Nobel Prize winner reports new model for neurotransmitter release

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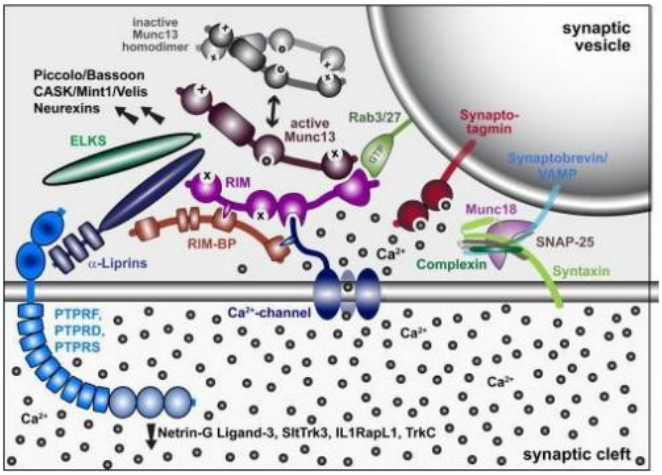

This is a molecular model of the active zone protein complex and its relation to the synaptic vesicle fusion machinery, Ca2+ channels, and synaptic cell-adhesion molecules. Credit: *Neuron*, Volume 75, Issue 1, 11-25, 12 July 2012, Sudhof

In a *Neuron* article published online October 10th, recent Nobel Laureate Thomas C. Südhof challenges long-standing ideas on how neurotransmitter gets released at neuronal synapses. On October 7th, Südhof won the Nobel Prize in Physiology or Medicine, alongside James Rothman and Randy Schekman, for related work on how vesicles—such as those in neurons that contain neurotransmitter—are transported within cells.

Neurotransmitter-containing vesicles are found inside neurons very close to the end of the axon. Here, they can quickly fuse with the neuronal membrane surrounding the axon to spill their contents into the synapse. How these vesicles are able to fuse with the membrane has been controversial, however, and understanding this process would give researchers much greater insight how neurons communicate with each other.

Previously, it was thought that proteins found on the outside of the vesicles and on the axon membrane (called SNARE proteins) would come together and physically form a pore through which the contents of the vesicle—the neurotransmitter—could be released into the synapse. Now, the new findings from Südhof suggest that these proteins may not form a pore at all. Instead, their main role may be to physically force the vesicle and the axon membrane to get very close to each other; once they are forced into contact, the two appear able to fuse spontaneously.

"The importance of SNARE transmembrane regions has never been tested in a physiological fusion reaction," says Dr. Südhof. "We show that the SNARE transmembrane regions are dispensible for fusion as such but are important for maintaining the normal efficiency of regulated fusion. These findings rule out an essential participation of the SNARE transmembrane regions in fusion and are consistent with the notion that the SNAREs function in fusion as force generators, i.e., that their function is to force the membranes close together." The results are controversial due to years of research supporting the SNARE-protein pore hypothesis. These provocative findings could change long-held models for how neurotransmitters are released from neurons and suggest that there remain many open questions about the role of SNAREs in neurotransmitter release at synapses.

More information: *Neuron*, Zhou et al.: "Lipid-Anchored SNAREs Lacking Transmembrane Regions Fully Support Membrane Fusion during Neurotransmitter Release."

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