

PROGRESS IN NEUROSCIENCE PINS

Seminar Series of the Brain & Mind Research Institute Weill Cornell Medical College (WCMC) &



The Graduate Program in Neuroscience of WCMC and Sloan Kettering Institute

Thursday, 11/6/14, 4 PM, coffee at 3:45 PM Weill Auditorium

Complexin: Gatekeeper of Synaptic Vesicle Fusion

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Abstract:



Synapses continually replenish their synaptic vesicle (SV) pools while suppressing spontaneous fusion events, thus maintaining a high dynamic range in response to physiological stimuli. The presynaptic protein complexin (CPX) inhibits fusion through interactions between its highly conserved central helix and the SNARE complex. Two poorly conserved domains (the accessory helix and the C-terminal domain) on either side of the central helix (CH) are also required for inhibition of spontaneous fusion. We found that the C-terminal domain (CTD) binds lipids through a novel protein motif, permitting complexin to inhibit spontaneous exocytosis in vivo by targeting complexin to highly curved membranes such as SVs. Membrane curvature enhanced CPX binding and induced conformational changes in a critical amphipathic region of the CTD. The accessory helix (AH) of CPX contributes to the inhibition of exocytosis but the molecular mechanism for this function remains unknown. Several models have been proposed for the role of AH based on the concept that AH competes with VAMP for a binding site on the SNARE complex. Using a series of AH mutations and chimeras with mouse AH together with NMR and CD spectroscopy, electrophysiology, and behavioral assays, we identified key features of the AH and CH required for inhibition of SV fusion by CPX. We propose that the AH stabilizes the CH through nucleation and propagation of helical secondary structure, thereby facilitating binding of the CH to the SNARE complex.

Recent relevant publications:

Martin JA, Hu Z, Fenz KM, Fernandez J, Dittman J.S. 2011. Complexin has opposite effects on two modes of synaptic vesicle fusion. *Curr Biol.* Jan 25;21(2):97-105. PMCID: PMC3026084

Wragg, RT, Snead D, Dong Y, Ramlall TF, Menon I, Bai J, Eliezer D, Dittman JS. 2013. Synaptic vesicles position complexin to block spontaneous fusion. *Neuron* 77(2):323-334. PMID: 23352168

Snead, D, Wragg RT, Dittman, JS, Eliezer, D. 2014. Membrane curvature sensing by the C-terminal domain of complexin. *Nature Commun.* Sep 17;5:4955. doi: 10.1038/ncomms5955. PMID: 25229806



