Review Update: Cycling of Synaptic Vesicles

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A reader's guide to the revised STKE review "Cycling of synaptic vesicles: How far? How fast?", http://www.stke.org/cgi/content/full/sigtrans;2004/264/re19

Over the past three years since the publication of the original version of this article, we have witnessed a wealth of new information regarding the pathways of synaptic vesicle cycling, which have been incorporated into the revised version of the Review. These advances include the morphological identification of the physiologically defined readily releasable pool of synaptic vesicles, the identification of molecular players implicated in fast vesicle recycling, and the genetic and structural analysis of endocytotic adaptor proteins implicated in cargo selection and membrane deformation. Given the wealth of structural information now available for the major players in clathrin-mediated vesicle recycling, we are beginning to understand at the level of atomic resolution how membrane curvature is achieved and decoded. With ever more sensitive physiological techniques in hand, we are also starting to appreciate the different release and vesicle cycling properties of different types of synapses, which may rely on kinetically distinct vesicle cycling pathways to different degrees. Although the overall organization of the review has been maintained, we have tried to incorporate most of the new information into the sections describing fusion and fission mechanisms and clathrin-mediated endocytosis. Highlights of the updated review are summarized below.

Morphological Organization of the Readily Releasable Pool

- Improved staining techniques have allowed the visualization of the readily releasable pool of cycling vesicles by EM. Surprisingly, these vesicles appear to be randomly dispersed throughout the vesicle cluster (*1*).

Fast-Track Vesicle Cycling

- Fluorescent dye tracking studies of single vesicles undergoing exo- and endocytosis in hippocampal neurons have provided new evidence for fast-track cycling. Some of these vesicles appear to undergo incomplete fusion with the plasma membrane (*2*), whereas those fusing completely may, in part, constitute a stranded pool of vesicles (*3*).

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Regulation of Calcium-Triggered Membrane Fusion

- Synaptotagmin, a major calcium-binding synaptic vesicle protein, triggers SNARE-mediated membrane fusion in a calcium- and dose-dependent manner (*4, 5*).
- Phosphatidylinositol (4,5)-bisphosphate (PIP_2) facilitates calcium-induced membrane penetration of synaptotagmin in vitro, thus perhaps being a downstream effector of this important phospholipid (*6*) in membrane fusion (*7*).

Membrane Fission and Curvature Sensing

- Analysis of mutant flies reveals an essential role for dynamin, but not endophilin, in membrane fission (*8*, *9*).
- Endophilin, amphiphysin, and several other proteins contain lipid curvature-sensing BAR domains (*10*).

Structural Organization of Endocytotic Adaptor Proteins in Slow-Track Vesicle Cycling

- Alternative adaptors (*11*), such as epsin, bind to and, at least in the case of epsin, deform PIP_2-containing membranes by partitioning into and bending those membranes (*12*).
- The crystal structure of the heterotetrameric clathrin adaptor AP-2 suggests that this complex may require conformational activation elicited by phosphorylation and the presence of PIP_2 in the lipid bilayer (*13*).

Components that May Regulate the Choice Between Fast- and Slow-Track Vesicle Cycling

- Isoforms of synaptotagmin may regulate the choice between fast and slow modes of vesicle cycling (*14, 15*).
- Animal with mutations in synaptobrevin display impaired fast-track vesicle cycling (*16*).

References and Notes

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