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Molecular Simulations of Synaptotagmin-like Protein4-a during the Vesicle Docking and Fusion with Endothelial Cells upon Ca^{2+} Binding[1] JIN LIU, QUYEN DINH, PRASHANTA DUTTA, School of Mechanical and Materials Engineering, Washington State University, Pullman WA USA — Synaptotagmin-like protein4-a (Slp4-a) is a calcium sensor protein which plays critical roles in triggering the vesicle docking and fusion with blood-brain barrier endothelial cells during the exocytosis process. Upon binding Ca^{2+}, Slp4-a undergoes a series of global translational/rotational movements and conformational changes, actively interacts with the SNARE complex, penetrates into the membrane bilayer, and triggers the pore opening. The exact molecular mechanism of how Ca^{2+} binding to Slp4-a leads to vesicle-cell fusion is not fully understood. In this work, we implement a hybrid coarse-grained force field that couples the united-atom protein models with the coarse-grained MARTINI water/lipid, to investigate the responses of Slp4-a upon Ca^{2+} binding. The hybrid coarse-grained molecular simulations enable us to explore large scale protein changes while retaining detailed molecular interactions. Our simulation results show that the binding of calcium ions causes dramatic reorientation and structural reorganization of Slp4-a. These changes induce local re-arrangement of membrane lipids at the Slp4-a-membrane contact areas leading to stronger attractive force between vesicle and endothelial cell membranes, which clearly indicate the initial docking and fusion process.

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