Main steps involved in neurotransmission at chemical synapses

Neurotransmitter secretion is very fast (~100 times faster than insulin secretion by pancreatic β-cells) and is **induced by Ca^{++} increase in the presynaptic terminal**

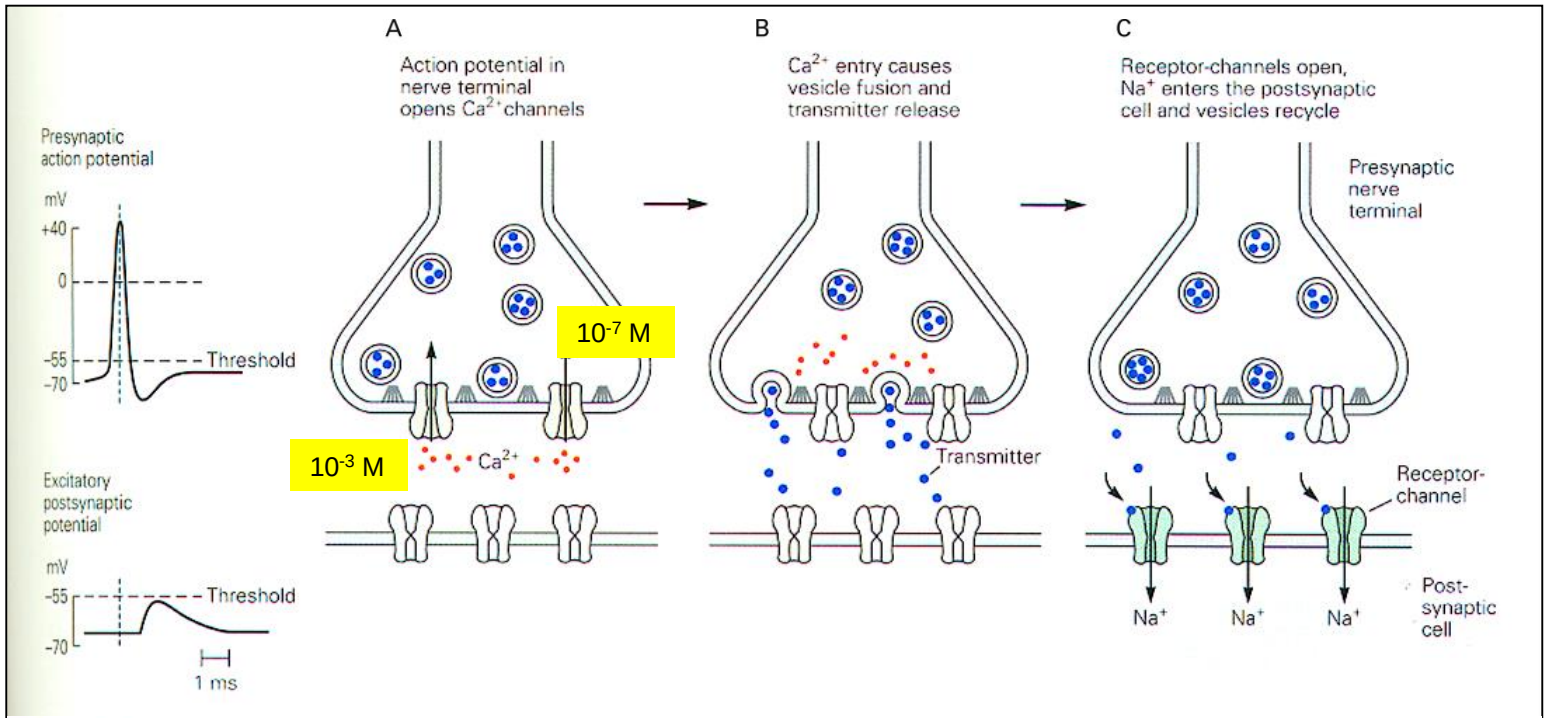


Figure 8–8 Synaptic transmission at chemical synapses involves several steps. The complex process of chemical synaptic transmission accounts for the delay between an action potential in the presynaptic cell and the synaptic potential in the postsynaptic cell compared with the virtually instantaneous transmission of signals at electrical synapses (see Figure 8–2B).

A. An action potential arriving at the terminal of a presynaptic axon causes voltage-gated Ca^{2+} channels at the active zone to open. The **gray filaments** represent the docking and release sites of the active zone.

B. The Ca^{2+} channel opening produces a high concentration of intracellular Ca^{2+} near the active zone, causing vesicles containing neurotransmitter to fuse with the presynaptic cell membrane and release their contents into the synaptic cleft (a process termed *exocytosis*).

C. The released neurotransmitter molecules then diffuse across the synaptic cleft and bind specific receptors on the postsynaptic membrane. These receptors cause ion channels to open (or close), thereby changing the membrane conductance and membrane potential of the postsynaptic cell.

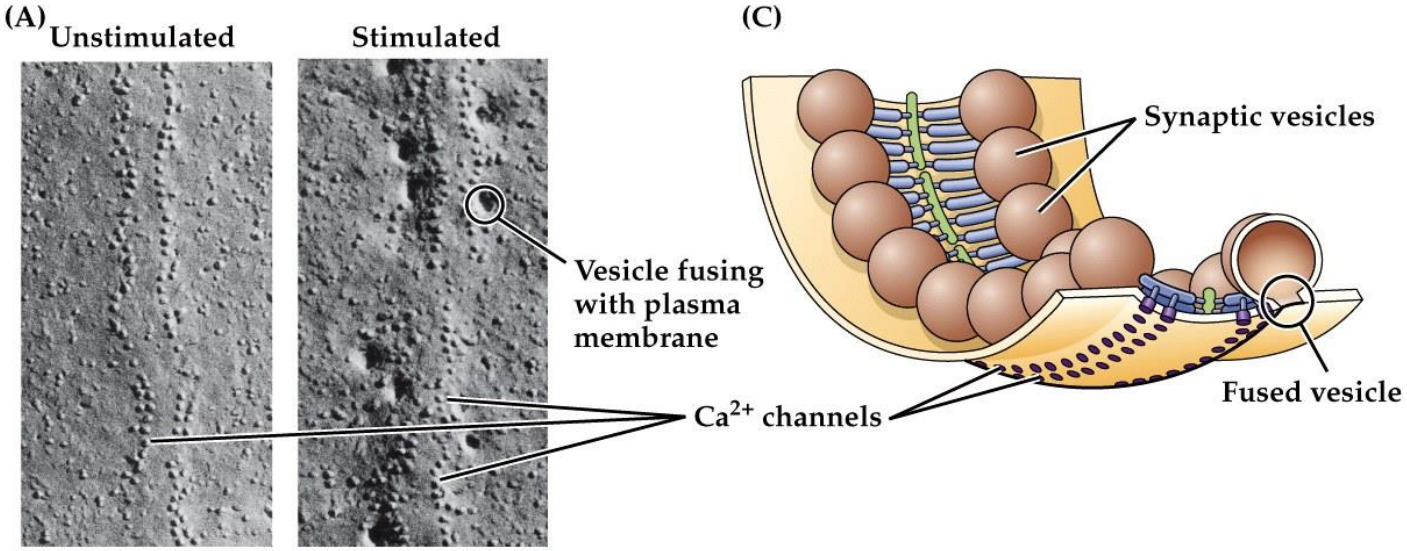
Release of neurotransmitter is quantal

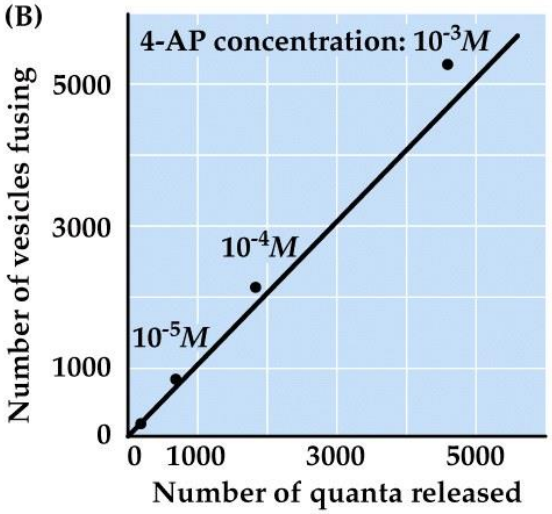
Bernard Katz

The anatomical specializations of the synapse and the properties of the pre-synaptic ion channels and postsynaptic receptors all contribute to achieve FAST, QUANTAL TRANSMISSION

For additional information on this subject, see Chapter 15 of the textbook 'From Molecules to Networks' by Byrne et al.

Relationship between synaptic vesicle exocytosis and quantal transmitter release





(A) Freeze-fracture microscopy was used to visualize the fusion of synaptic vesicles in presynaptic terminals of frog motor neurons

(B) Comparisons of the number of observed vesicles fusions to the number of quanta released by a presynaptic action potential

(C) Structural organization of vesicles fusion sites of frog presynaptic terminals

***NEUROSCIENCE 5e*, Figure 5.8**

Postsynaptic events leading to generation of action potential in the muscle fiber

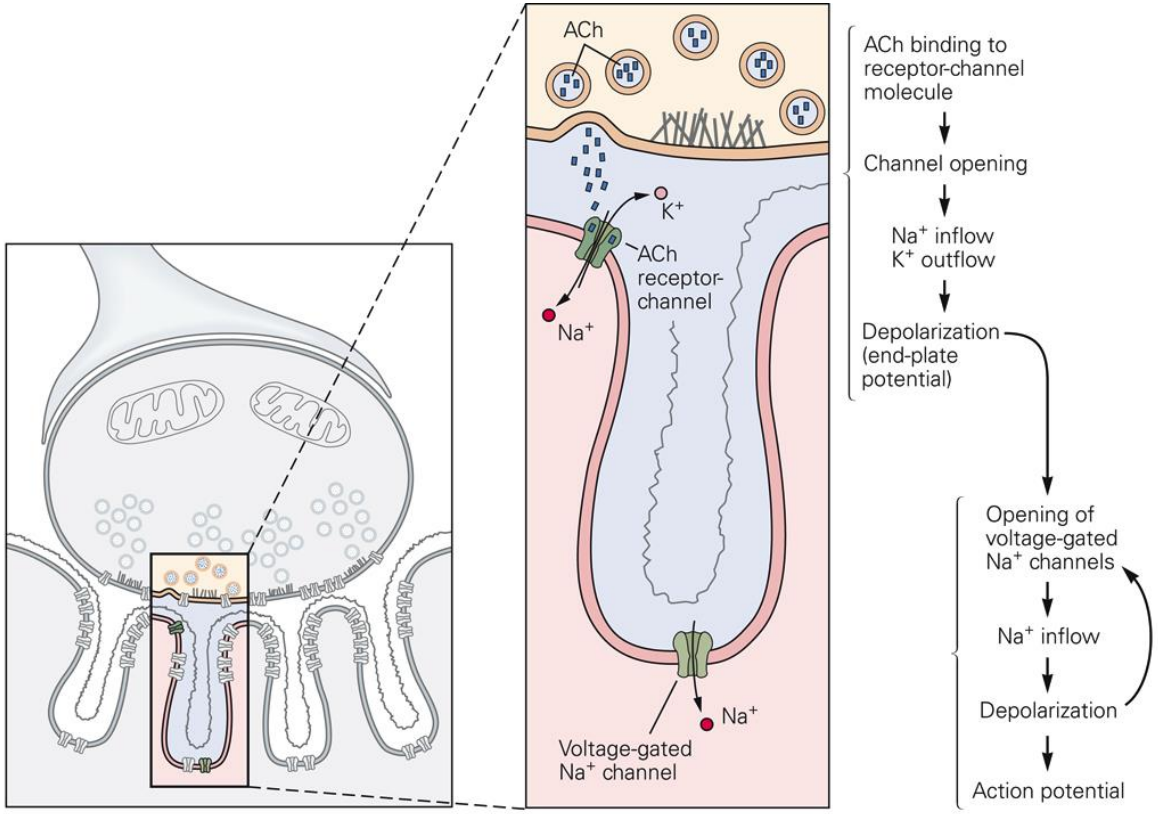


Figure 9–12 The depolarization resulting from the opening of ACh receptor-channels at the end-plate opens voltage-gated Na^+ channels. The depolarization of the muscle membrane during the end-plate potential opens neighboring voltage-gated Na^+ channels in the muscle membrane. The depolarization is normally large enough to open a sufficient number of Na^+ channels to exceed the threshold for an action potential. (Reproduced, with permission, from Alberts et al. 1989.)

Kandel, Principles of Neural Sciences, 2013

Calcium channels are concentrated at the active zone

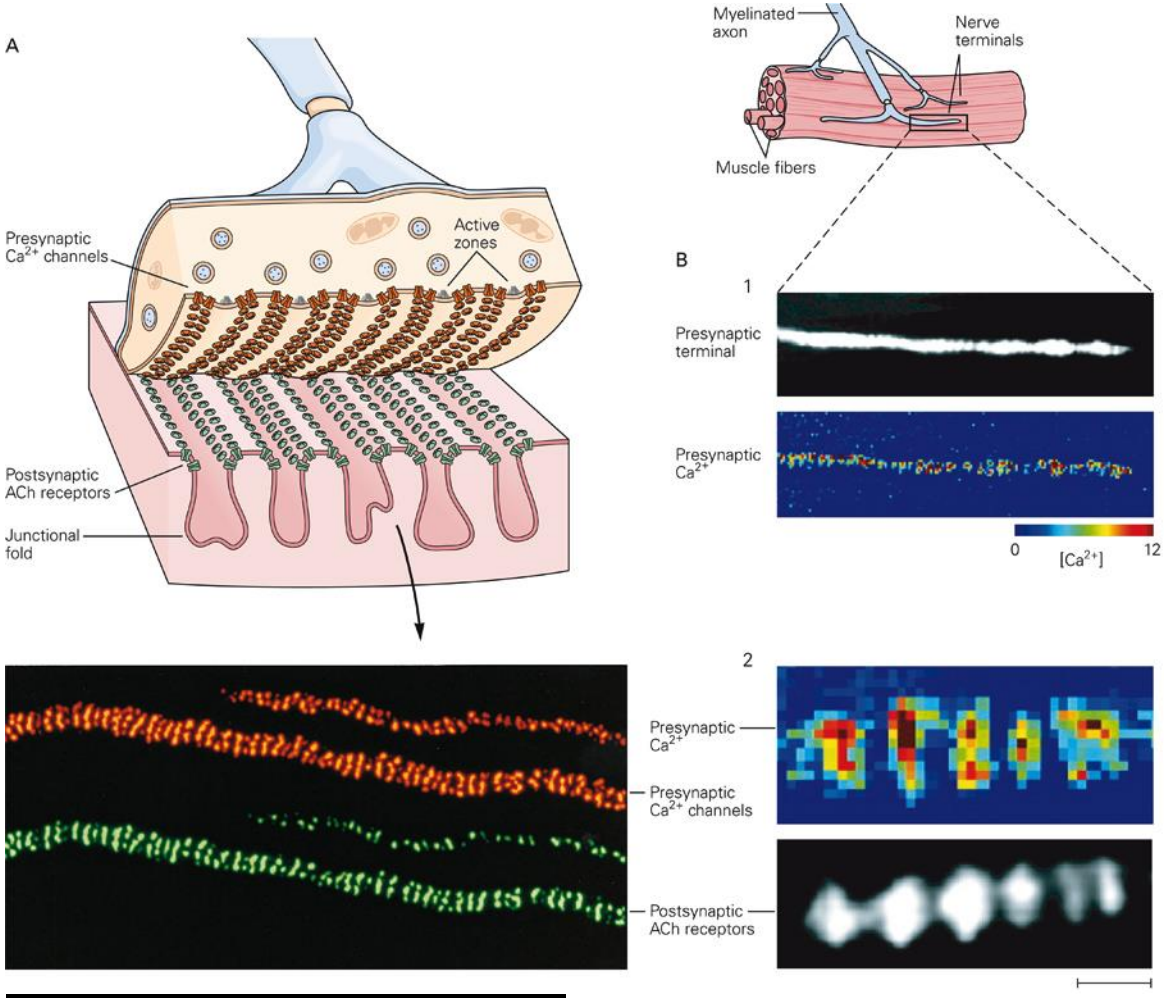


Figure 12–4 **Calcium flowing into the presynaptic nerve terminal during synaptic transmission at the neuromuscular junction is concentrated at the active zone.** Calcium channels in presynaptic terminals at the end-plate are concentrated opposite clusters of nicotinic acetylcholine (ACh) receptors on the postsynaptic muscle membrane. Two drawings show the frog neuromuscular junction.

A. The enlarged view shows the microanatomy of the neuromuscular junction with the presynaptic terminal peeled back. A fluorescent image shows the presynaptic Ca^{2+} channels (labeled with a Texas red-coupled marine snail toxin that binds to Ca^{2+} channels), and postsynaptic ACh receptors (labeled with fluorescently tagged α-bungarotoxin, which binds selectively to ACh receptors). The two images are normally superimposed but have been separated for clarity. The patterns of labeling with both probes are in almost precise register, indicating that the active zone of the presynaptic neuron is in almost perfect alignment with the postsynaptic membrane containing the high concentration of ACh receptors. (Reproduced, with permission, from Robitaille, Adler, and Charlton 1990.)

B. Calcium influx in presynaptic terminals is localized at active zones. Calcium can be visualized using calcium-sensitive fluorescent dyes. **1.** A presynaptic terminal at a neuromuscular junction filled with the dye fura-2 under resting conditions is shown in the black and white image. The fluorescence intensity of the dye changes as it binds Ca^{2+}. In the color image, color-coded fluorescence intensity changes show local hot-spots of intracellular Ca^{2+} in response to a single presynaptic action potential. **Red** indicates regions with a large increase in Ca^{2+}; **blue** indicates regions with little increase in Ca^{2+}. Regular peaks of Ca^{2+} are seen along the terminal, corresponding to the localization of Ca^{2+} channels at the active zones. **2.** The color image shows a high-magnification view of the peak increase in terminal Ca^{2+} levels. The corresponding black-and-white image shows fluorescence labeling of nicotinic ACh receptors in the postsynaptic membrane, illustrating the close spatial correspondence between areas of presynaptic Ca^{2+} influx and areas of postsynaptic receptors. The scale bar represents 2 μm. (Reproduced, with permission, from Wachman et al. 2004.)

Kandel, Principles of Neural Sciences, 2013

Microdomains with high Ca^{2+} concentrations form near open Ca^{2+} channels and trigger the exocytosis of synaptic vesicles

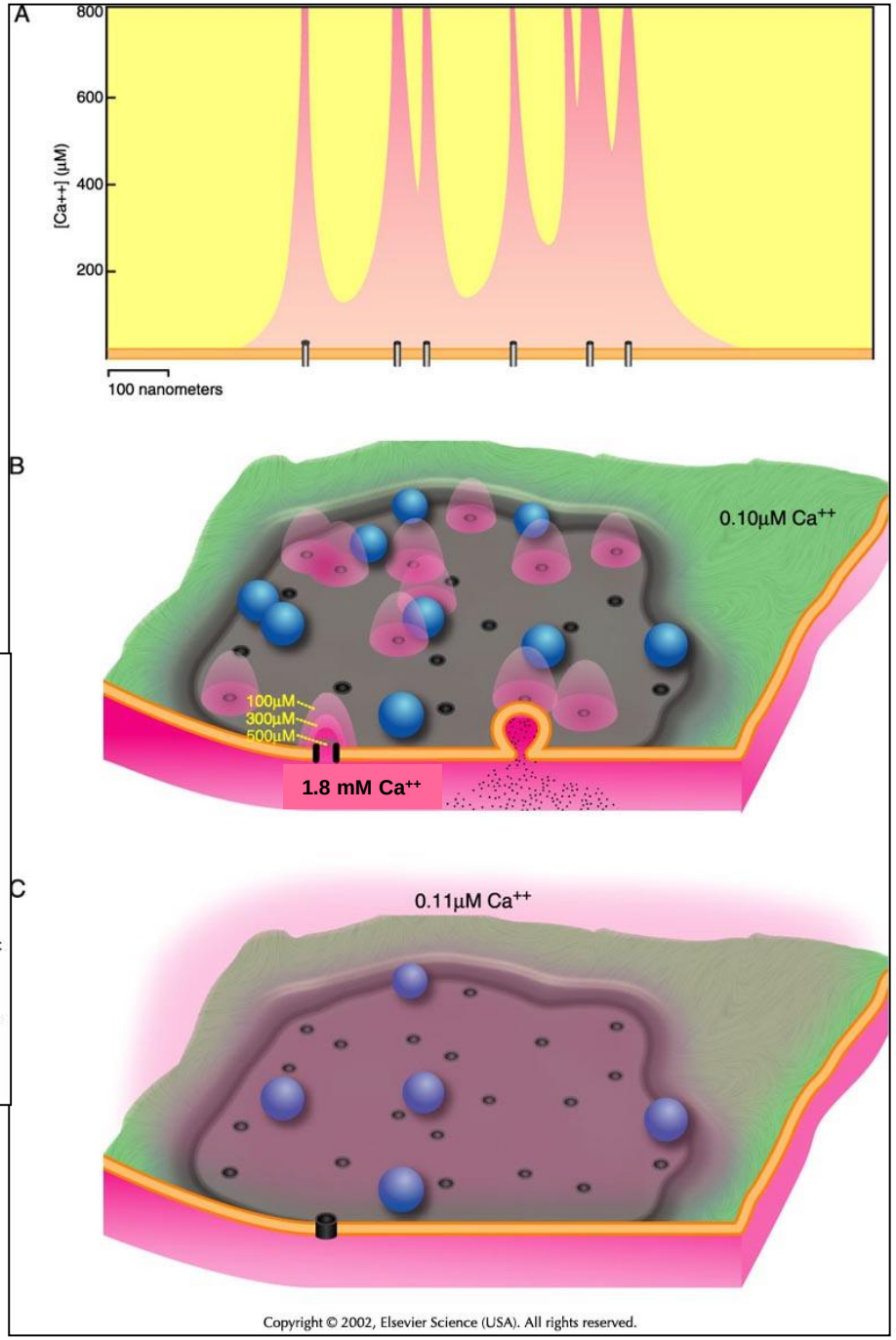
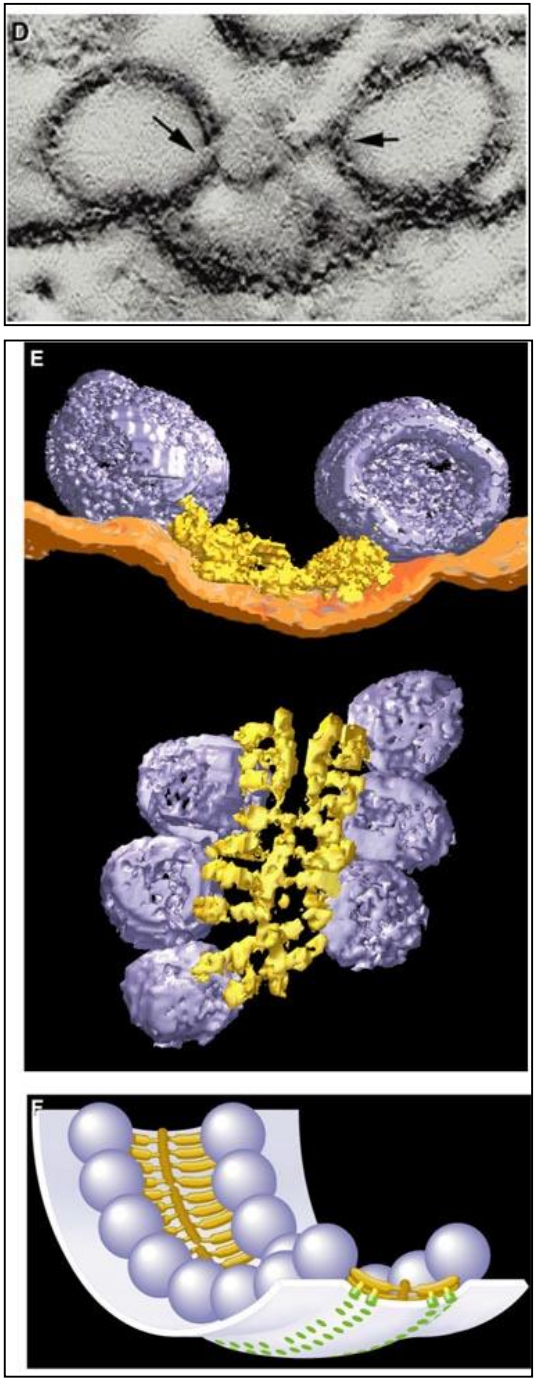


FIGURE 3 Microdomains with high Ca^{2+} concentrations form in the cytosol near open Ca^{2+} channels and trigger the exocytosis of synaptic vesicles. (A) In this adaptation of a model of Ca^{2+} dynamics in the terminal, a set of Ca^{2+} channels is spaced along the x axis, as if in a cross section of a terminal. The channels have opened and, while they are open, the cytosolic Ca^{2+} concentration (y axis) is spatially inhomogeneous. Near the mouth of the channel, the influx of Ca^{2+} drives the local concentration to as high as 800 μM, but within just 50 nm of the channel, the concentration drops off to 100 μM. Channels are spaced irregularly but are often sufficiently close to one another that their clouds of Ca^{2+} can overlap and sum. (B) In the active zone (gray), an action potential has opened a fraction of the Ca^{2+} channels and microdomains of high cytosolic Ca^{2+} (pink) arise around these open channels as Ca^{2+} flows into the cell. In the rest of the cytoplasm, the Ca^{2+} concentration is at resting levels (0.10 μM), but within these microdomains, particularly near the channel mouth, Ca^{2+} concentrations are much higher, as in A. Synaptic vesicles docked and primed at the active zone may come under the influence of one or more of these microdomains and thereby be triggered to fuse with the membrane. (C). A few milliseconds after the action potential, the channels have closed and the microdomains have dispersed. The overall Ca^{2+} concentration in the terminal is now slightly higher (0.11 μM) than before the action potential. If no other action potentials occur, the cell will pump extra Ca^{2+} out across the plasma membrane and restore the initial condition after several 100 ms.

Byrne, From Molecules to Networks, 2014

Reconstruction of the active zones at the neuromuscolar junction by electron tomography



The fine structure of the active zone at a frog neuromuscular junction as seen with electron tomography. (D) In a cross-sectional image from tomographic data, two vesicles are docked at the plasma membrane and additional electron-dense elements are seen. When these structures are traced and reconstructed through the volume of the EM section (E), proteins of the active zone (gold) appear to form a regular structure adjacent to the membrane that connects the synaptic vesicles (silver) and plasma membrane (white). Viewed from the cytoplasmic side (E, lower image), proteins are seen to extend from the vesicles and connect in the center. (F) Schematic rendering of an active zone based on tomographic analysis. An ordered structure aligns the vesicles and connects them to the plasma membrane and to one another.

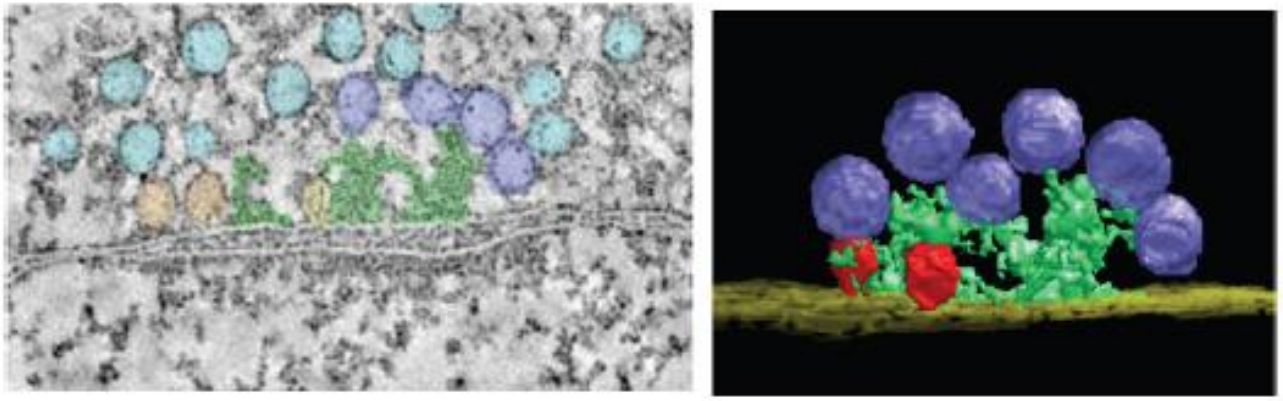
(D–F)

After Harlow *et al.*, (2001).

Squire, Fundamental Neuroscience, 2013

CNS synapses: the presynaptic terminal

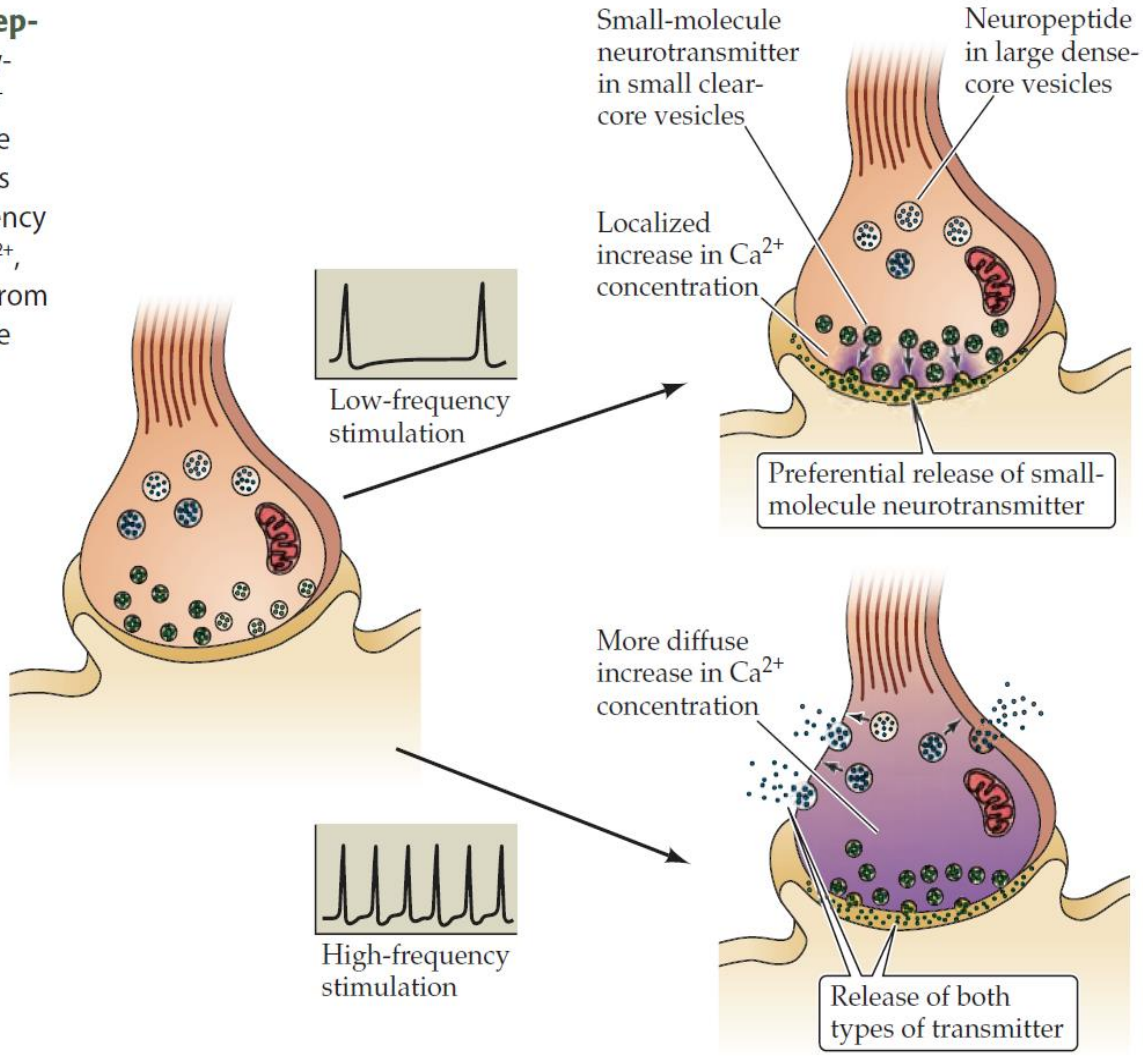
Architecture of the presynaptic Active Zone



Reconstruction of two dense projections (green) showing their relationship with six synaptic vesicles (blue) and two fusing vesicles (red).
(electron tomography)

Burette et al., Microsc Microanal 13(Suppl 2), 2007

FIGURE 5.12 Differential release of neuropeptide and small-molecule co-transmitters. Low-frequency stimulation preferentially raises the Ca^{2+} concentration close to the membrane, favoring the release of transmitter from small clear-core vesicles docked at presynaptic specializations. High-frequency stimulation leads to a more general increase in Ca^{2+}, causing the release of peptide neurotransmitters from large dense-core vesicles, as well as small-molecule neurotransmitters from small clear-core vesicles.



Purves, Neuroscience, 2012

Calcium controls:

1) exocytosis

2) mobilization of synaptic vesicles

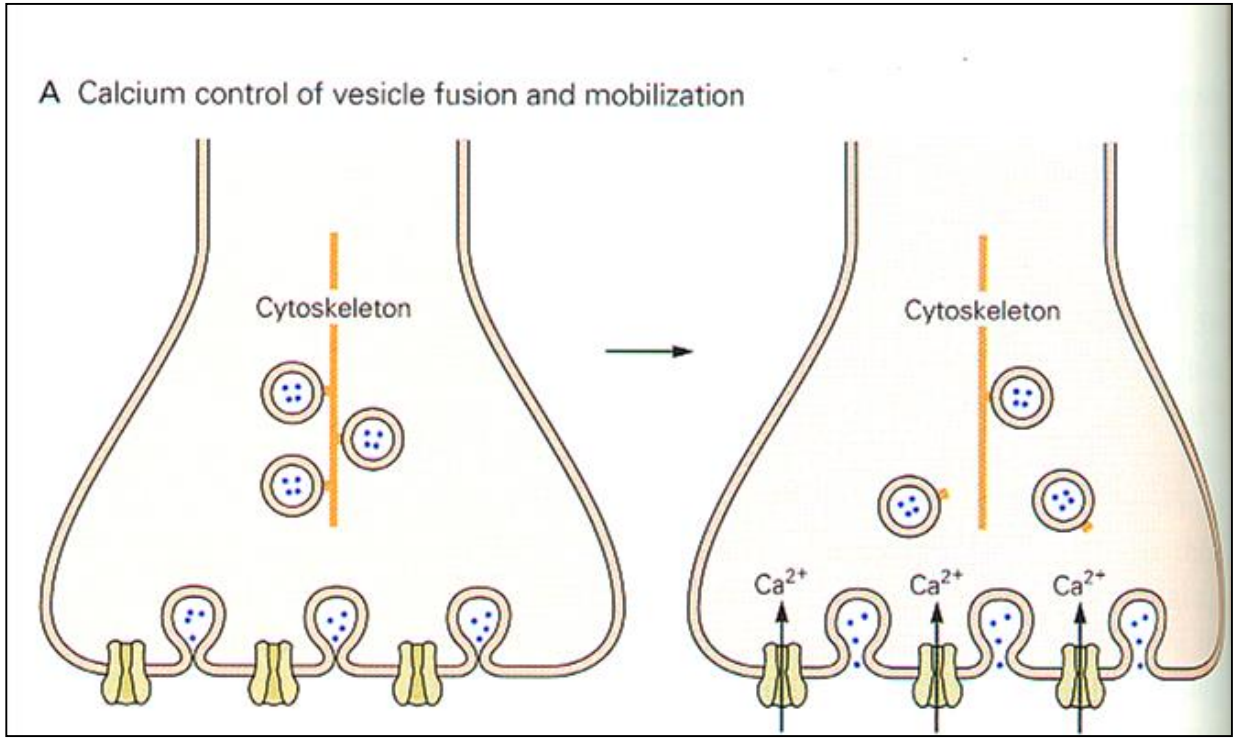


Figure 14-14 The mobilization, docking, and function of synaptic vesicles are controlled by Ca^{2+} and low-molecular-weight GTP-binding proteins.

A. Synaptic vesicles in nerve terminals are sequestered in a *storage compartment* where they are tethered to the cytoskeleton, as well as in a *releasable* compartment where they are docked to the presynaptic membrane. Entry of Ca^{2+} into the nerve terminal leads to the opening of the fusion pore complex and neurotransmitter release. Calcium entry also frees vesicles from the storage compartment through phosphorylation of synapsins, thus increasing the availability of vesicles for docking at the presynaptic plasma membrane.

Dephosphorilated Synapsin 1 (Syn 1) links vesicles to the actin cytoskeleton.

Phosphorilation of Syn 1 induces vesicle mobilization, increasing the number of vesicles available for docking/fusion with the plasma membrane

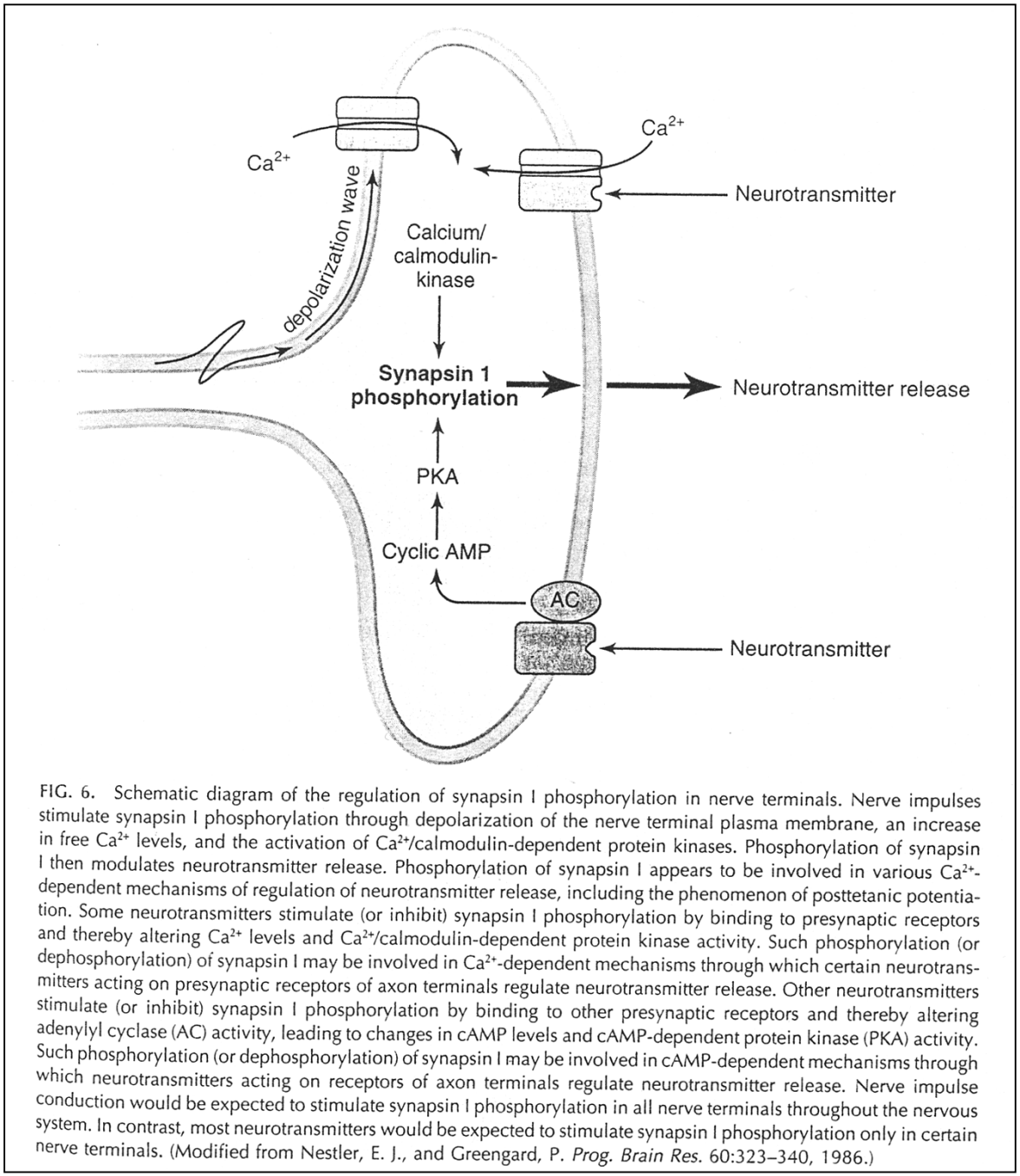
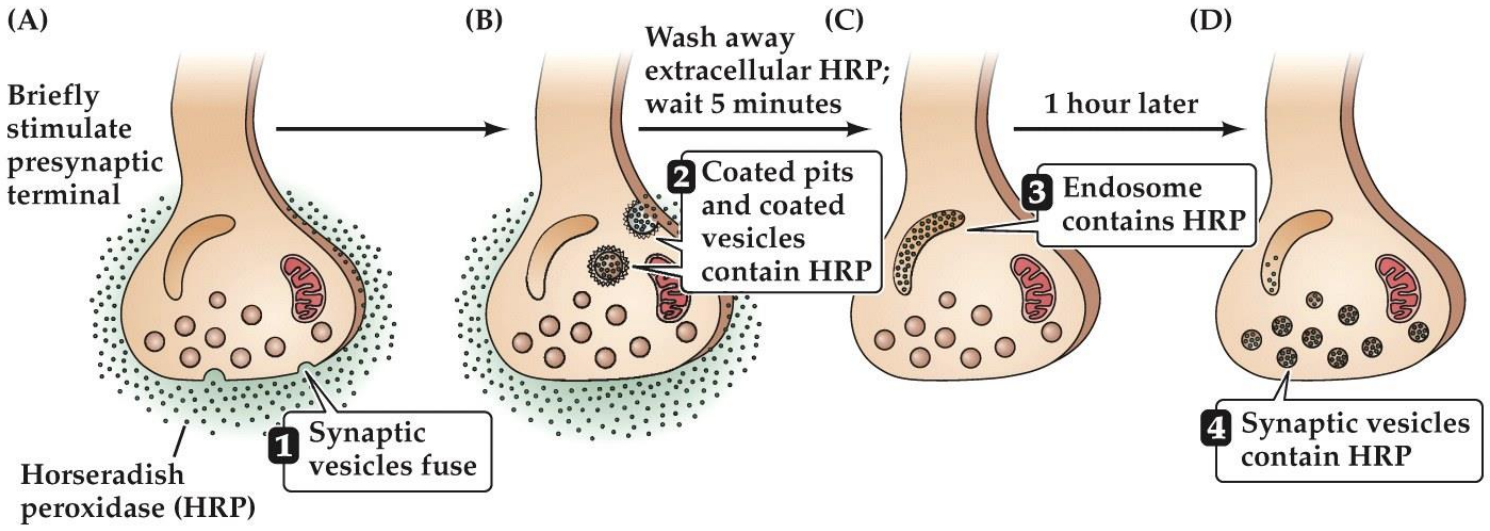


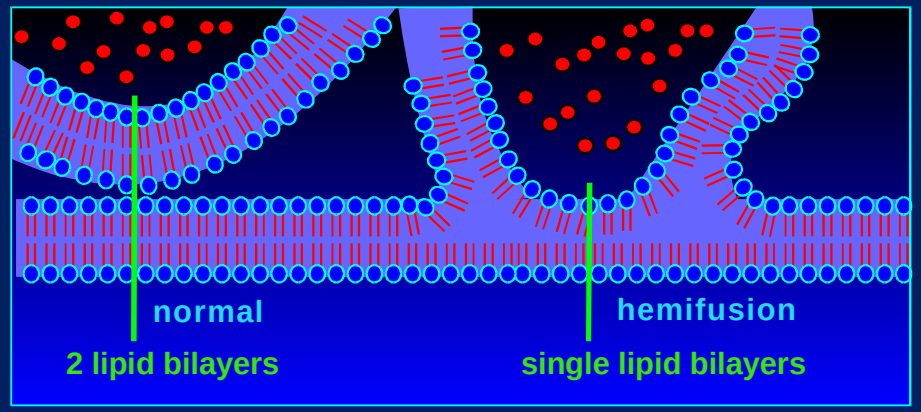
FIG. 6. Schematic diagram of the regulation of synapsin I phosphorylation in nerve terminals. Nerve impulses stimulate synapsin I phosphorylation through depolarization of the nerve terminal plasma membrane, an increase in free Ca^{2+} levels, and the activation of Ca^{2+}/calmodulin-dependent protein kinases. Phosphorylation of synapsin I then modulates neurotransmitter release. Phosphorylation of synapsin I appears to be involved in various Ca^{2+}-dependent mechanisms of regulation of neurotransmitter release, including the phenomenon of posttetanic potentiation. Some neurotransmitters stimulate (or inhibit) synapsin I phosphorylation by binding to presynaptic receptors and thereby altering Ca^{2+} levels and Ca^{2+}/calmodulin-dependent protein kinase activity. Such phosphorylation (or dephosphorylation) of synapsin I may be involved in Ca^{2+}-dependent mechanisms through which certain neurotransmitters acting on presynaptic receptors of axon terminals regulate neurotransmitter release. Other neurotransmitters stimulate (or inhibit) synapsin I phosphorylation by binding to other presynaptic receptors and thereby altering adenylyl cyclase (AC) activity, leading to changes in cAMP levels and cAMP-dependent protein kinase (PKA) activity. Such phosphorylation (or dephosphorylation) of synapsin I may be involved in cAMP-dependent mechanisms through which neurotransmitters acting on receptors of axon terminals regulate neurotransmitter release. Nerve impulse conduction would be expected to stimulate synapsin I phosphorylation in all nerve terminals throughout the nervous system. In contrast, most neurotransmitters would be expected to stimulate synapsin I phosphorylation only in certain nerve terminals. (Modified from Nestler, E. J., and Greengard, P. *Prog. Brain Res.* 60:323–340, 1986.)

Demonstration of synaptic vesicle recycling in the presynaptic terminal



Purves, Neuroscience, 2012

The Nine Steps of the Synaptic Vesicle Cycle



8 Exocytosis

NT

7 Docking

6 Endosome Fusion

Endosome

9 Translocation

5 Translocation

H^+

1 Docking

2 Priming

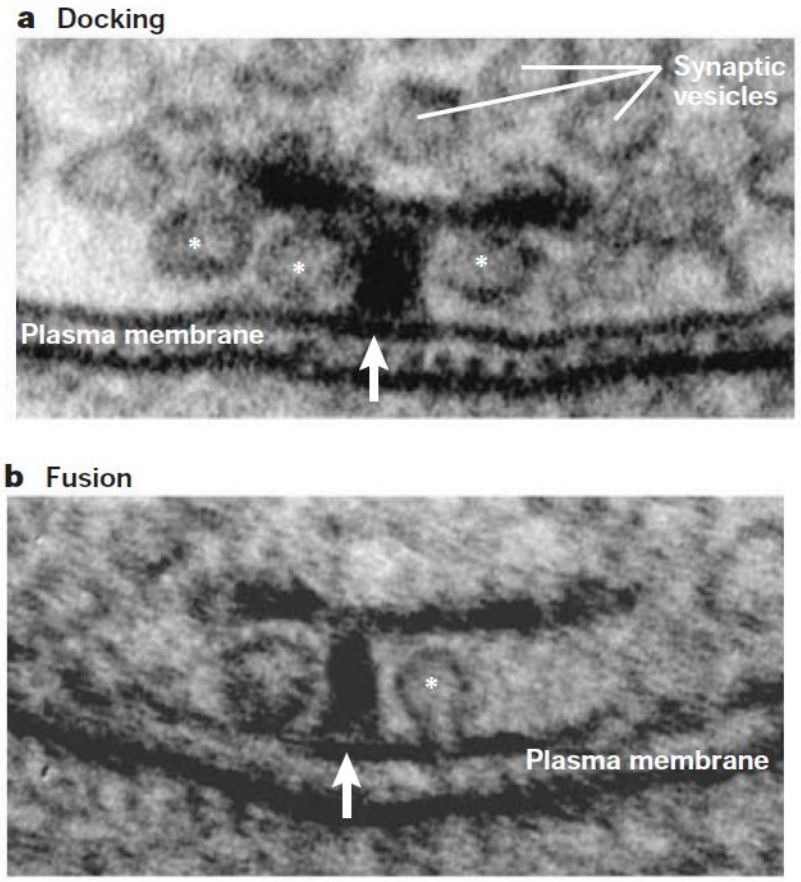
3 Fusion/Exocytosis

4 Endocytosis

ATP

5 Ca^{2+}

Ca^{2+}



Chlatrin-mediated endocytosis

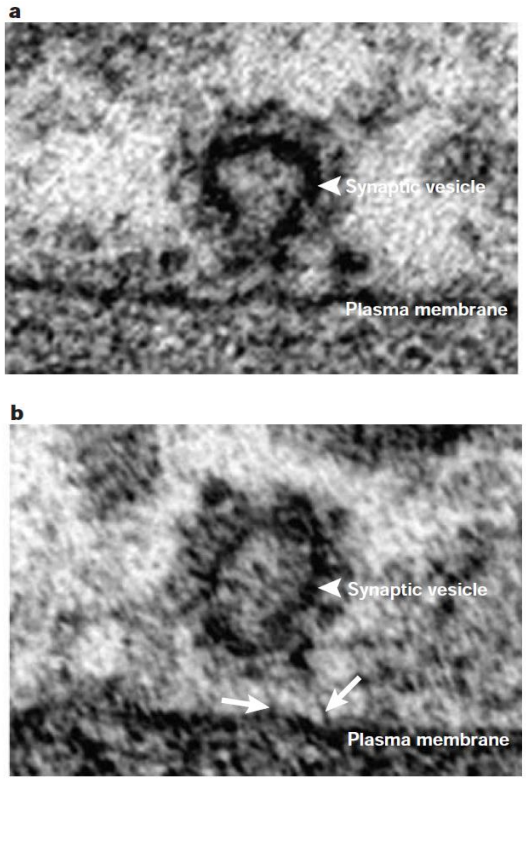
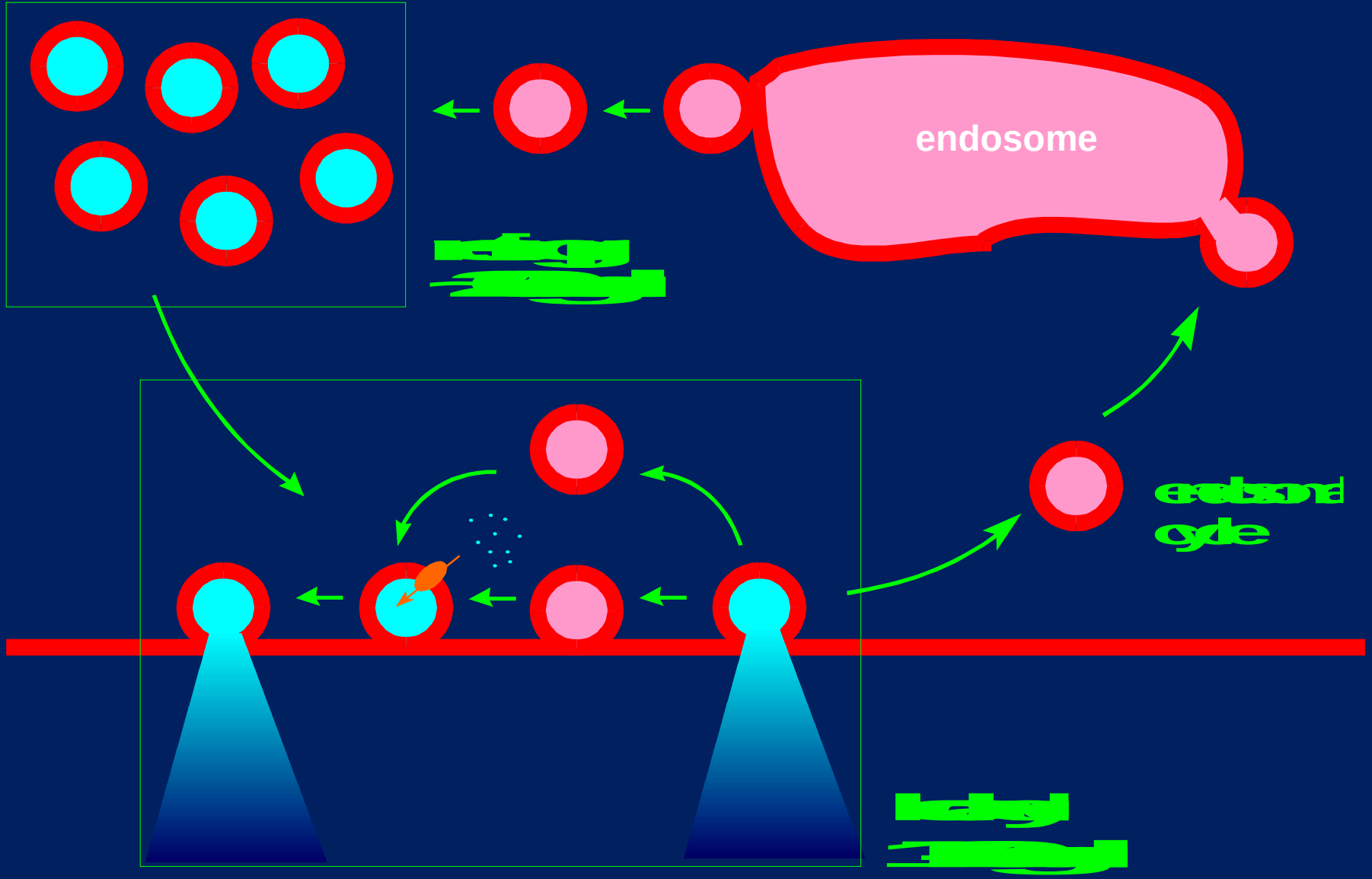


Figure 2 | **Regulation of synaptic vesicle exocytosis by lipid raft environment. a,b** | Electron micrographs of the *Drosophila melanogaster* neuromuscular junction presynaptic active zone, showing electron-dense 'T-bar' release sites (white arrows). Panel **a** shows morphologically docked synaptic vesicles (asterisks) close to or in direct contact with the active zone. Panel **b** shows fusion of a synaptic vesicle (asterisk) at the active zone.

Rohrbough & Broadie , 2005
Nature Reviews Neurosci
doi:10.1038/nrn1608



The synaptic vesicle cycle revisited

Schematic representation of the **three vesicle pools** found in the presynaptic terminal

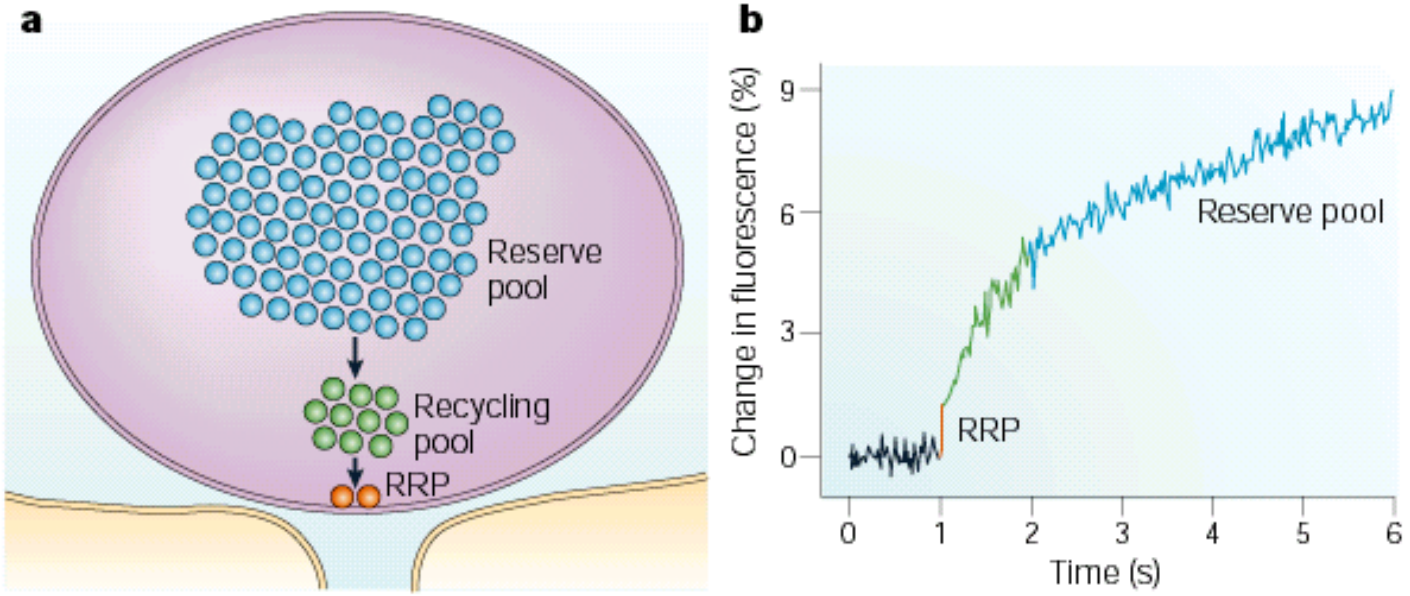


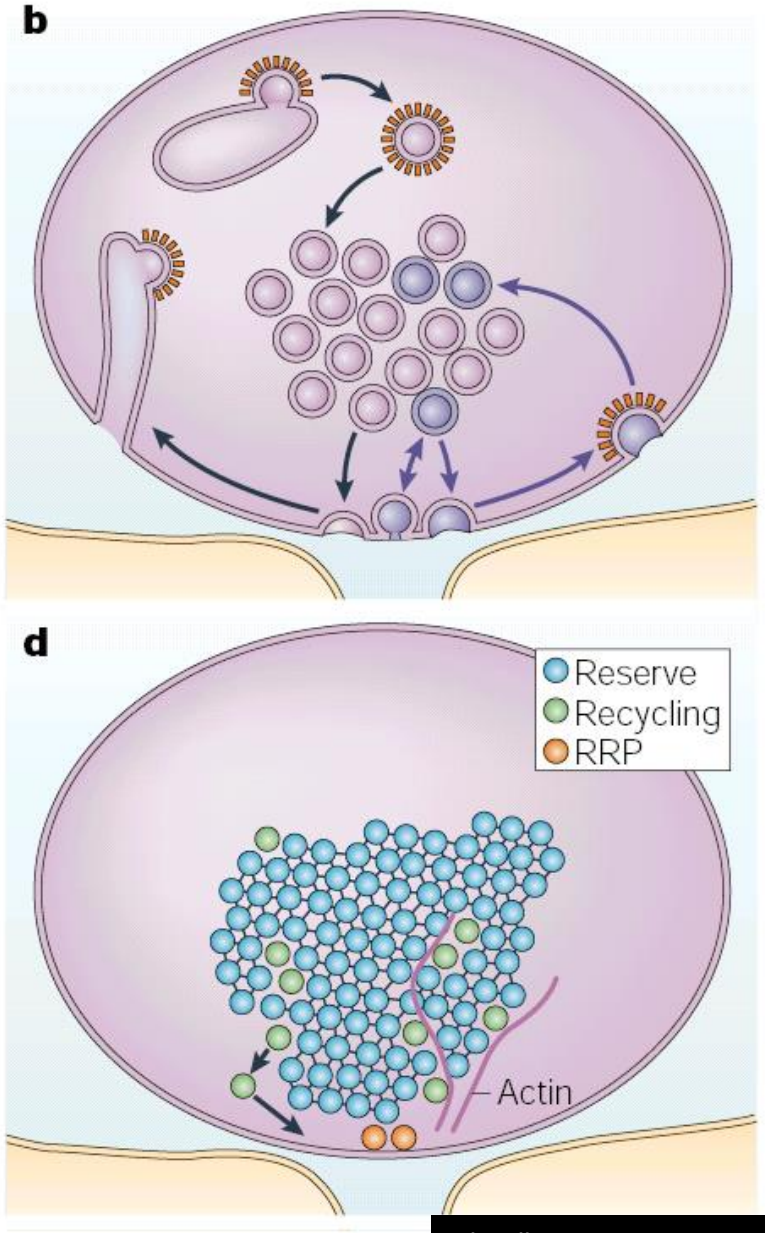
Figure 1 | **Three vesicle pools. a** | The classic three-pool model. The reserve pool makes up ~80–90% of the total pool, and the recycling pool is significantly smaller (~10–15%). The readily releasable pool (RRP) consists of a few vesicles (~1%) that seem to be docked and primed for release. **b** | Three kinetic components of release (indicating release of three vesicle pools) on depolarization of goldfish bipolar cells. The cell was stimulated in the presence of the styryl dye FM 1-43, and the increase in fluorescence gives a direct measure of exocytosis. Panel **b** modified, with permission, from REF. 12 © (1999) Blackwell Scientific Publishing.

Rizzoli & Betz, 2005
NATURE REVIEWS **NEUROSCI**
doi:10.1038/nrn1583

Recycling and mobilization of vesicle pools

b) Proposed recycling model. The **reserve pool (pink)** recycles slowly, through formation of infoldings and their break-off through clathrin coat-dependent mechanisms. The **recycling pool (purple)** cycles through direct endocytosis from the plasma membrane. This process might be clathrin coat dependent, or might rely on transient fusion (kissand-run). Kiss-and-run might be used especially by **readily releasable pool** (**RRP**) vesicles.

d) Proposed model of mobilization. The **RRP** vesicles are docked and do not require mobilization. The **reserve vesicles** form most of the cluster and are tightly crosslinked, possibly by **synapsin**. The **recycling pool vesicles** are not as heavily crosslinked, so are more mobile. They might be able to diffuse to the active zone (arrows, left). Alternatively (right), they might have access to cytoskeletal elements (for example, actin118) that direct them towards the active zone.



Rizzoli & Betz, 2005
NATURE REVIEWS **NEUROSCI**
doi:10.1038/nrn1583

Synapses can be «presynaptically silent»

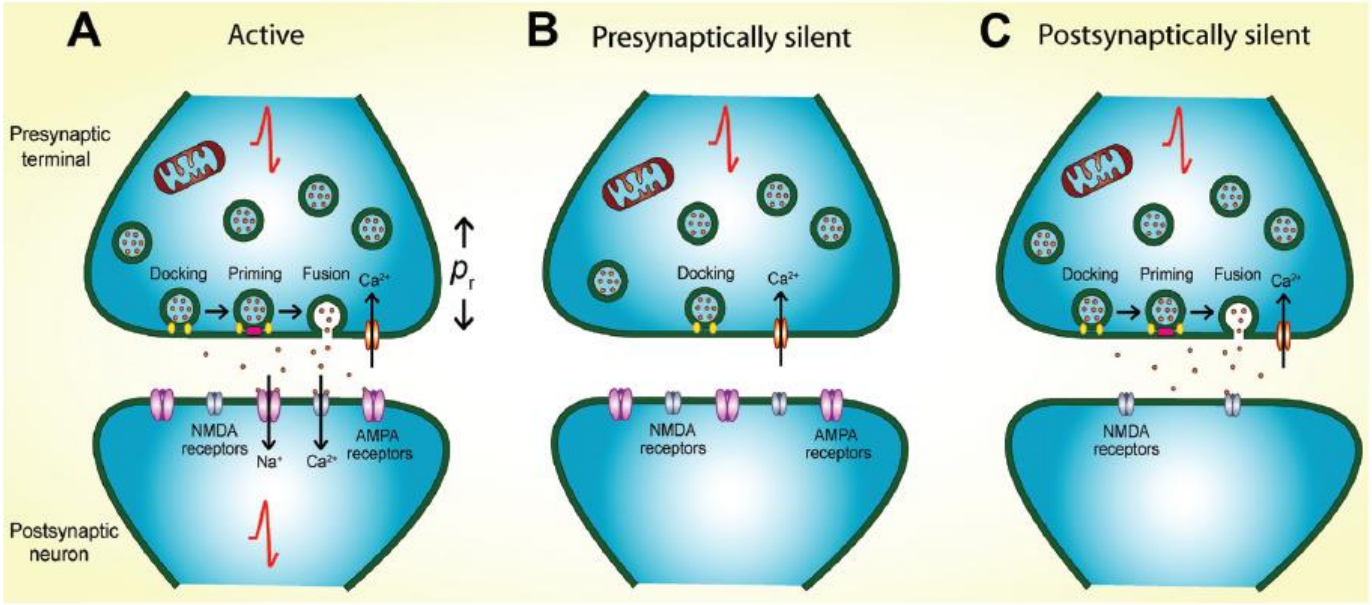
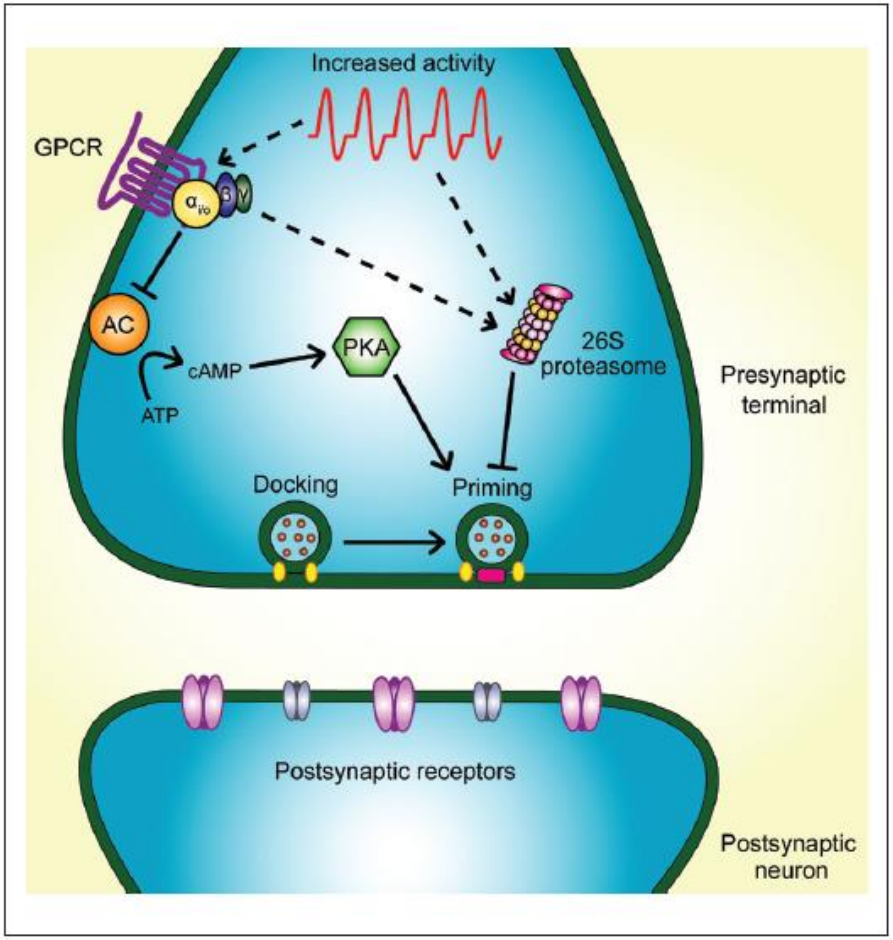


Figure 1. Categories of silent synapses. (A) Active synapses consist of presynaptic terminals with functional vesicle docking, priming, and release upon calcium influx, all powered primarily by mitochondrial ATP production. The probability of vesicle release (p_r) is modulated without altering the qualitative release competence of the terminal. Neurotransmitter released from active presynaptic terminals binds to postsynaptic receptors and causes a postsynaptic response. At glutamate synapses, for example, glutamate released via presynaptic vesicle fusion will bind to AMPA receptors, allowing net cation influx that directly depolarizes the target cell and relieves voltage-dependent magnesium block of NMDA receptors (not depicted). Depolarizing effects of activated AMPA and NMDA receptors contribute to action potential generation. (B) In presynaptically silent synapses, vesicle docking is intact, but priming and fusion are impaired, even with strong depolarization and calcium influx that overcome low vesicle release probability. Without transmitter release, there is no postsynaptic response. (C) Postsynaptically silent synapses maintain active presynaptic terminals, but the postsynaptic membrane is missing receptors necessary to generate a response. At glutamate synapses, AMPA receptors are absent, leaving NMDA receptors unable to overcome voltage-dependent block.

Crawford & Mennerick, 2012, The Neuroscientist
DOI: 10.1177/1073858411418525

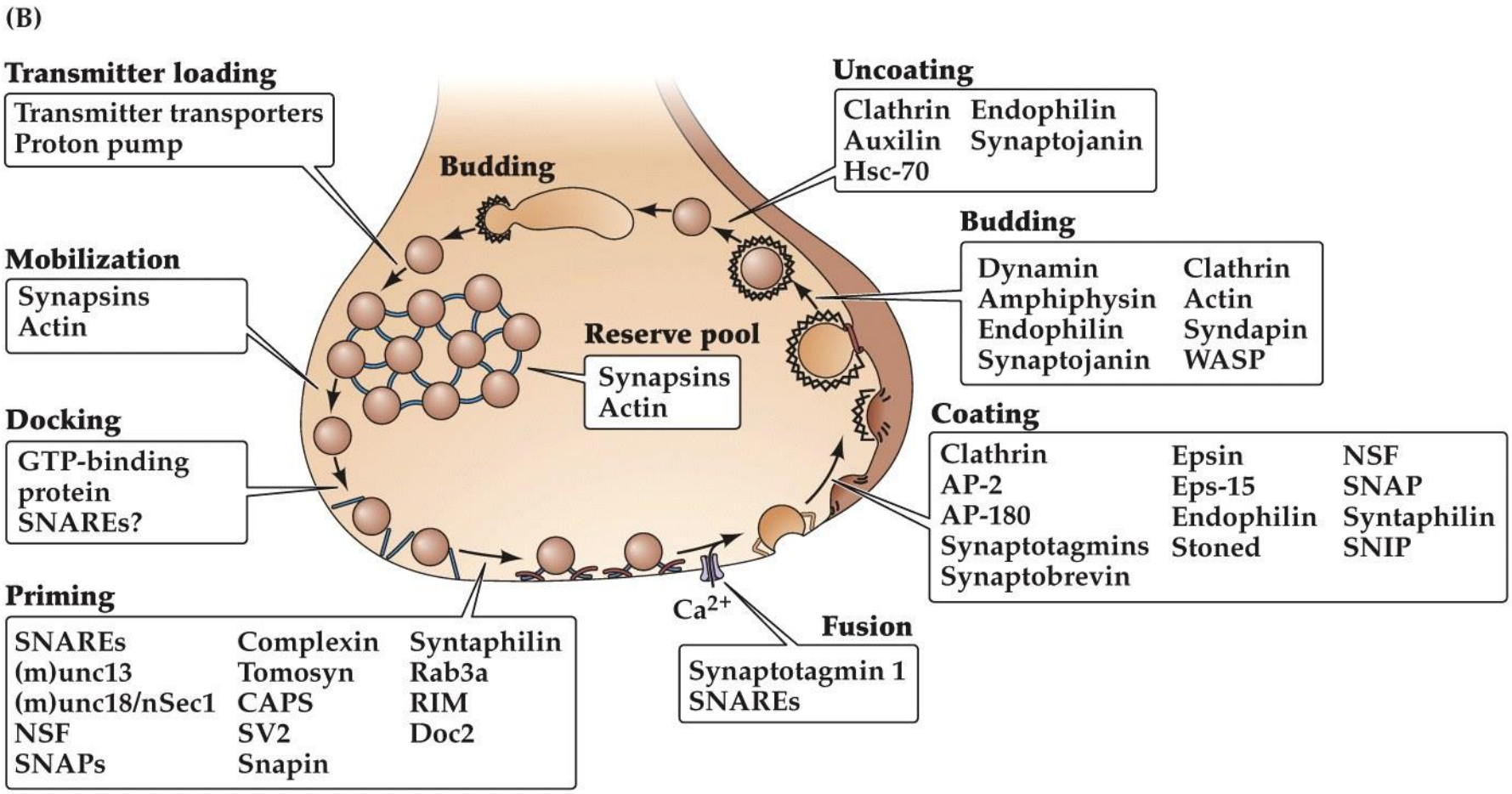
Signaling cascades participating in presynaptic dormancy induction

Figure 3. Signaling cascades participating in presynaptic dormancy induction. Prolonged strong depolarization or increased action potential firing induces presynaptic dormancy in glutamatergic neurons through activation of inhibitory G proteins and through activation of the ubiquitin-proteasome system. Depolarization increases proteasome activity through unknown mechanisms. Both depolarization- and G protein–coupled receptor (GPCR) agonist–induced silencing require proteasome activity. Dormancy is also induced via reduced cAMP signaling, so inhibitory actions of the Gα subunit on adenylyl cyclase (AC) likely reduce cAMP and protein kinase A (PKA) signaling during silencing induction. PKA phosphorylates presynaptic priming proteins like Rim1, a modification that may render Rim1 resistant to proteasome degradation; therefore, less Rim1 phosphorylation is expected after depolarization. Increased proteasome activity, combined with a vulnerable presynaptic protein population, may then lead to priming protein degradation. This model provides a plausible mechanism for priming protein level reduction and dormancy induction by depolarization. Postsynaptic protein levels are unaltered by induction of presynaptic dormancy.



Crawford & Mennerick, 2012
The Neuroscientist
DOI: 10.1177/1073858411418525

Presynaptic proteins and their roles in synaptic vesicle cycling

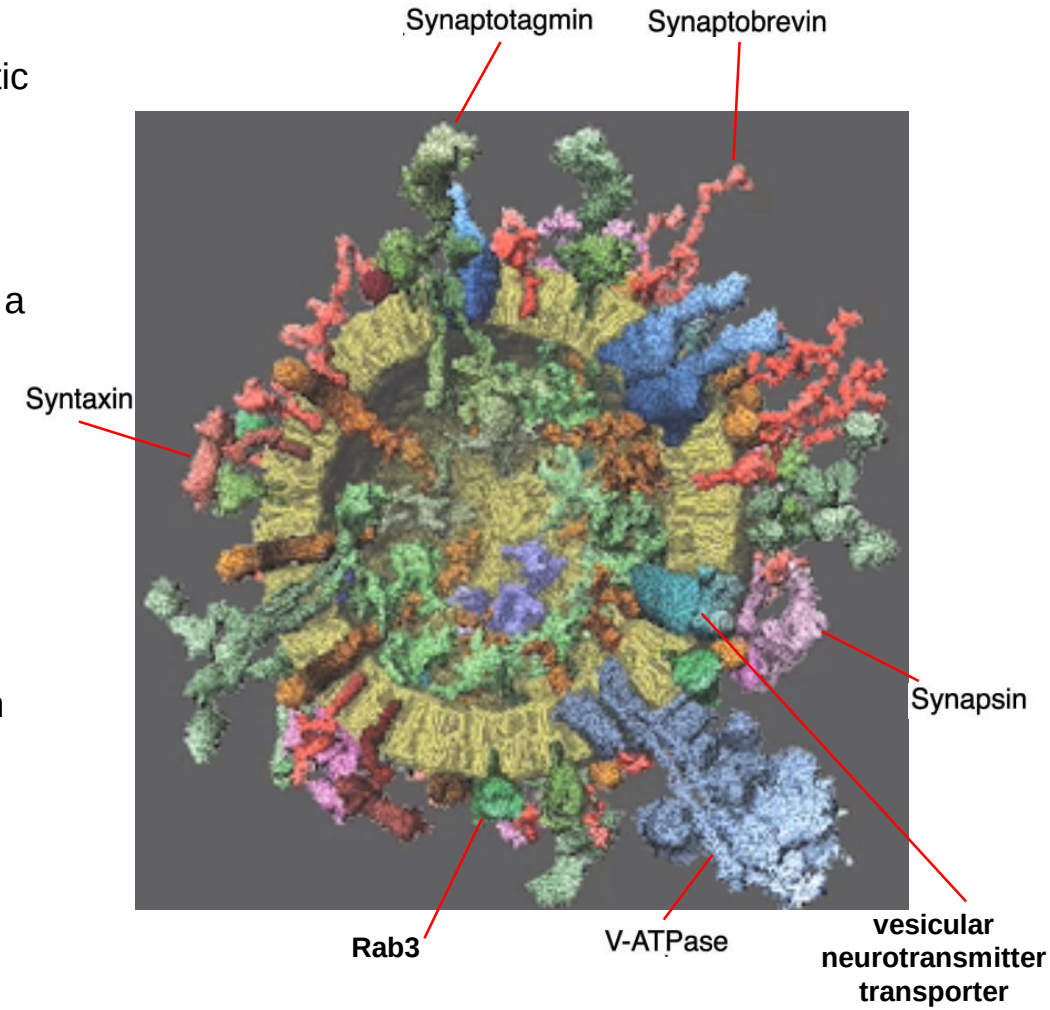


NEUROSCIENCE 5e, Figure 5.13 (Part 2)

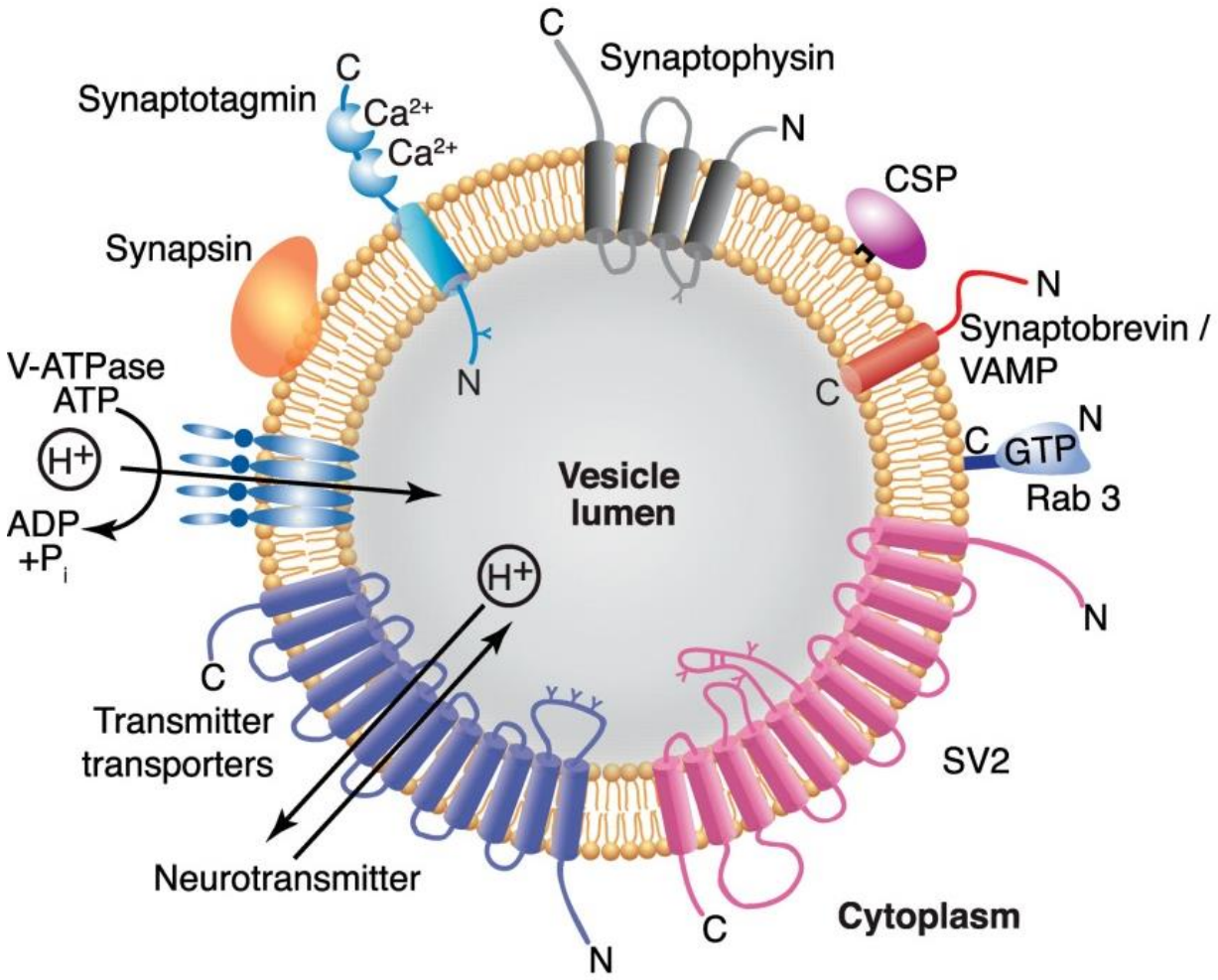
The molecular anatomy of a synaptic vesicle

This model represents a cutaway view of a synaptic vesicle, with the membrane lipids and proteins drawn to scale. Each synaptic vesicle membrane contains close to 50 different integral membrane protein molecules, which vary widely in their relative abundance. The most abundant protein is a SNARE protein, called v-SNARE **synaptobrevin**. This molecule participates in membrane fusion at the synaptic terminal, and there are about 70 copies of this protein per vesicle. By contrast, the vesicle contains only one to two copies of **V-ATPase**. V-ATPase uses energy from ATP hydrolysis to pump H^+ into the vesicle lumen. The resulting electrochemical gradient provides the energy to import neurotransmitter molecules, such as glutamate, into the vesicle.

This model was created, in part, from an electron tomogram of a real synaptic vesicle. Other data, including structural data of the synaptic vesicle's proteins, have been combined with the data from the tomogram to create the three-dimensional model. Note, only 70% of the membrane proteins estimated to be present in the membrane are depicted in the model.



Luo, Principles of Neurobiology, 2016



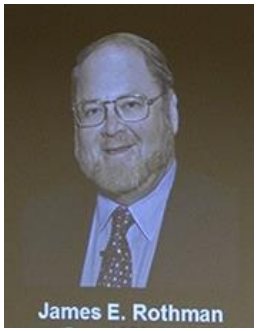
Schematic representation of the structure and topology of the major synaptic vesicle membrane proteins . N, amino terminal; C, carboxy terminal.

Byrne, From Molecules to Networks, 2014

Critical questions in neurotransmitter release:

- How do the synaptic vesicle and the plasma membrane fuse during transmitter release?
- How does calcium trigger synaptic vesicle fusion?
- How is calcium influx localized to release sites in order to enable the fast coupling of an action potential to transmitter release?

The mechanism of synaptic vesicle exocytosis was co-opted from general vesicle trafficking common to all eukariotes



Discovery of SNARE proteins in membrane fusion

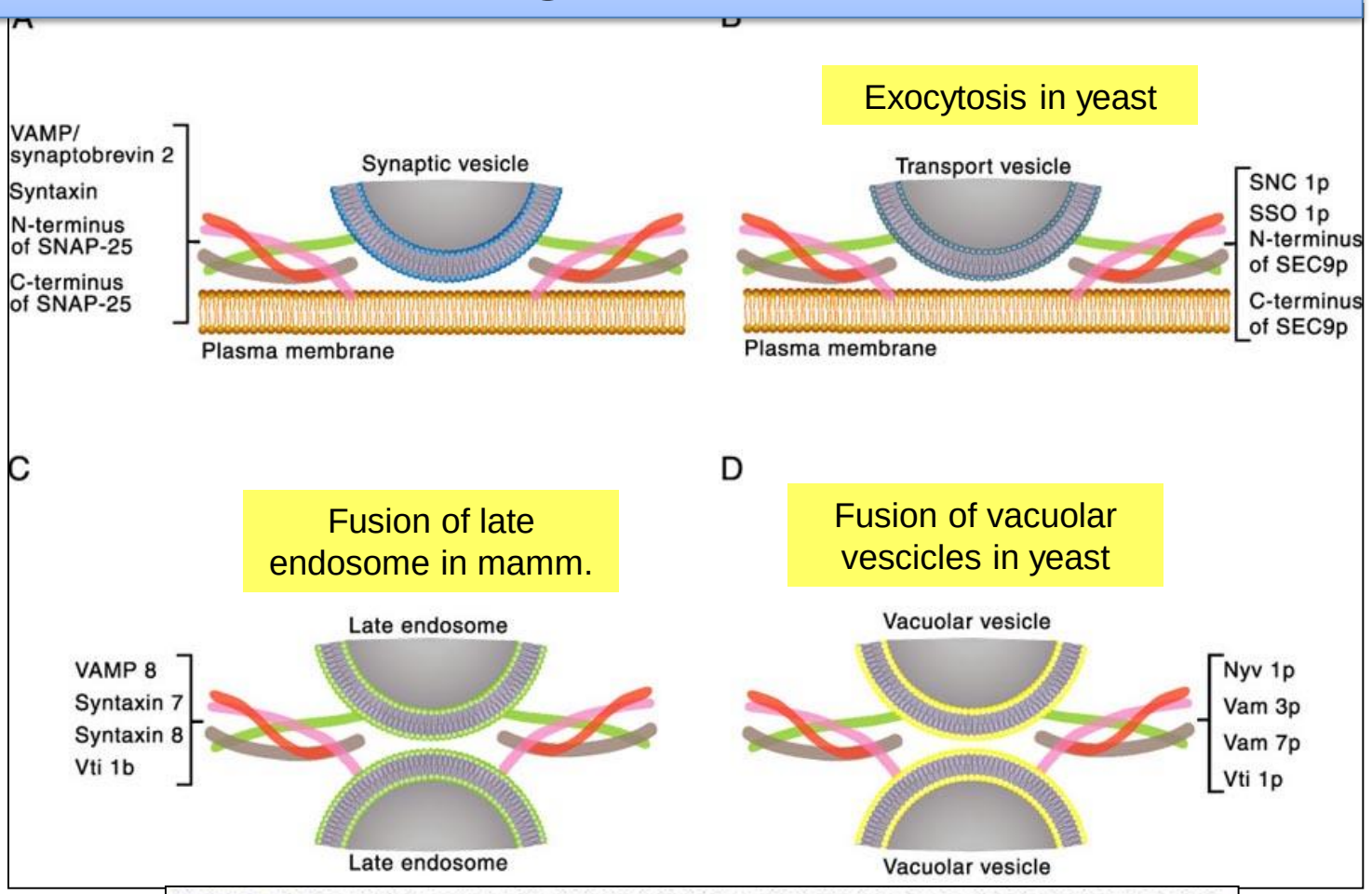


FIGURE 7 Neurotransmitter release shares a core mechanism with many membrane fusion events within eukaryotic cells. The fusion of synaptic vesicles (A) is driven by a particular complex of four coiled-coil domains contributed by three different proteins. Exocytosis in yeast (B), the fusion of late endosomes in mammalian cells (C), and the fusion of vacuolar vesicles in yeast (D) exemplify the closely related four-stranded coiled–coil complexes required to drive fusion in other membrane-trafficking steps.

Squire, Fundamental Neuroscience, 2013

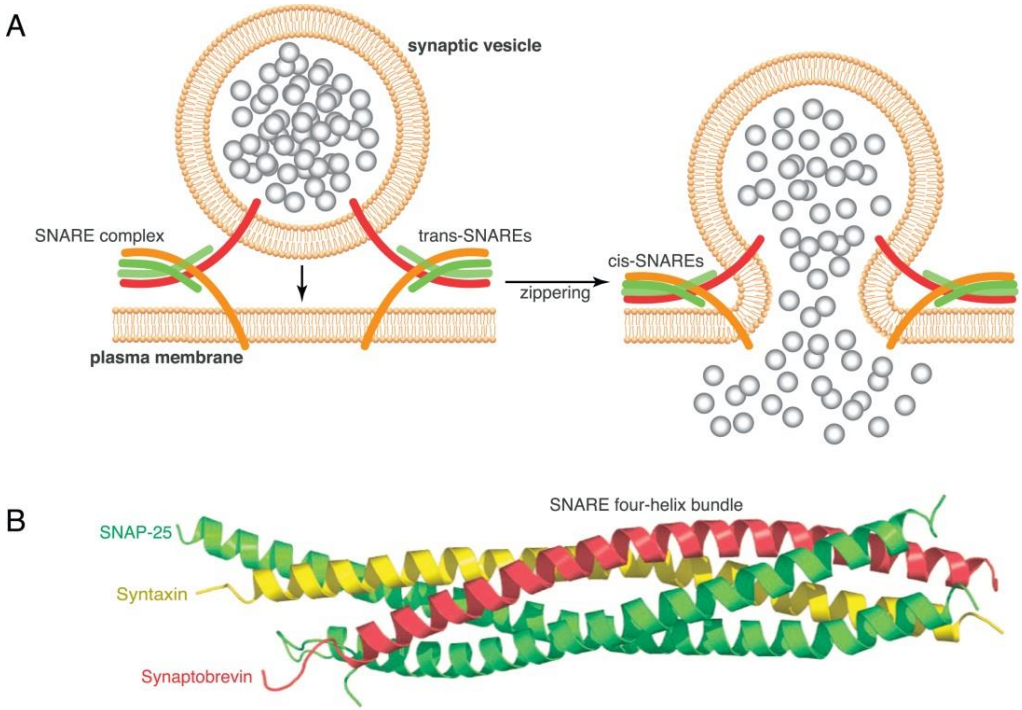


Figure 15.6 The mechanism of membrane fusion.
(A) Fusion of synaptic vesicles is driven by a *trans*-SNARE complex of four coiled-coil domains contributed by three different proteins located on the vesicular and the target membrane. Zippering of this complex from the N- to the C-terminus forces the two membranes together for fusion. Once fused, the SNARE complex is in a *cis* configuration. Neurotransmitter release shares this core mechanism with membrane fusion events within eukaryotic cells. (B) Structural ribbon rendition of a tightly assembled SNARE complex. The four-helix bundle consists of one SNARE motif from synaptobrevin and synataxin, while SNAP-25 contributes two SNARE motifs.
Adapted from Rizo and Südhof (2012); structure originally published in Sutton et al. (1998).

Byrne, From Molecules to Networks, 2014

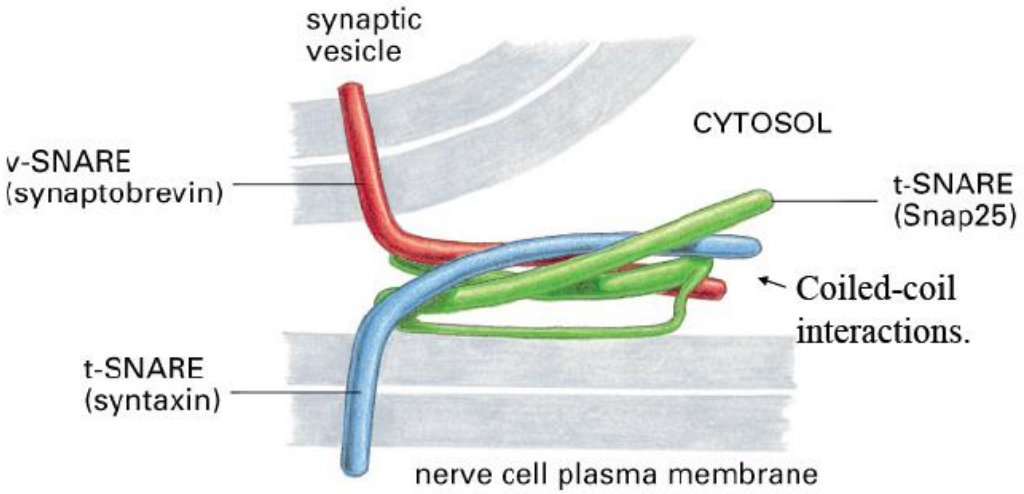
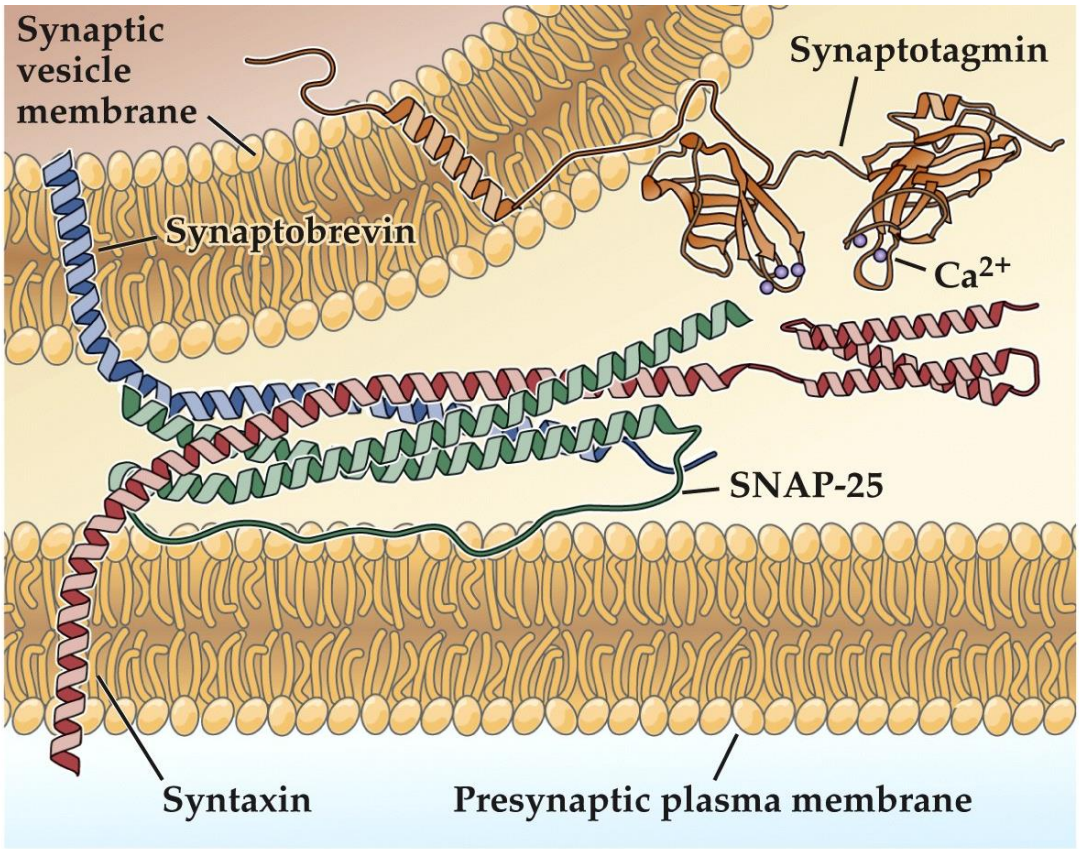


Figure 13–12. Molecular Biology of the Cell, 4th Edition.

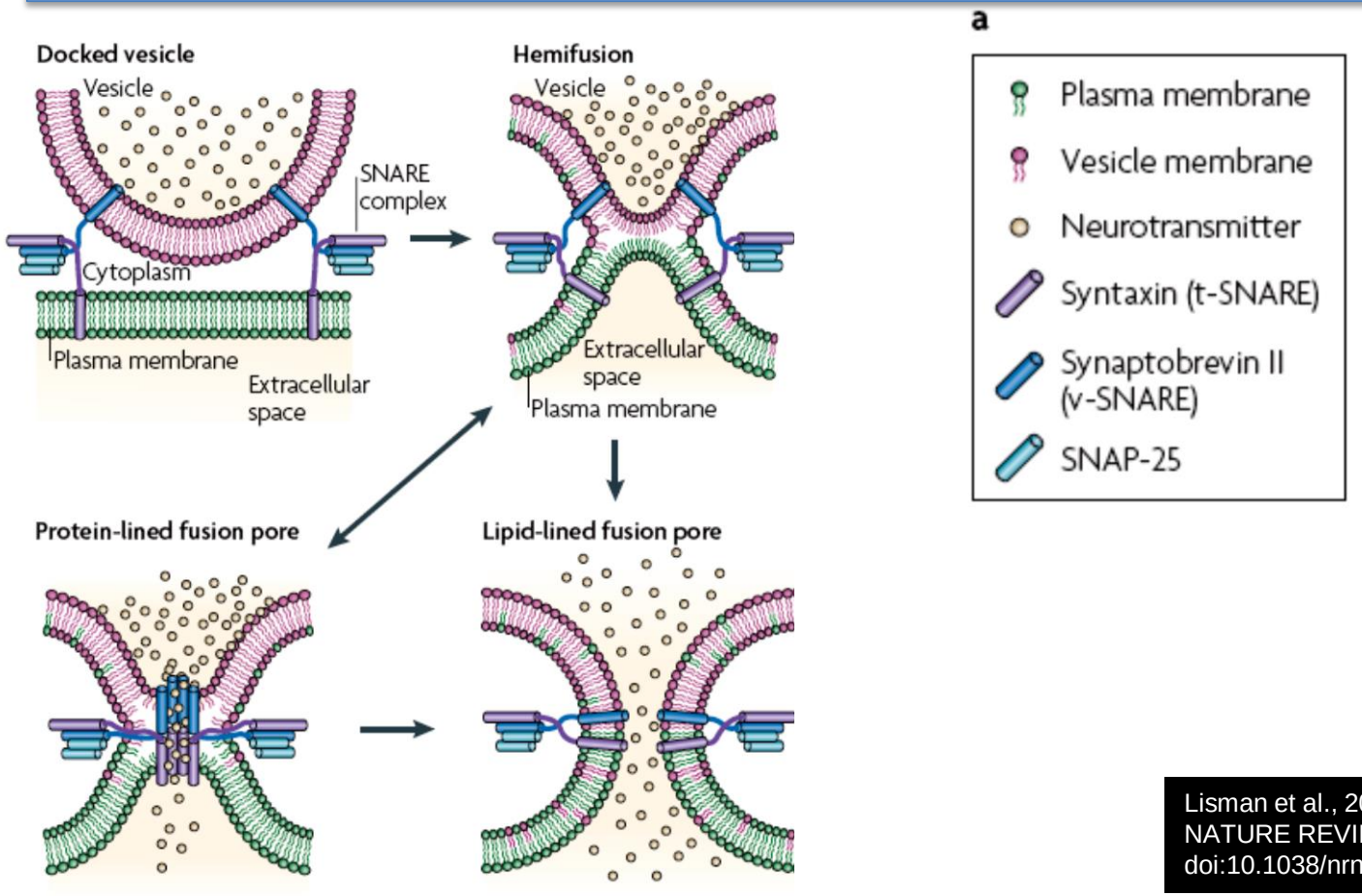
Structure of the SNARE complex

SNARE = SNAP receptors



NEUROSCIENCE 5e, Figure 5.14 (Part 1)

Vesicle fusion and potential mechanisms of formation of the fusion pore



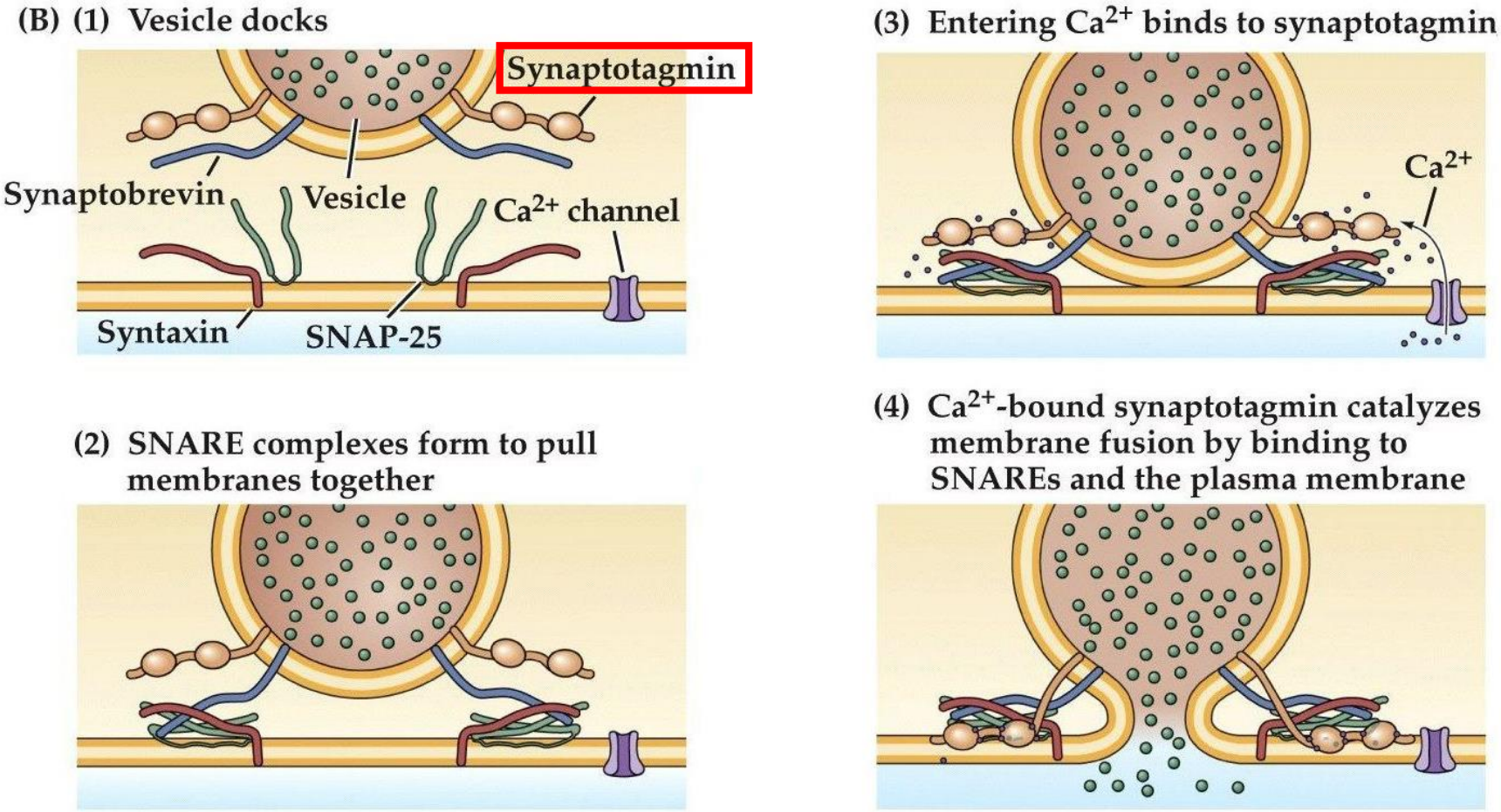
Lisman et al., 2007
NATURE REVIEWS NEUROSCI
doi:10.1038/nrn2191

Figure 4 | **Vesicle fusion and fusion pores. a** | Two potential mechanisms of formation of the fusion pore between the synaptic vesicle (upper membrane; pink) and the plasma membrane (lower membrane; green). In the top left panel the vesicle is in the 'docked' state in which it is held near the plasma membrane by the SNARE complex. In the top right panel, the vesicle and plasma membrane have their distal leaflets in a hemifused state that is primed for release. During the release process, a protein-lined pore (lower left panel) is formed by two of the SNARE proteins, syntaxin and synaptobrevin. This step may be reversible, or may be followed by a transition to a lipid-lined pore (bottom right panel). An alternative model is that fusion pore opening always involves the formation of a lipid-lined pore. **b** | Kiss-and-run

Critical questions in neurotransmitter release

- How do the synaptic vesicle and the plasma membrane fuse during transmitter release?
- How does calcium trigger synaptic vesicle fusion?
- How is calcium influx localized to release sites in order to enable the fast coupling of an action potential to transmitter release?

Synaptotagmin is the **Ca^{++} sensor** that triggers vesicle fusion



NEUROSCIENCE 5e, Figure 5.14 (Part 2)

In the absence of Ca++ synaptotagmin may serve as a brake for release. Ca++ removes the brake

Electrophysiological analyses of Syt1 knockout mice revealed that Syt1 is required for all fast synchronous synaptic fusion in forebrain neurons but is dispensable for other types of fusion

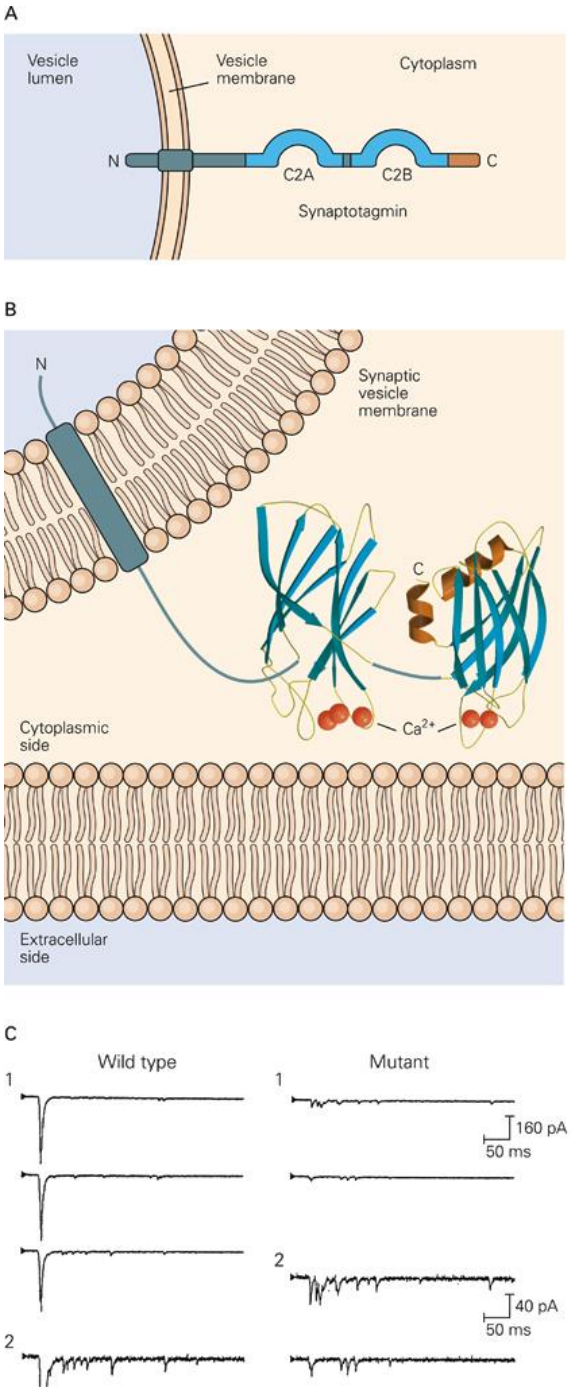


Figure 12–13 The structure of synaptotagmin and genetic evidence for its role in transmitter release.

A. Synaptotagmin is an integral membrane protein of synaptic vesicles. The short N-terminal tail, which resides in the vesicle lumen, is followed by a single hydrophobic domain that spans the vesicle membrane and a long cytoplasmic tail that contains two C2 domains (C2A and C2B) near the C terminus. The C2 domains are calcium- and phospholipid-binding motifs found in many other proteins, including PKC.

B. The X-ray crystal structure of the two C2 domains is shown here. The C2A domain binds three Ca^{2+} ions and the C2B domain two Ca^{2+} ions. The structures of the other regions of synaptotagmin have not yet been determined and are drawn here for illustrative purposes. The membrane and structures are drawn to scale.

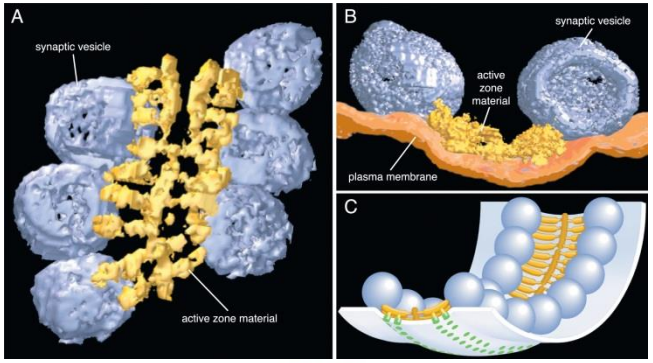
C. Fast calcium-triggered transmitter release is absent in mutant mice lacking synaptotagmin. Recordings show excitatory postsynaptic currents evoked in vitro by stimulation of cultured hippocampal neurons from wild-type mice or mutant mice in which synaptotagmin has been deleted by homologous recombination (1). Neurons from wild-type mice show large, fast excitatory postsynaptic currents evoked by three successive presynaptic action potentials, reflecting the fact that synaptic transmission is dominated by the rapid synchronous release of transmitter from a large number of synaptic vesicles. In the bottom trace, where the synaptic current is shown at a highly expanded current scale (2), one can see that a small, prolonged phase of asynchronous release of transmitter follows the fast phase of synchronous release. During this slow phase there is a prolonged increase in frequency of individual quantal responses. In neurons from a mutant mouse a presynaptic action potential triggers only the slow asynchronous phase of release; the rapid synchronous phase has been abolished.

Kandel, Principles of Neural Sciences, 2013

Critical questions in neurotransmitter release

- How do the synaptic vesicle and the plasma membrane fuse during transmitter release?
- How does calcium trigger synaptic vesicle fusion?
- How is calcium influx localized to release sites in order to enable the fast coupling of an action potential to transmitter release?

What type of molecular structure links Ca++ channels to membrane docked synaptic vesicles?



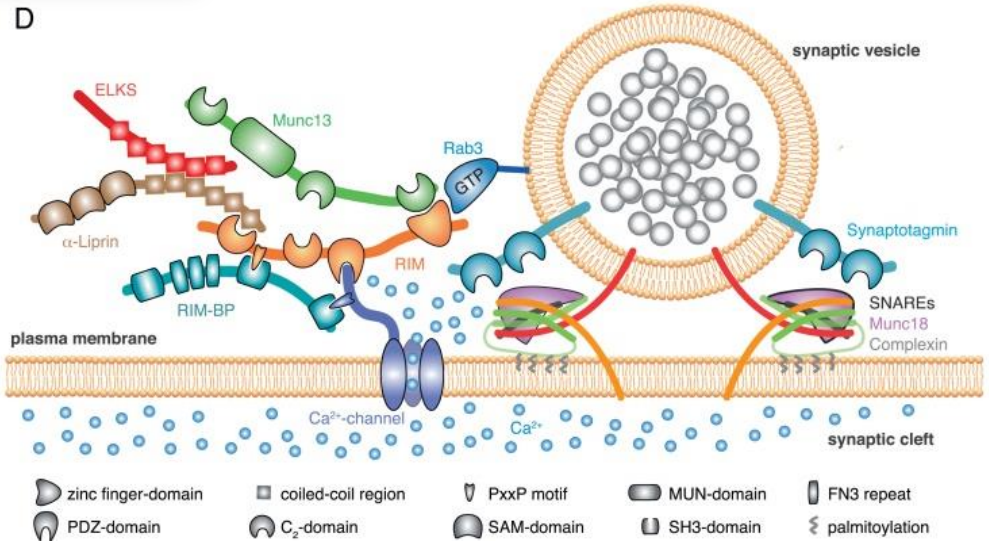
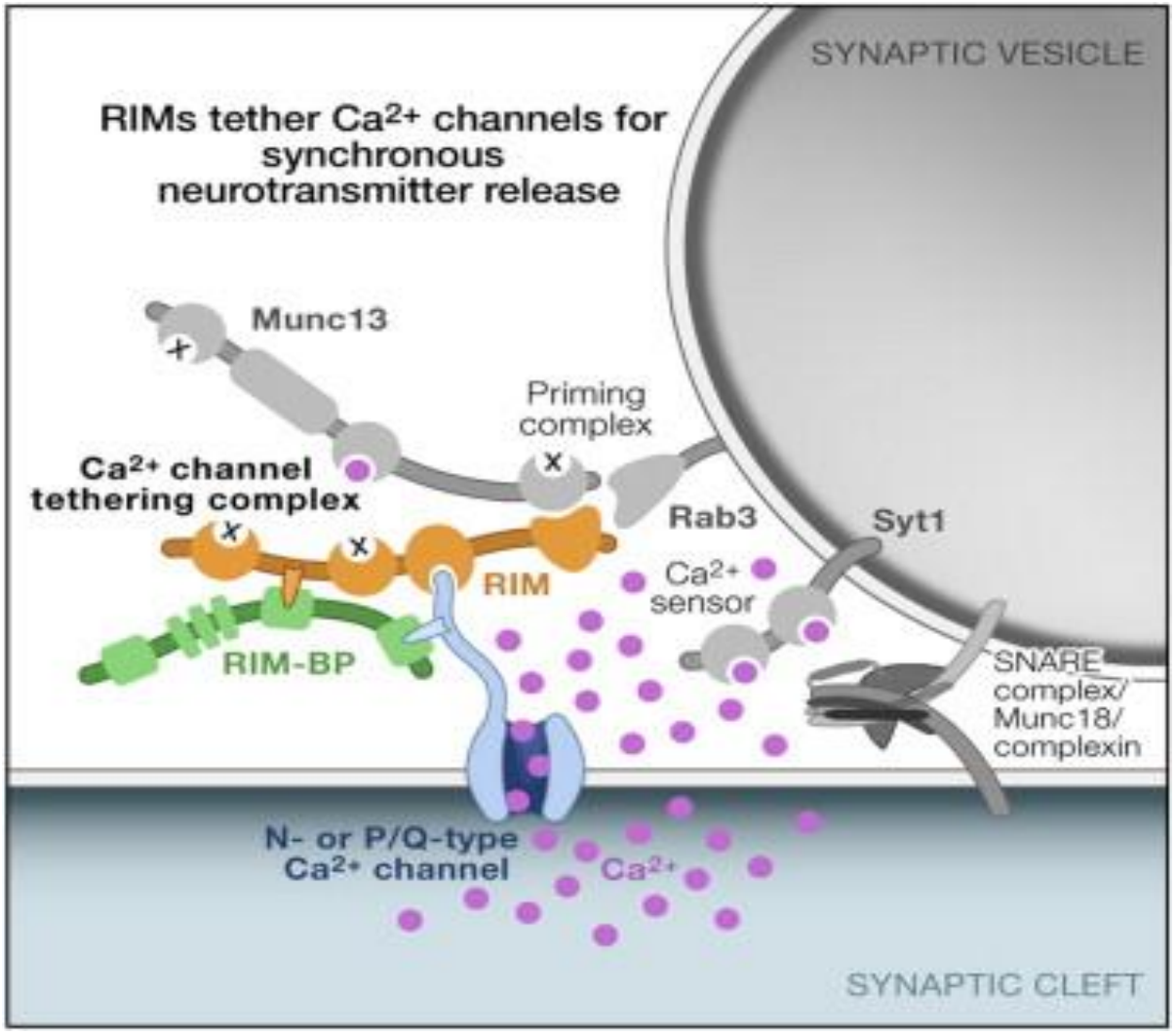


Figure 15.8 Models of the presynaptic active zone.
(A–C) Fine structure of the active zone at a neuromuscular junction. (A) Active zone (yellow) as revealed by electron tomography, viewed from the side of the plasma membrane with adjacent synaptic vesicles (blue). Active zone protein material extends from the vesicles and connects to a central beam in an organized fashion. (B) Transverse view of active zone material and docked synaptic vesicles adjacent to the plasma membrane (orange). (C) Schematic rendering of an active zone based on the tomographic analysis. An ordered structure aligns the vesicles and connects them to the plasma membrane and to one another. (D) Protein interactions in the active zone of a central nervous synapse. Several families of large multidomain proteins form a dense network that connects to synaptic vesicles and tethers Ca^{2+} channels close by.
(A–C) Adapted with permission from Macmillan Publishers Ltd. (Harlow et al., 2001). (D) Adapted from Kaeser et al. (2011).

Molecular machinery mediating Ca^{2+}-triggered vesicle fusion



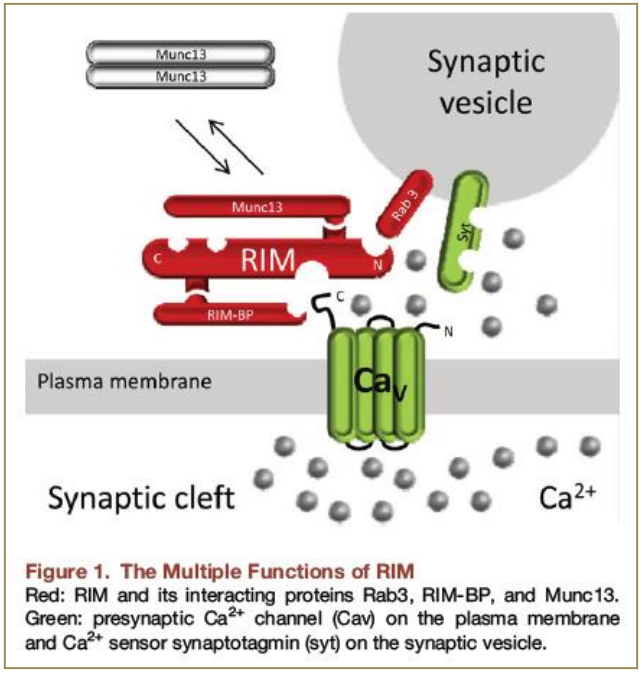
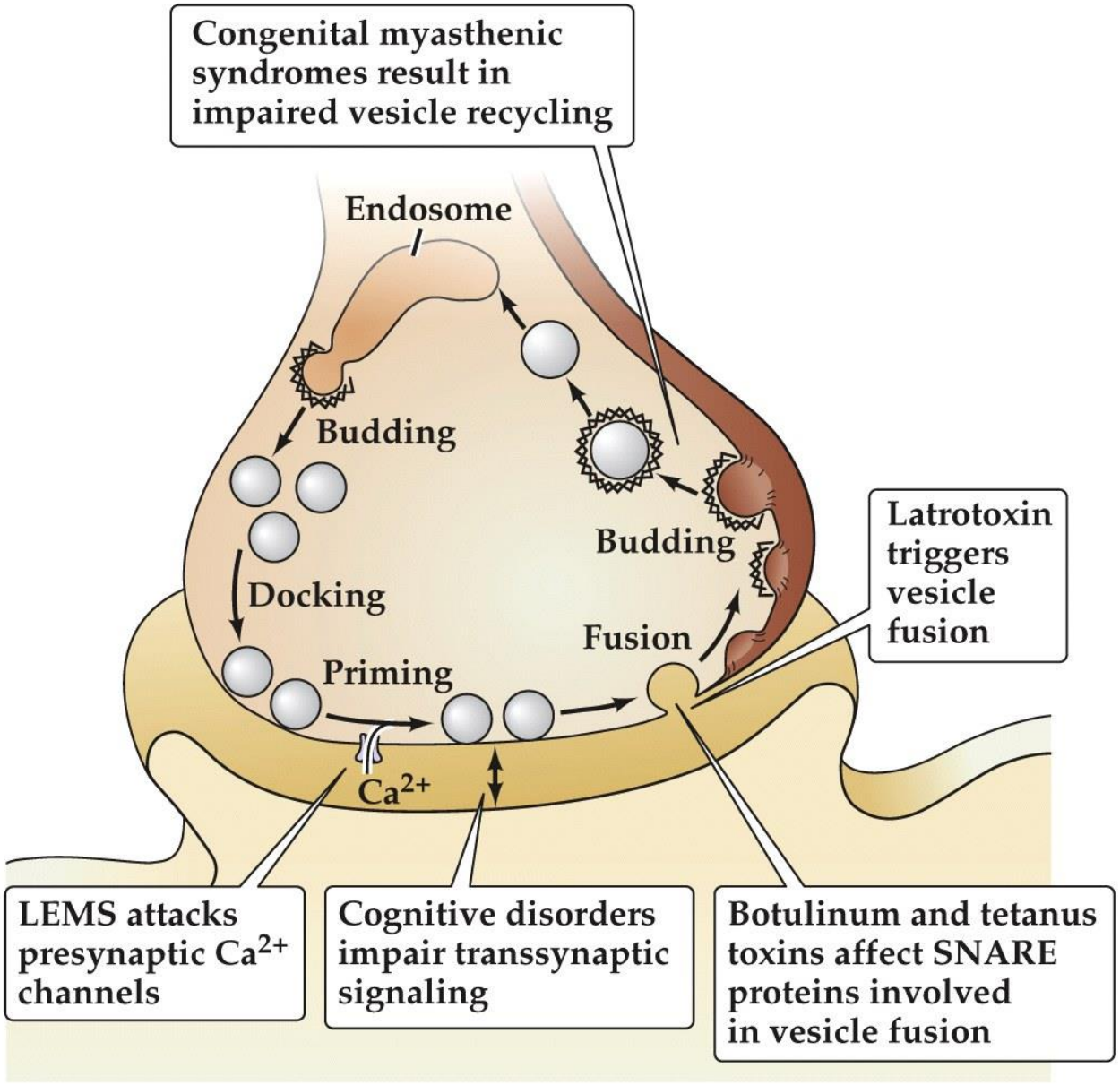


Figure 1. The Multiple Functions of RIM
Red: RIM and its interacting proteins Rab3, RIM-BP, and Munc13. Green: presynaptic Ca^{2+} channel (Cav) on the plasma membrane and Ca^{2+} sensor synaptotagmin (syt) on the synaptic vesicle.

At presynaptic active zones, Ca^{2+} channels bind to PDZ domains of RIM proteins ► Deletion of RIM proteins decreases presynaptic Ca^{2+} influx and vesicle priming ► **RIMs tether Ca^{2+} channels to presynaptic active zones for fast, synchronous release**

Kaeser et al, 2011
Cell 144:282-9

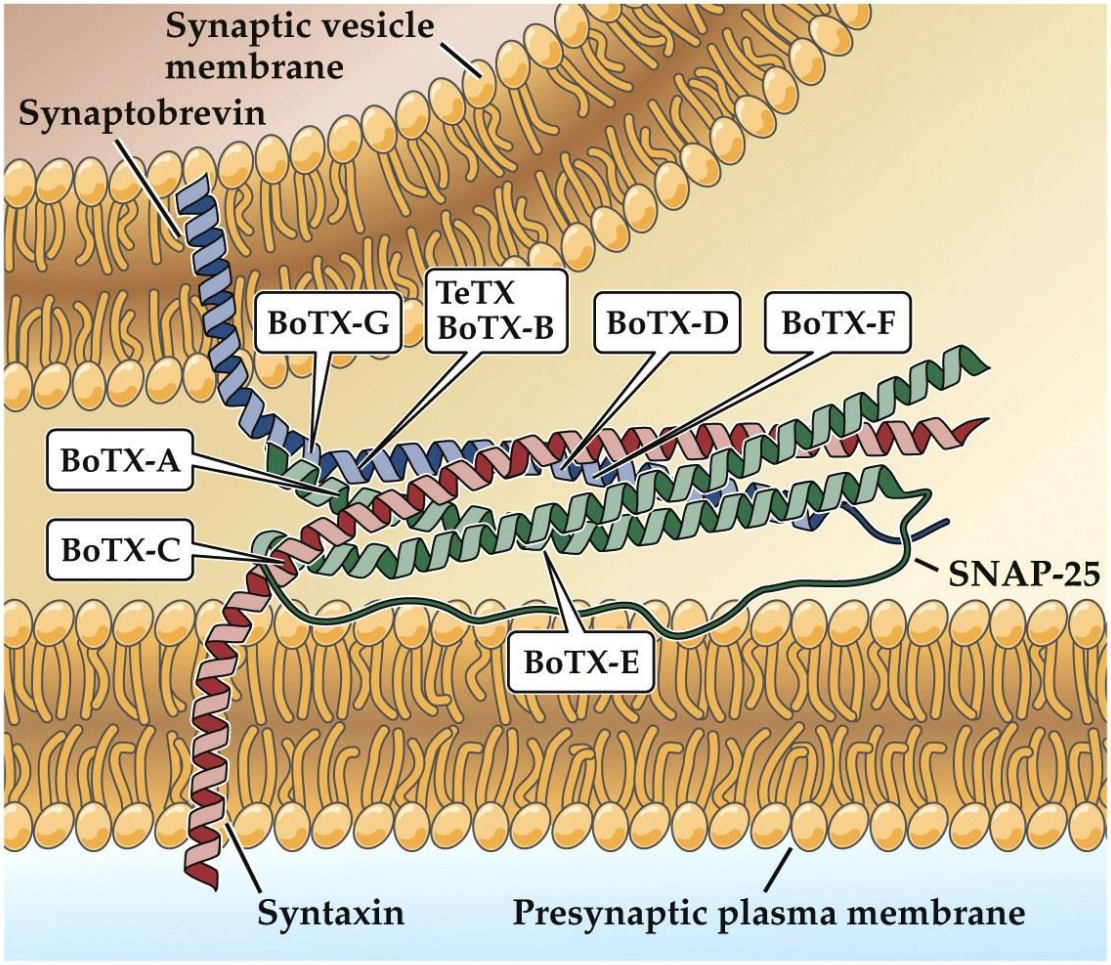
The presynaptic terminal is the target of numerous neurological deseases



LEMS = Lambert-Eaton myasthenic syndrome

NEUROSCIENCE 5e, Box 5B (Part 1)

Neurotoxins affecting synaptic vesicle exocytosis



NEUROSCIENCE 5e, **Box 5B (Part 2)**

FIGURE 6 SNARE proteins and the action of clostridial neurotoxins. The SNARE complex shown at the left brings the vesicle and plasma membranes into close proximity and likely represents one of the last steps in vesicle fusion. Vesicular VAMP, also called synaptobrevin, binds with syntaxin and SNAP-25 that are anchored to the plasma membrane. Tetanus toxin and the botulinum toxins, proteases that cleave specific SNARE proteins as shown, can block transmitter release.

Purves, Neuroscience, 2012