Communication

Transmembrane Structures of Amyloid Precursor Protein Dimer Predicted by Replica-Exchange Molecular Dynamics Simulations

Naoyuki Miyashita, John E. Straub, D. Thirumalai, and Yuji Sugita

*J. Am. Chem. Soc.*, **2009**, 131 (10), 3438-3439• DOI: 10.1021/ja809227c • Publication Date (Web): 20 February 2009

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML
Aggregation of amyloid β peptide (Aβ) in the brain is the primary element in the pathogenesis of Alzheimer’s disease (AD). Aβ is produced from amyloid precursor protein (APP), which is a type-I transmembrane (TM) glycoprotein in neural and non-neural cells. APP is first cleaved on the β-site by β-secretase, and the extracellular domain of APP is dissociated from the remaining protein (APP-C99). γ-Secretase then cleaves the γ-site (Gly38-Thr43), which is located in the TM domain of APP-C99. Finally, Aβ is released to the extracellular region. Because the γ-site contains several cleavage points [see Supporting Figure (SF) 1 in the Supporting Information], Aβ’s having different chain lengths are observed. Of these, Aβ1-40 and Aβ1-42 are primary and secondary isosforms, respectively.

Structural information on Aβ and its aggregated forms has been accumulated by NMR spectroscopy and X-ray crystallography. A number of molecular dynamics (MD) simulations of the aggregation of Aβ in solution have also been performed. In contrast, little is known about the TM structures of APP and APP-C99. Since the amyloid accumulation depends on the chain length of Aβ, it is relevant to understand how Aβ is cleaved by γ-secretase and released from APP-C99. To address this key question, we have determined the monomer structure of the APP-C99 fragment (Aβ1–53), which has two α-helical regions from His13 to Val18 and from Ala30 to Lys53, by replica-exchange MD (REMD) simulations. APP-C99 contains three Gly-XXX-Gly motifs in the TM and juxtamembrane (JM) regions. This motif is known to promote dimerization of polypeptides via C=H⋯O hydrogen bonds between two segments in a membrane environment. A pairwise replacement of Gly (Gly29 and Gly33) with Leu (Leu29 and Leu33) in APP enhances the homodimerization but leads to a drastic reduction of Aβ1-40 and Aβ1-42 secretion. To resolve this apparent discrepancy, it would be useful to predict the homodimer conformations of APP-C99 in the membrane. Understanding these homodimer conformations is essential for elucidating the last step in the formation of Aβ-associated AD.

We performed REMD simulations of two APP fragments (Aβ23–53) in a membrane environment for both the wild-type (WT) sequence and a mutant in which Gly29 and Gly33 are replaced by Leu29 and Leu33. MMTSB toolsets with the CHARMm 19 EEF1.1 force field were used for the calculations (the simulation details are given in the Supporting Information). The effects of the solvent and the membrane on the APP fragments were included implicitly using the IMM1 implicit membrane model.

At 300 K, secondary and tertiary structures of the mutant APP fragments differ from those of the WT. In Figure 1, we compare the α-helicity of each residue in the WT with the corresponding one in the mutant. The similarity of α-helicity in the top (red) and bottom (green) plots indicates that the REMD simulations were able to sample all of the possible configurations of the APP fragments in the membrane. Marked contrasts in the α-helices of the WT and the mutant are observed for residues 29–38. This region was observed to be unwound in the WT, whereas it formed an α-helix in the mutant. In Figure 2, Leu29 in the mutant was located in the membrane, whereas Gly29 in the WT was in the extracellular region. The position of Leu29 was not altered by the mutation. Each mutant APP fragment was, therefore, more tilted (see SF 3). As a result, the γ-site in the mutant was shifted toward the center of the membrane.

We also investigated the homodimer conformations of the WT and mutant APP fragments at 300 K by principal component analysis (PCA) of the backbone atoms in the region from Gly29 to...
mutated Leu29 and Leu33 contributed significantly. In addition to observed mainly in the mutant (PM1 in Figure 3b), because the intervened between two APP fragments. This conformation was in the WT, was stabilized by Cγ of APP fragments in the membrane. The first type, observed only hydrogen bonds between the two fragments for these classifications, not classify major dimer structures. Instead, we used Cγ–H···O hydrogen bonds at Gly38. These changes likely induce mismatched interactions between the γ-site of APP-C99 and the active site of γ-secretase, which would reduce the secretion of Aβ1–40 or Aβ1–42.5

In summary, we have predicted the APP fragment (Aβ32–53) dimer structures of the WT and a mutant protein using REMD simulations and found drastic changes in the dimer structures due to the mutation.5 The results are in good agreement with the existing experimental data5,10 and provide fundamental insight into the initial steps in the amyloid formation.

Acknowledgment. This research was supported in part by a Grant for Scientific Research on a Priority Area “Membrane Interface” (to Y.S.), the Development and Use of the Next-Generation Supercomputer Project of the Ministry of Education Culture, Sports, Science and Technology (MEXT), and by CREST & BIRD, Japan Science and Technology Agency (JST) (to Y.S.). D.T. and J.E.S. are thankful for the support of a grant from the National Institutes of Health (RO1 GM076688). We thank the RIKEN Super Combined Cluster (RSCC) for providing computational resources.

Supporting Information Available: Simulation methods, Supporting Figures 1–6, and complete ref 6b (as ref 2 in the reference list). This material is available free of charge via the Internet at http://pubs.acs.org.

References


JA809227C