

HOW Ca²⁺ TRIGGERS NEUROTRANSMITTER RELEASE

Thomas C. Südhof

Department of Molecular Genetics, Center for Basic Neuroscience, Howard Hughes Medical Institute, UT Southwestern Medical Center, Dallas, TX 75390-9111, USA.

At a synapse, release of neurotransmitters initiates synaptic transmission. Our laboratory is interested in how a presynaptic terminal releases neurotransmitters in a tightly regulated and topologically restricted manner. Neurotransmitter release occurs by synaptic vesicle exocytosis that is triggered by influx of Ca²⁺ into the presynaptic terminal. Ca²⁺-evoked synaptic vesicle exocytosis is one of the fastest, most tightly controlled, and most modulated reactions in biology. The speed and plasticity of neurotransmitter release are major factors in shaping the exquisite precision of synaptic networks.

In a longstanding program, we are investigating the molecular cascades that orchestrate synaptic vesicle exocytosis and neurotransmitter release. Hundreds, maybe thousands of proteins are involved in release. We envision that these proteins mediate release in a hierarchy of reactions: At the lowest level of this hierarchy, release is effected by exocytosis. Exocytosis in turn is controlled by Ca²⁺, and the Ca²⁺-dependent release machinery is embedded in the active zone of the presynaptic terminal by a protein scaffold that integrates signalling during synaptic plasticity. At the top level of the hierarchy, a transsynaptic cell adhesion apparatus organizes the position and activation of the release machinery with respect to the postsynaptic specializations.

We are trying, in conjunction with other laboratories, to achieve a description of the molecular machinery that mediates the execution and plasticity of neurotransmitter release. Major players at each level of the presynaptic hierarchy have been identified. Exocytosis is largely mediated by SNAREs (e.g., synaptobrevin, syntaxin and SNAP-25) and SM proteins (e.g., Munc18-1), and is controlled by synaptotagmins as Ca²⁺-sensors. As Ca²⁺-sensors, synaptotagmins not only translate voltage-gated Ca²⁺-influx into the release reaction, but also participate in the fusion machinery, and contribute to presynaptic plasticity. Indeed, Ca²⁺-binding to synaptotagmins is the central event in the release process, and is modulated by active zone proteins. Key components of the protein scaffold of the active zone, such as Munc13s, RIMs, and ELKS integrate synaptic vesicle exocytosis and mediate synaptic plasticity. An initial, sketchy description of the molecular machinery that executes neurotransmitter release has thus emerged, a description that hopefully will form the basis for a mechanistic understanding of this central process in synaptic transmission.

Selected References

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