Abstract Submitted
for the MAR11 Meeting of
The American Physical Society

MD-simulations of Beta-Amyloid Protein Insertion Efficiency and Kinetics into Neuronal Membrane Mimics LIMING QIU, CREIGHTON BUIE, MARK VAUGHN, KWAN CHENG, Texas Tech University — Early interaction events of beta-amyloid (Aβ) peptides with the neuronal membranes play a key role in the pathogenesis of Alzheimer's disease. We have used all-atom MD simulations to study the protein insertion efficiency and kinetics of monomeric Aβ_{40} and Aβ_{42} into phosphatidylcholine lipid bilayers (PC) with and without 40 mole% cholesterol (CHOL) that mimic the cholesterol-enriched and depleted lipid nanodomains of the neuronal plasma membranes. Independent replicates of 200-ns simulations of each protein pre-inserted in the upper lipid layer were generated. In PC bilayers, only 25% of Aβ_{40} and 50% of Aβ_{42} in the replicates showed complete insertion into the lower lipid layer, whereas the percentages increased to 50% and 100%, respectively, in PC/CHOL bilayers, providing evidence that cholesterol improves the protein insertion efficiency into the bilayers. The rate of protein insertion was proportional to the hydrophobic, transmembrane helix length of the inserted peptide and depended on the cholesterol content. We propose that the lysine snorkeling and C-terminus anchoring of Aβ to the PC headgroups at the upper and lower lipid/water interfaces represent the dual-transmembrane stabilization mechanisms of Aβ in the neuronal membrane domains.

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Date submitted: 18 Nov 2010 Electronic form version 1.4