonstrated before by solid-state NMR studies and MD simulations for regular Aβ fibrils,[20,23,32,58] their membrane-bound counterparts may be characterized by a similarly polymorphic nature that could lead to a variety of amyloid channel structures. While it is possible that some of these structures are still stabilized by a large fraction of inter-peptide hydrogen bonds, leading to the formation of β-strands (as illustrated in **Fig. 3**), they may also present a significant helical content in peptide regions (e.g., termini) that are subject to interactions with lipid tails rather than with neighboring Aβ peptides. Due to their implications in understanding the molecular processes that lead to the cytotoxicity of amyloid fibrils, oligomers and channels, we expect that structural studies using both modern experimental and computational techniques will continue to be central to amyloid-related research.[19,24-26,30,32,47,55-57,59-71]

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