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Molecular organization of the reserve pool of synaptic vesicles

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Neuronal synapses accumulate clusters of vesicles (SVs) filled with neurotransmitters at presynaptic active zones. These vesicles fuse with the membrane and release their content during synaptic activity. Clusters of SVs are comprised of several functional pools. The reserve pool of synaptic vesicles serves to replenish the ready releasable pool during strong activation of synapses and to sustain neurotransmitter release. Overexpression and/or mutations in genes encoding the proteins organizing synaptic vesicles in the reserve pool in synapses are implicated in several neurological disorders, such as Down syndrome, epilepsy, and autism. How exactly the proteins, which organize the reserve pool interact at different stages of the synaptic vesicle cycle is still largely unknown. Using genetic approaches and acute perturbation of the protein-protein interactions in model synapses in *Drosophila*, mouse, and lamprey we show that the scaffolding protein intersectin 1 (ITSN1) is a component of an extravesicular matrix of the reserve pool of SVs. It regulates the function of the SV-associated protein synapsin 1 by forming a dynamic complex. The complex formation with synapsin 1 is mediated by SH3A (Src-homology 3 A) domain of ITSN1, which binds to the D domain of synapsin I. An intramolecular switch within ITSN1 regulates the interaction between the proteins allowing ITSN1 and synapsin 1 come into interaction during synaptic activity. Our data uncover the mechanism that serves to sequester synapsin 1 within the reserve pool when it dissociates from SV during stimulation and promotes efficient reclustering when stimulation ceased by releasing dephosphorylated synapsin within the reserve pool.

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