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Protein machinery regulating the synaptic vesicle fusion

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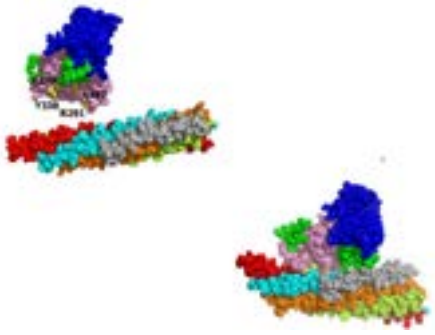
Neuronal transmitters are released *via* the fusion of synaptic vesicles with the plasma membrane. Vesicles dock to the membrane *via* a protein complex termed SNARE, which contains membrane attached (t-SNARE) and vesicle attached (v-SNARE) proteins. The fusion occurs in response to a calcium inflow, and the vesicle protein Synaptotagmin (Syt) serves as a calcium sensor. A cytosolic protein Complexin (Cpx) interacts with the SNARE complex, restricting the spontaneous fusion. Although molecular interactions of these proteins have been extensively studied, it is still debated how Syt dynamically interacts with the SNARE protein complex, Cpx, and lipid bilayers to trigger lipid merging. To elucidate these mechanisms, we combined molecular dynamics (MD) simulations with molecular biology and genetic approaches in *Drosophila*. Basing on MD simulations, we created a model of the protein fusion machinery wherein Cpx dynamically interacts with v-SNARE, preventing full SNARE assembly. Our MD simulations also elucidated how Syt interacts with lipid bilayers, causing lipid bulging that may precede the formation of the stalk and the fusion pore opening. Finally, our simulations predicted direct interactions of Syt with the SNARE-bound Cpx. The developed molecular model enabled us to predict new mutations in v-SNARE and Cpx that alter the fusion process. To test these predictions, we generated *Drosophila* lines with single point mutations and investigated how these mutations affect the kinetics of transmitter release. The results of these experiments suggest that our model creates the basis for systematic approach to manipulating the fusion machinery based on theoretical predictions derived from MD simulations.



Biography

Maria Bykhovskaia is an expert in synaptic transmission. Her lab combines molecular modeling and computations with electrophysiology, microscopy, and molecular biology approaches. She holds a Professor's position in the Washington State University. Her PhD training was in protein molecular modeling, and subsequently she used a Postdoc in Computational Neuroscience to initiate a career devoted to the study of presynaptic mechanisms and plasticity. As a PI, she has developed in her lab expertise in electrophysiology, live confocal imaging, and electron microscopy. The lab combines these experimental approaches with mathematical modeling to understand the fundamental mechanisms of release of neuronal transmitters.

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