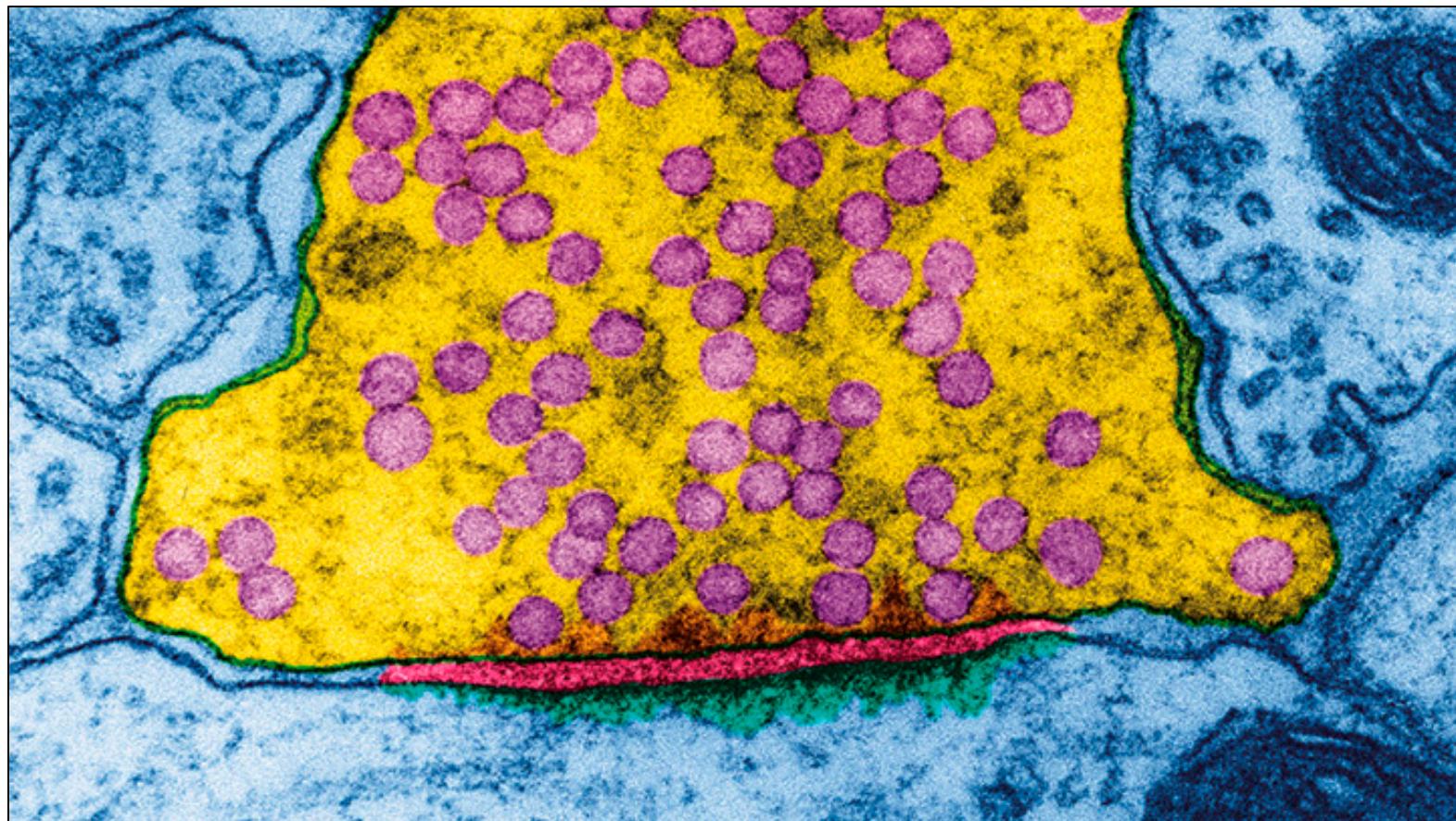
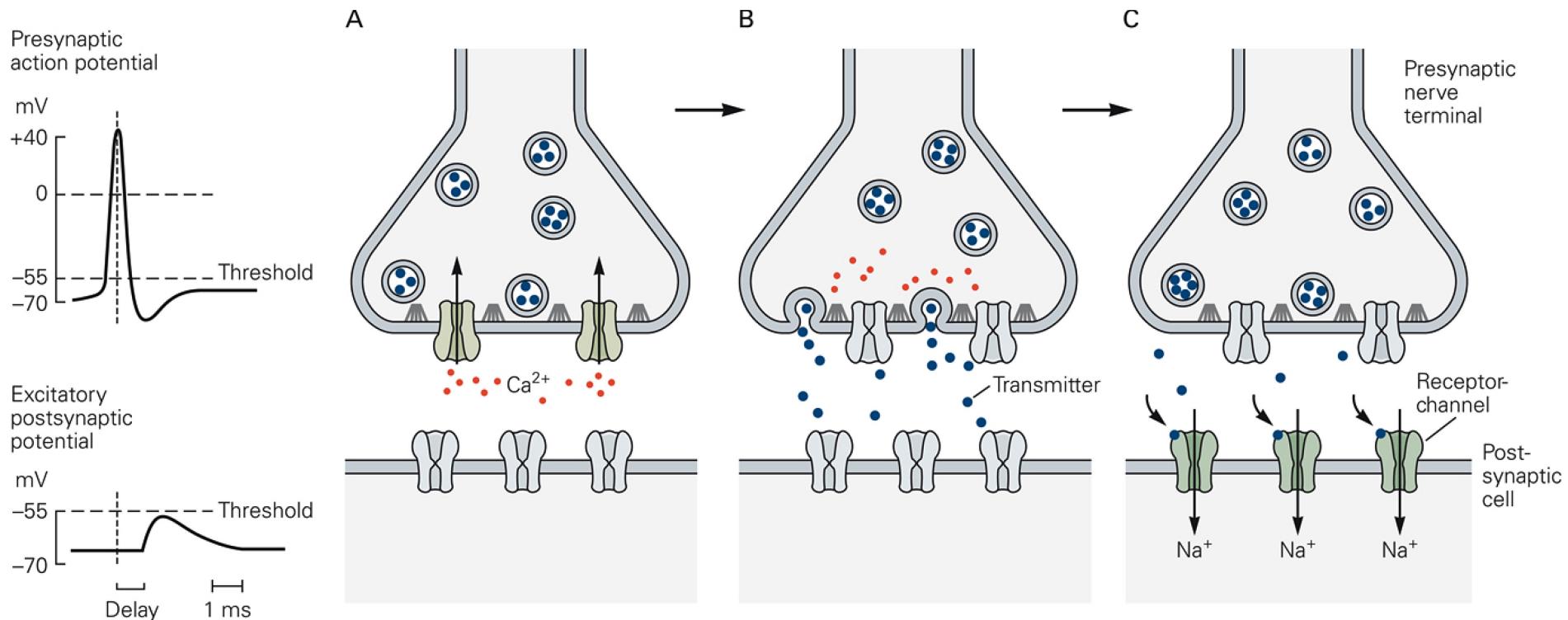


Chapter 15:

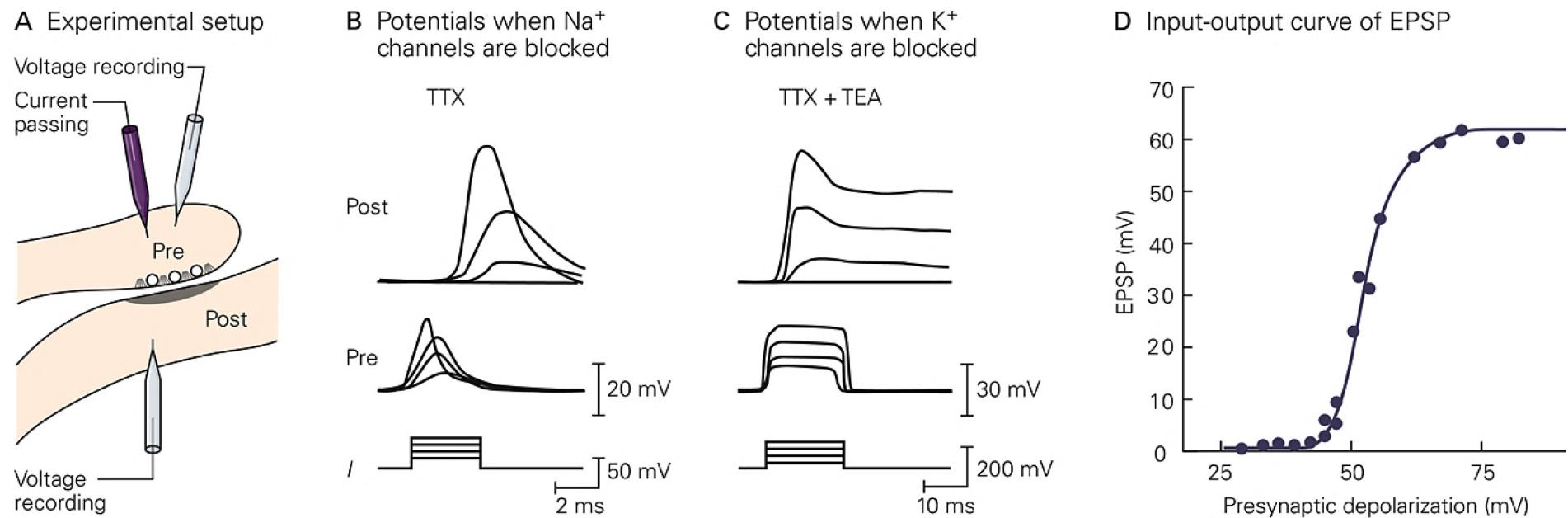
Transmitter Release



Basic Model of Transmitter Release



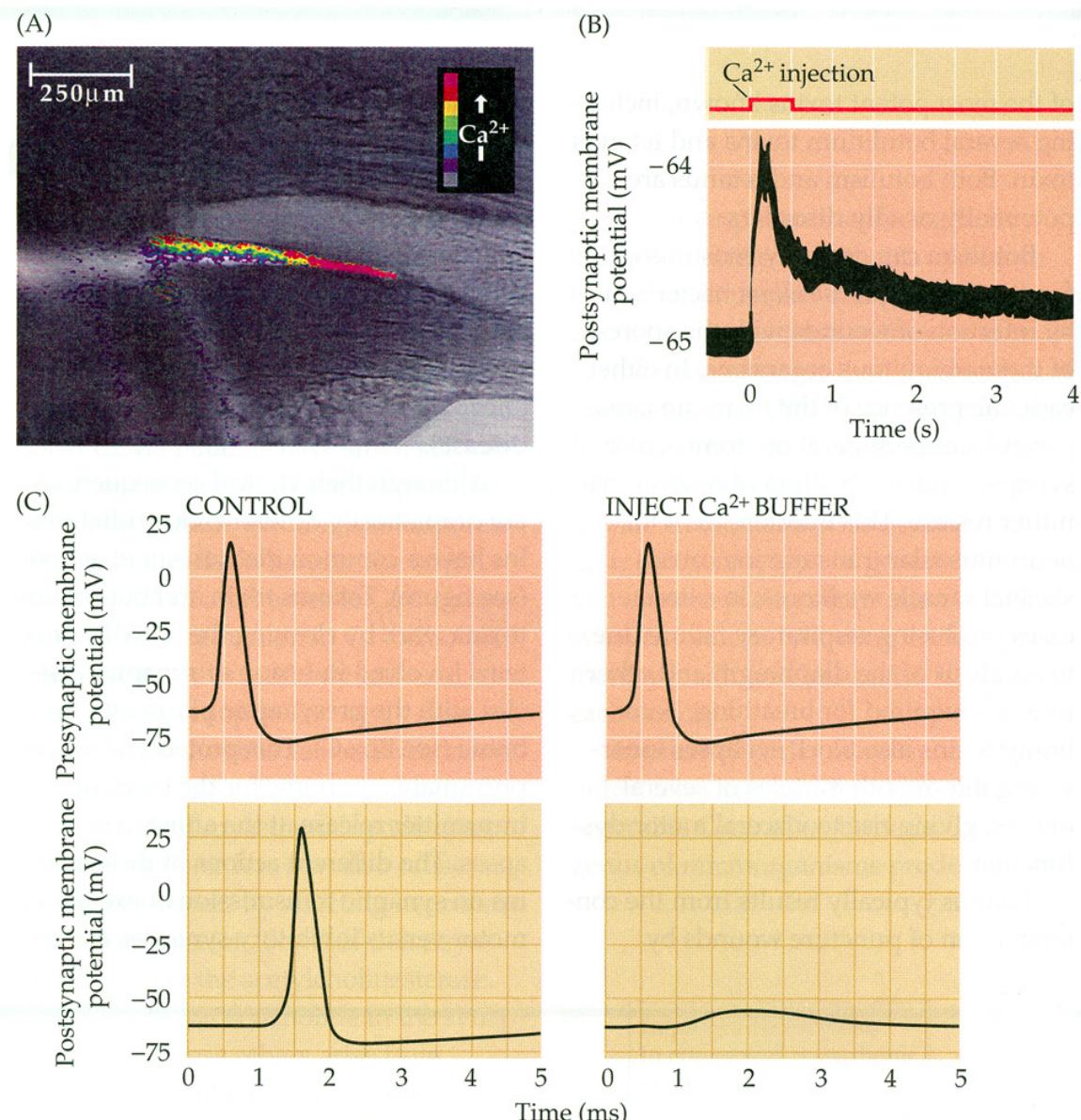
Transmitter Release is Stimulated by Presynaptic Depolarization



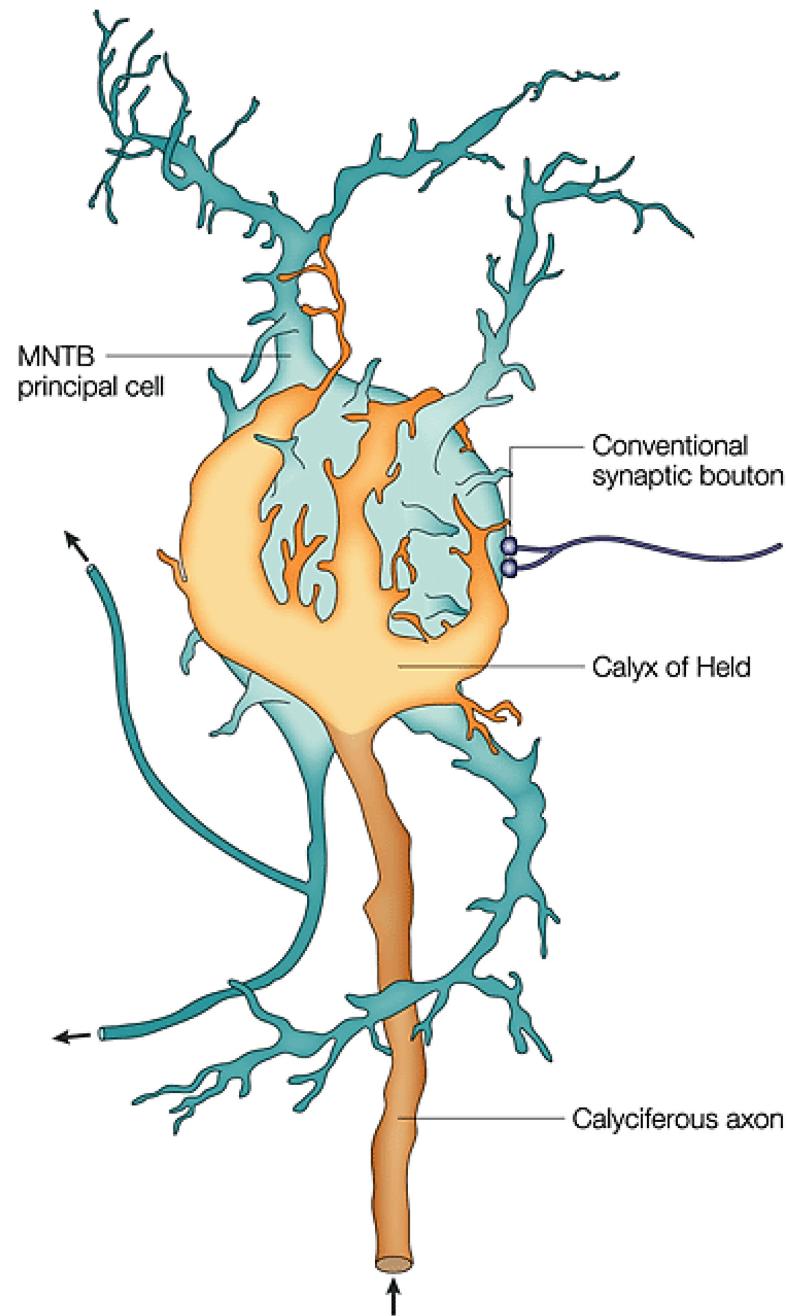
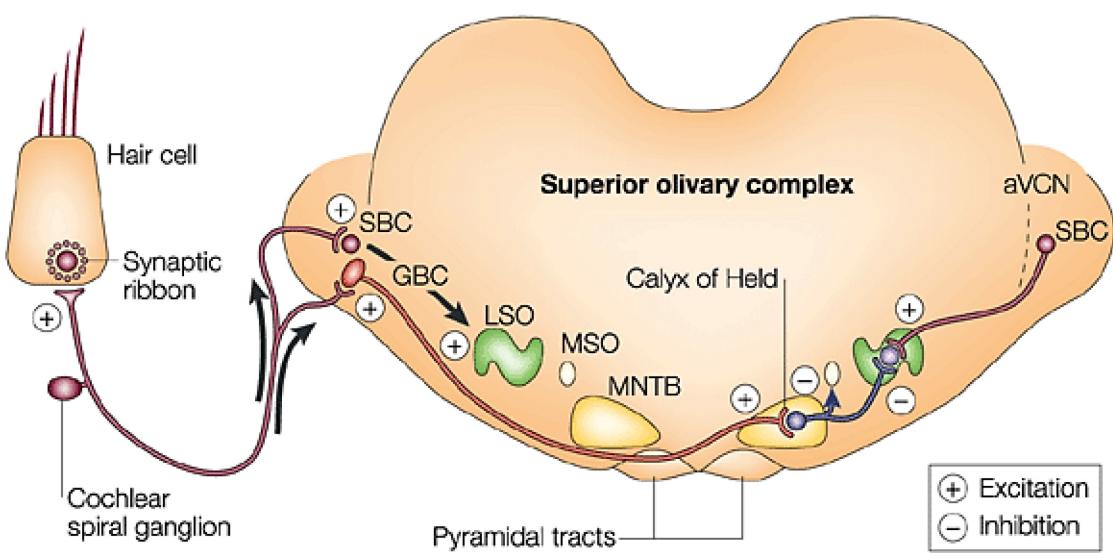
Ca^{2+} Influx Triggers Transmitter Release

Figure 5.11 Evidence that a rise in pre-synaptic Ca^{2+} concentration triggers transmitter release from presynaptic terminals. (A) Fluorescence microscopy measurements of presynaptic Ca^{2+} concentration at the squid giant synapse (see Figure 5.8A). A train of presynaptic action potentials causes a rise in Ca^{2+} concentration, as revealed by a dye (called fura-2) that fluoresces more strongly when the Ca^{2+} concentration increases. (B) Microinjection of Ca^{2+} into a squid giant presynaptic terminal triggers transmitter release, measured as a depolarization of the postsynaptic membrane potential. (C) Microinjection of BAPTA, a Ca^{2+} chelator, into a squid giant presynaptic terminal prevents transmitter release. (A from Smith et al., 1993; B after Miledi, 1971; C after Adler et al., 1991.)

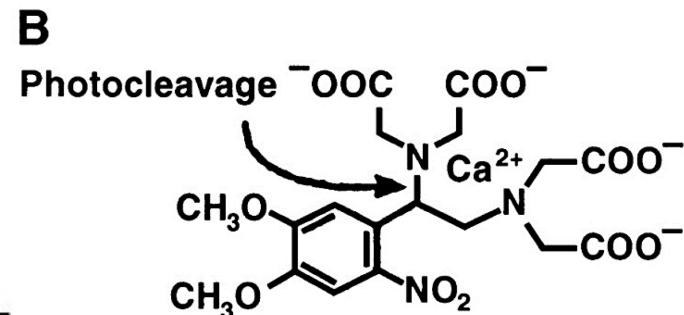
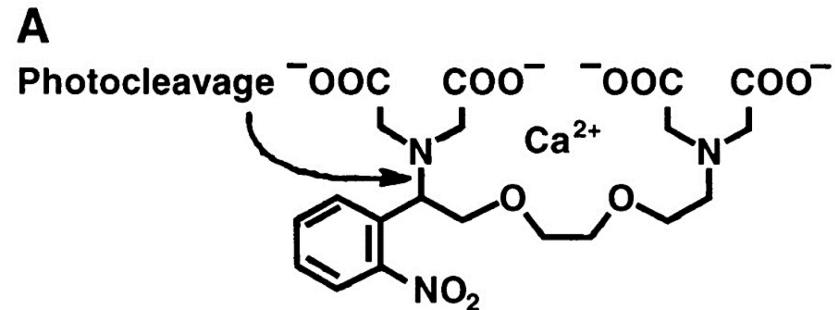
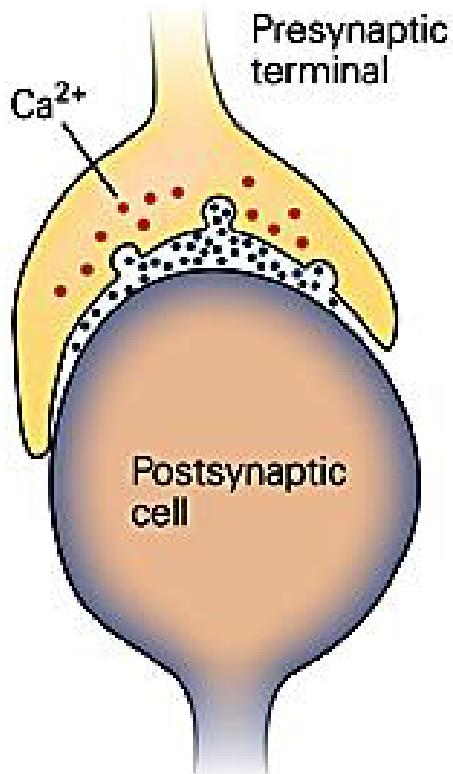
Figure 5.11, Purves



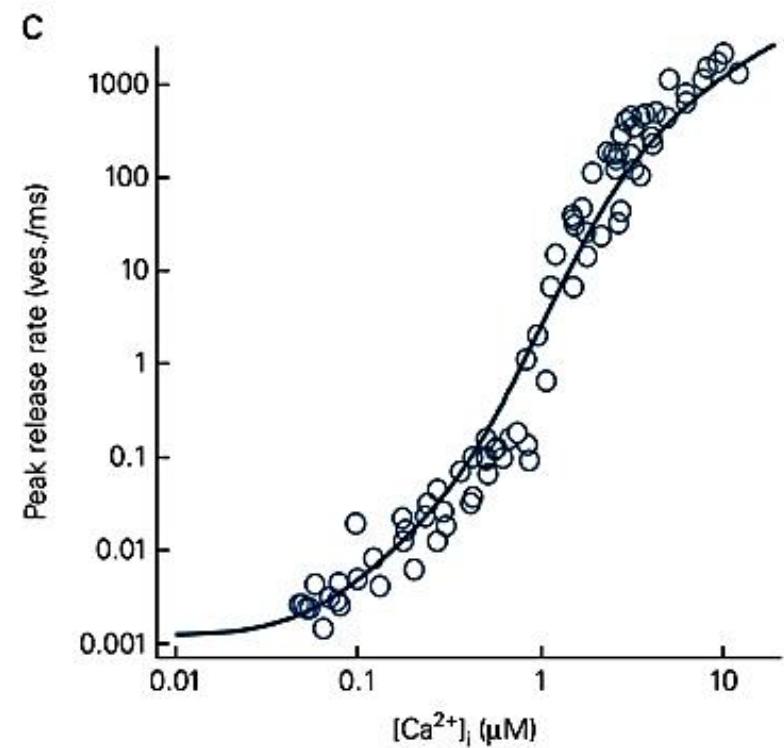
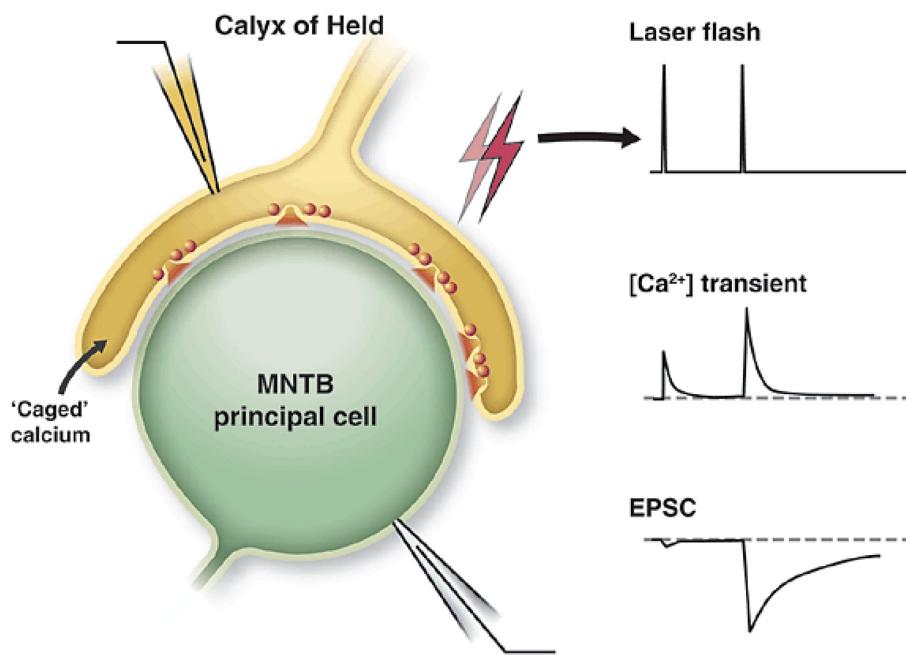
The Calyx of Held – a Special Synapse



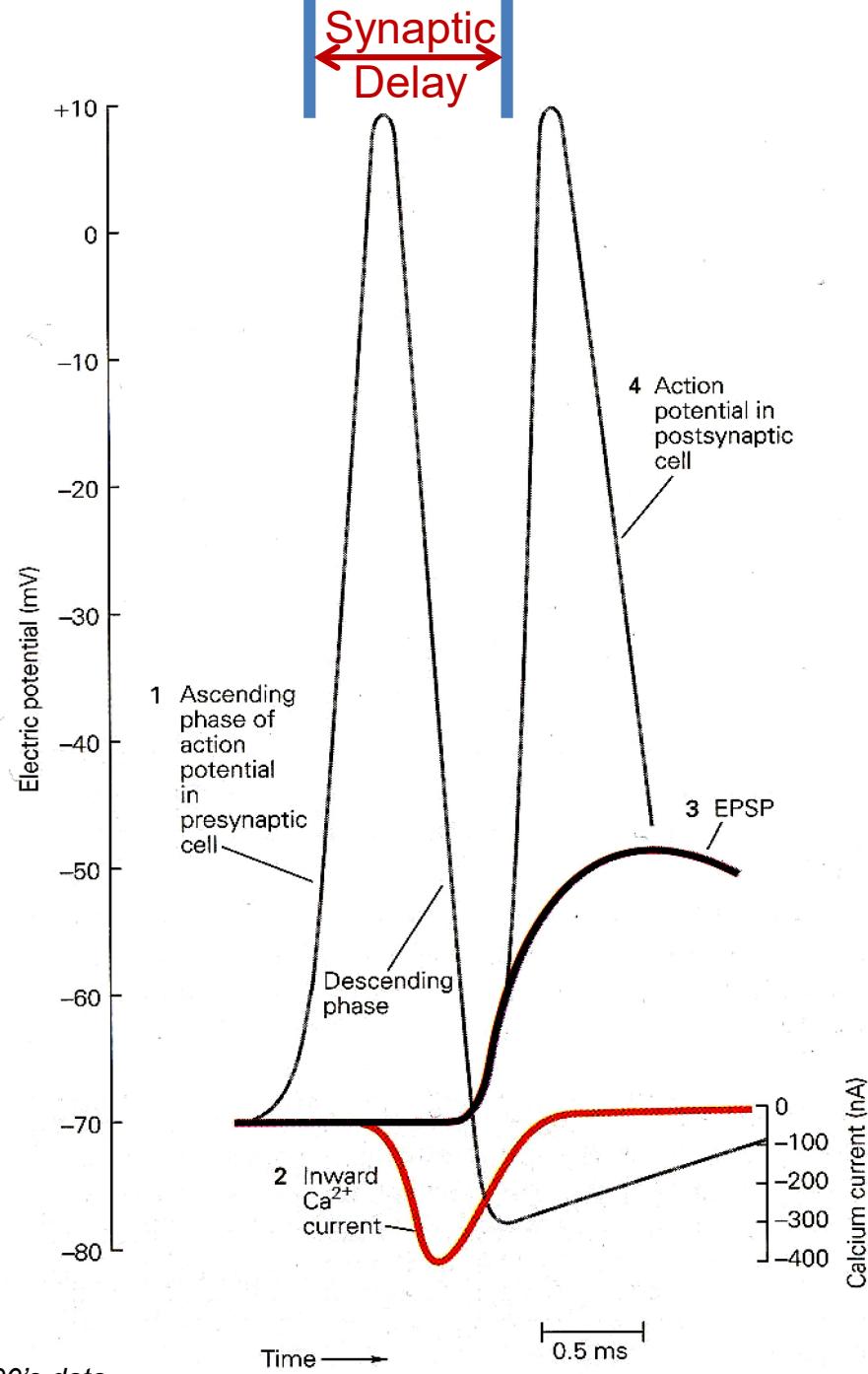
Simulating Calcium Influx with Caged Calcium



Presynaptic Ca^{2+} levels determine the strength of synaptic transmission



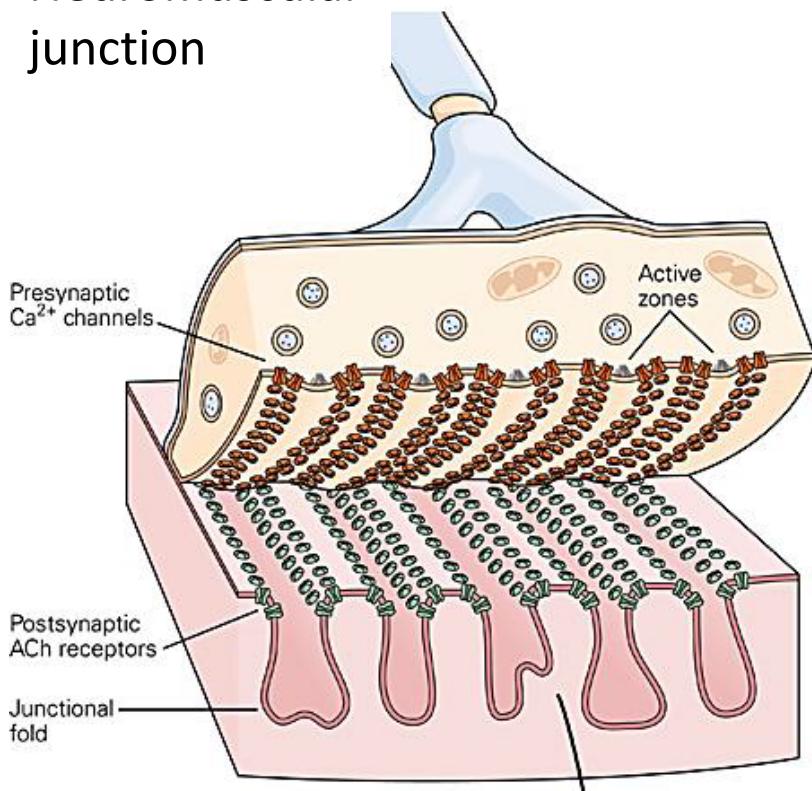
The timing of presynaptic Ca^{2+} influx determines the onset of synaptic transmission



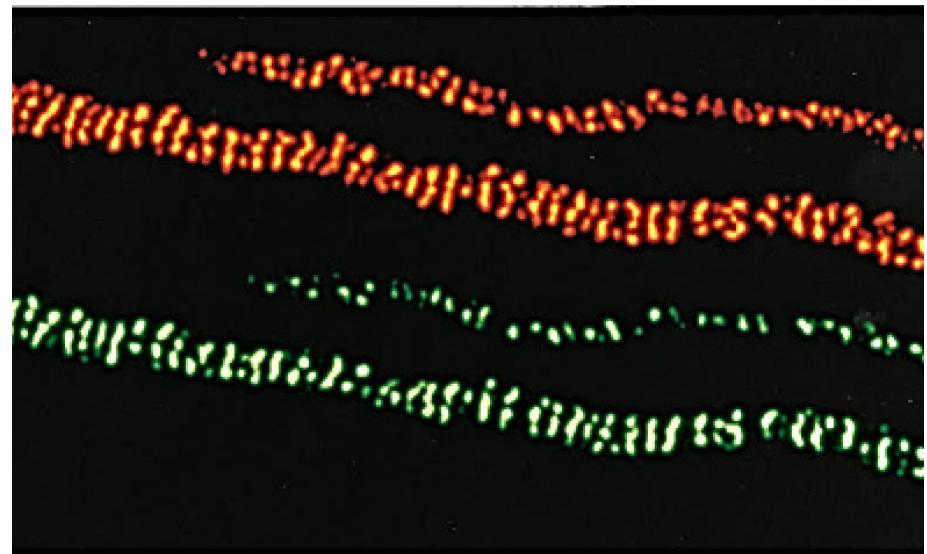
- The synaptic delay is largely attributable to the time required to open Ca^{2+} channels.

Presynaptic Ca^{2+} Channel Location

Neuromuscular junction



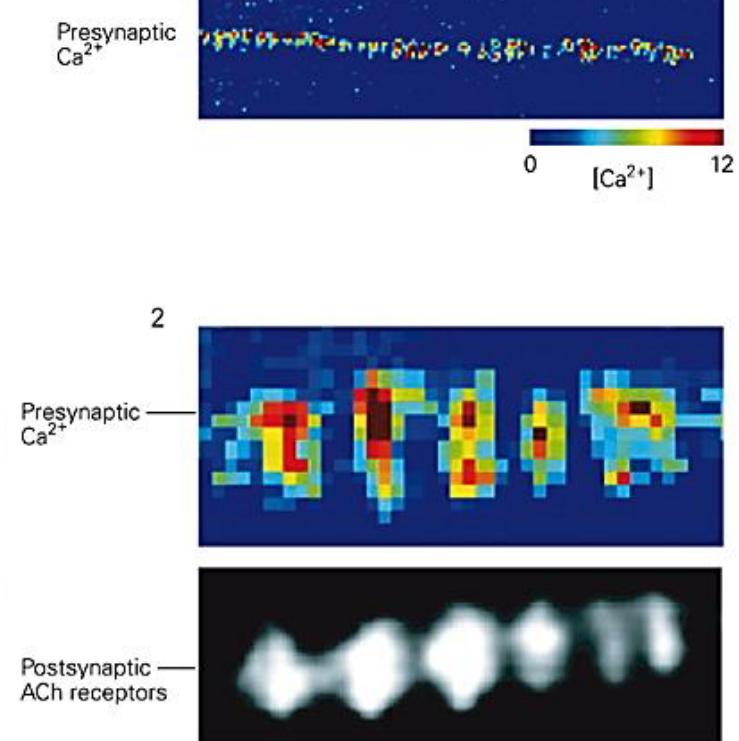
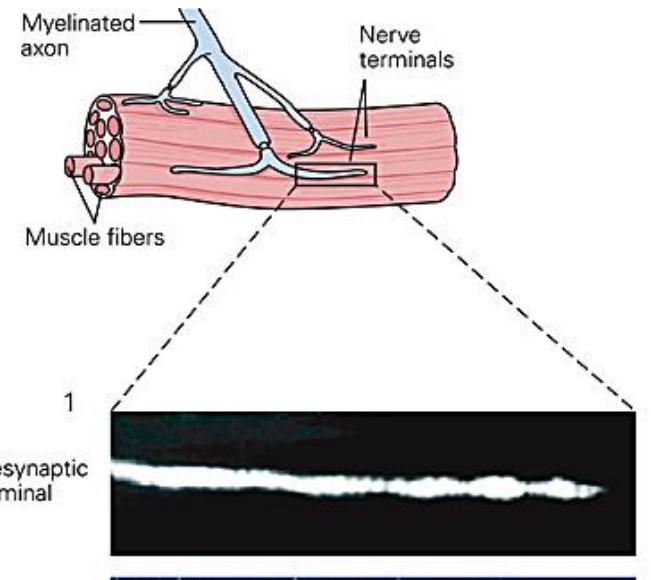
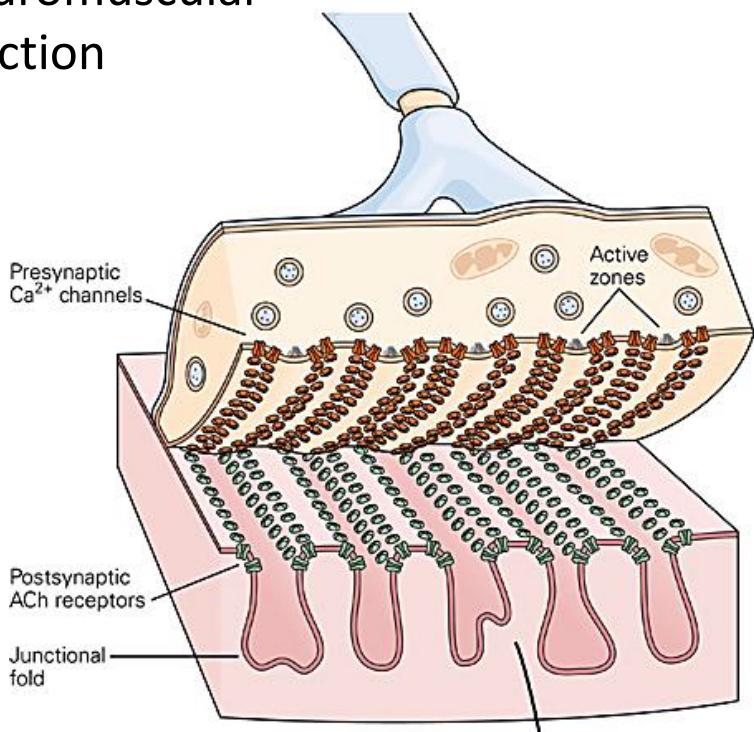
Presynaptic Ca^{2+} channels



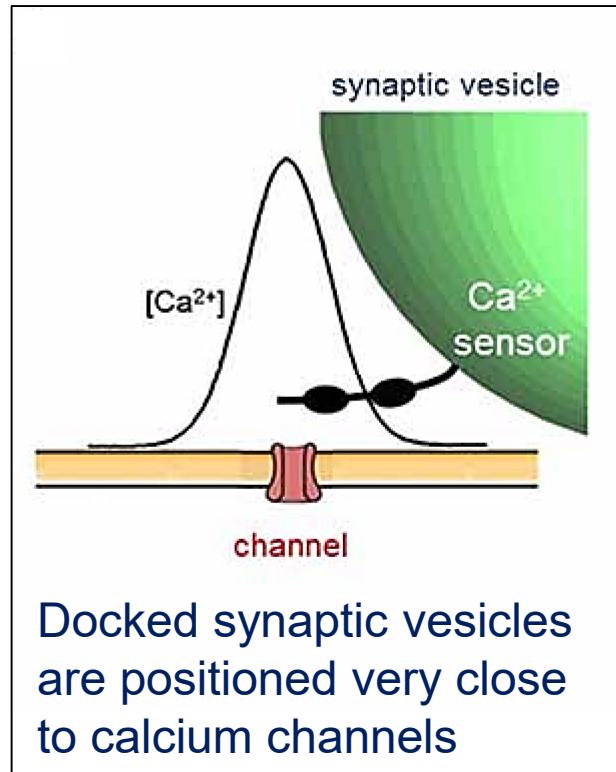
Postsynaptic ACh receptors

Presynaptic Calcium Microdomains

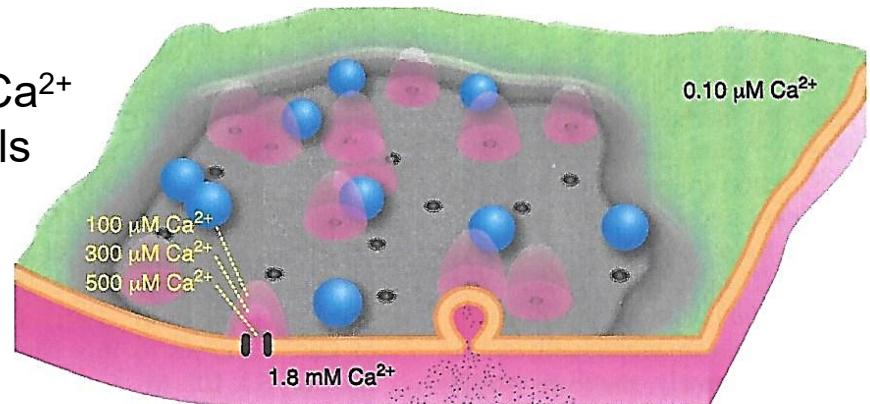
Neuromuscular junction



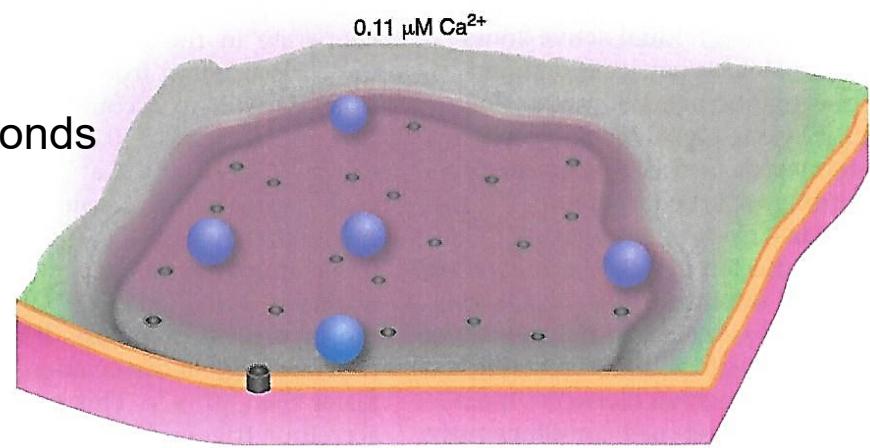
Presynaptic Calcium Microdomains



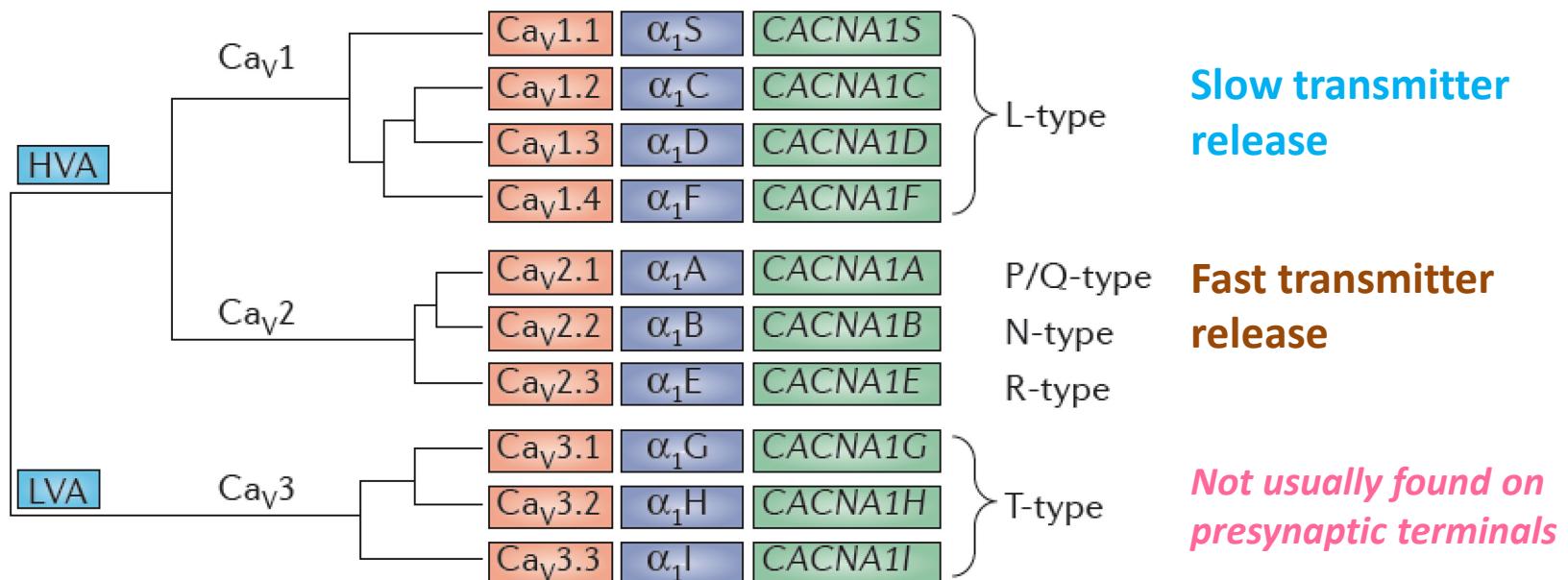
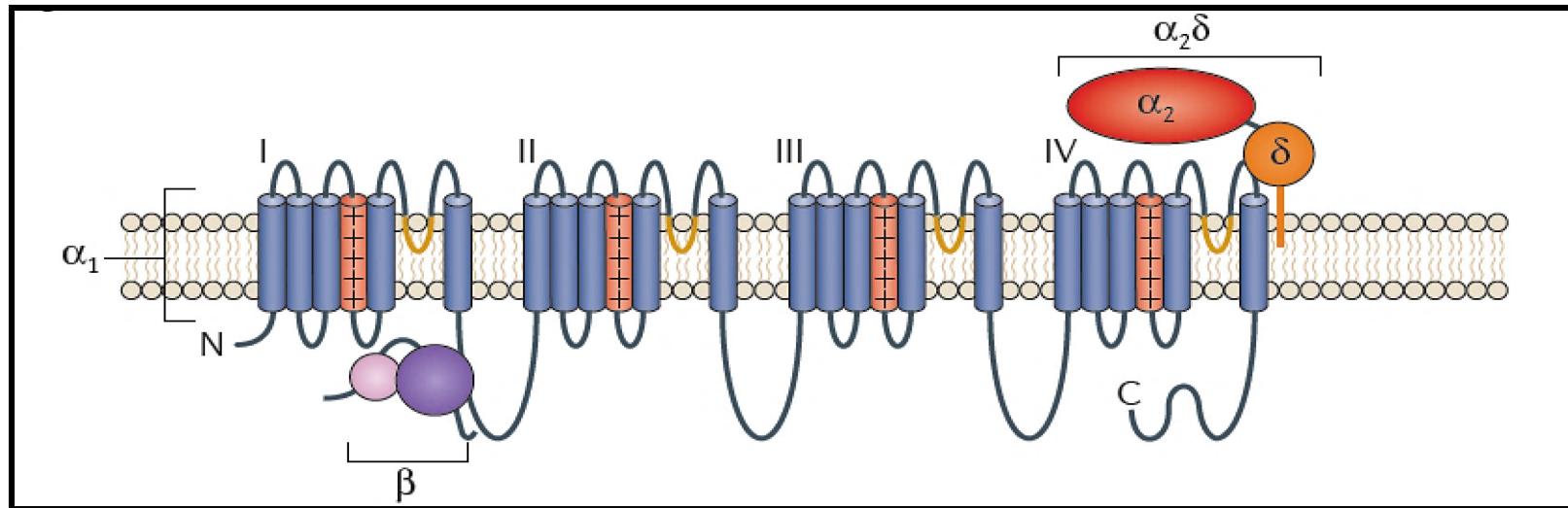
When Ca^{2+} channels open...



A few milliseconds later...

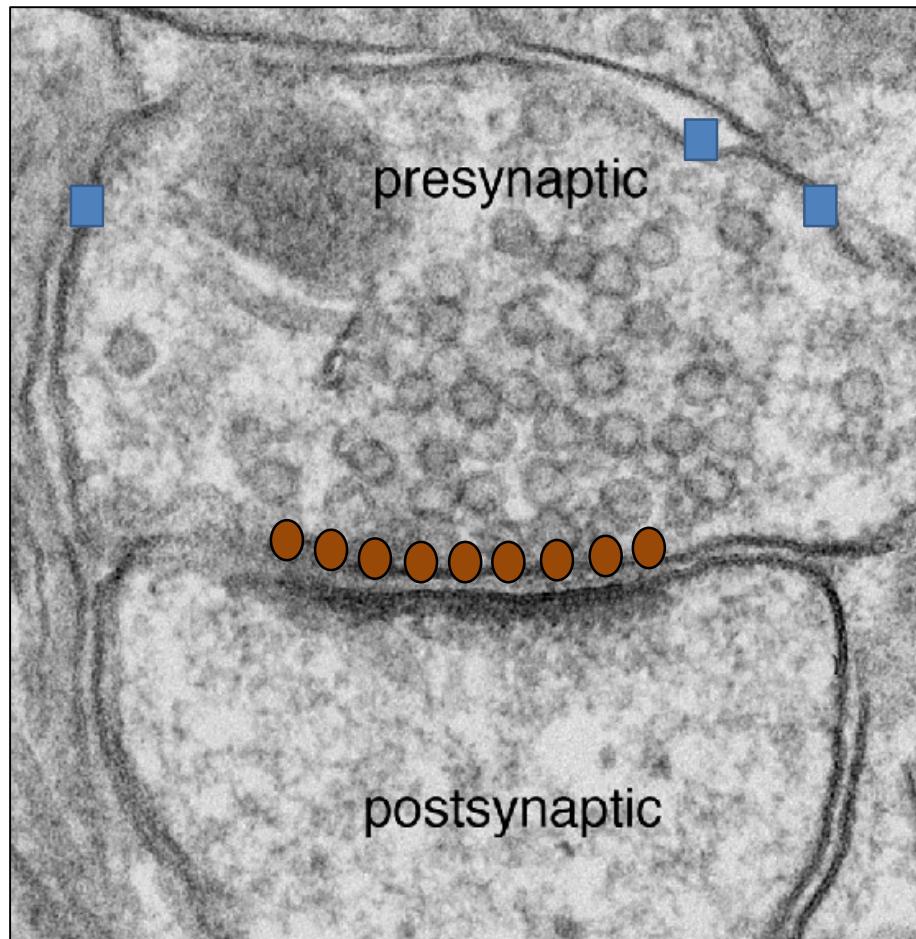
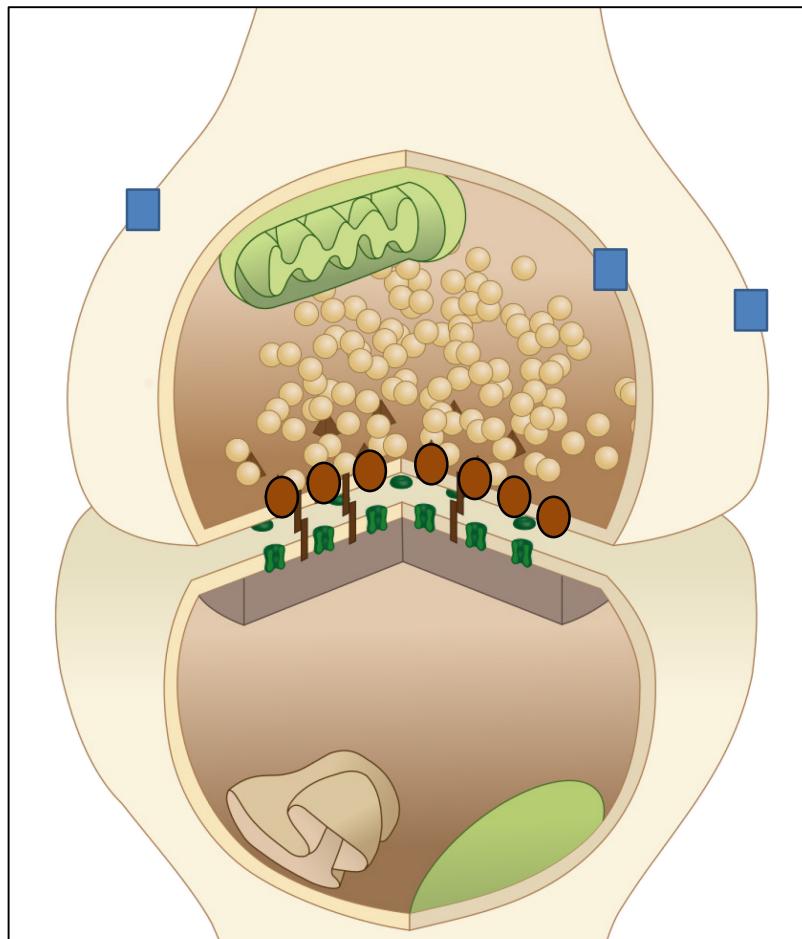


Types of Voltage-Gated Ca²⁺ Channels



Presynaptic Ca^{2+} Channels in the CNS

- N and P/Q type voltage-gated Ca^{2+} channels at active zones.
- L type voltage-gated Ca^{2+} channels are located outside of active zones.



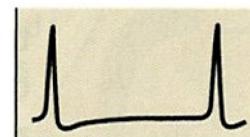
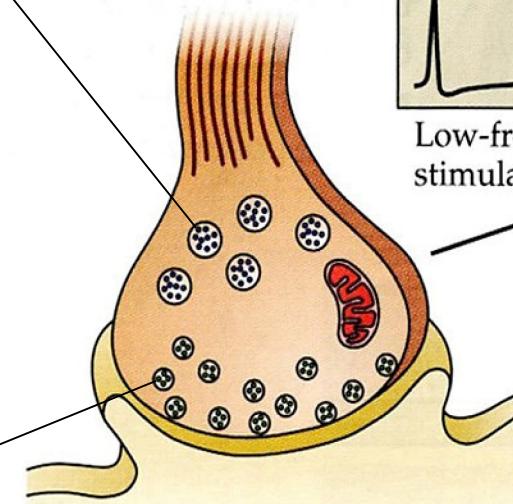
Neurotransmitter Co-Transmission

Neuropeptide transmitters:

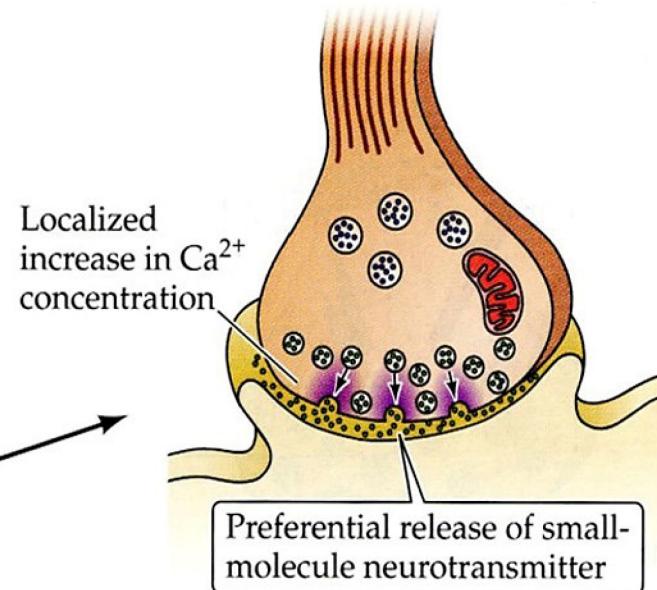
- Vesicles are located further back in the axon terminal
- Vesicles are not released at active zones

Small-molecule transmitters:

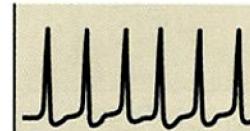
- ACh, NE, DA, 5-HT, Glu, GABA
- Vesicles are docked and released at active zones



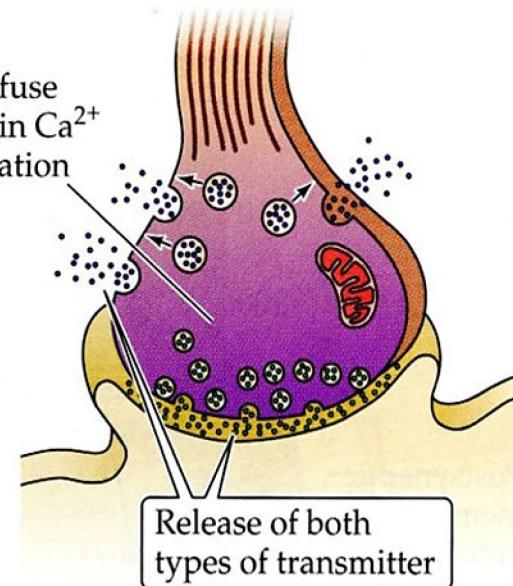
Low-frequency stimulation



More diffuse increase in Ca^{2+} concentration



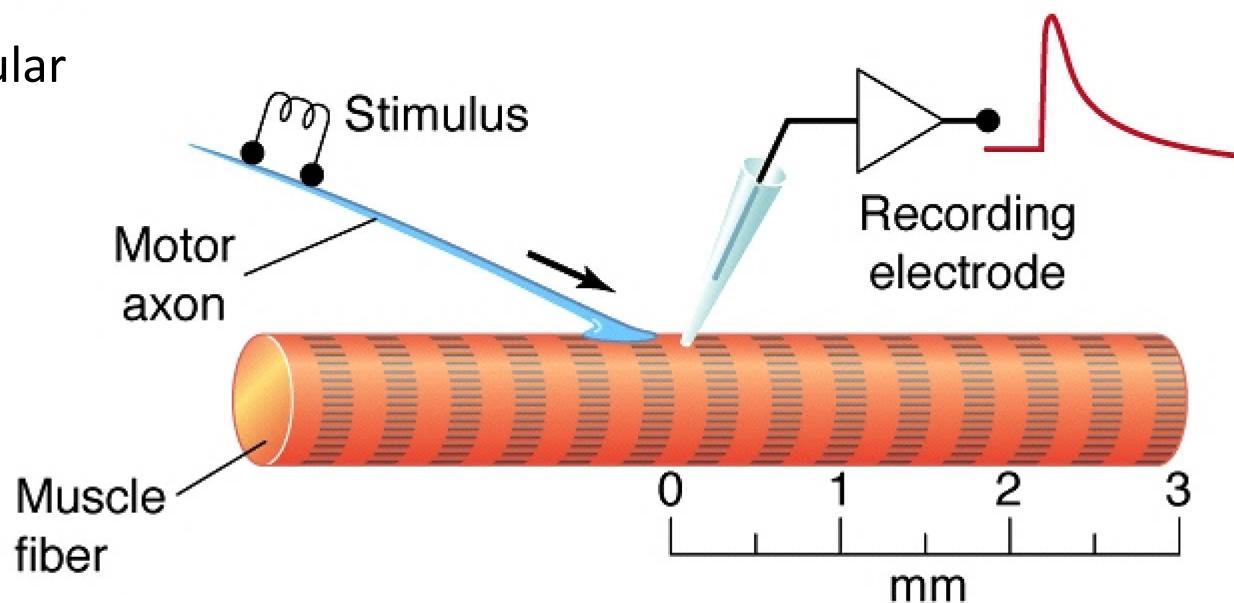
High-frequency stimulation



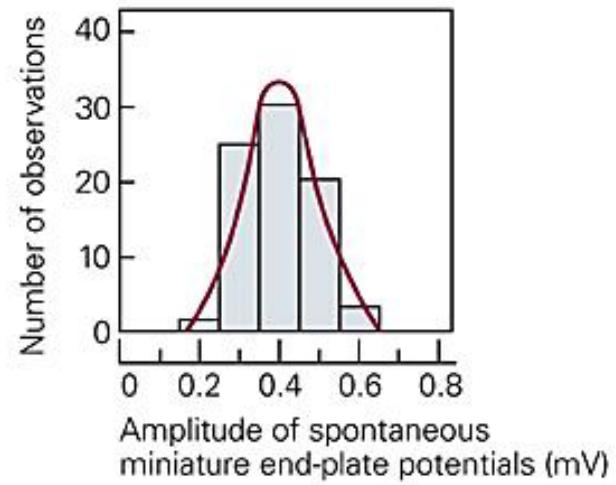
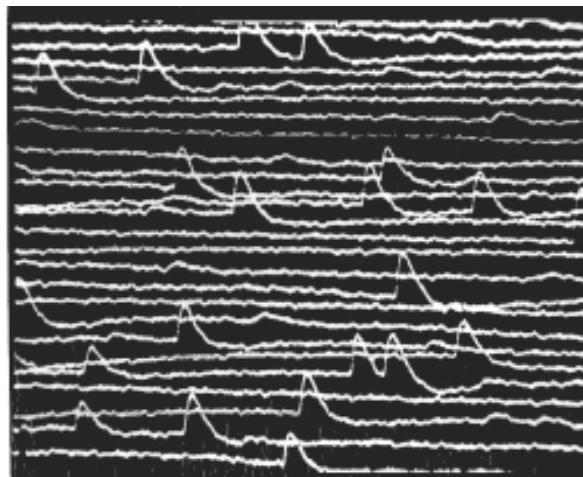
Release of both types of transmitter

Miniature End-Plate Potentials (MEPPs)

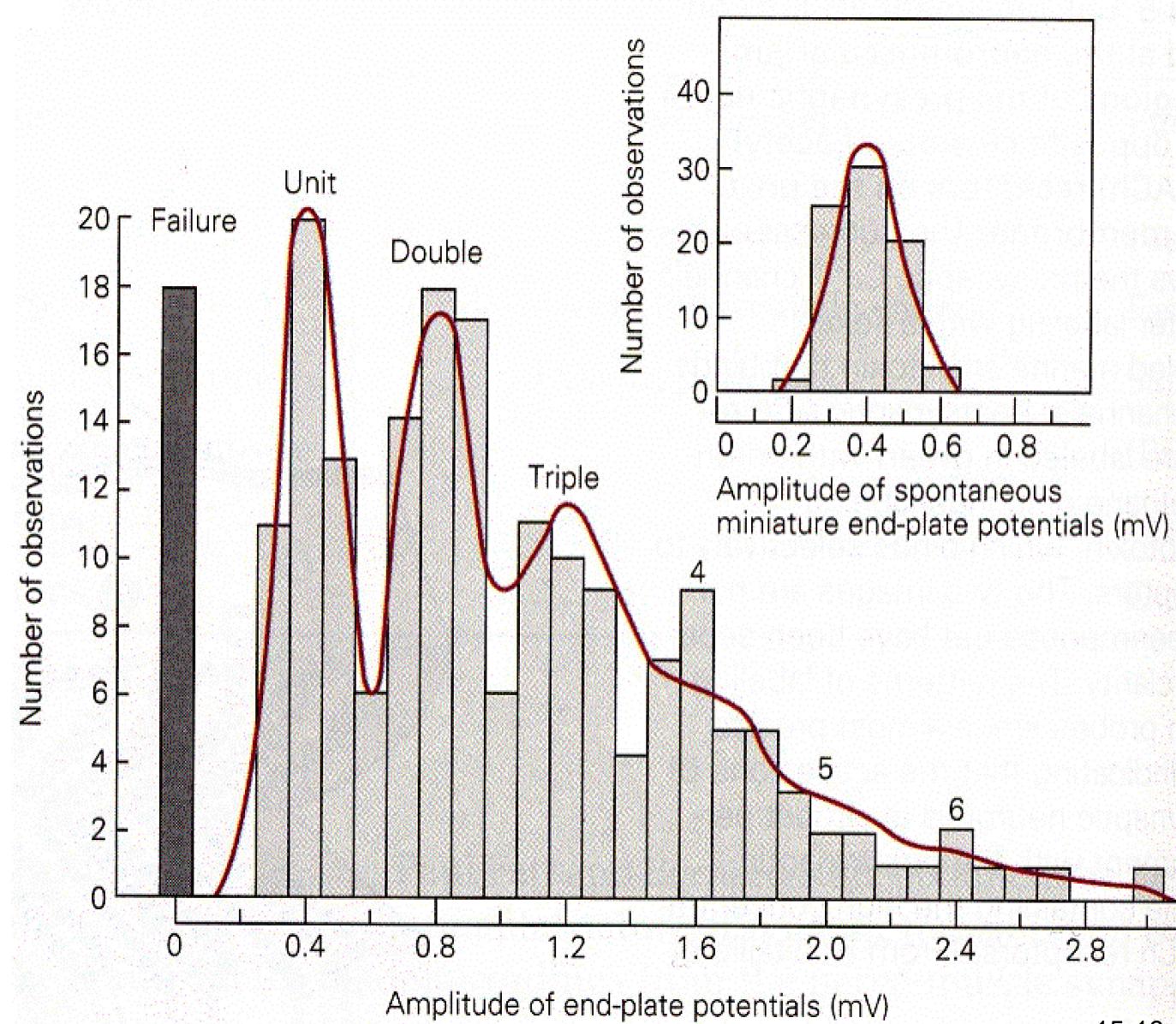
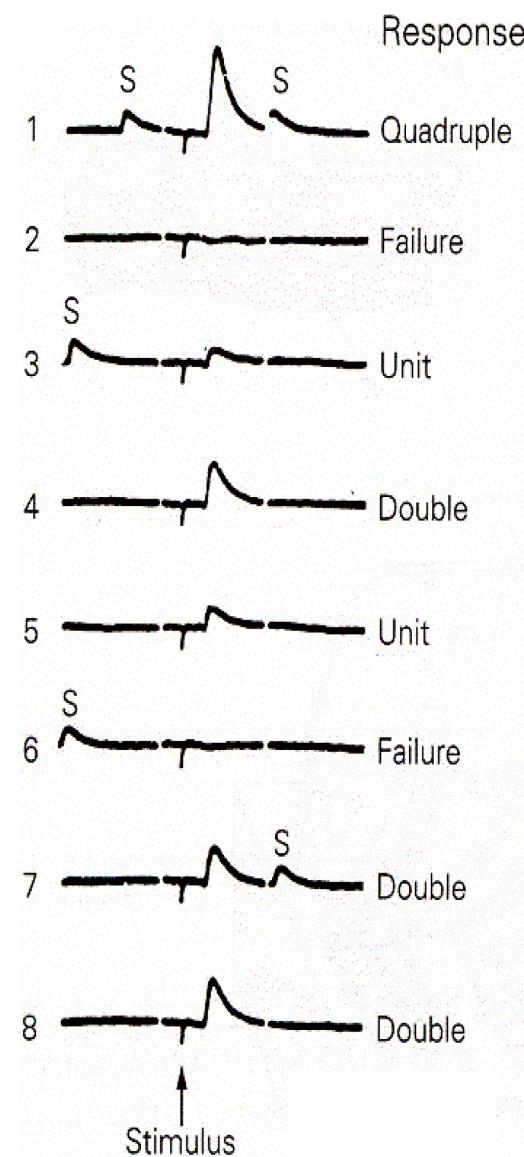
Neuromuscular junction



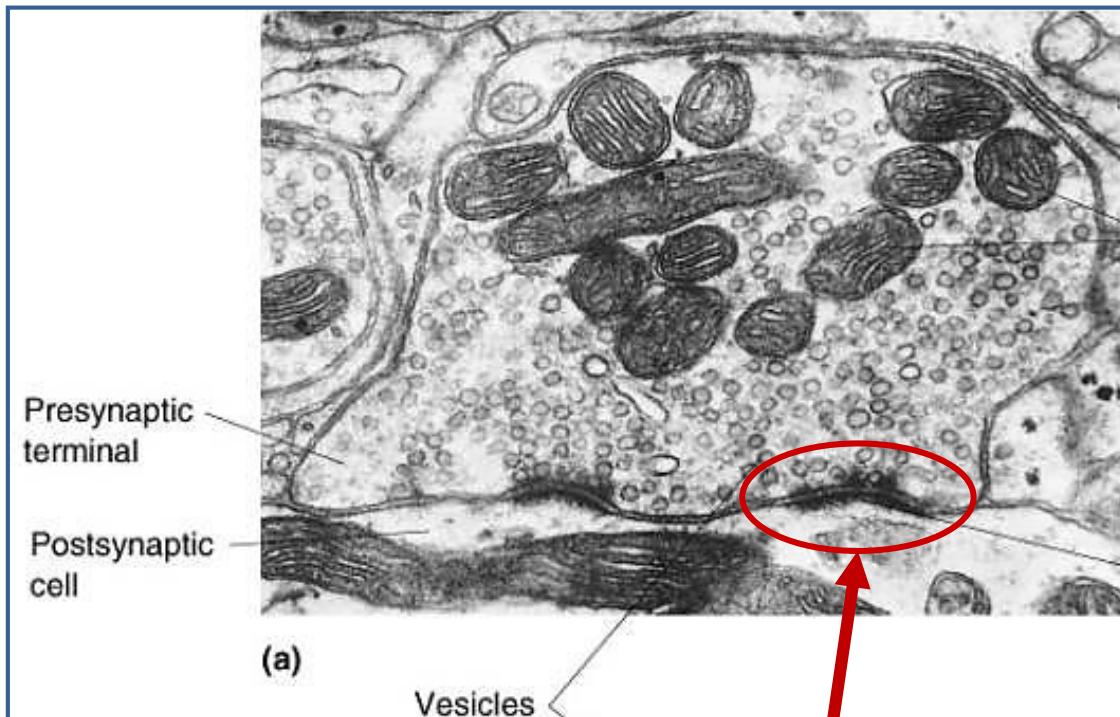
Recording without stimulating the motor axon:



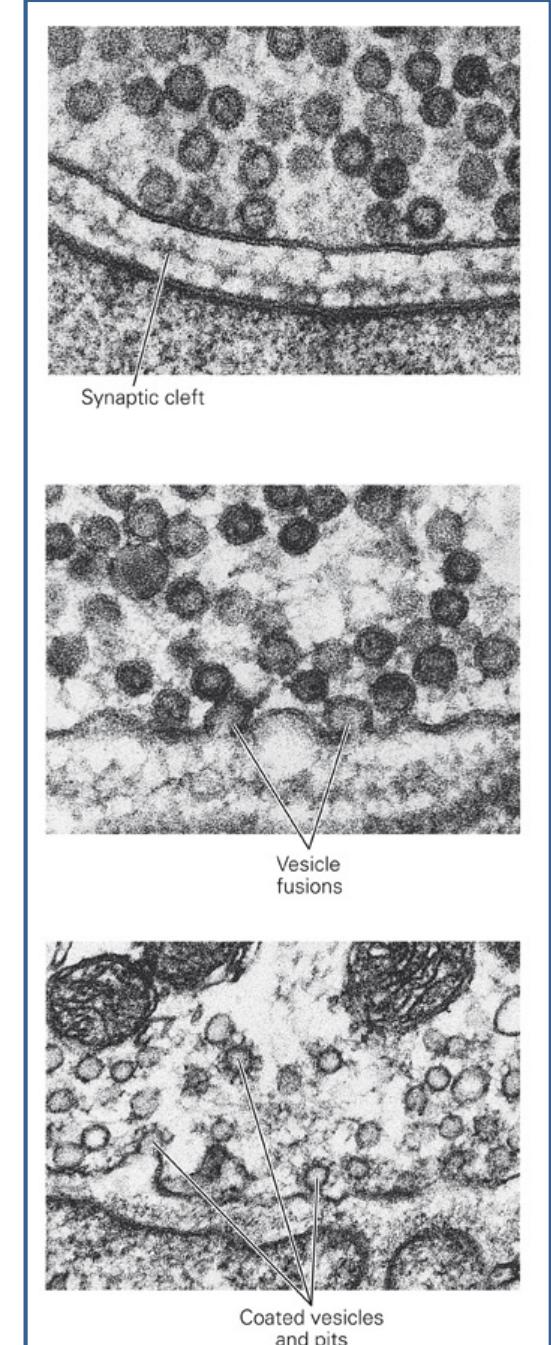
Transmitter is Released in Quantal Units



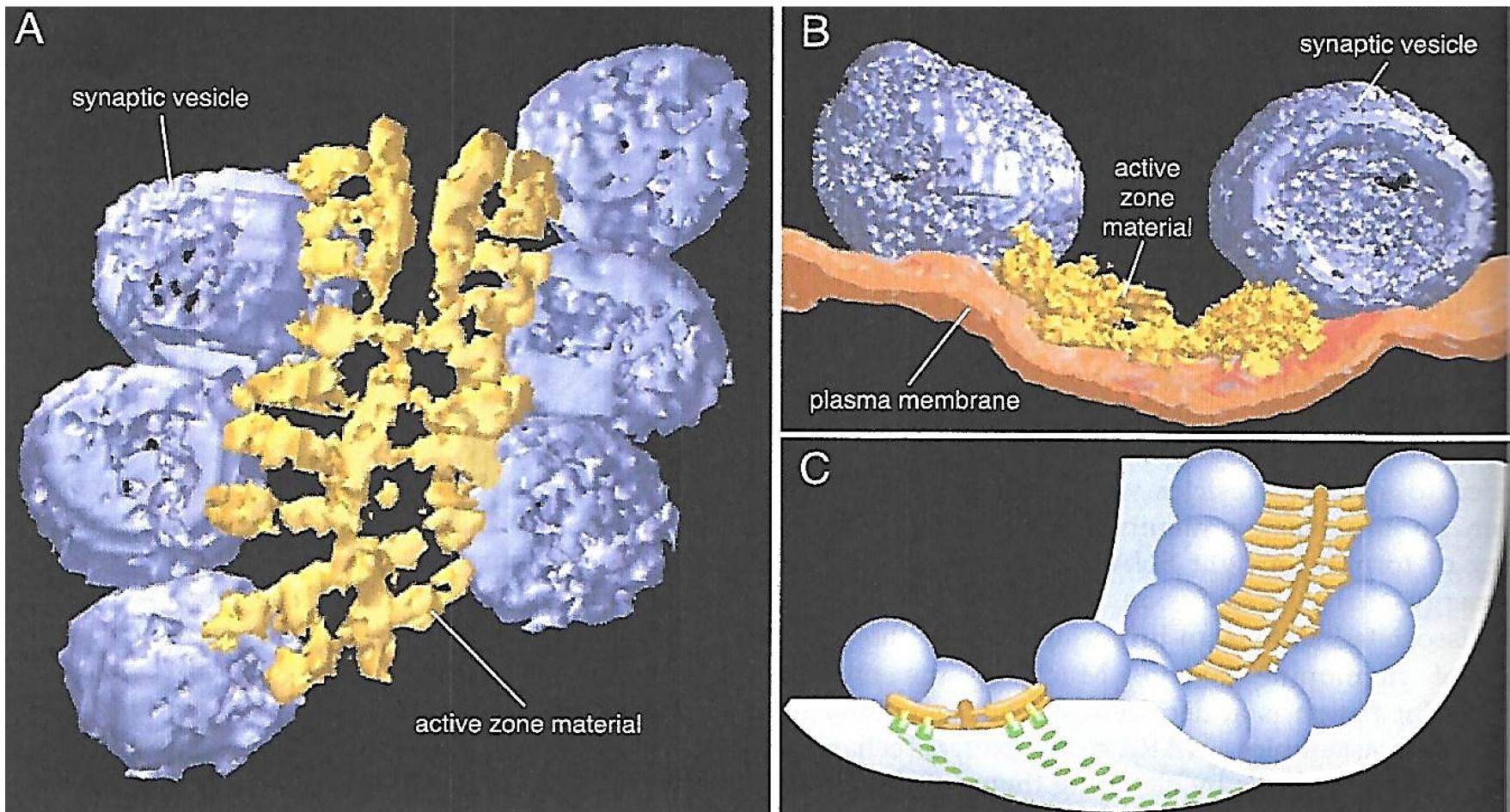
Vesicular Release of Neurotransmitter



Active Zone

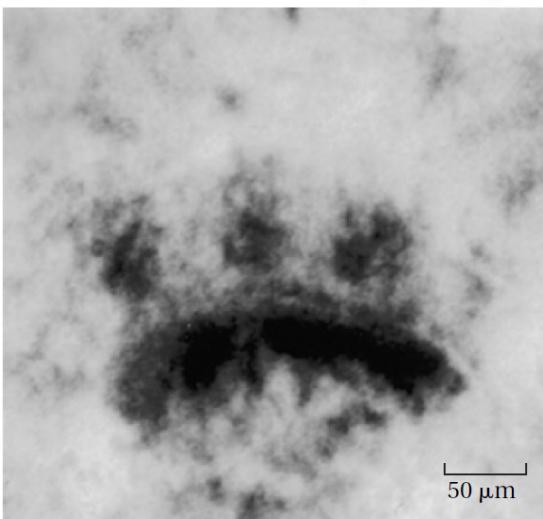


NMJ Active Zone Organization

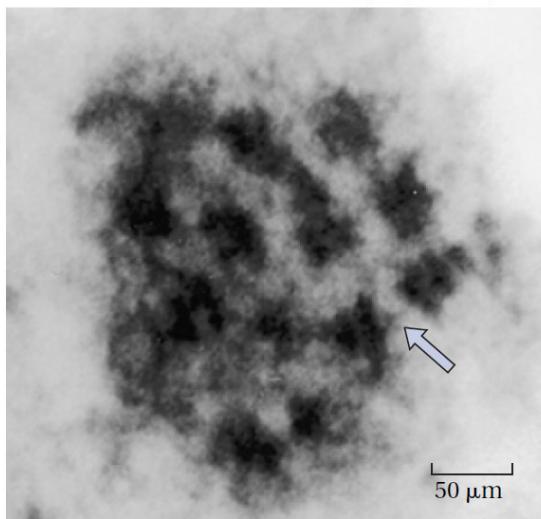


CNS Active Zone Organization

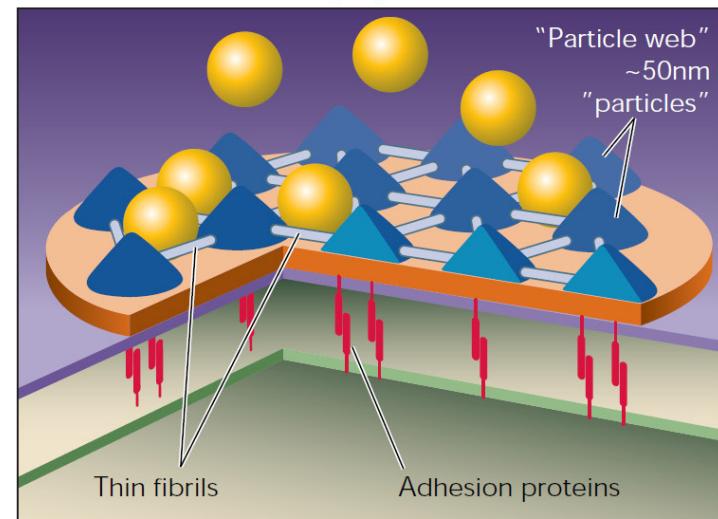
E Mammalian active zone (side view)



F Mammalian active zone (top view)



G Mammalian central synapse

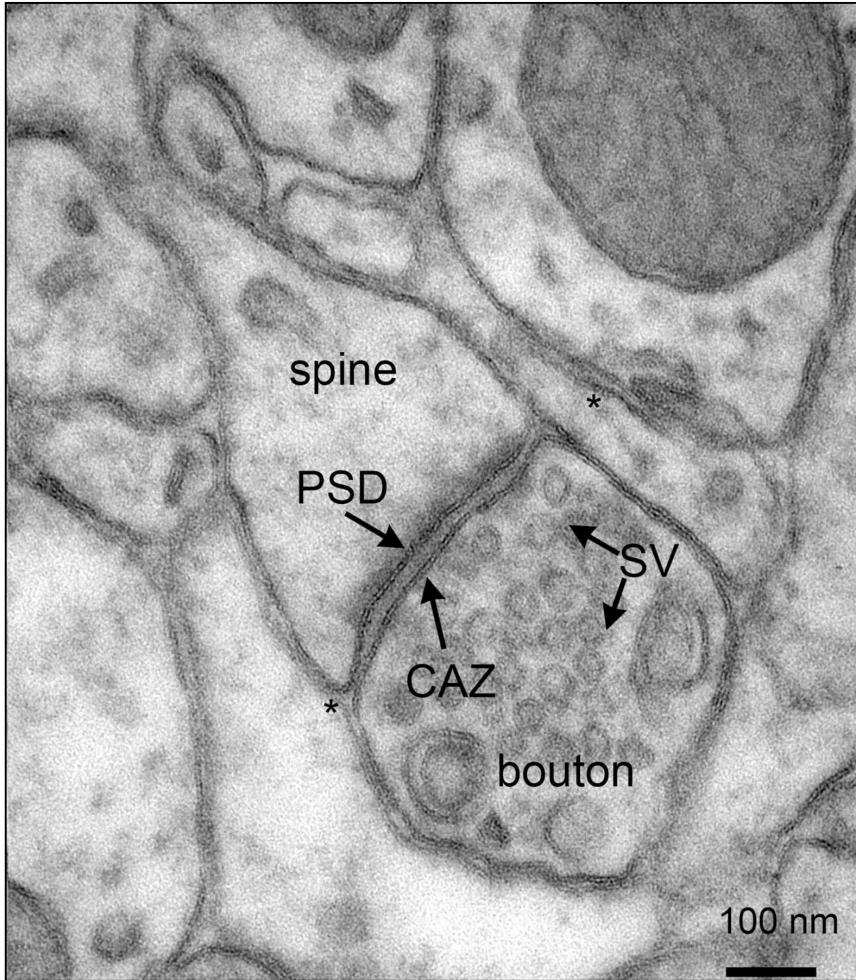


A typical active zone in the CNS has 10-20 vesicle docking/release sites, but the probability of any one vesicle fusing in response to an action potential is quite low (5-10% chance).

- *Note: this probability can go up or down based on the active zone's anatomy & physiology, which can be modified by synaptic experience.*

This means that, on average, one vesicle fuses with the membrane for each action potential arriving at the active zone.

Transmitter Release at CNS Synapses



Electron micrograph of cortex showing pre- and postsynaptic structures. CAZ, cytomatrix at the active zone; PSD, postsynaptic density; SV, synaptic vesicles. *Molecular & Cellular Proteomics* 15 (2) 368-381

Most CNS synapses have only one active zone; therefore, an average of one vesicle is released per synapse for each action potential.

How might the number of vesicles released by a presynaptic neuron onto a postsynaptic neuron be increased?

The Neuromuscular Junction and the Calyx of Held each have hundreds of active zones. What effect does this have?

Types of Vesicular Release

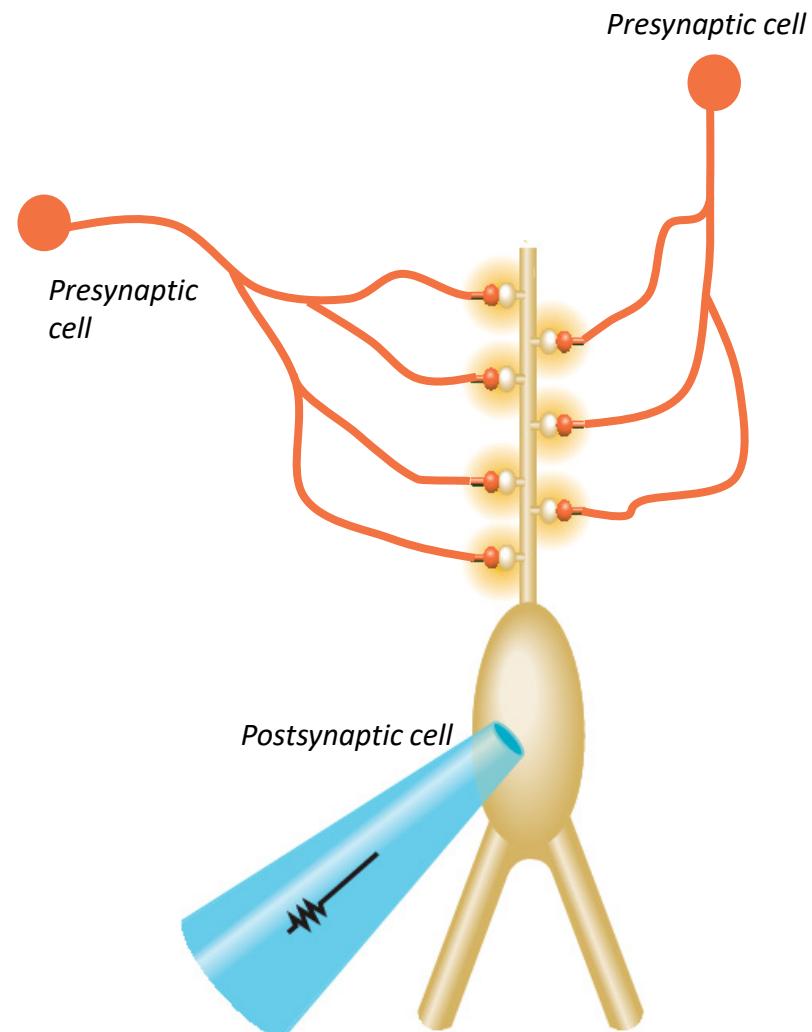
Spontaneous Release

- Caused by spontaneous release of one vesicle at an axon terminal
- Results in mini EPSCs (mEPSCs) and mini IPSCs (mIPSCs)



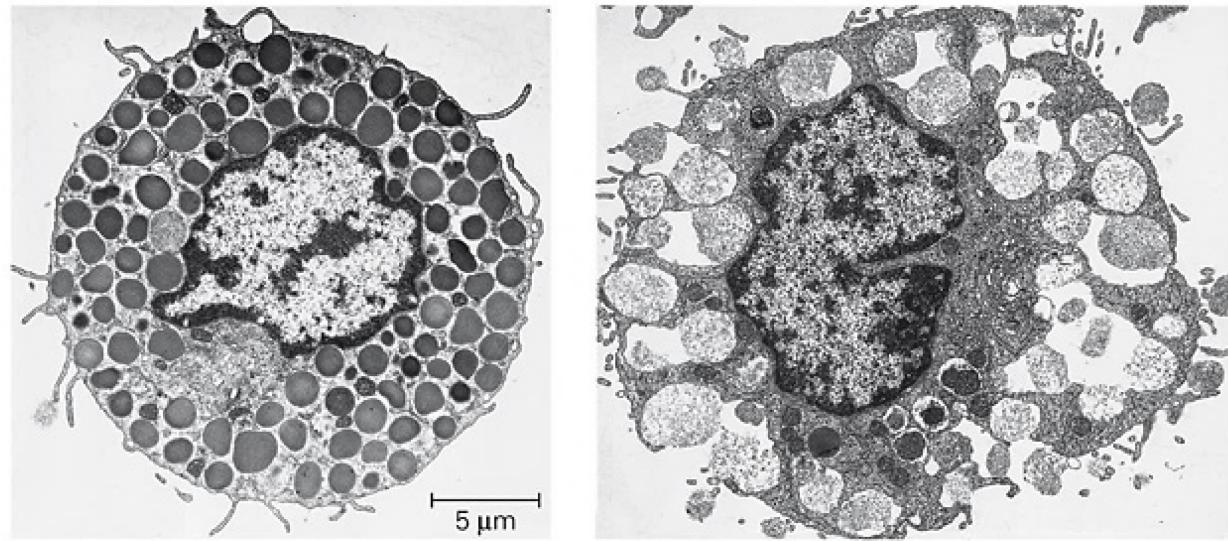
Evoked Release

- Caused by action potentials arriving at the axon terminal
- Results in traditional EPSCs and IPSCs

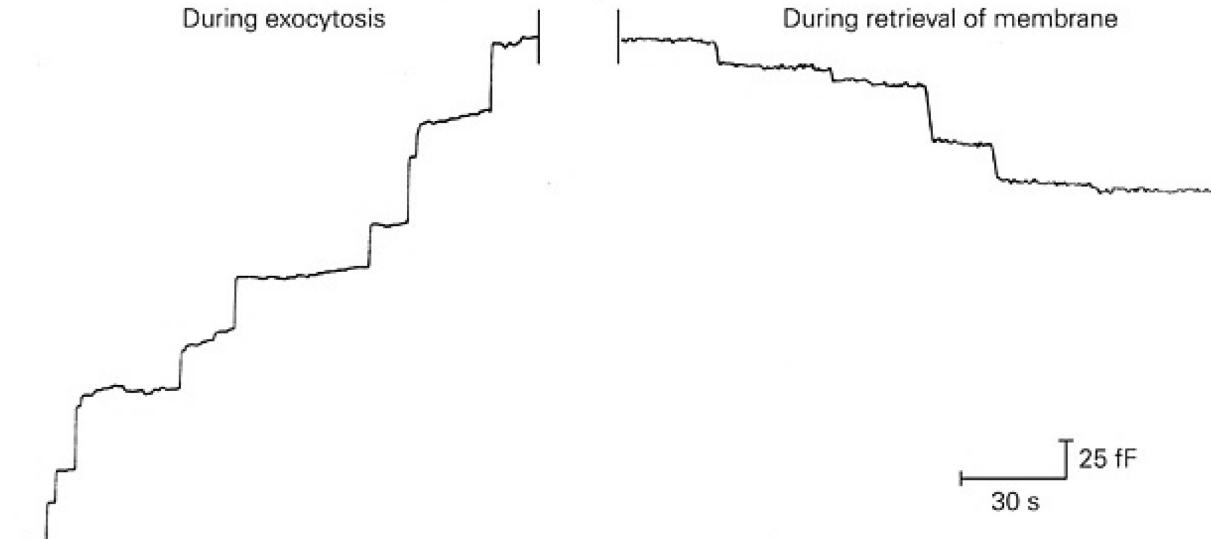


Measuring Transmitter Release by Monitoring Membrane Capacitance

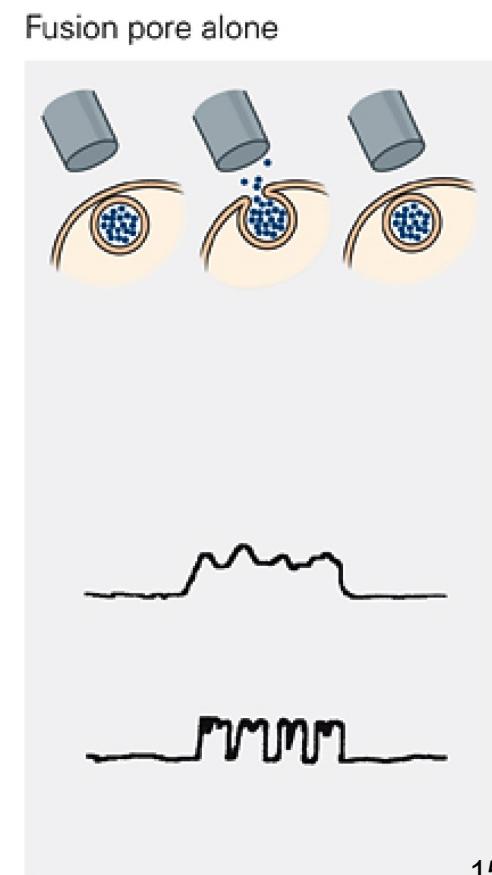
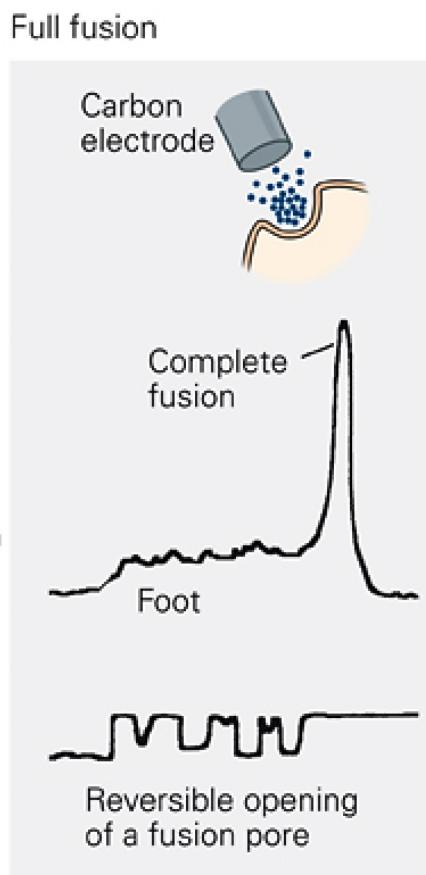
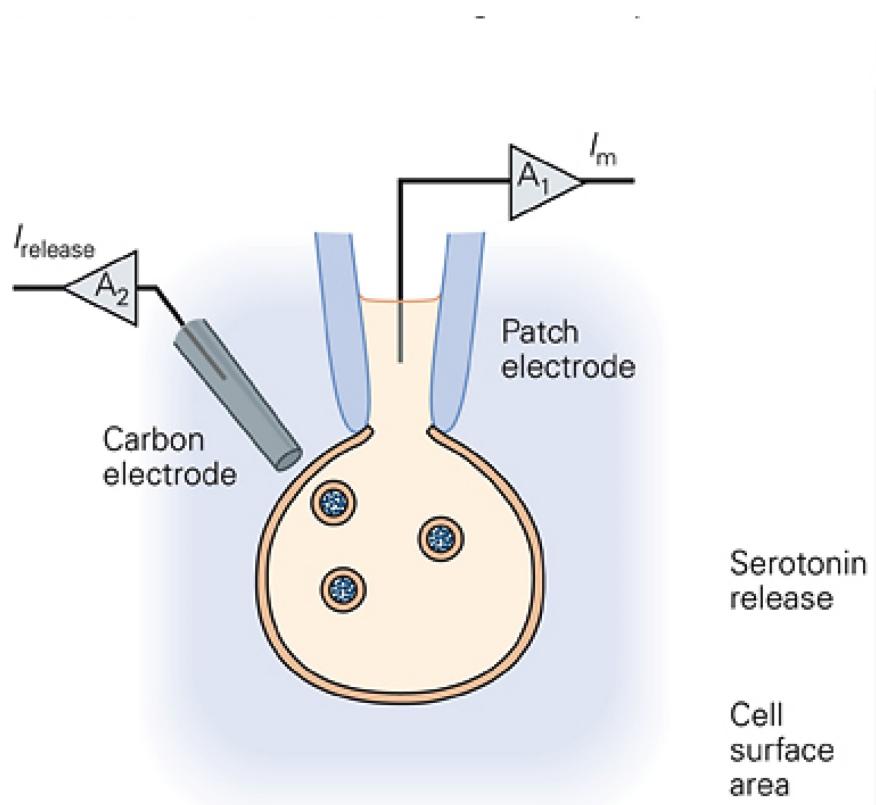
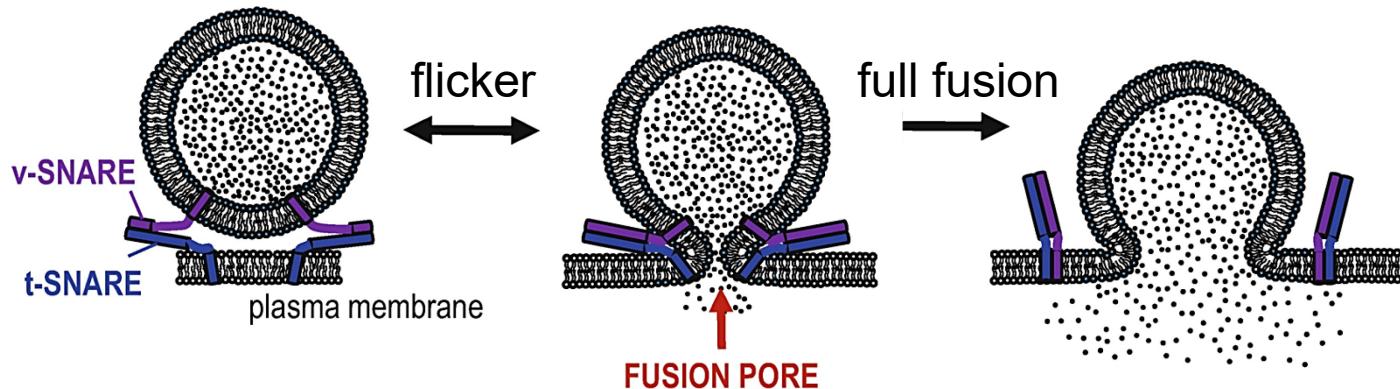
A Mast cell before and after exocytosis of secretory vesicles



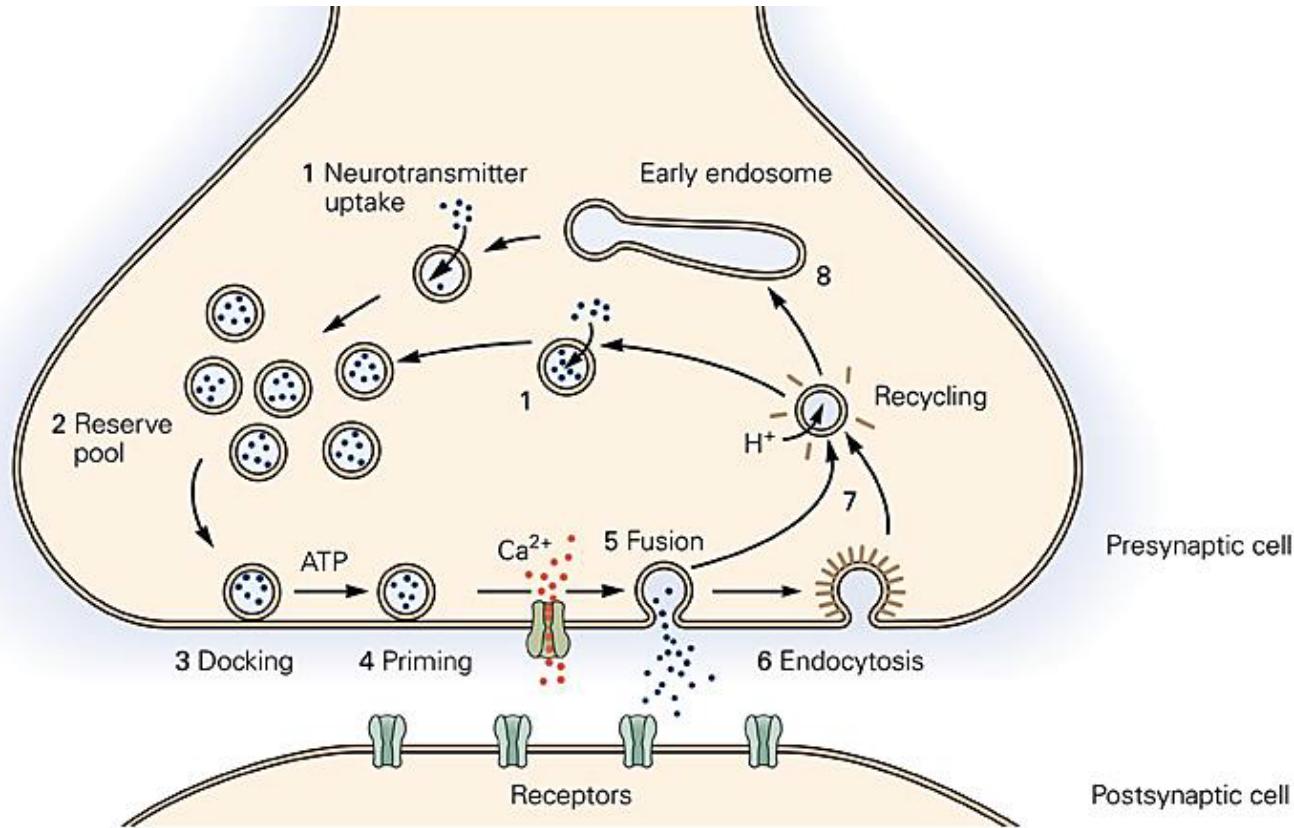
B Membrane capacitance during and after exocytosis of mast cell vesicles



The Fusion Pore

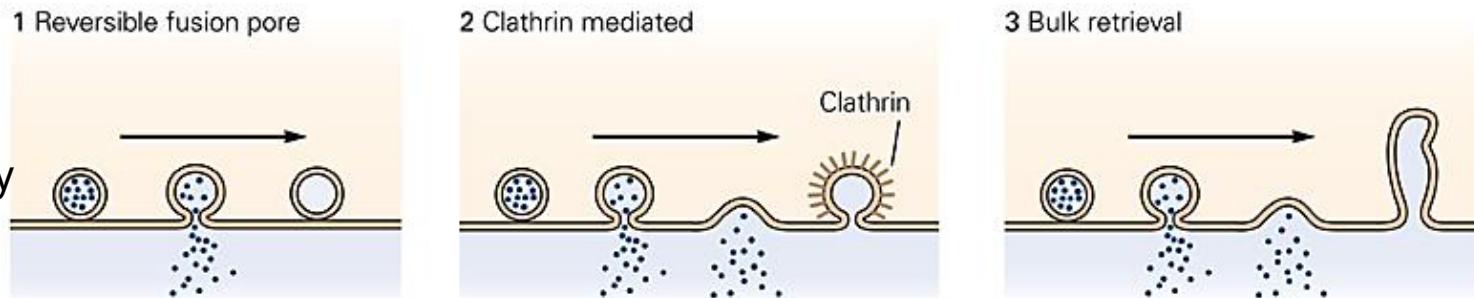


The Synaptic Vesicle Cycle



B Mechanisms for recycling synaptic vesicles

1 Reversible fusion pore



Flicker
Kiss & run
Kiss & stay

Vesicle Storage and Movement

Storage:

Synapsins link vesicles to the cytoskeleton

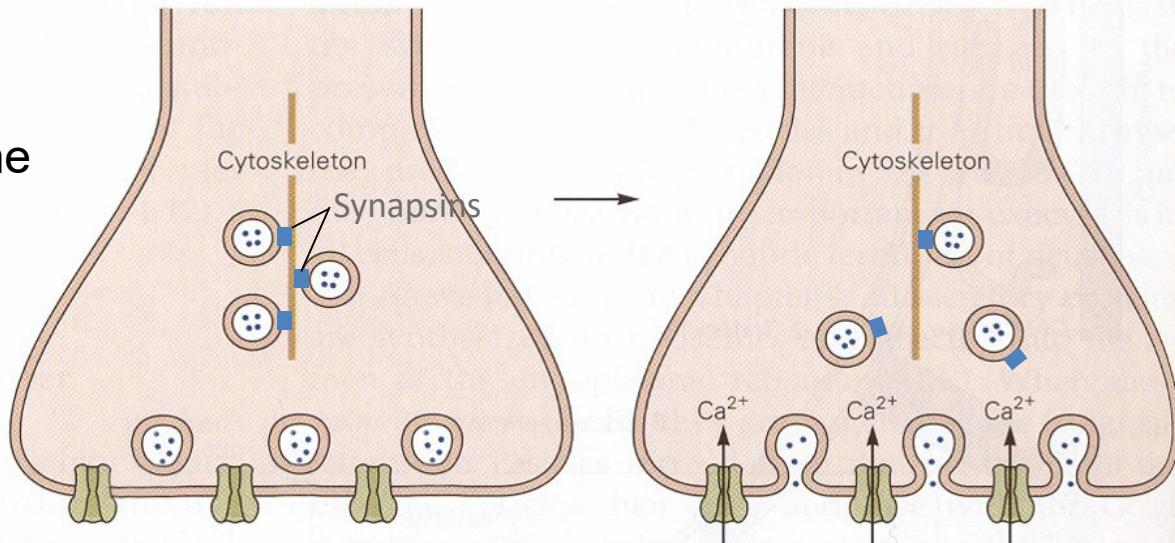
Mobilization:

Calcium influx cause synapsins to be phosphorylated, releasing vesicles from the cytoskeleton.

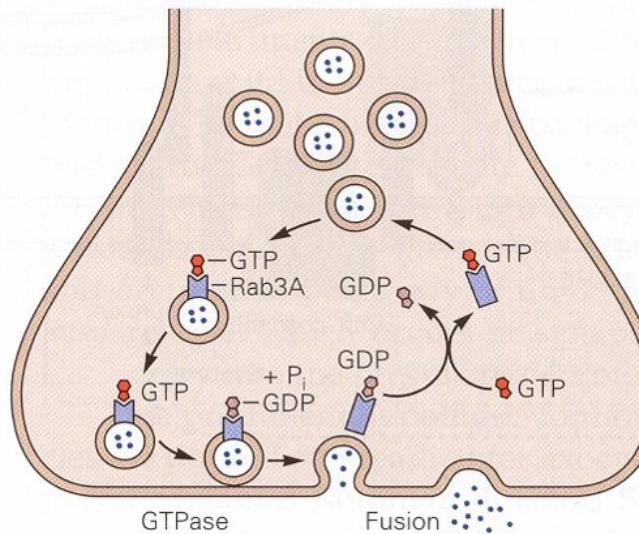
Trafficking:

Targeting of vesicles to the active zone is mediated by rab3A

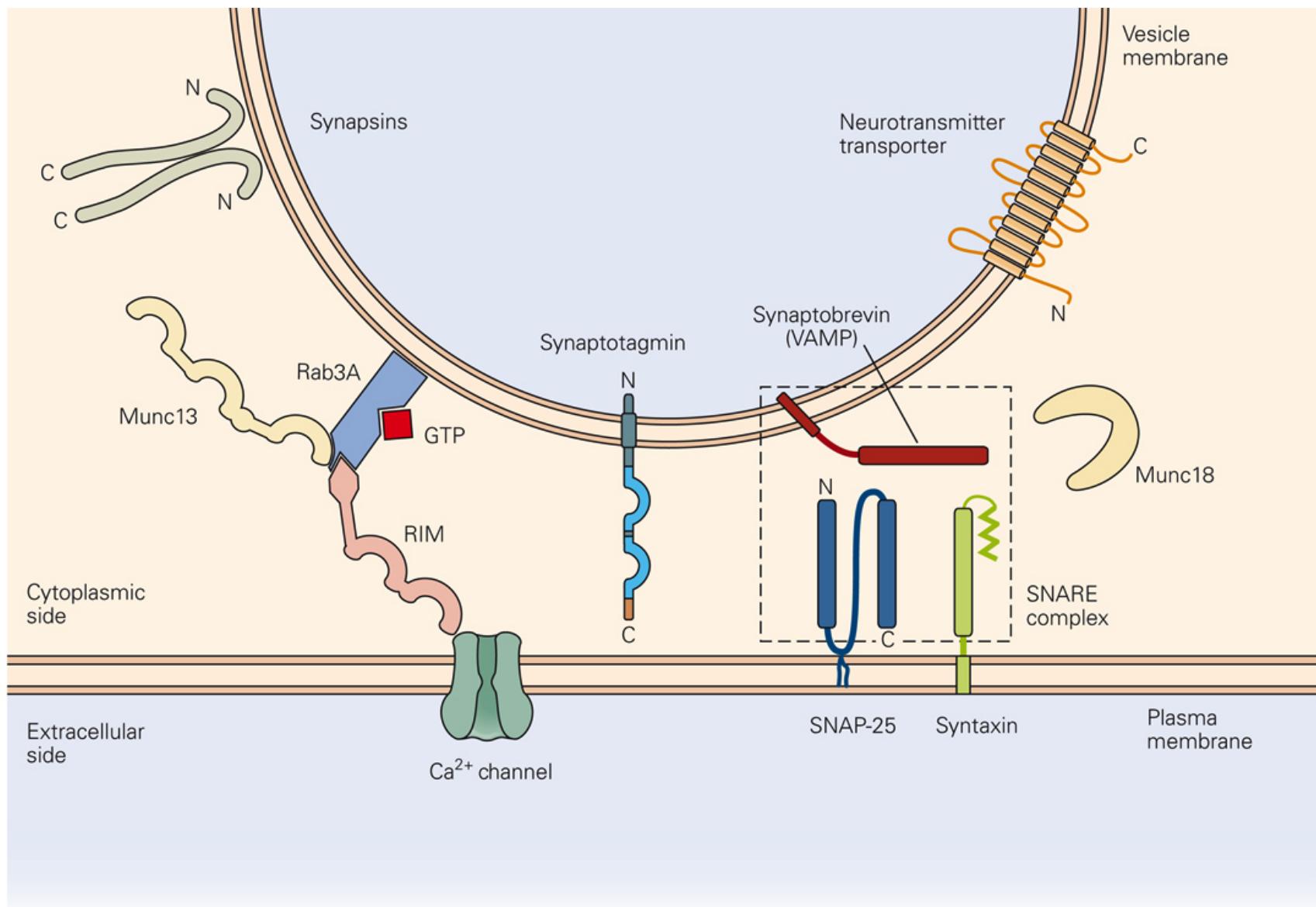
A Calcium control of vesicle fusion and mobilization



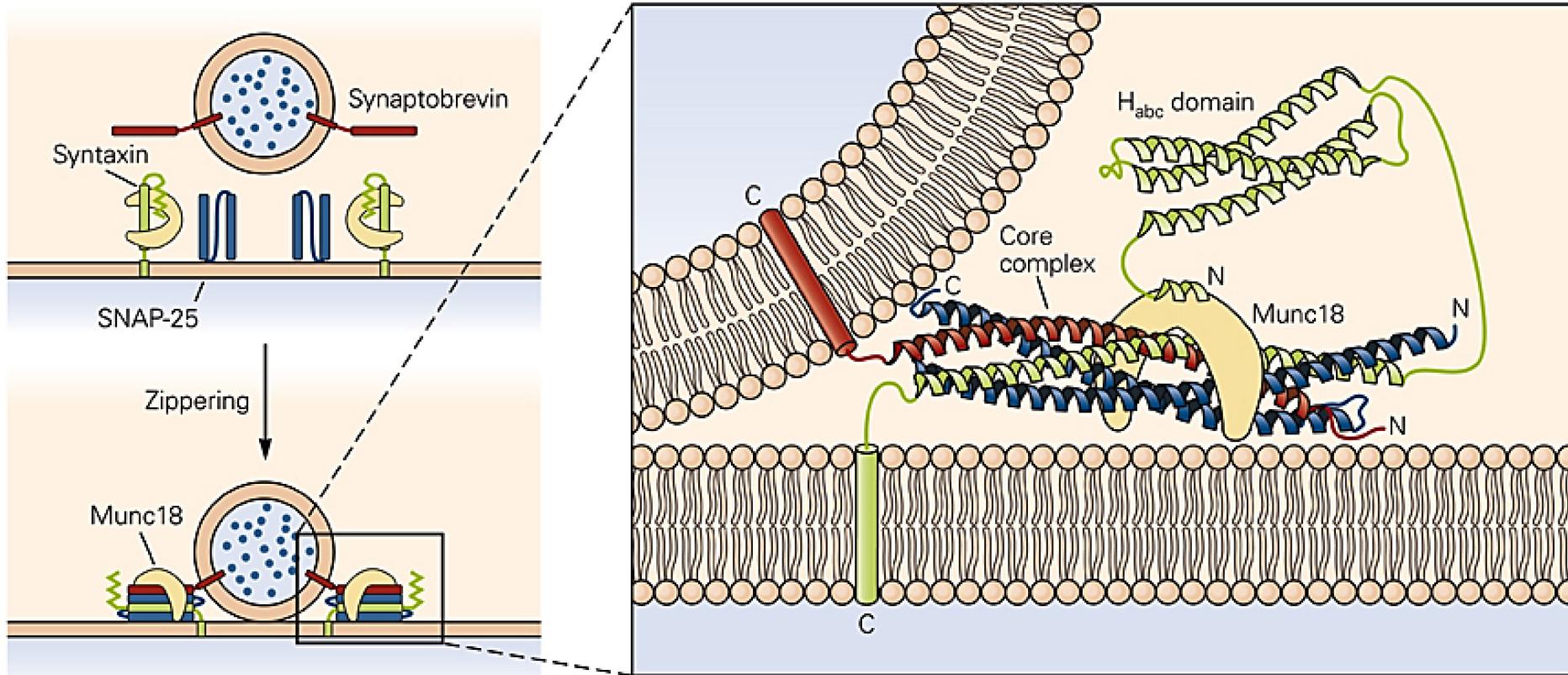
B Rab3A control of vesicle fusion



Proteins Regulate Vesicle Exocytosis

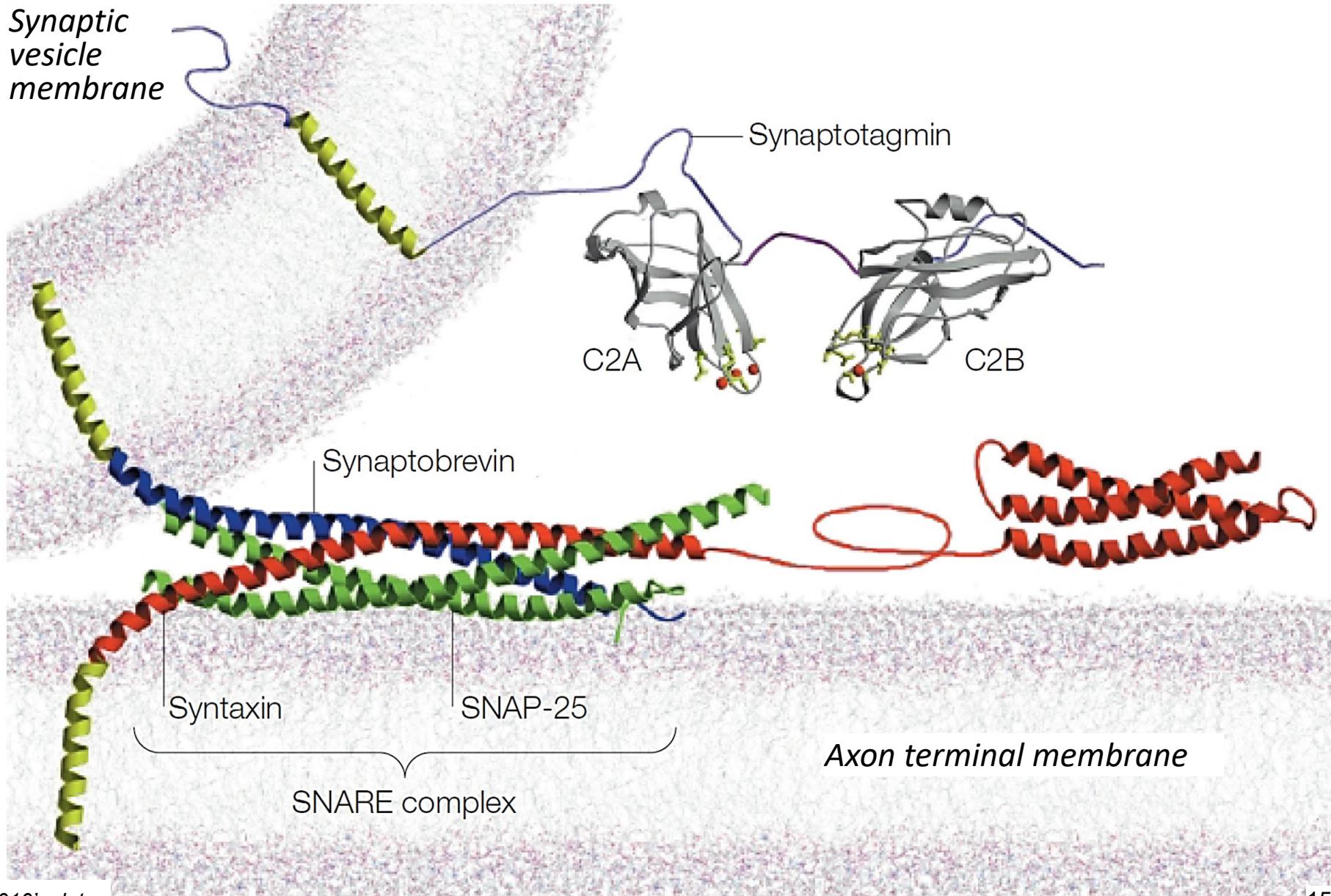


The SNARE Complex

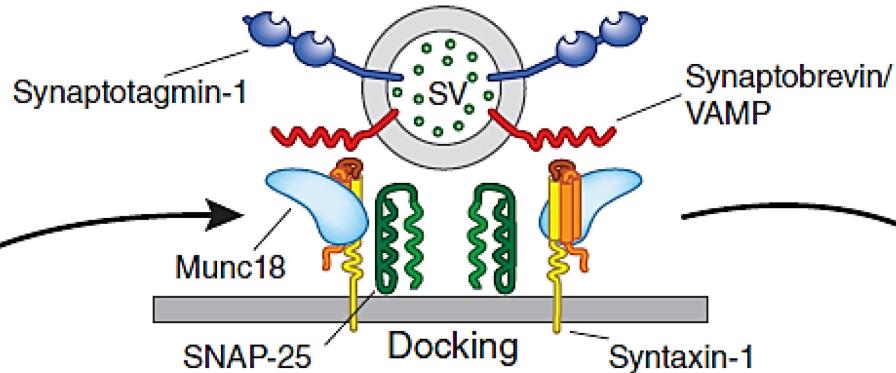


v-SNAREs bind with t-SNAREs to bring membranes together and induce fusion (exocytosis).

Synaptotagmin is the Ca^{2+} Sensor

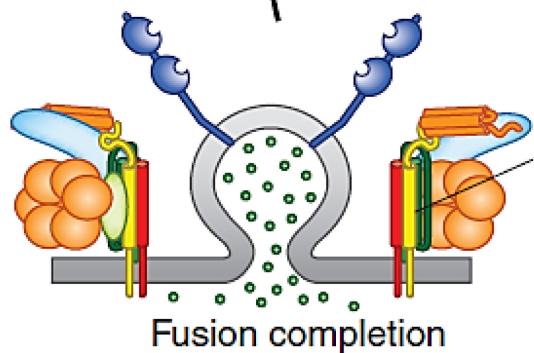


NSF and SNAP-mediated disassembly of SNARE complex



Assembly of SNARE complex

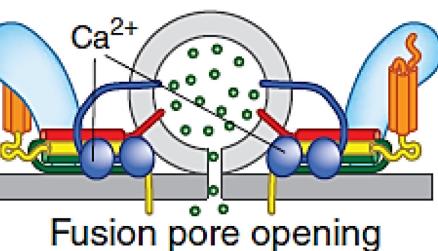
ADP +
 P_i
NSF SNAPS



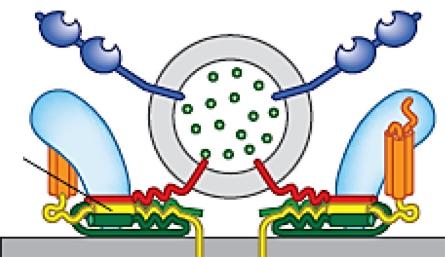
Fusion completion

Fusion pore expansion

ATP
NSF SNAPS

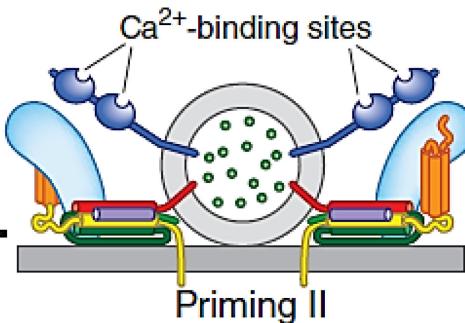


Ca^{2+} triggered fusion pore opening



Priming I

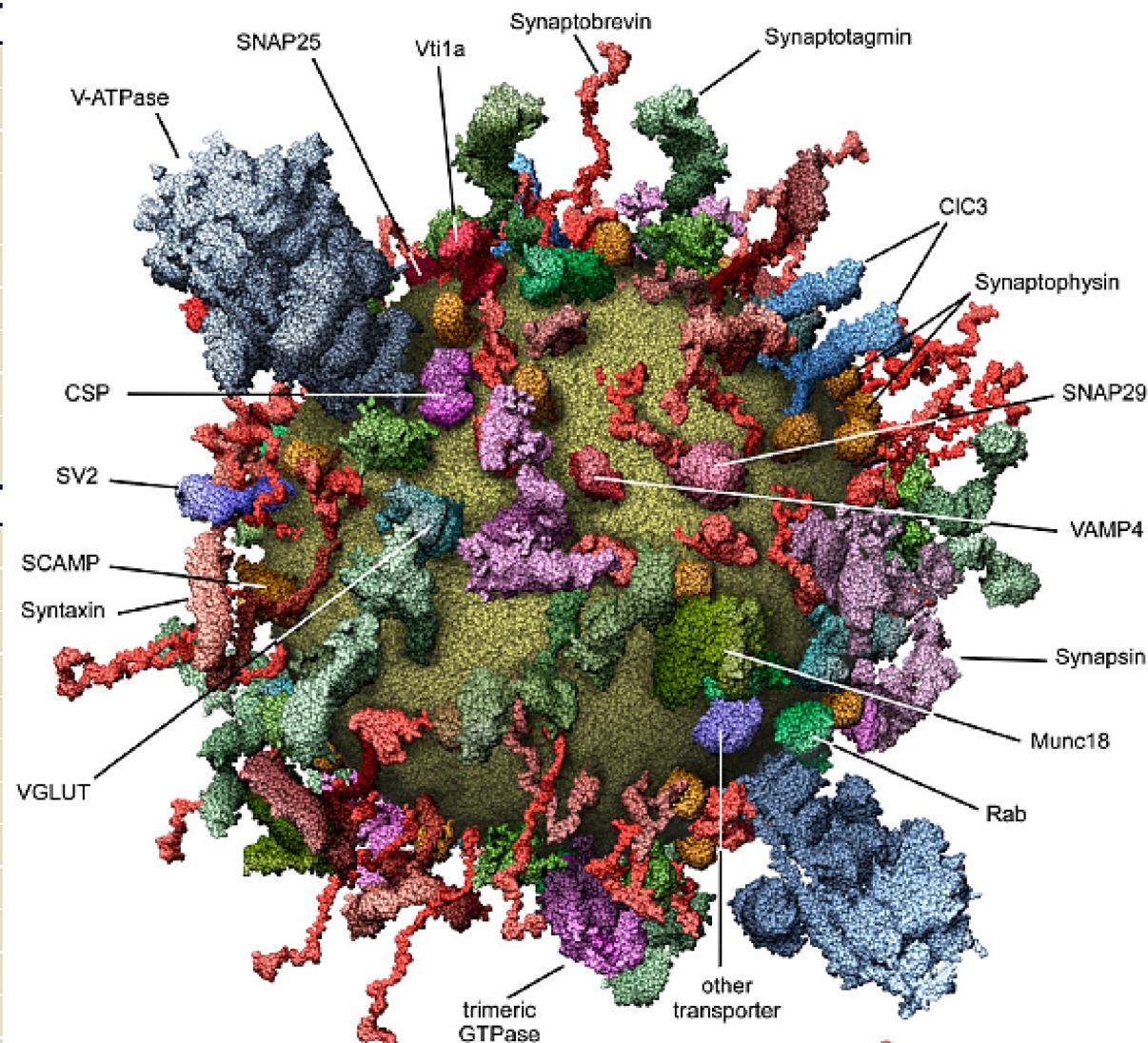
Additional proteins bind



Priming II

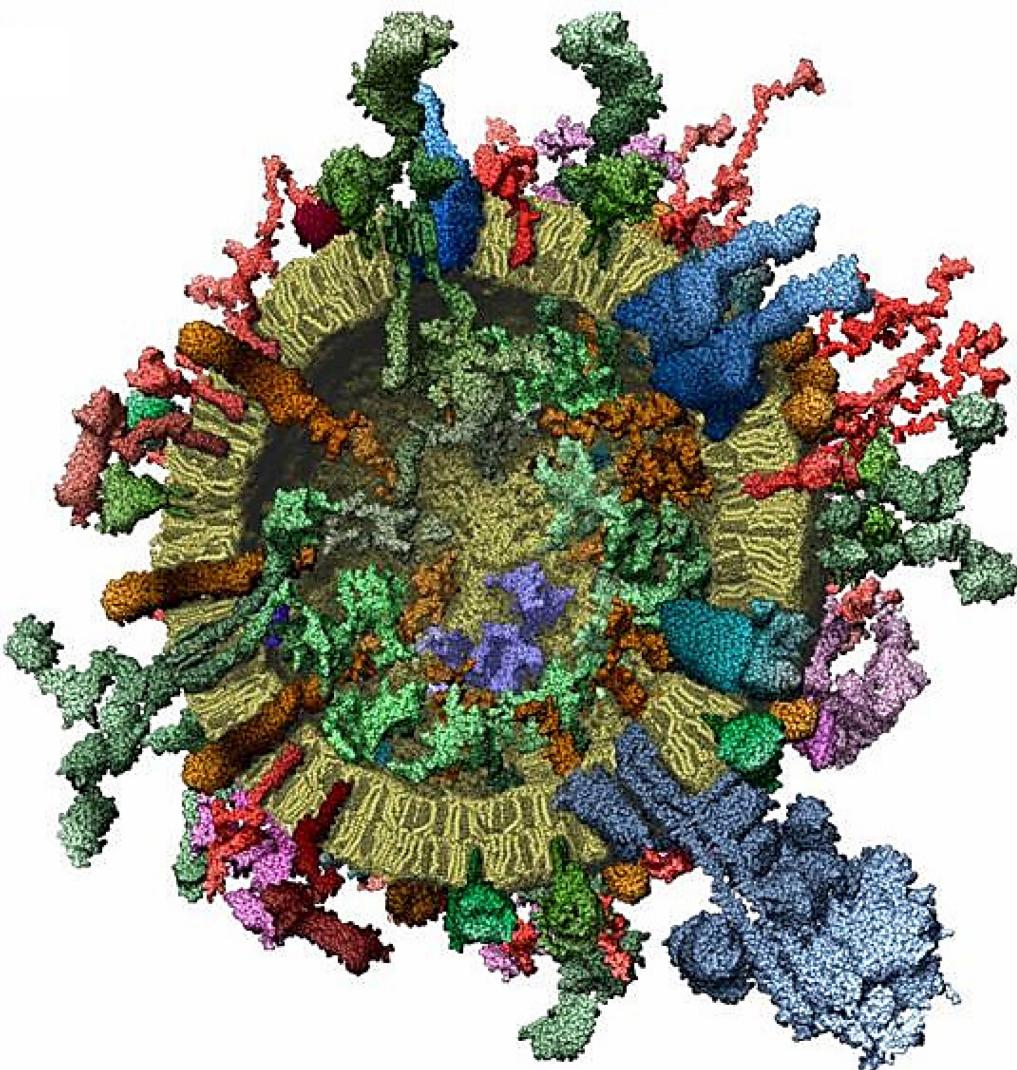
Molecular Scale Model of a Synaptic Vesicle

Physical Parameters	
Density (g/ml)	1.10
Outer diameter (nm)	41.6
Inner aqueous volume (l)	19.86×10^{-21}
Number of neurotransmitter molecules (at 150 mM)	1790
Mass (g) ^a	29.6×10^{-18}
Mass (MDa) ^a	17.8
Protein:phospholipids (w:w)	1.94
Phospholipids:cholesterol (mol:mol)	1:0.8
Transmembrane domains (number/% of surface coverage) ^b	600/20.0
Protein Stoichiometry (Copies/Vesicle)	
Synaptophysin	31.5
Synaptobrevin/VAMP2	69.8
VGLUT1 ^c	9.0
VGLUT2 ^c	14.4
Synapsins	8.3
Syntaxin 1	6.2
SNAP-25	1.8
Synaptotagmin	15.2
Rab3A	10.3
SV2	1.7
Synaptogyrin	2.0
SCAMP1	0.8
CSP	2.8
V-ATPase ^d	1.4

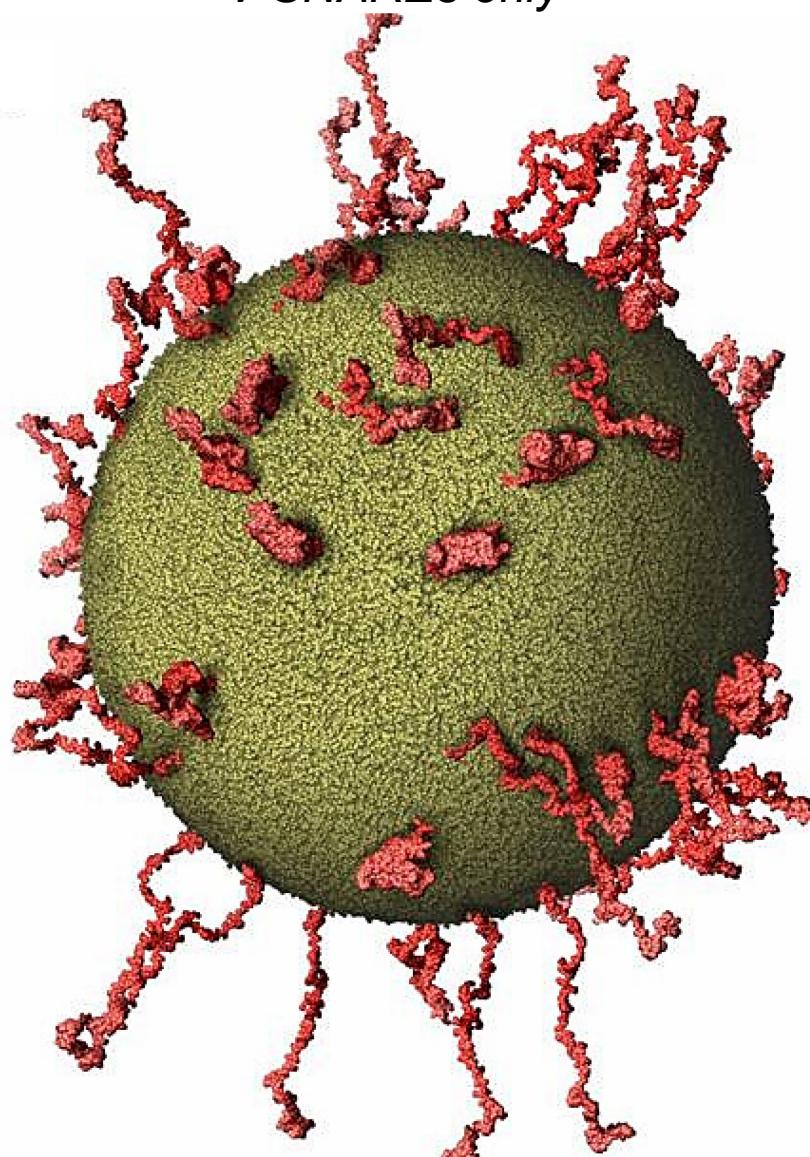


Molecular Scale Model of a Synaptic Vesicle

Cut-away view

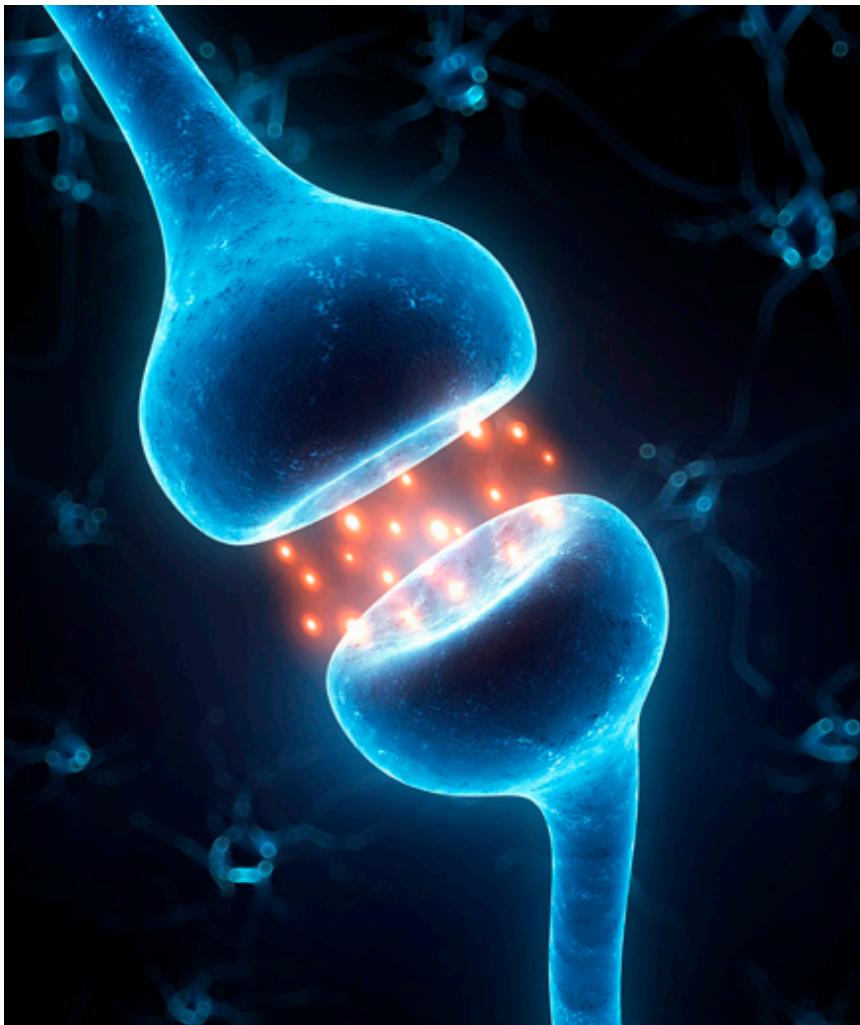


v-SNAREs only



Synaptic Plasticity

The ability of a synapse to change in strength



Short-Term Plasticity

(lasts milliseconds to minutes)

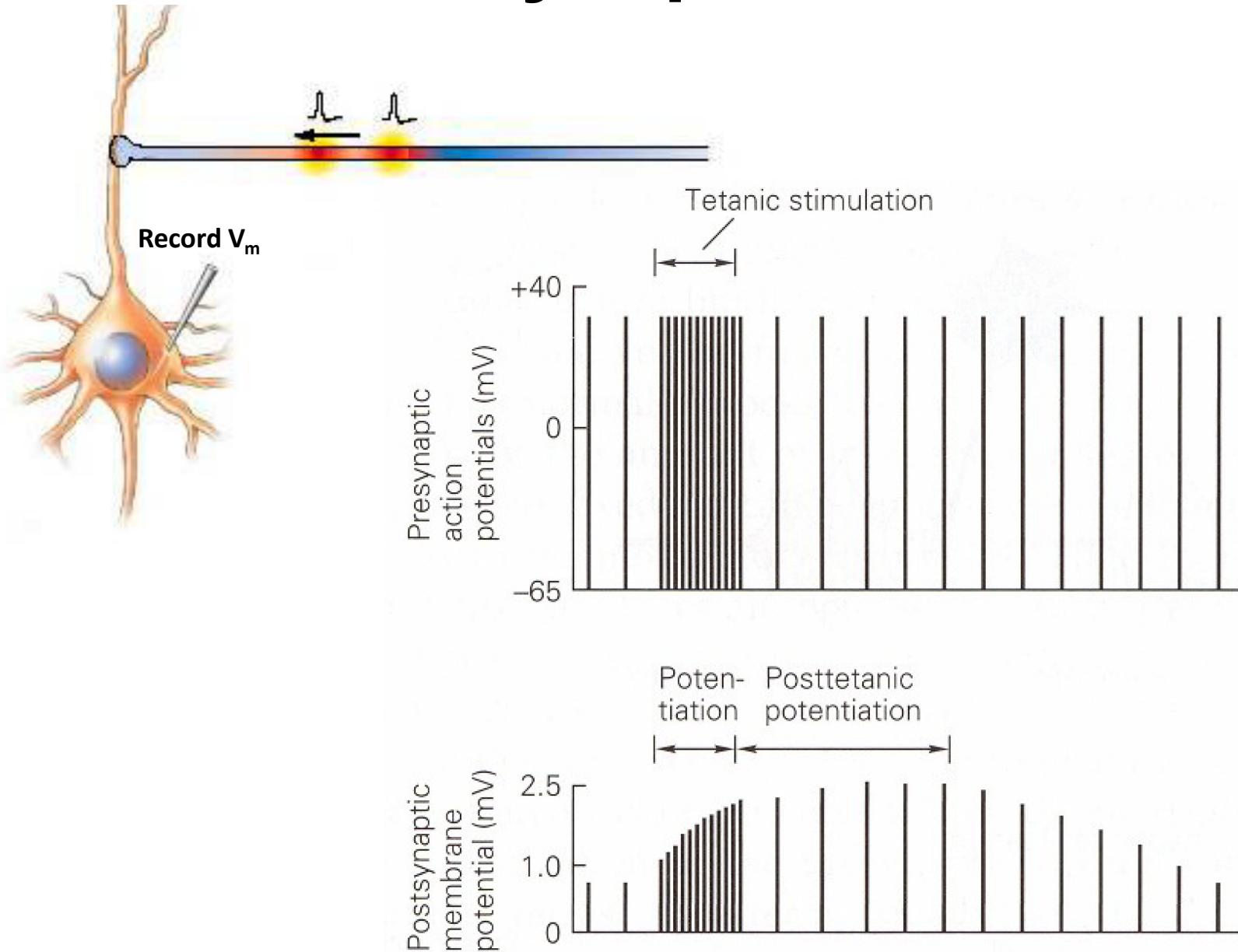
- Short-term synaptic facilitation/potentiation
- Short-term synaptic depression
- Paired pulse facilitation
- Paired pulse depression
- Presynaptic facilitation
- Presynaptic inhibition

Long-Term Plasticity

(lasts hours or longer)

- Long-term potentiation
- Long-term depression

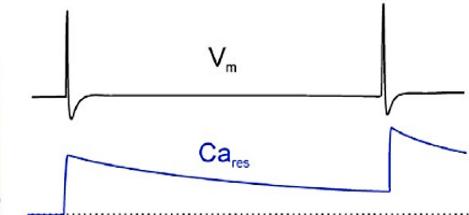
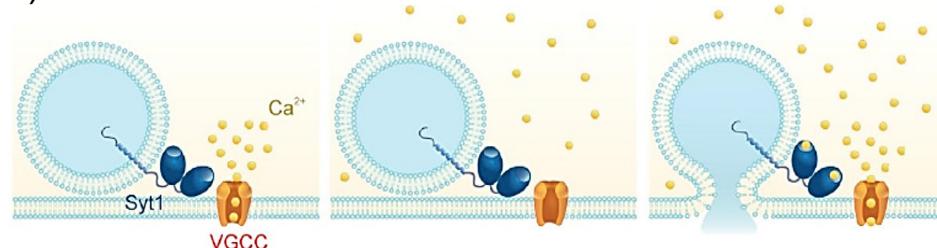
Short-Term Synaptic Potentiation



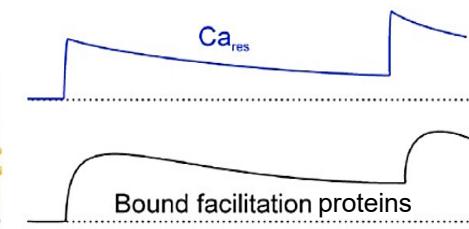
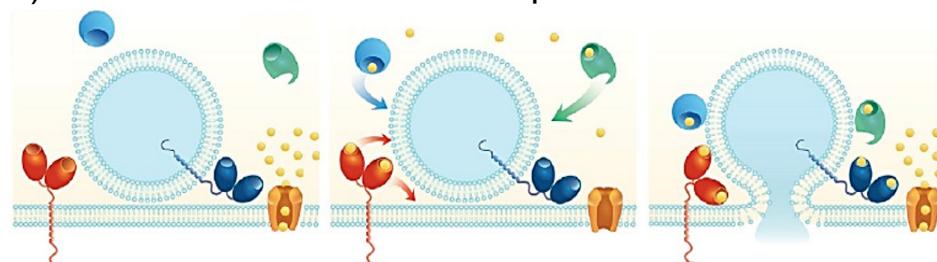
Short-Term Synaptic Potentiation

Effects of Residual Calcium

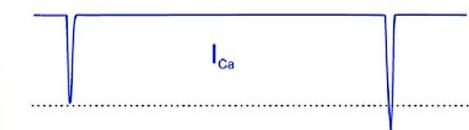
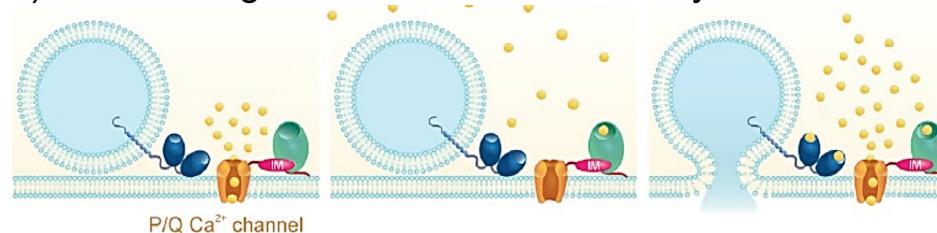
A) Calcium concentrations summate



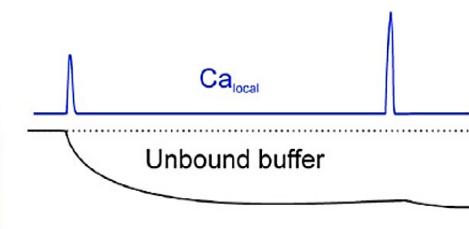
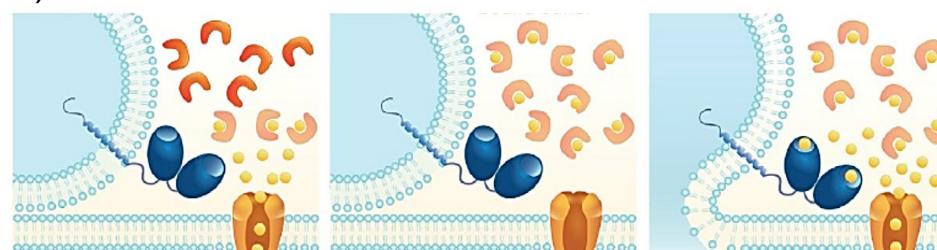
B) Calcium activates facilitation proteins



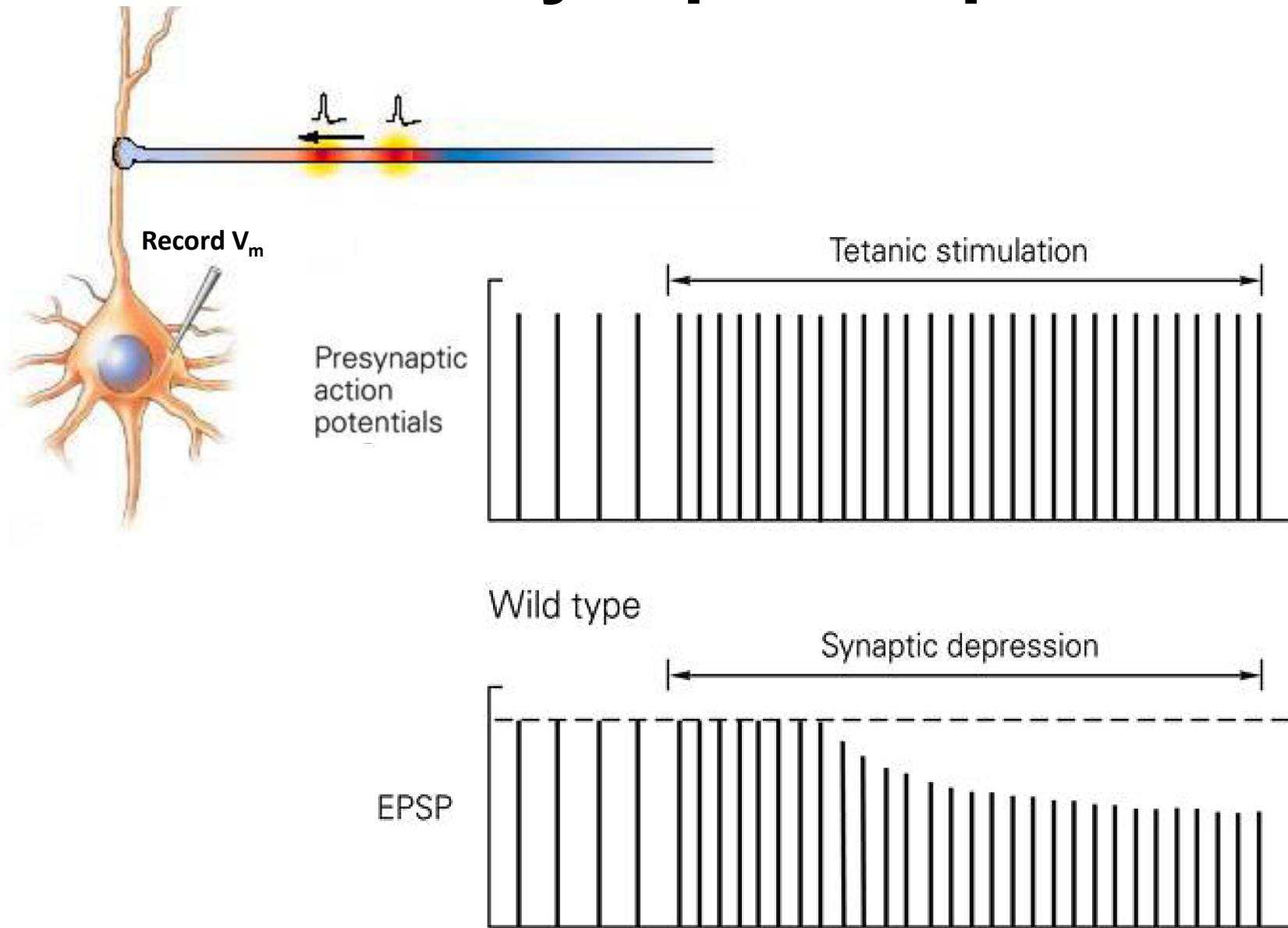
C) Calcium augments Ca^{2+} channel activity



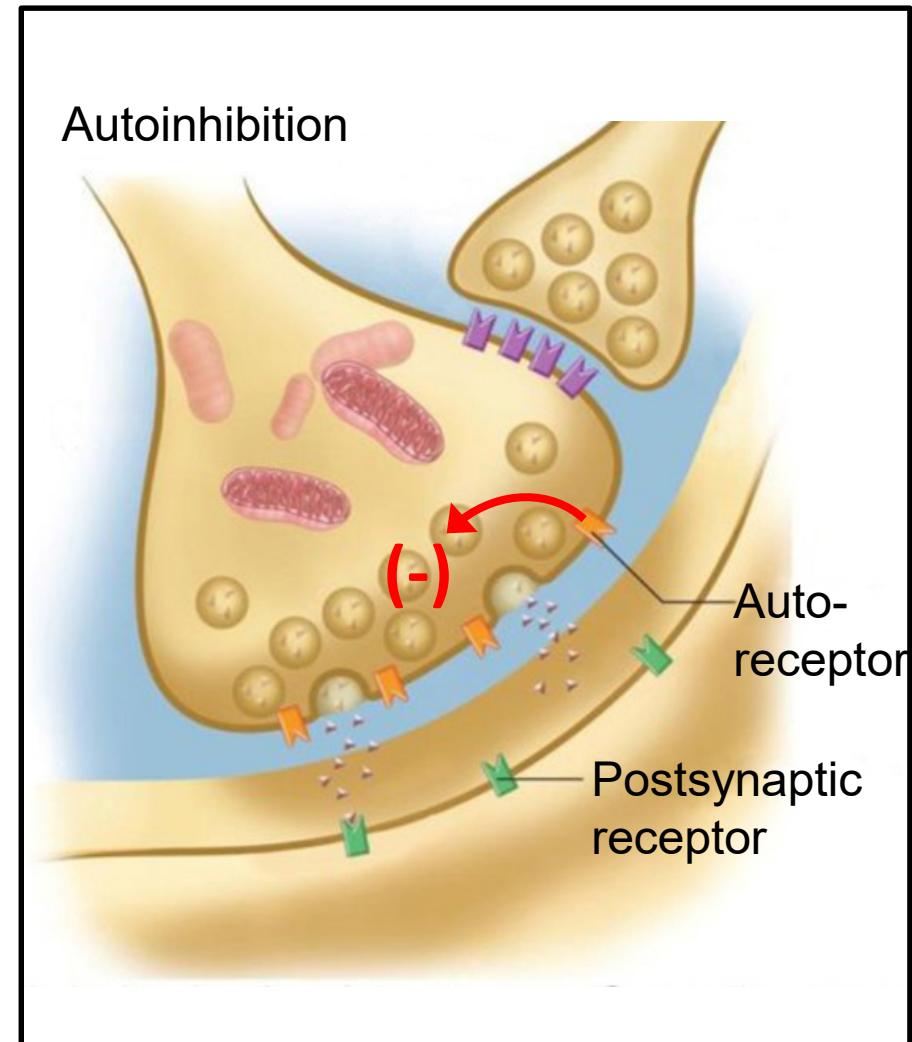
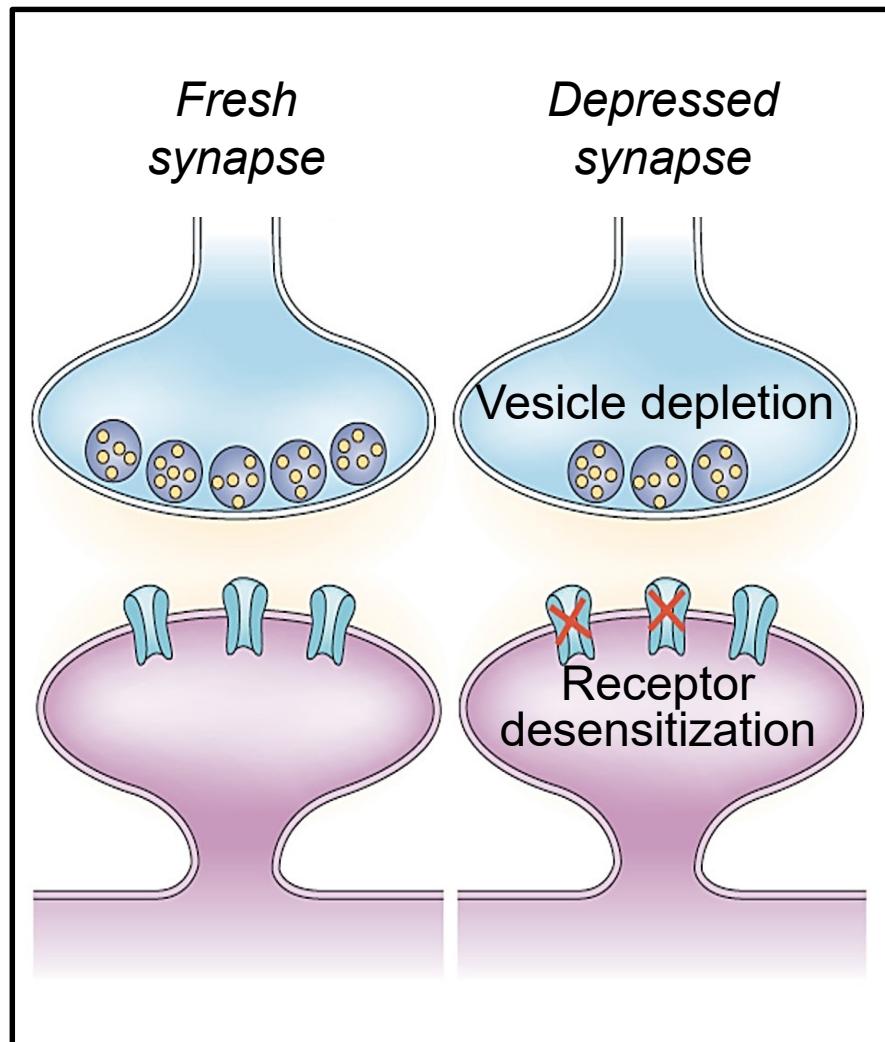
D) Calcium buffer saturation



Short-Term Synaptic Depression

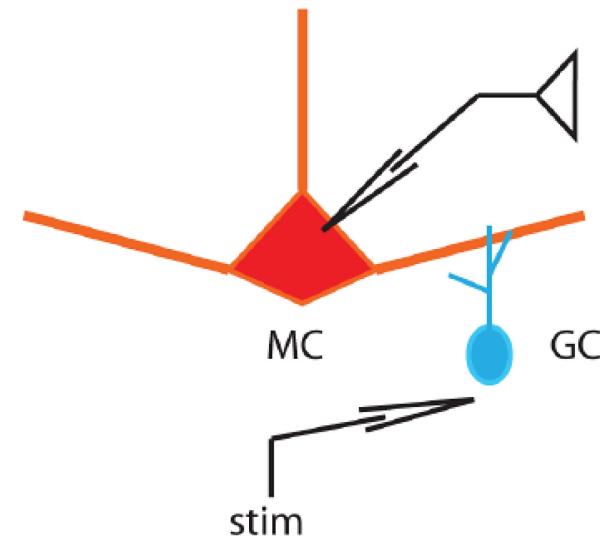


Short-Term Synaptic Depression

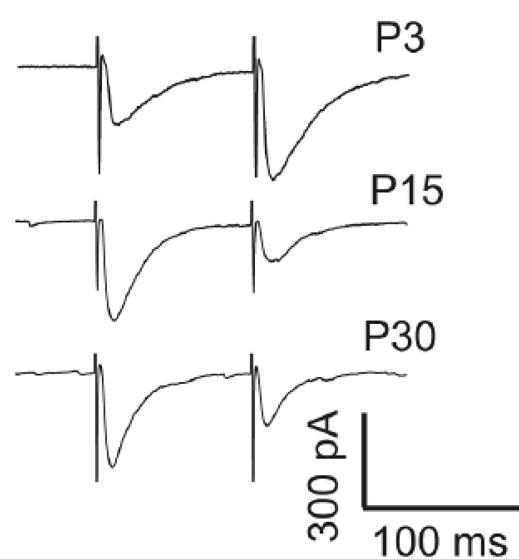


Paired Pulse Facilitation and Paired Pulse Depression

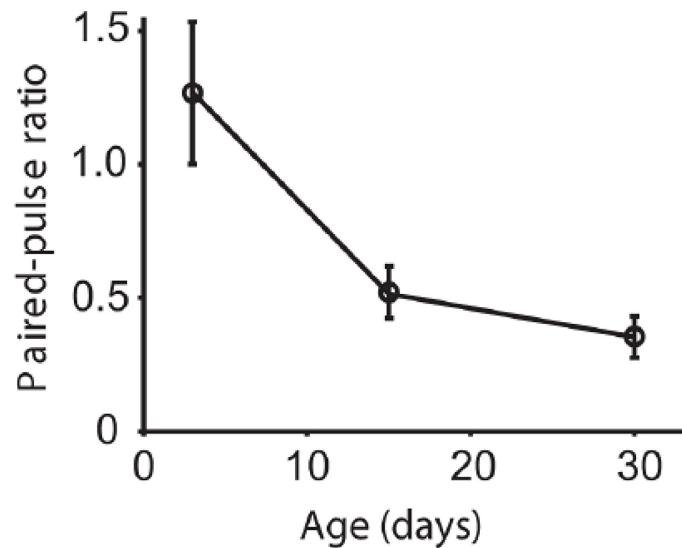
A



B



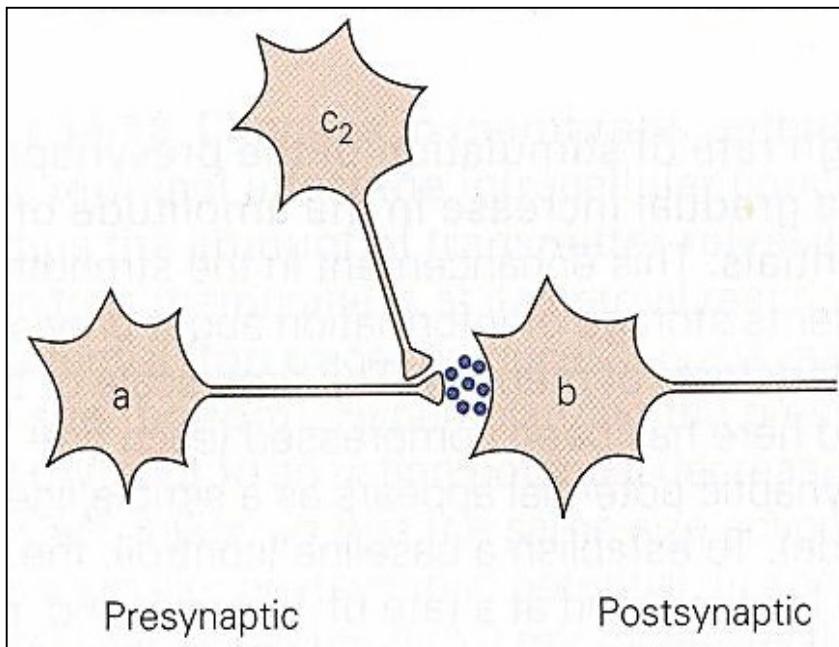
C



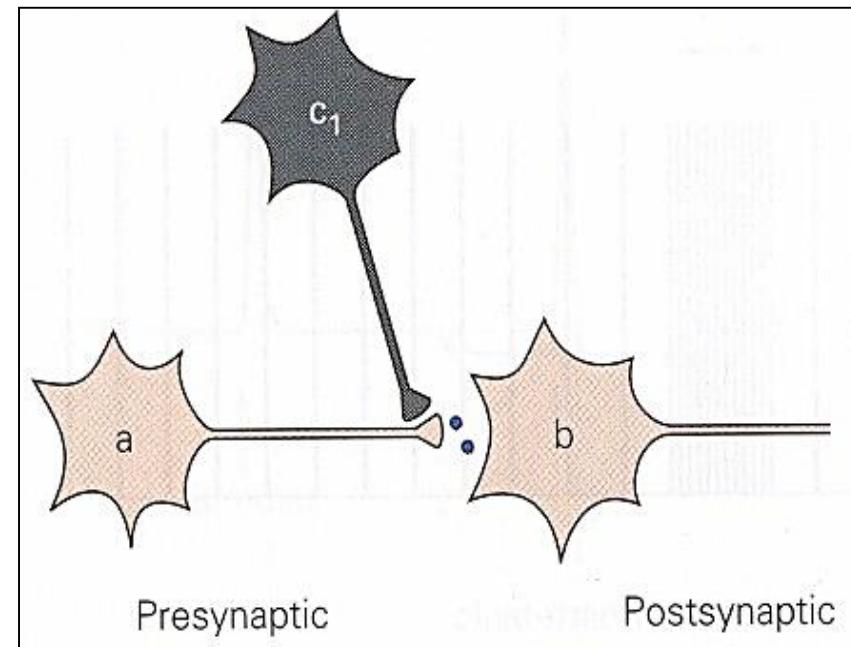
Presynaptic Facilitation and Inhibition

(involve axo-axonic synapses)

Presynaptic Facilitation



Presynaptic Inhibition



Neuron C stimulates the axon terminal of neuron A, augmenting transmitter release

Neuron C inhibits the axon terminal of neuron A, causing a decrease in transmitter release

Presynaptic Facilitation and Inhibition

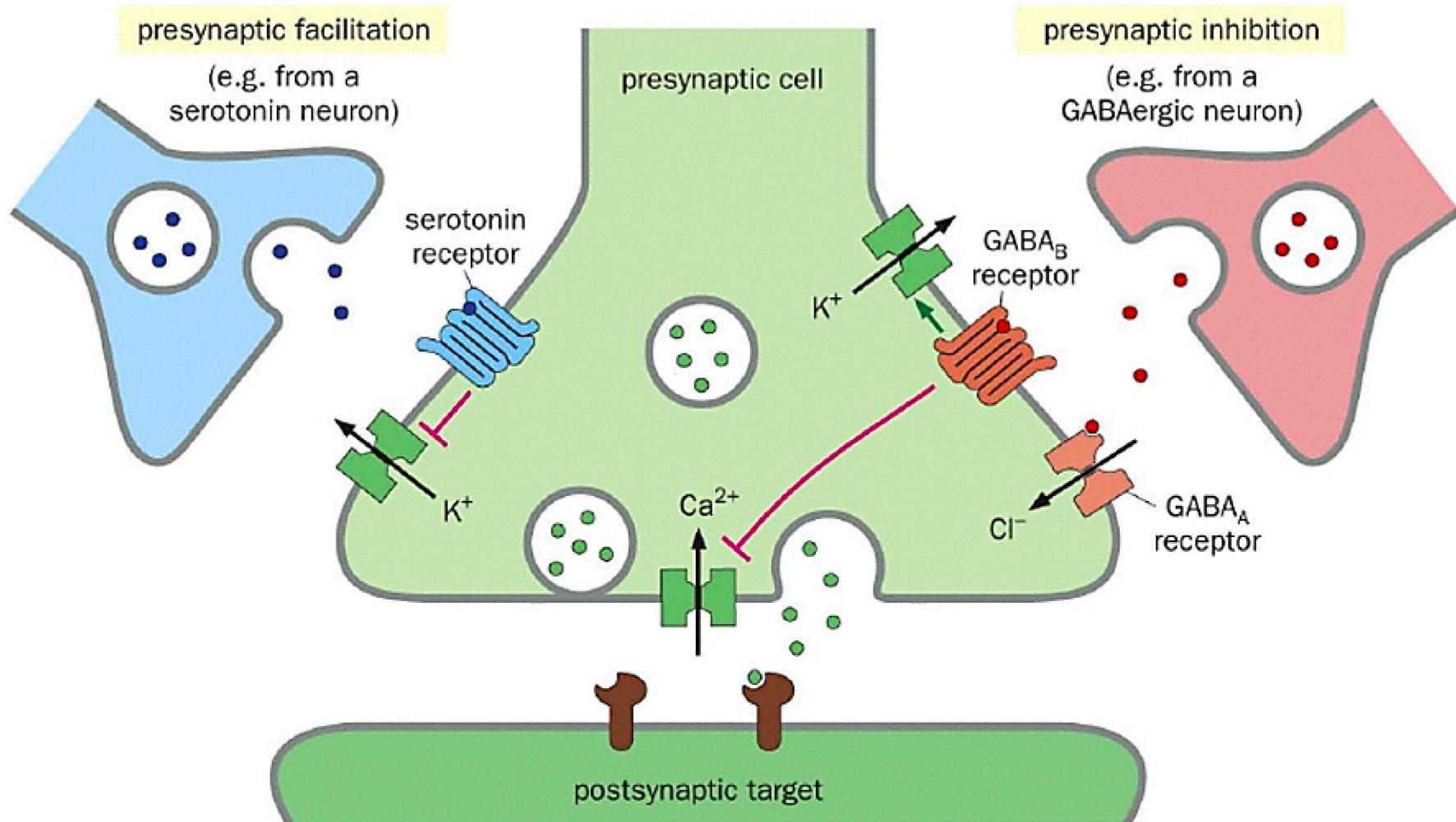


Figure 3-37 Principles of Neurobiology (© Garland Science 2016)