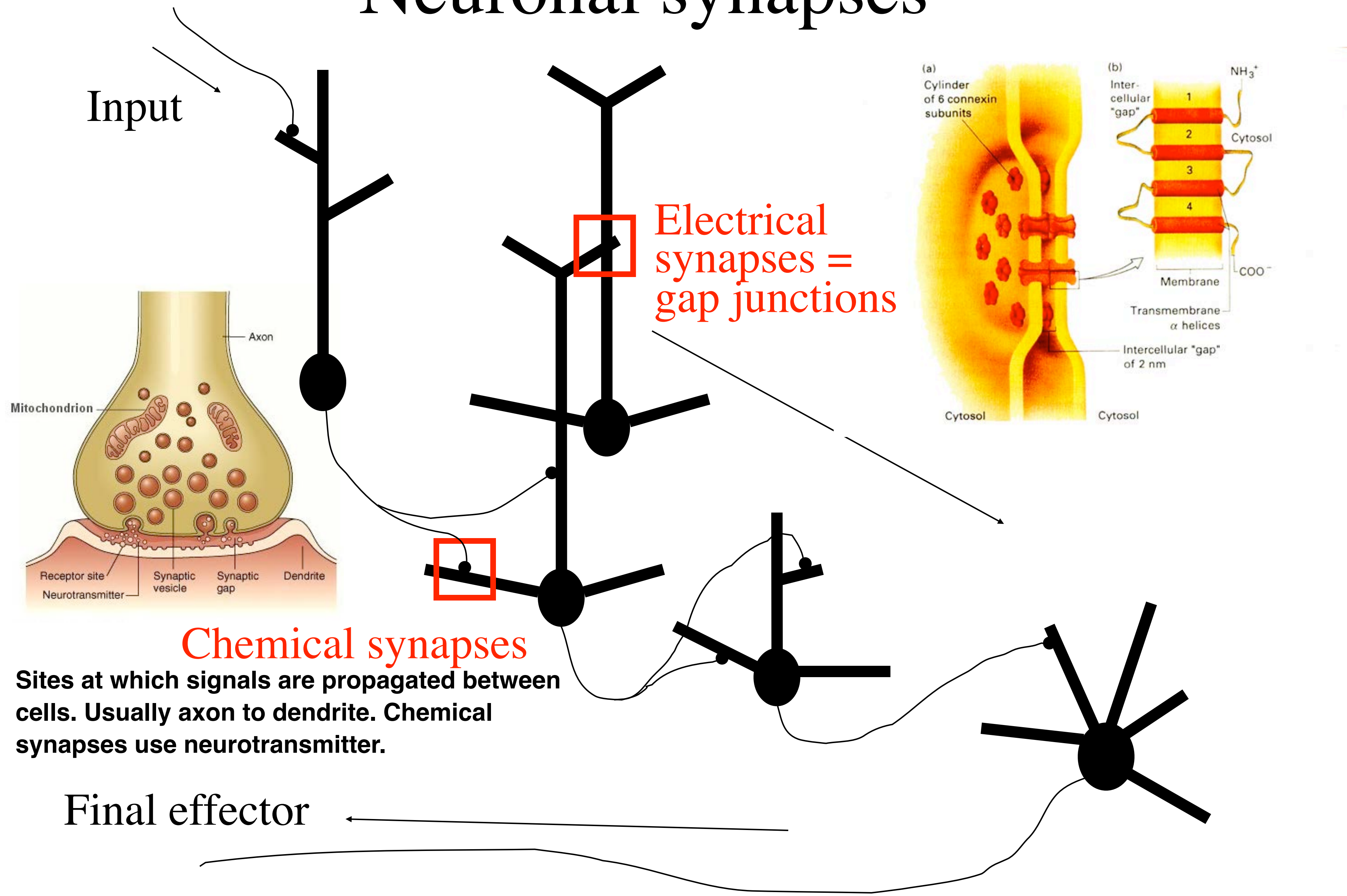
Synapses

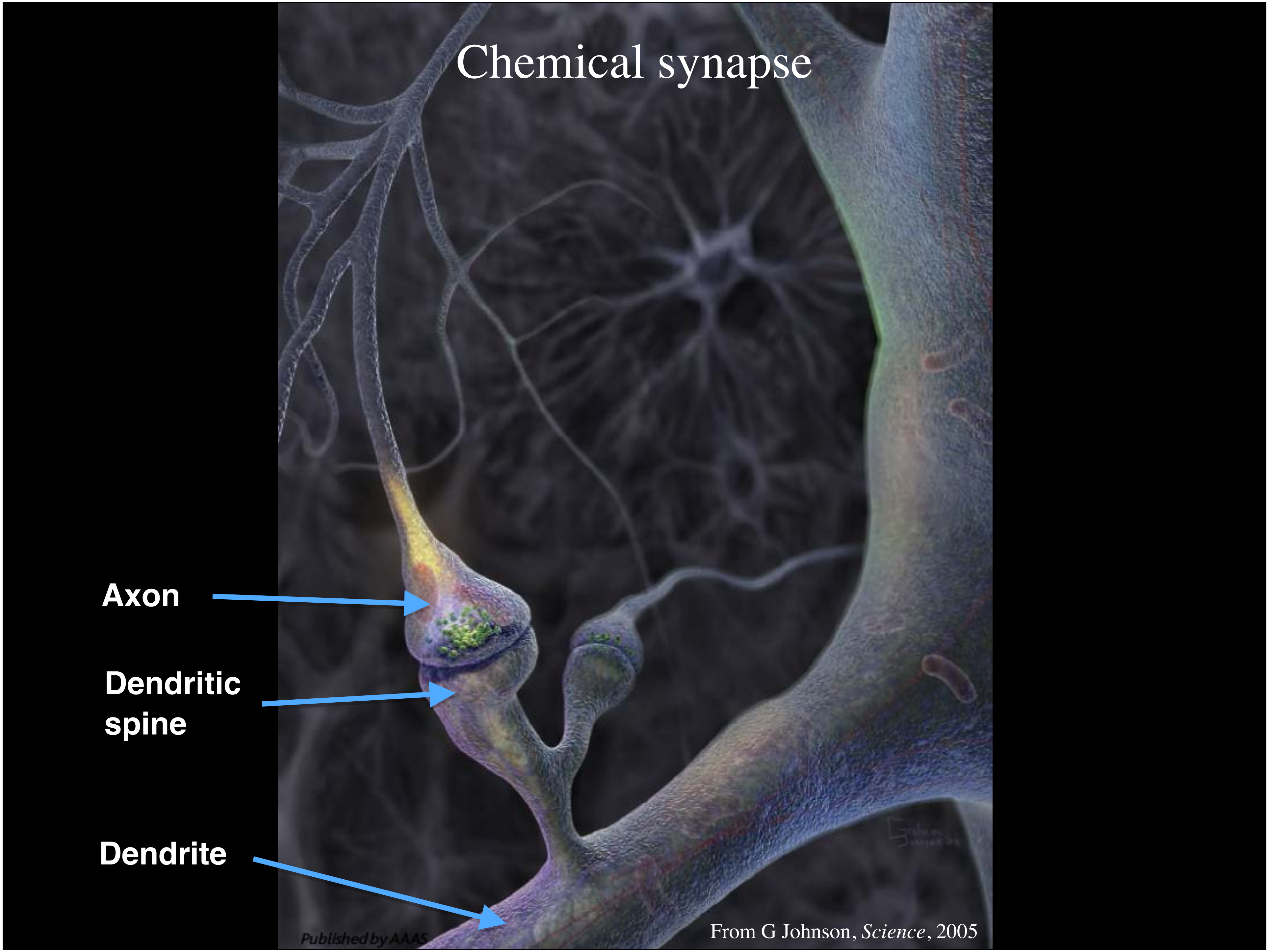
Pietro De Camilli

October 12, 2012

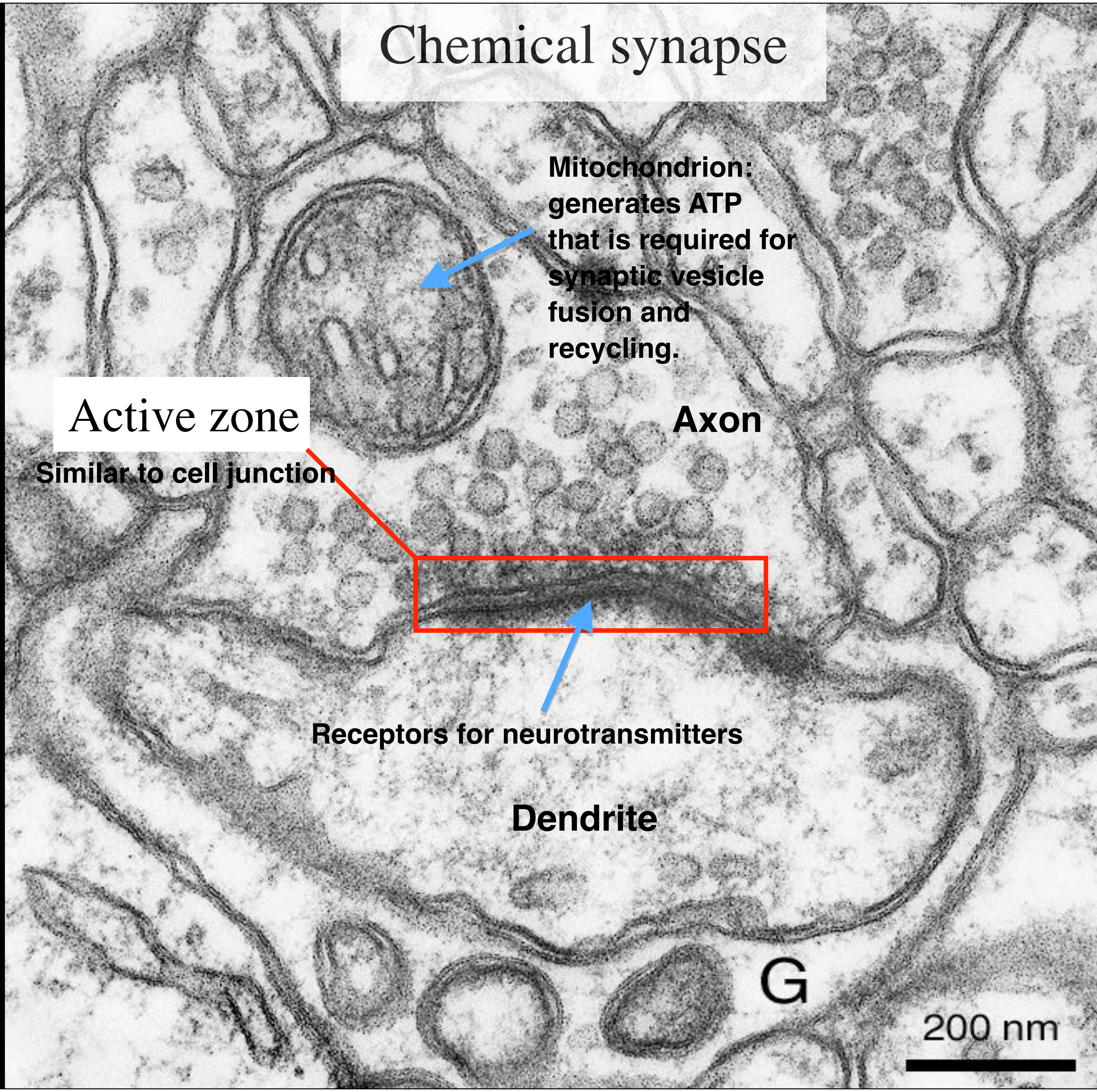
Neuronal synapses



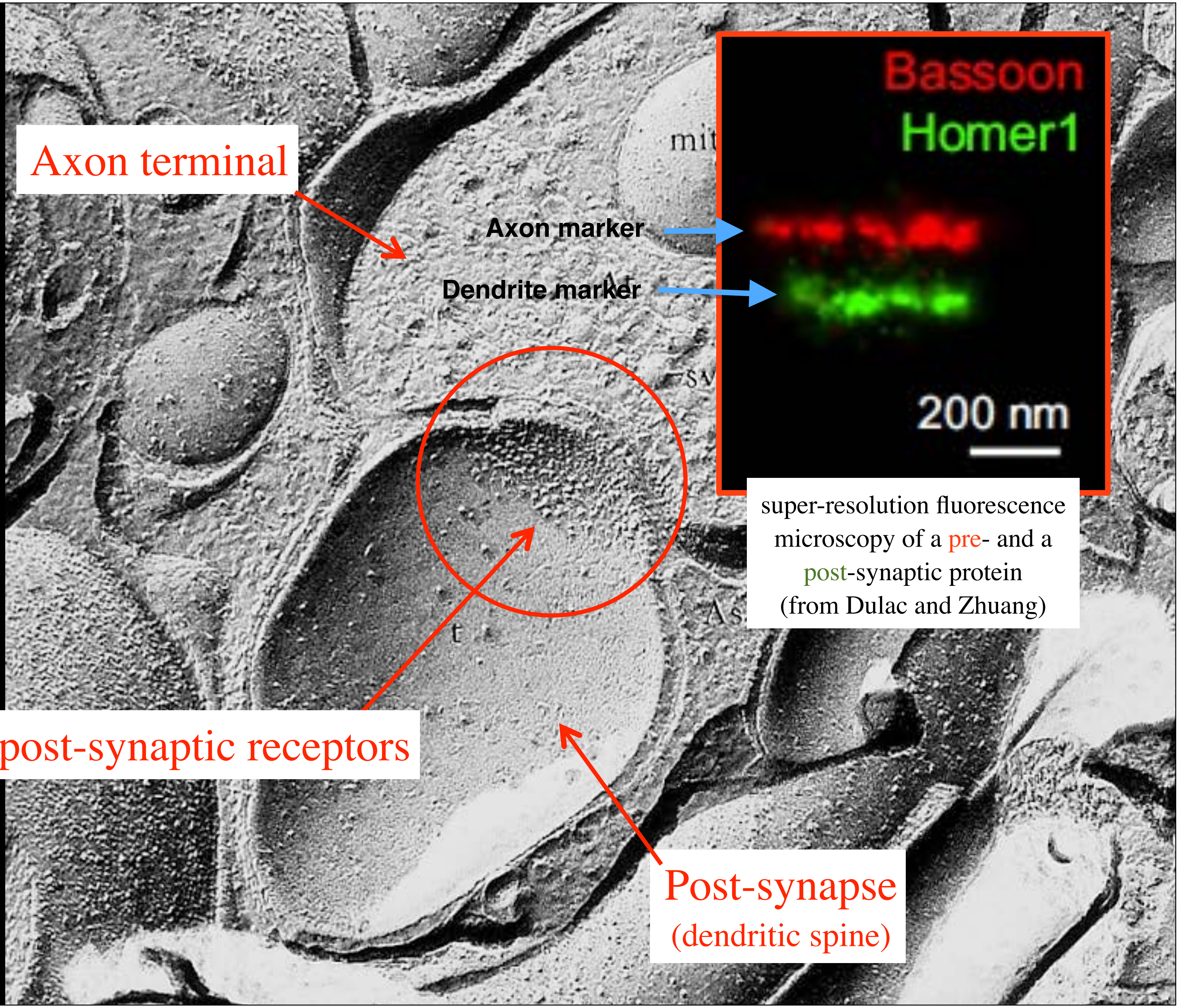
Sites at which signals are propagated between cells. Usually axon to dendrite. Chemical synapses use neurotransmitter.


Chemical synapse
Axon
Dendritic
spine
Dendrite
Published by AAAS
From G Johnson, *Science*, 2005

Chemical synapse



Freeze-fracture view

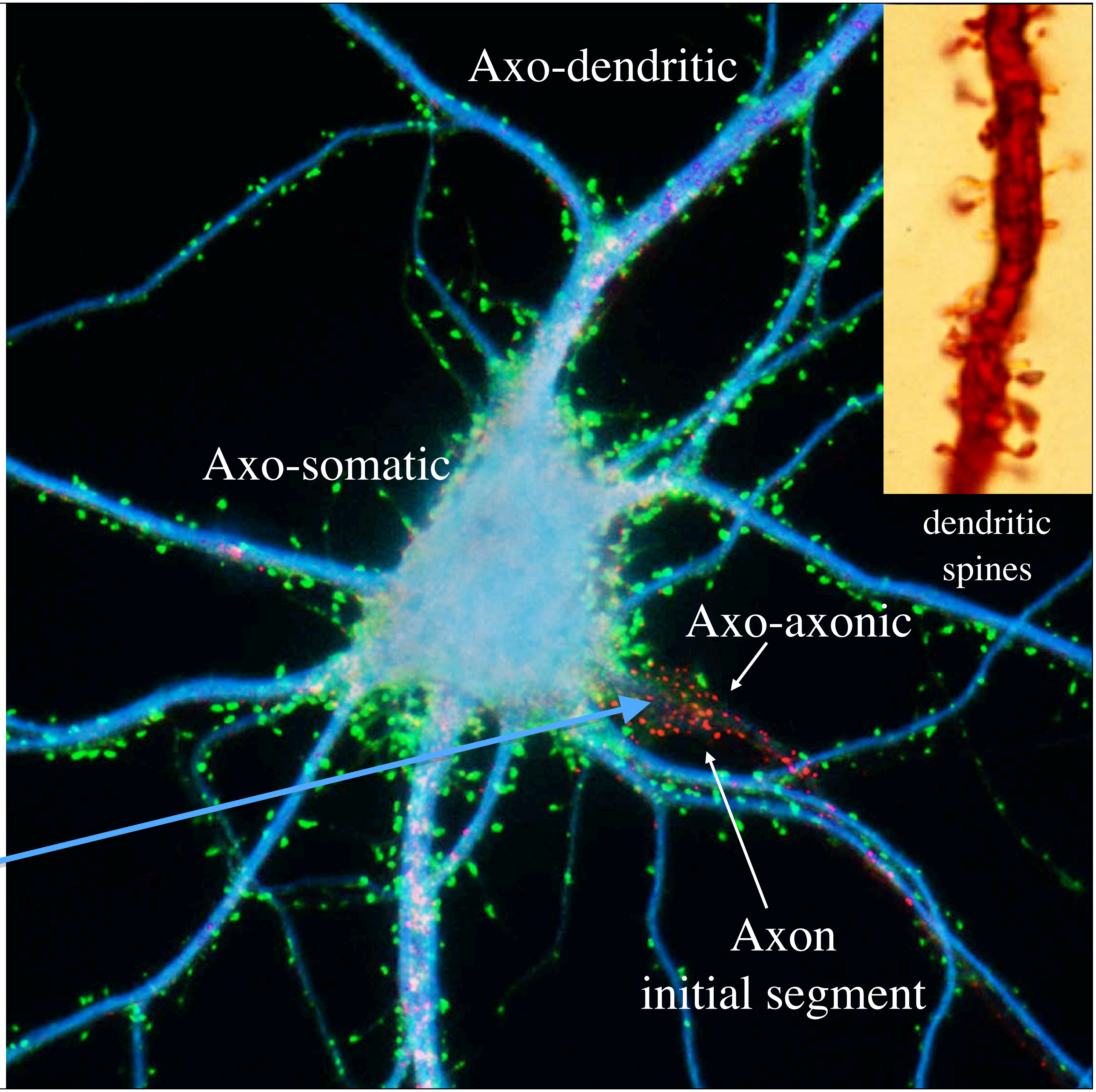


super-resolution fluorescence microscopy of a pre- and a post-synaptic protein (from Dulac and Zhuang)

Green = glutamatergic (excitatory) synapses

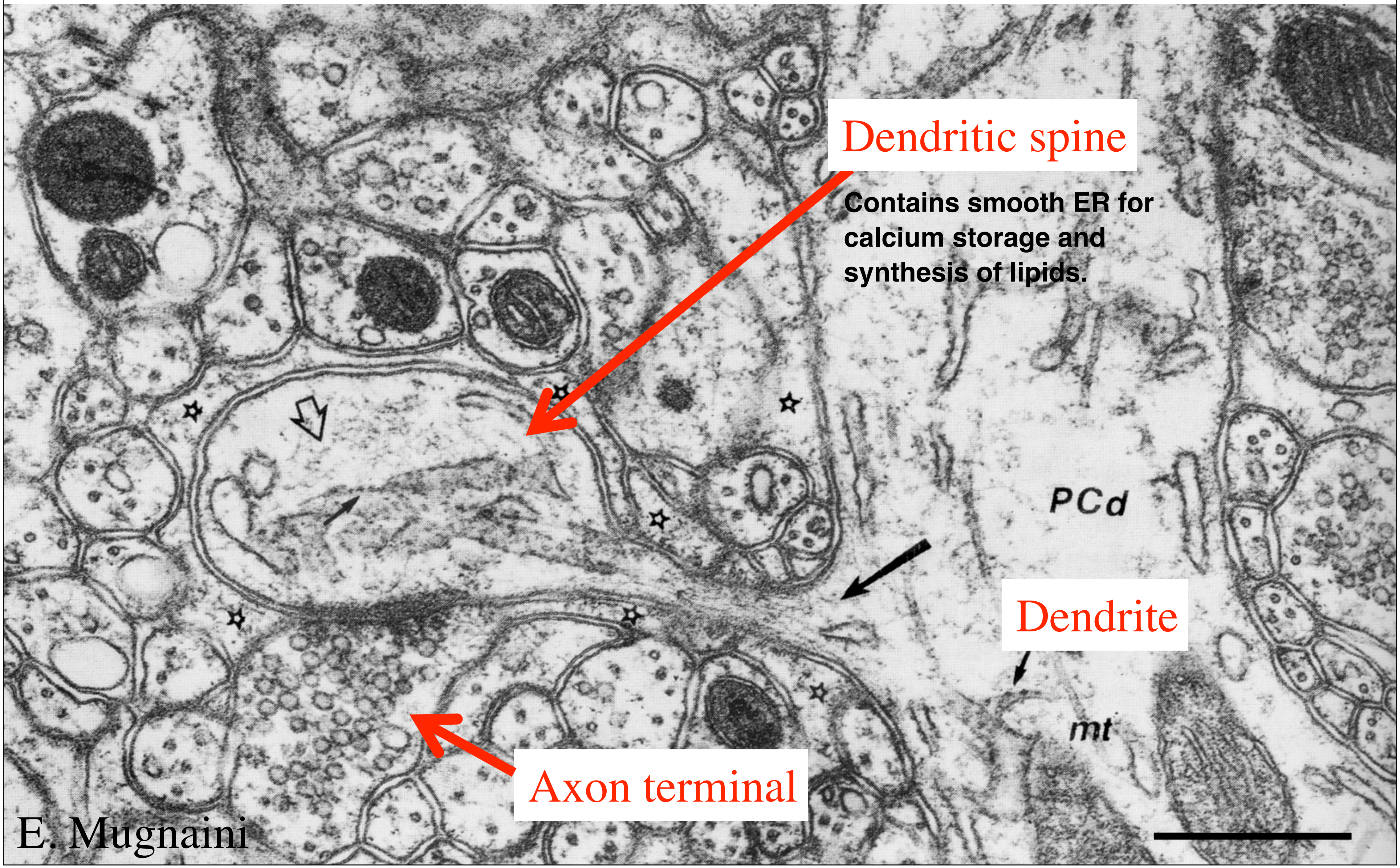
Red = GABA-ergic (inhibitory) synapses

Majority of inhibitory synapses on initial segment of axon. Place where decision to generate action potential is made.

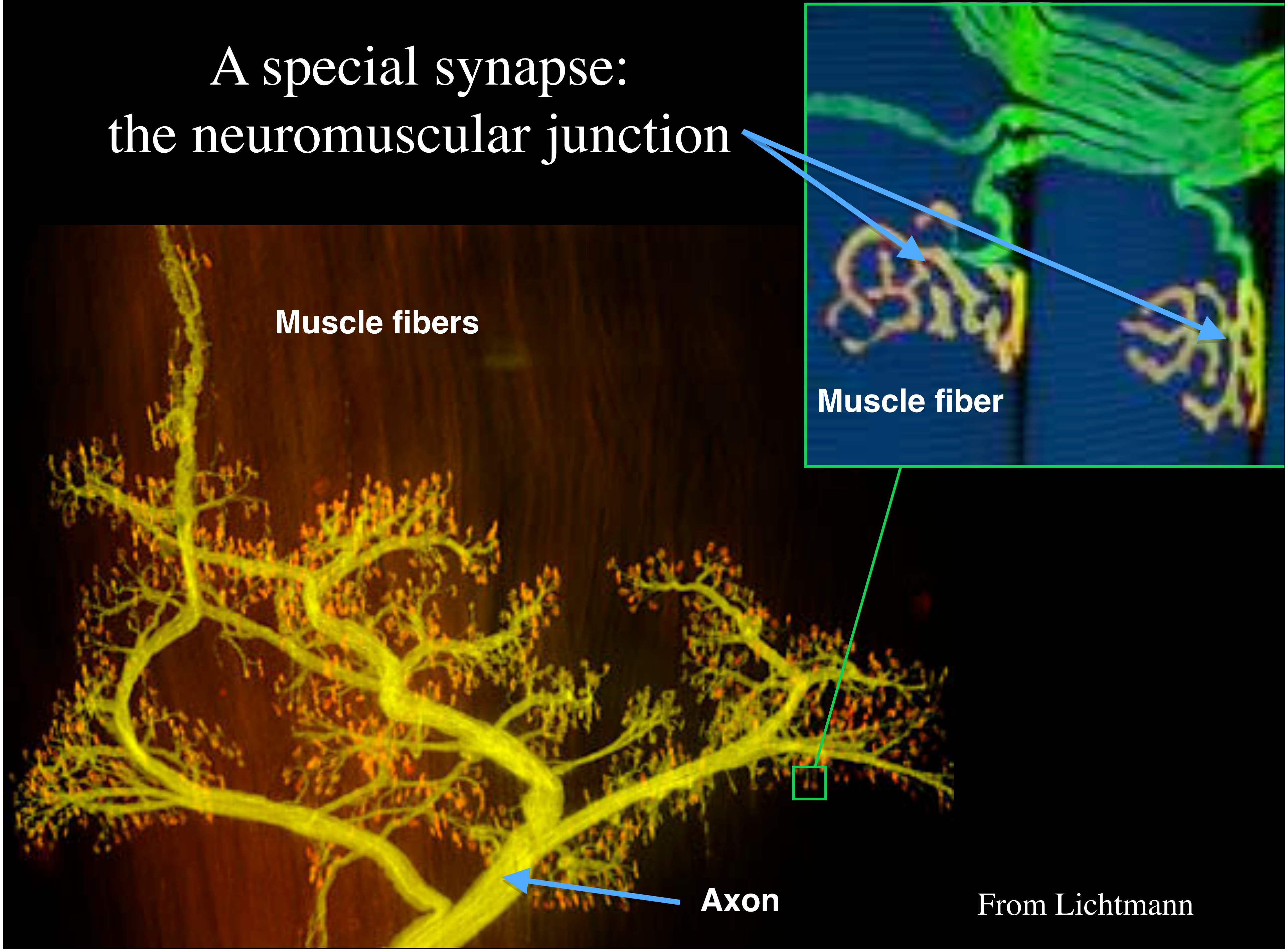


From Craig A.M.

spine synapse (cerebellum)



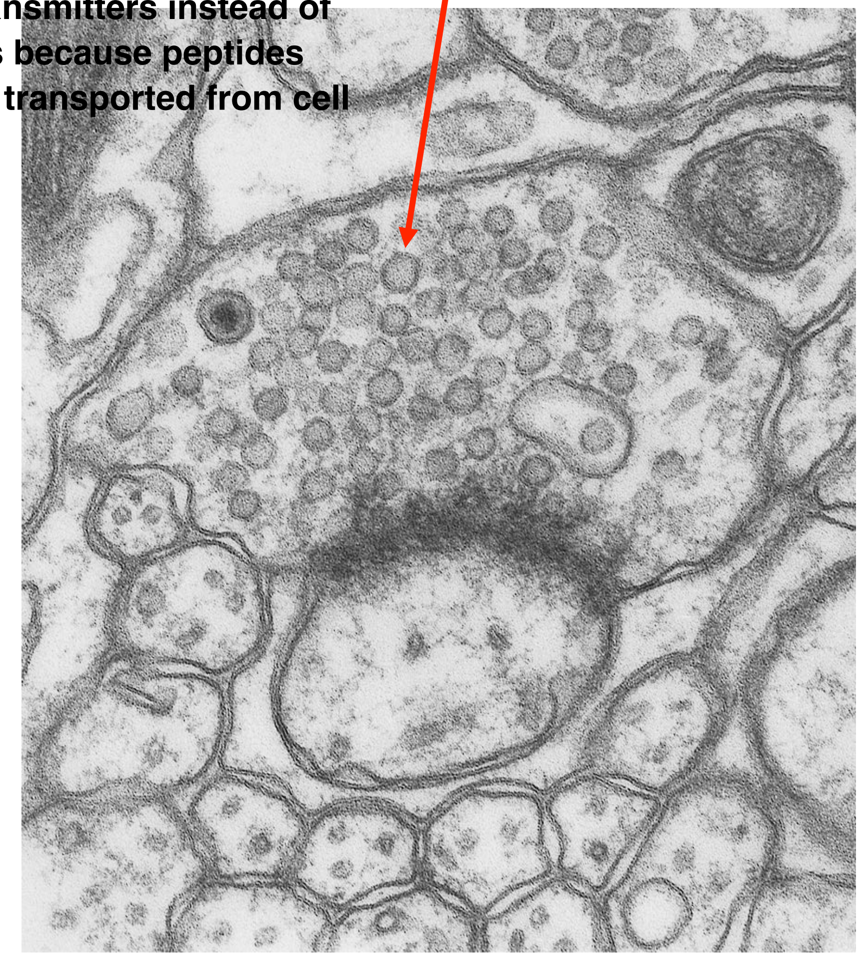
A special synapse: the neuromuscular junction



From Lichtmann

Synaptic vesicles store fast-acting neurotransmitters

Because axon terminus must continuously release vesicles over short period of time, vesicles are recycled through endocytosis. Neurons use small metabolites for neurotransmitters instead of peptides because peptides must be transported from cell body.



Neurotransmitters contained in synaptic vesicles:

	Gaba, glycine	inhibitory
CNS	Glutamate	excitatory
NMJ	Ach	excitatory
	Amines	excitatory

+ *small non peptide molecules*
+ *fast acting (although can also have slow actions)*

Synaptic vesicles are continuously regenerated in nerve terminals by local membrane recycling

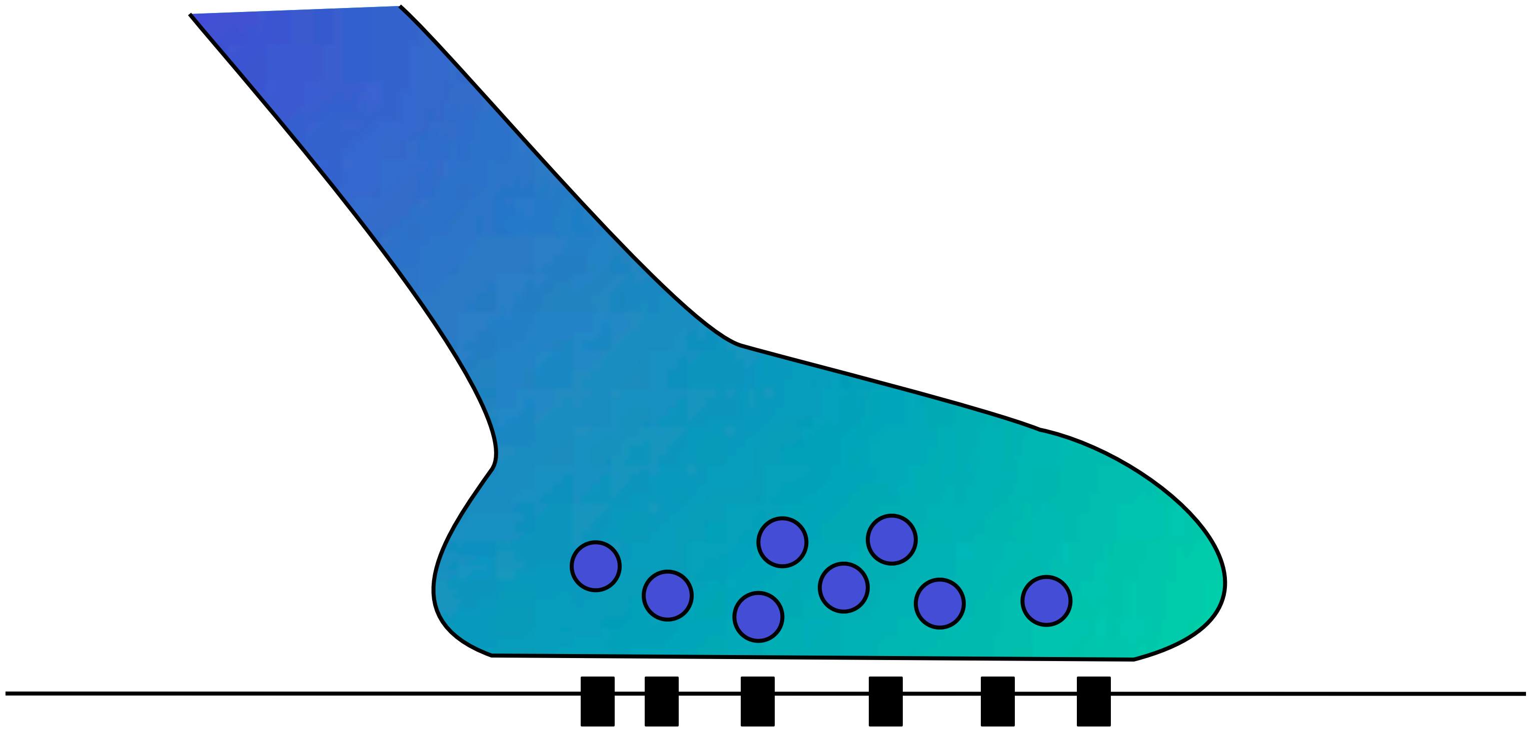
Large dense-core vesicles store neuropeptides

Are assembled in the cell body

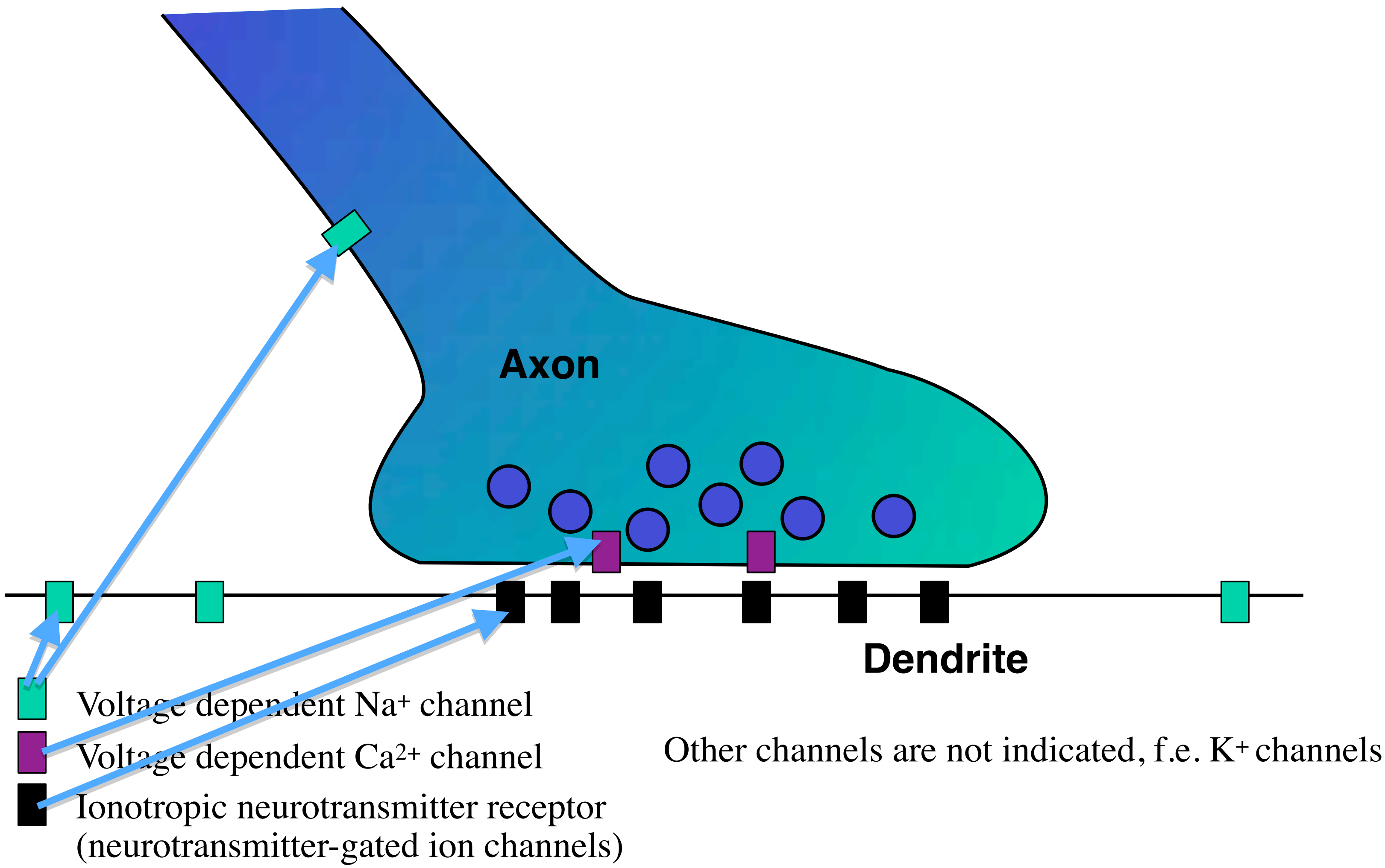
neuropeptides (peptide neurotransmitters) have slow modulatory actions

If axon releases a large amount of neurotransmitter, it will also release neuropeptides that modulate the response of the post-synaptic cell. The neuropeptide prepares the post-synaptic cell to receive a barrage of neurotransmitter.

Key Steps in Synaptic Transmission

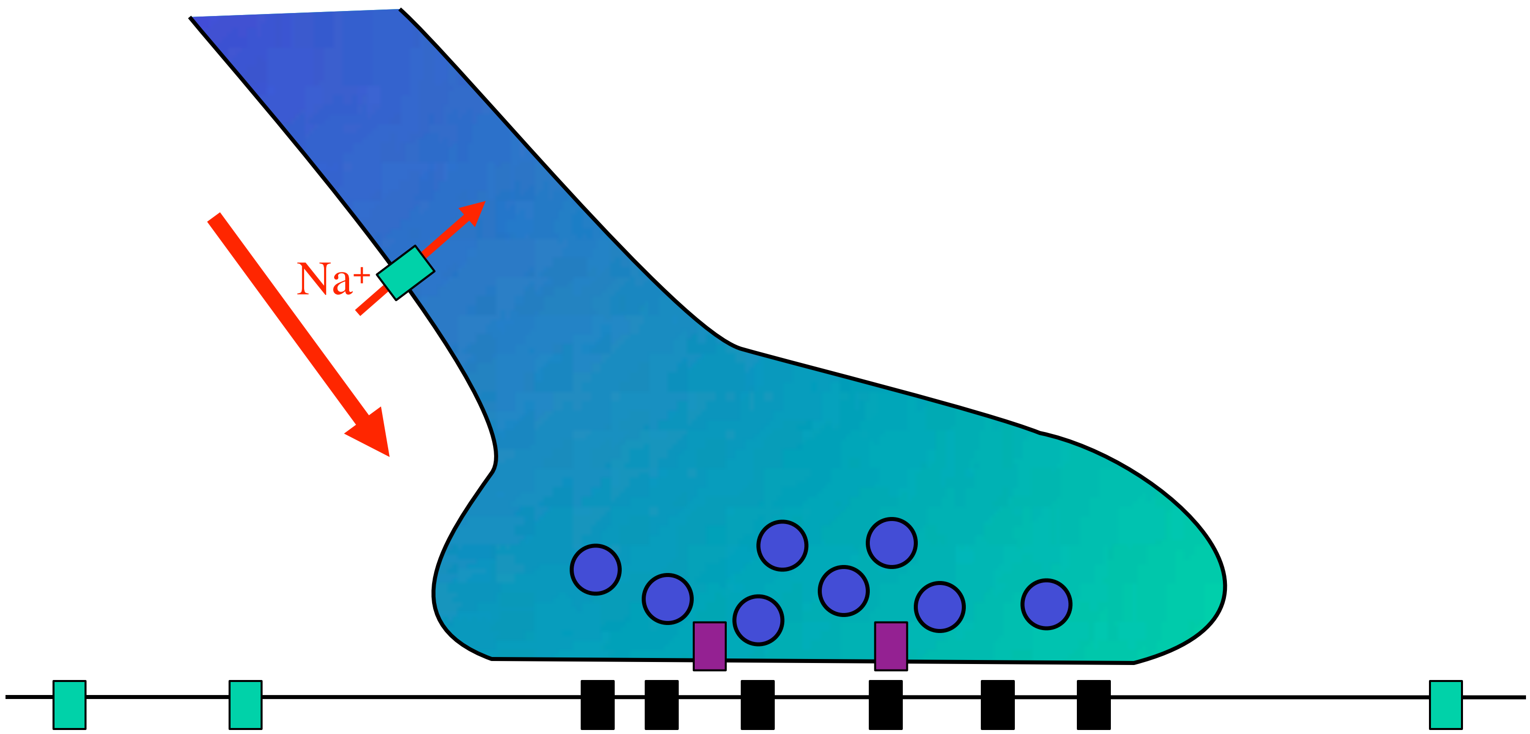


Key Steps in Synaptic Transmission



Key Steps in Synaptic Transmission

The ACTION POTENTIAL travels down the axon:
Opening of voltage-gated Na^+ channels



Key Steps in Synaptic Transmission

The ACTION POTENTIAL travels down the axon:
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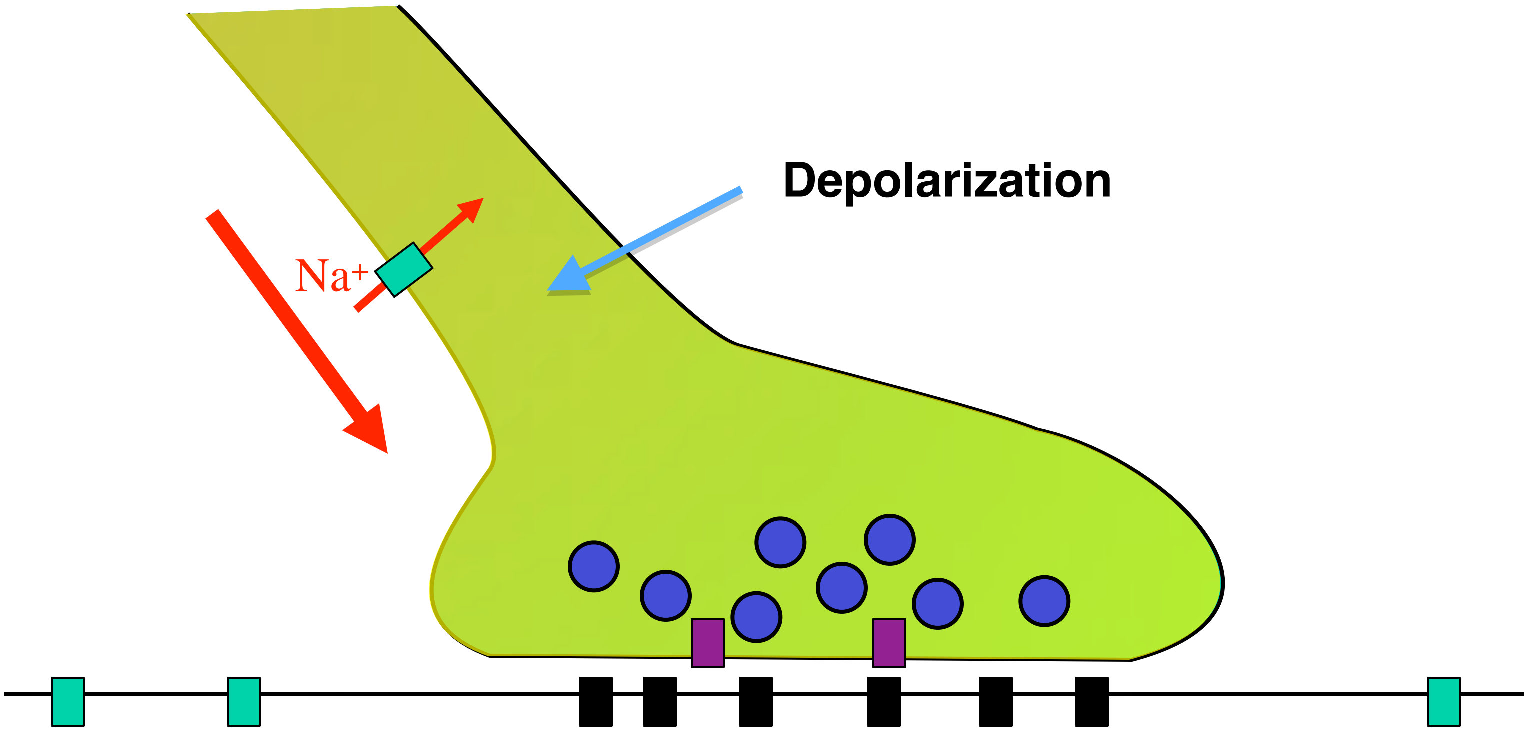
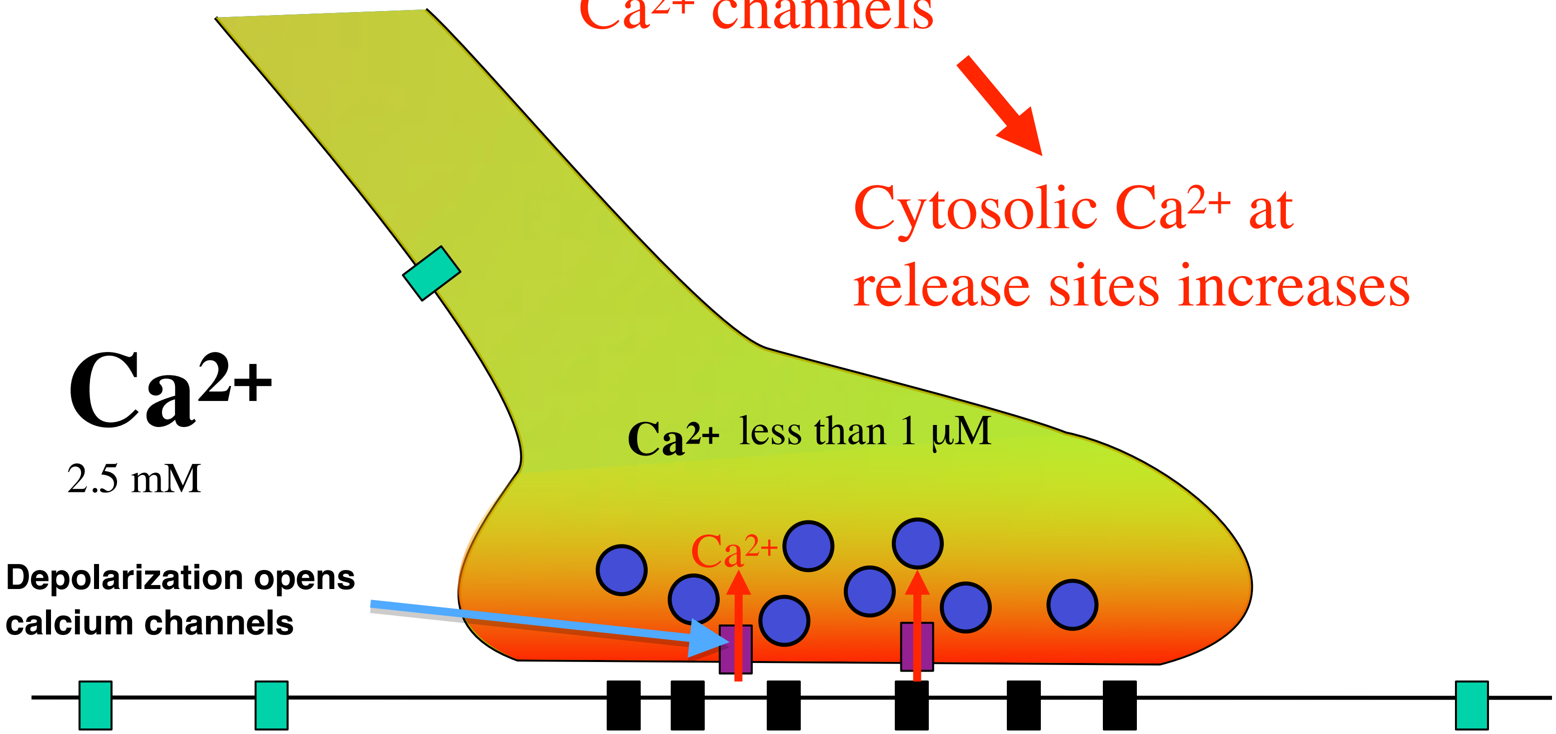


Key Steps in Synaptic Transmission

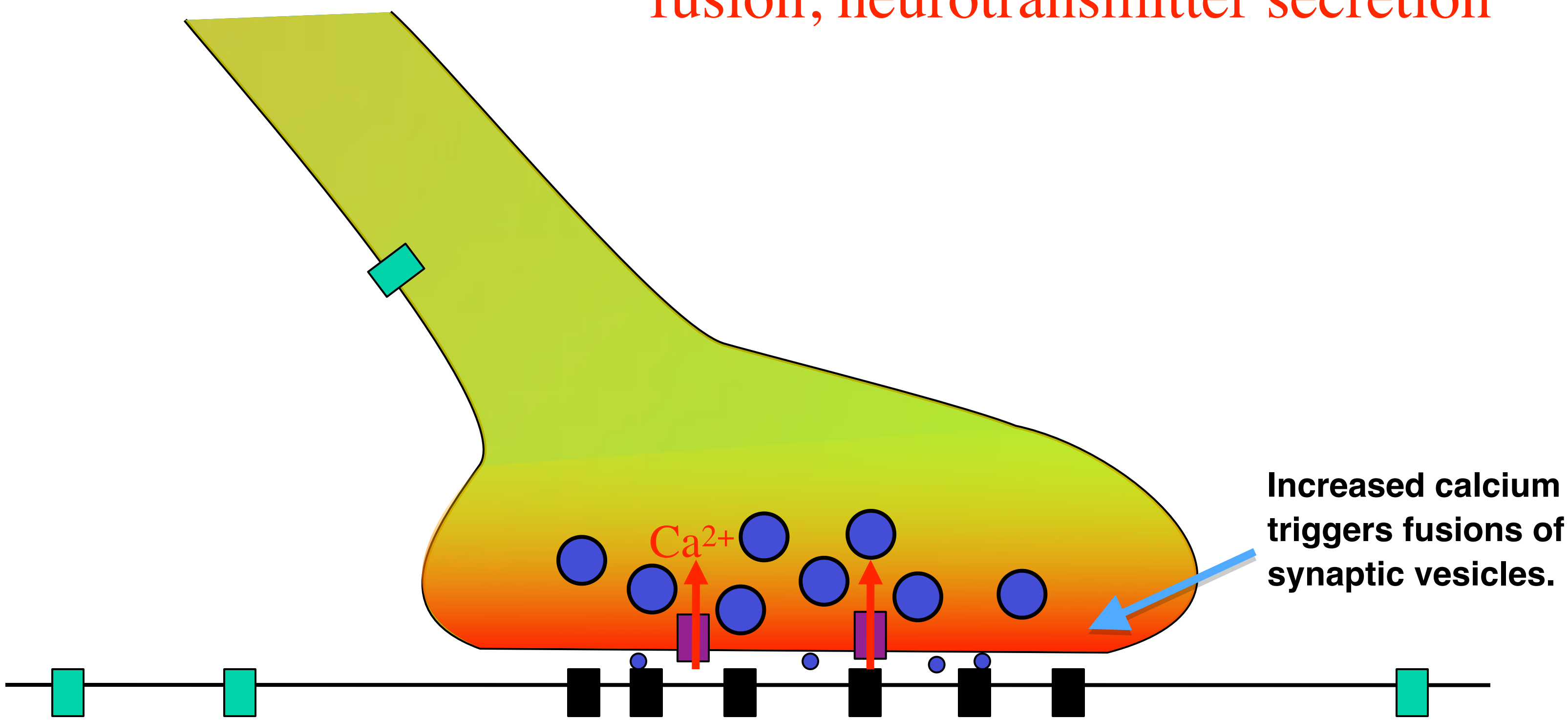
The ACTION POTENTIAL invades the nerve terminal: opening of voltage-gated Ca^{2+} channels

Cytosolic Ca^{2+} at release sites increases



Key Steps in Synaptic Transmission

Ca^{2+} triggers synaptic vesicle fusion, neurotransmitter secretion

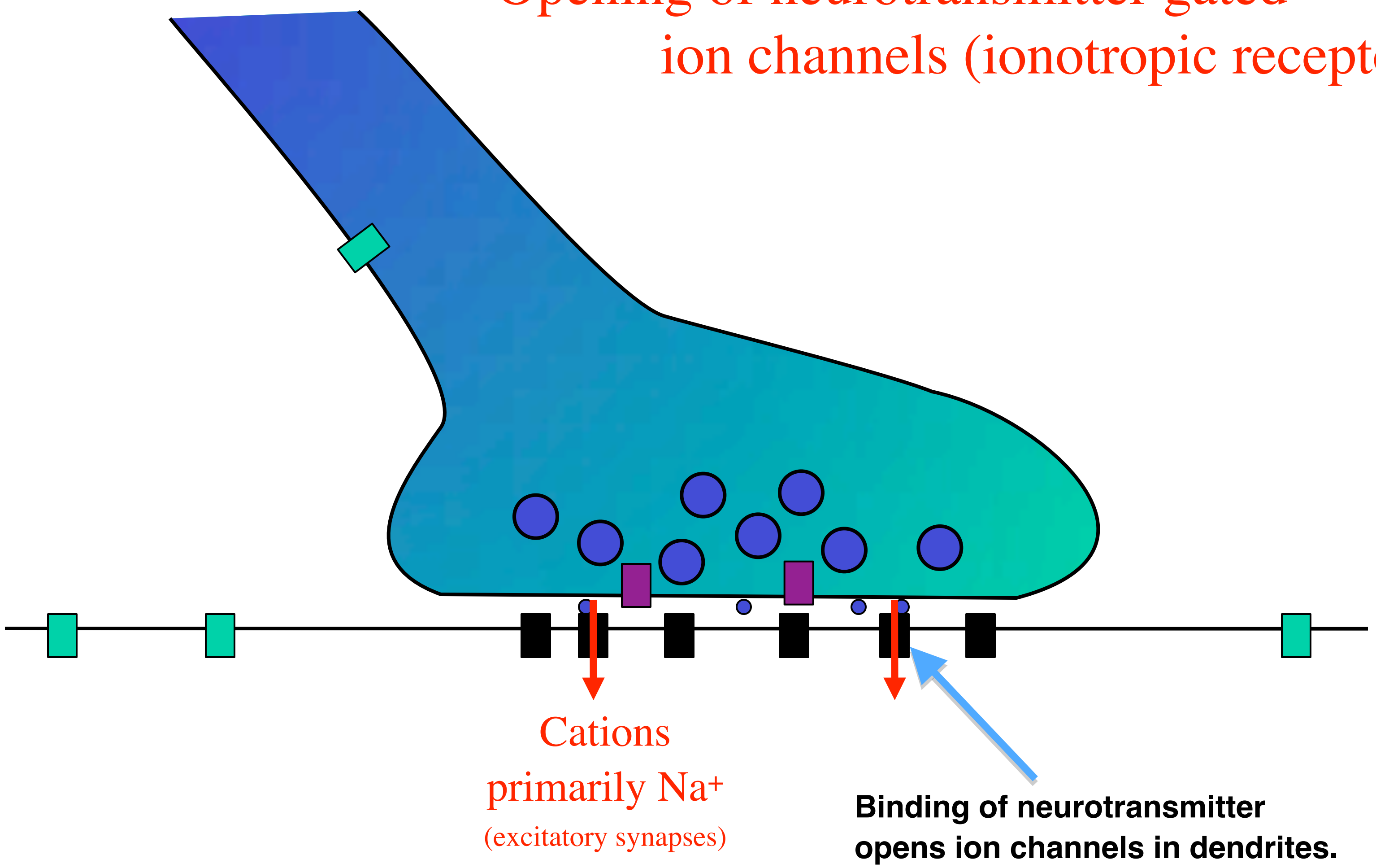


Neurotransmitter content of one vesicle = quantum of neurotransmitter

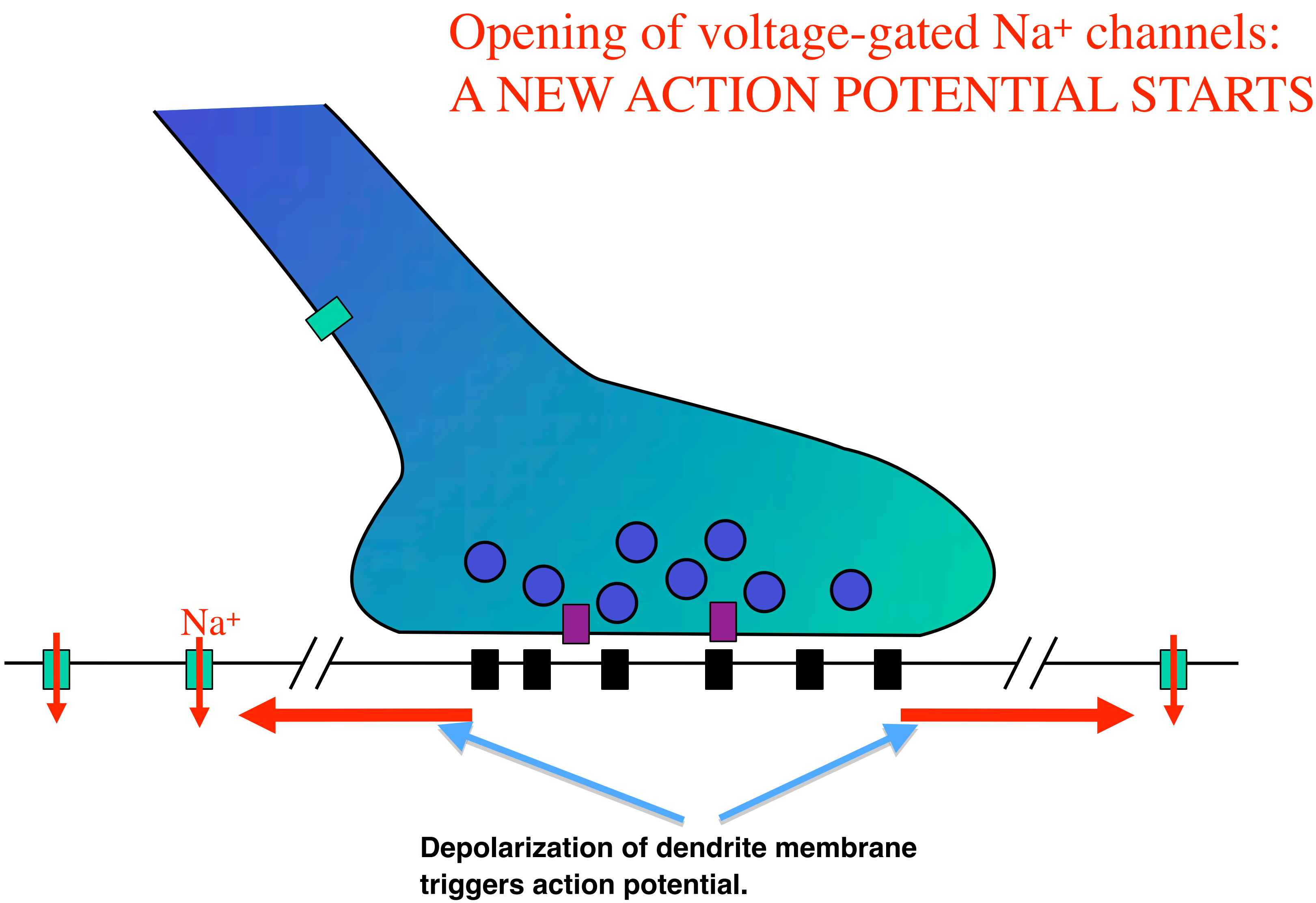
Key Steps in Synaptic Transmission

Post-synaptic effects at excitatory synapses

Opening of neurotransmitter gated ion channels (ionotropic receptor)



Key Steps in Synaptic Transmission

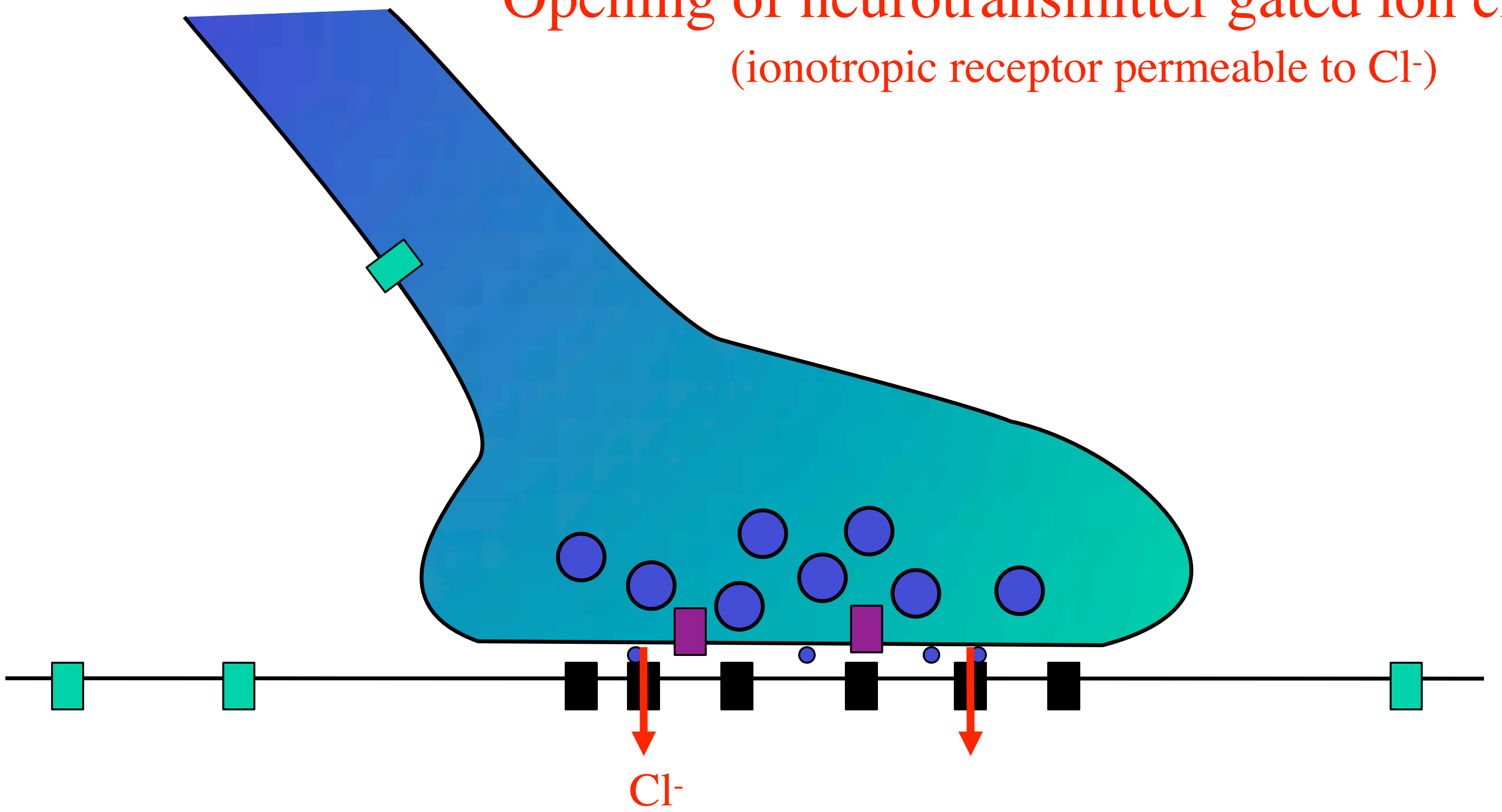


Key Steps in Synaptic Transmission

Post-synaptic effects at inhibitory synapses

Opening of neurotransmitter gated ion channel

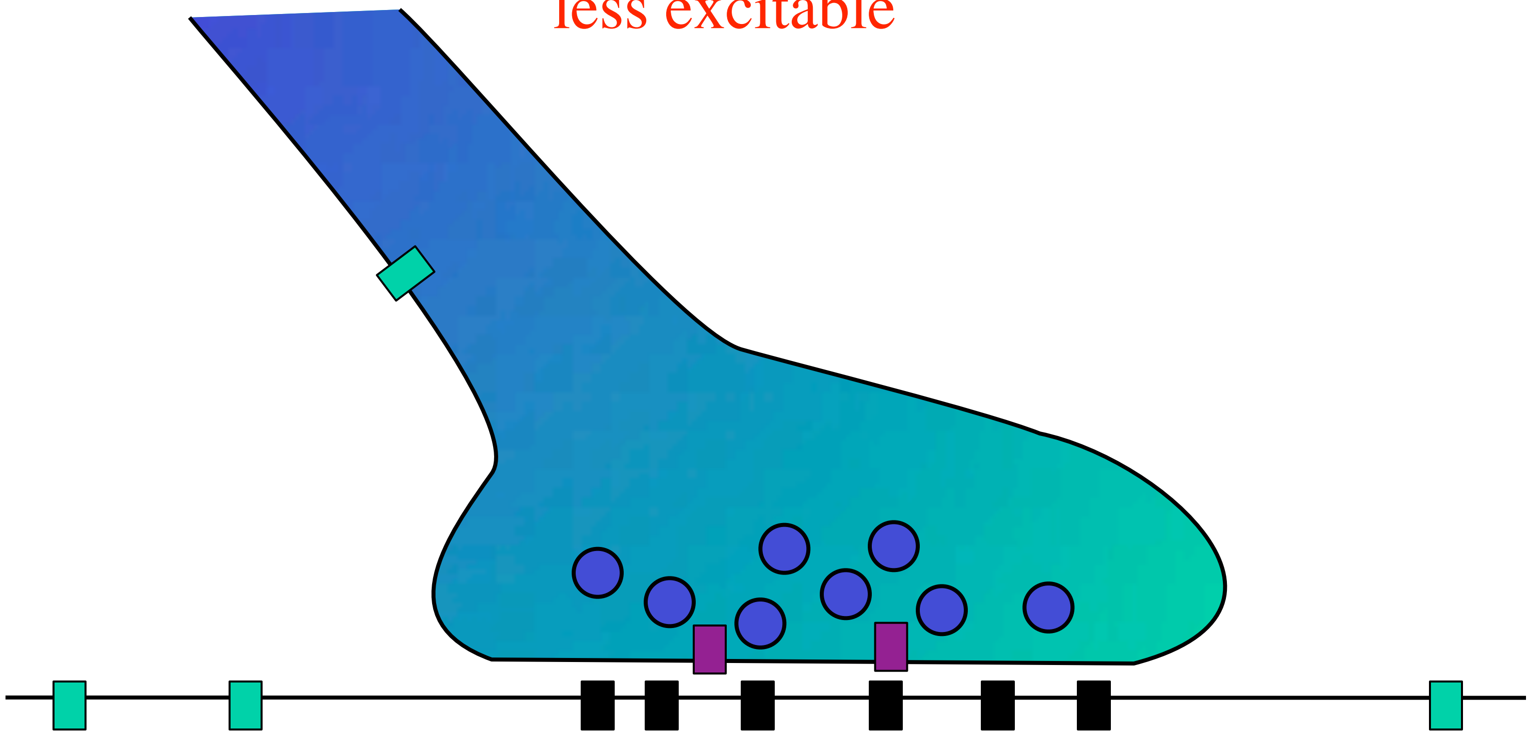
(ionotropic receptor permeable to Cl^-)



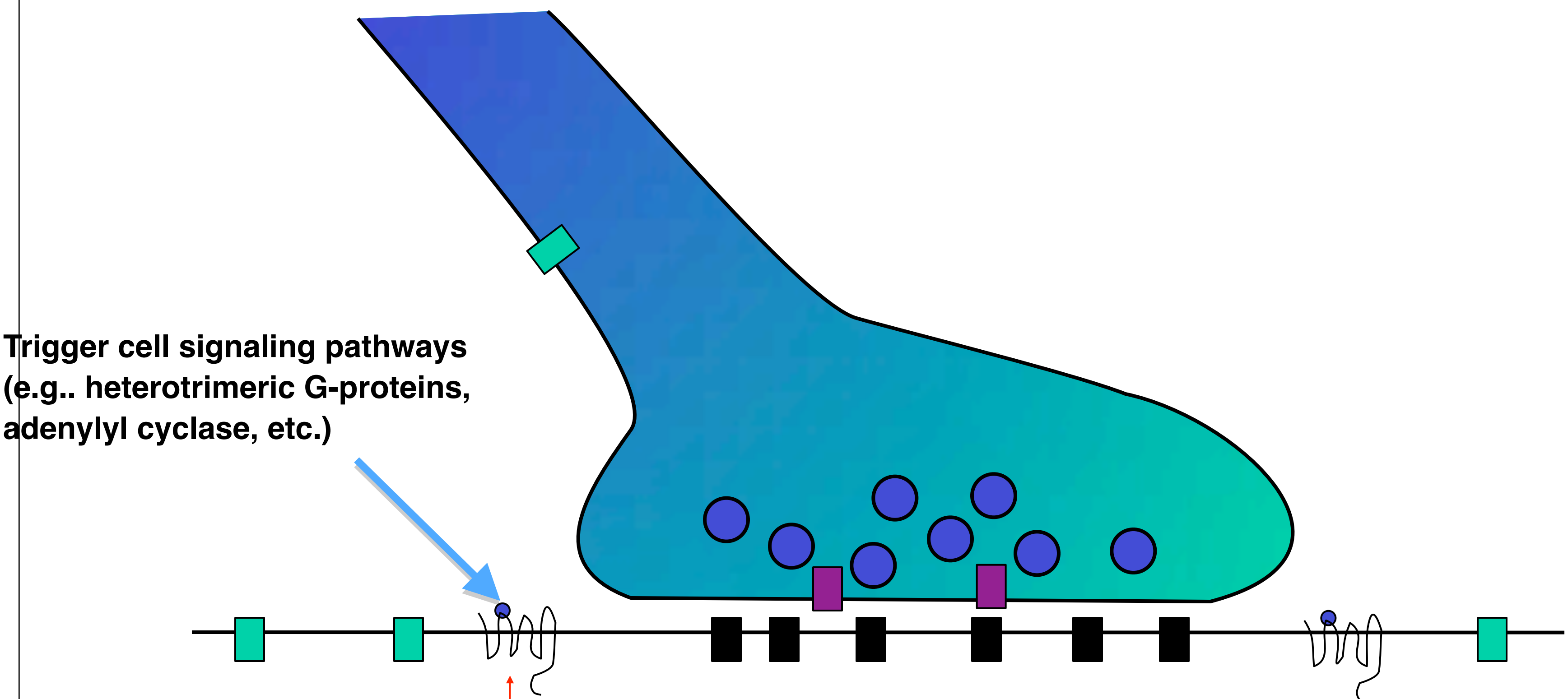
Entry of chloride make membrane hyperpolarized (cytoplasm has higher negative charge due to chloride ion. Hyperpolarization makes it more difficult to initiate an action potential. Need much more neurotransmitter to open more ion channels.

Key Steps in Synaptic Transmission

Cell become hyperpolarized, no action potential generated and cell becomes less excitable

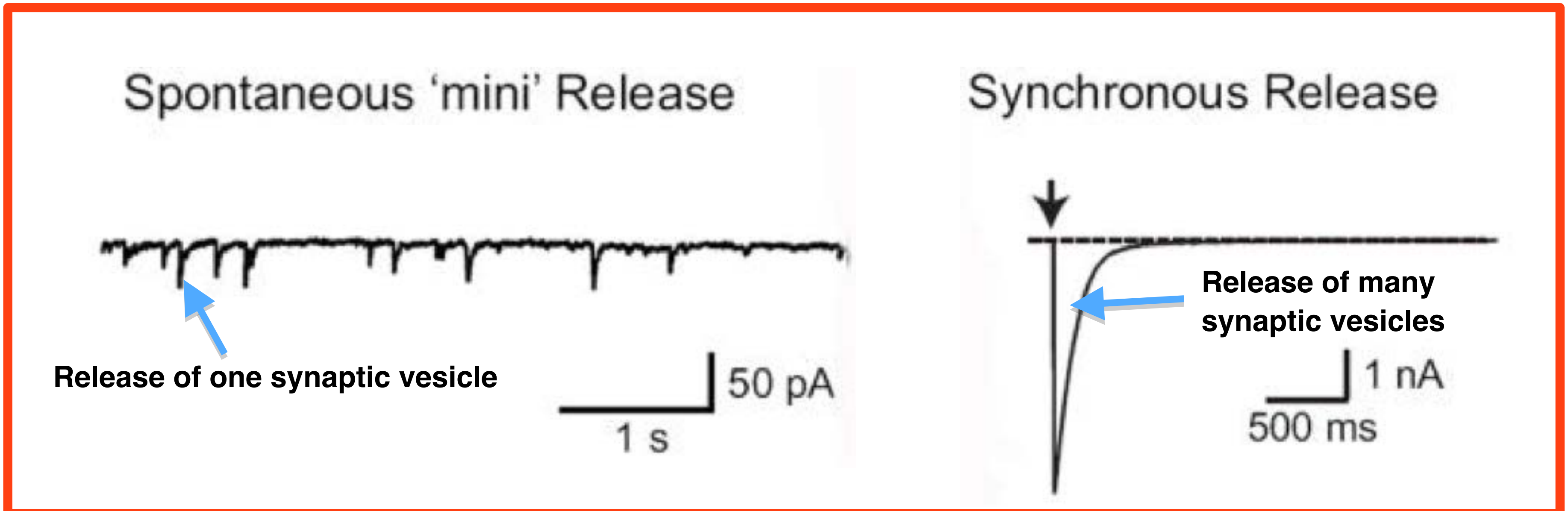


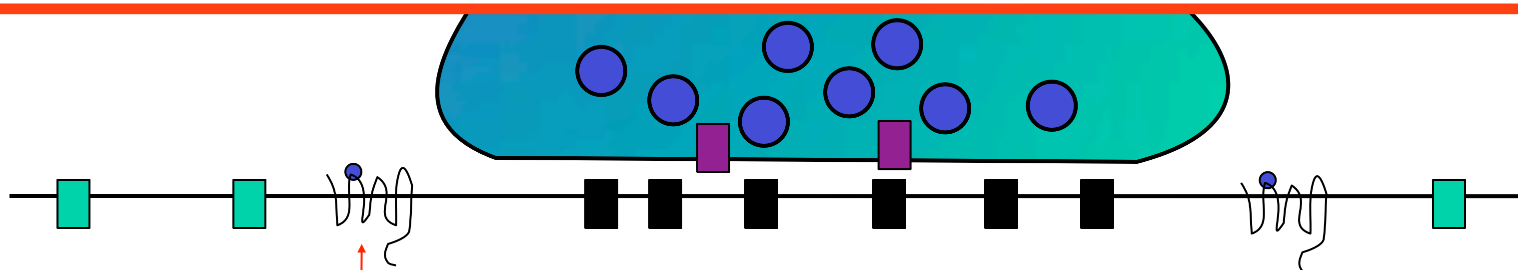
Neurotransmitters secreted via synaptic vesicles may also be involved in slow modulatory signaling



Metabotropic receptors (second messangers-linked receptors) for neurotransmitters, modulate the post-synaptic electrical response and mediate trophic effects

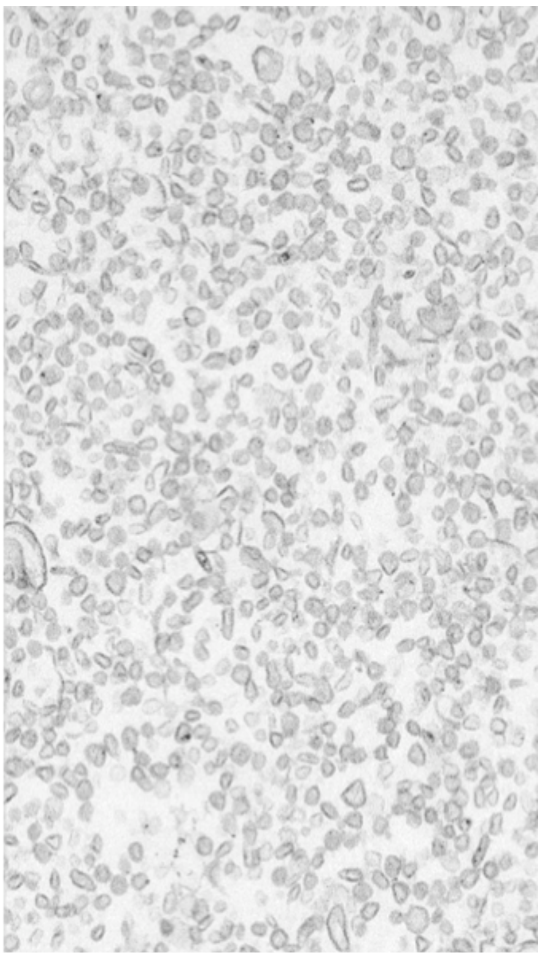
Neurotransmitters secreted via synaptic vesicles may also be involved in slow modulatory signaling



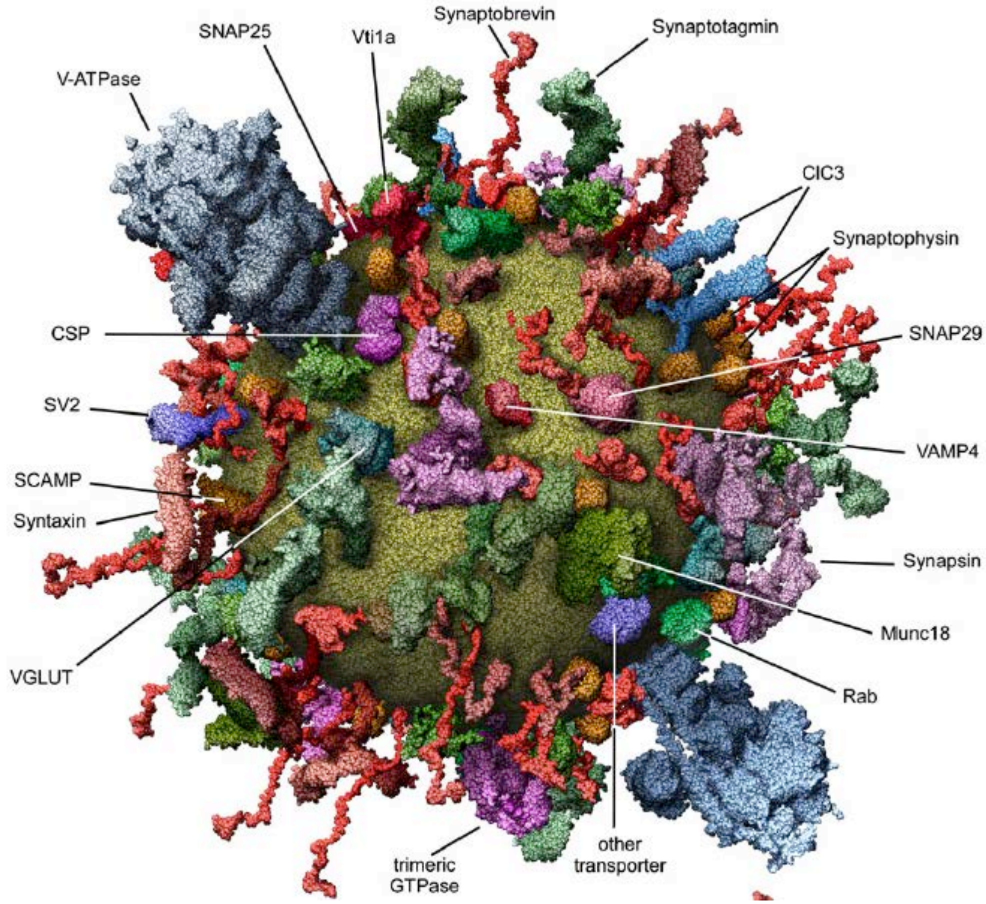


Metabotropic receptors (second messangers-linked receptors) for neurotransmitters, modulate the post-synaptic electrical response and mediate trophic effects

Synaptic vesicles are well characterized organelles

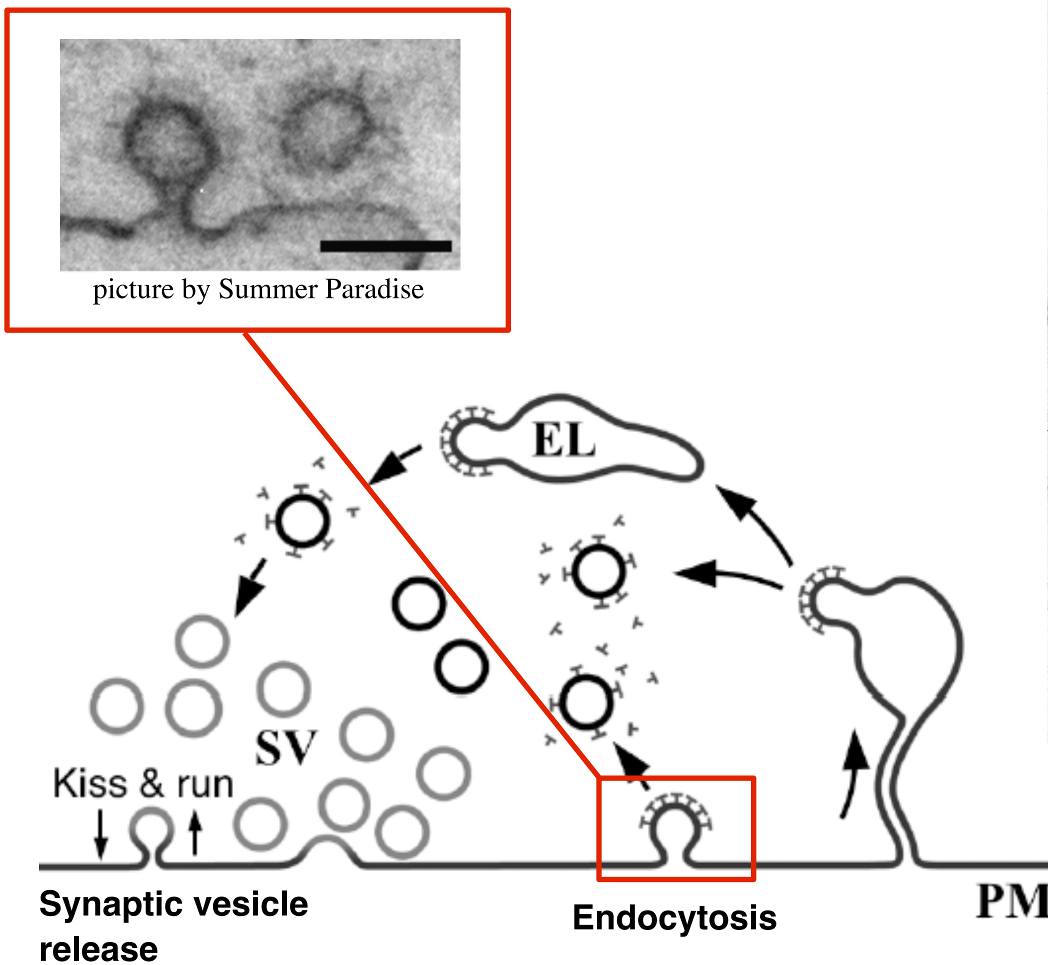


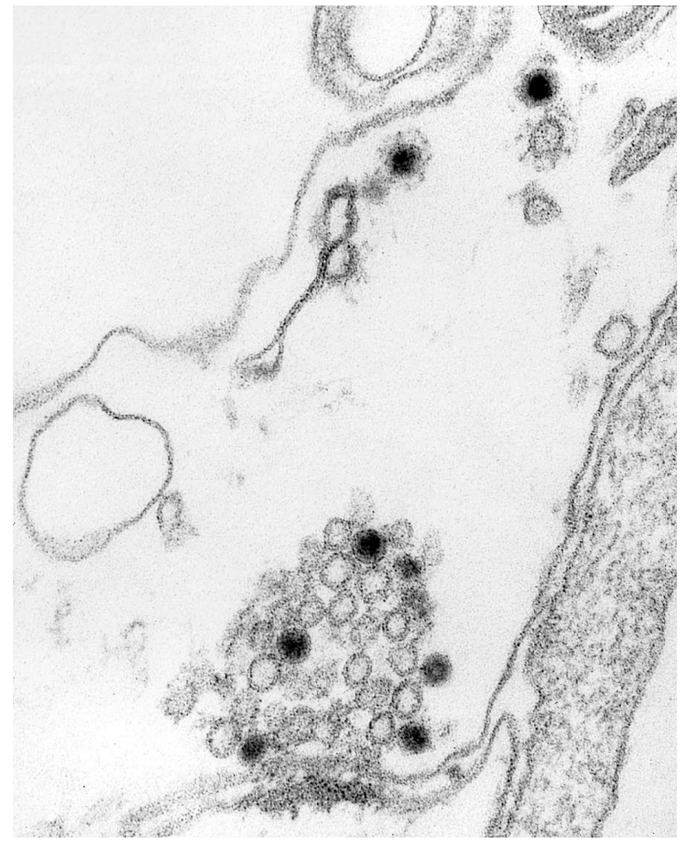
from Huttner, Greengrad, De Camilli et al. 1983



Takamori et al. (Jahn lab) 2006

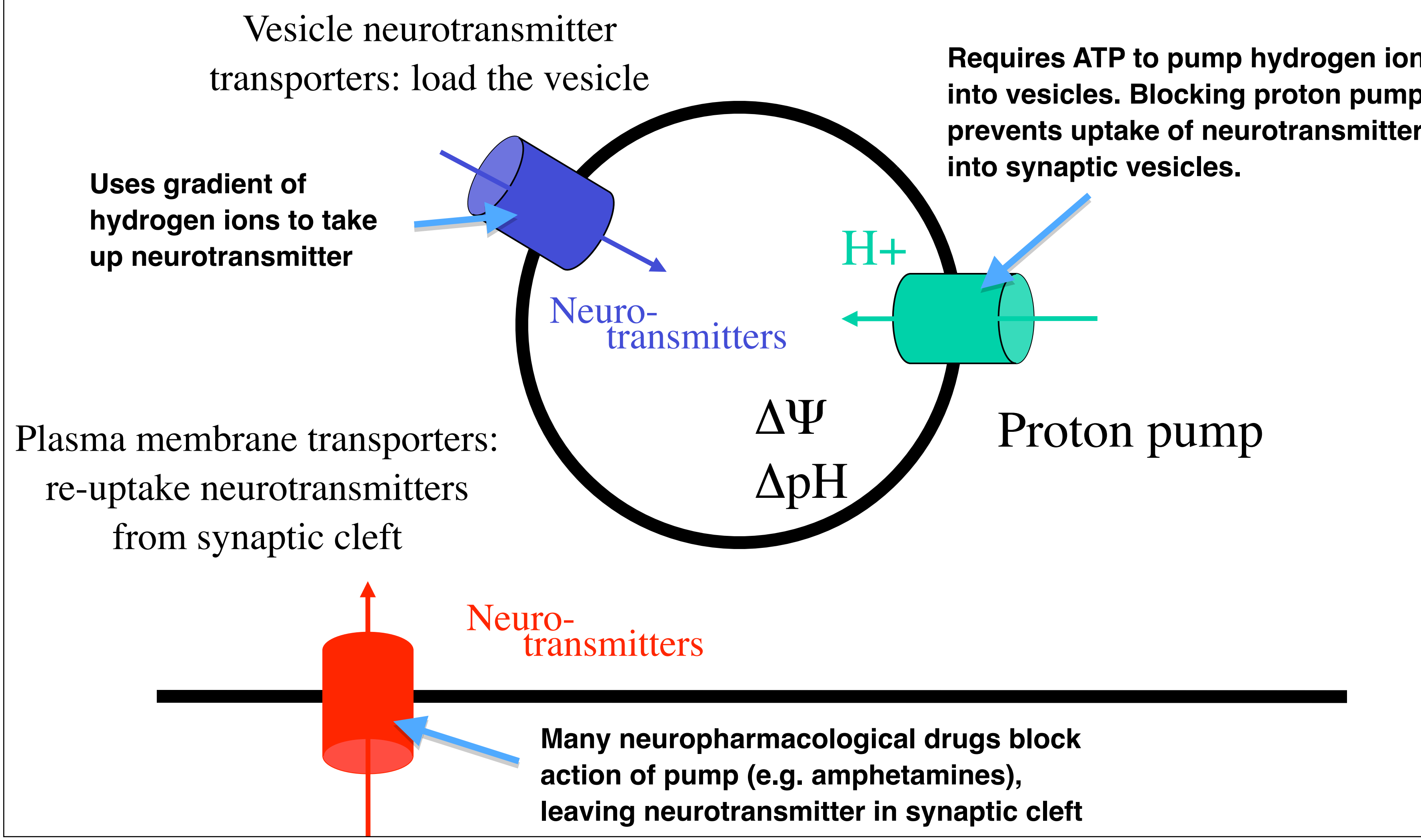
Synaptic vesicles undergo recycling





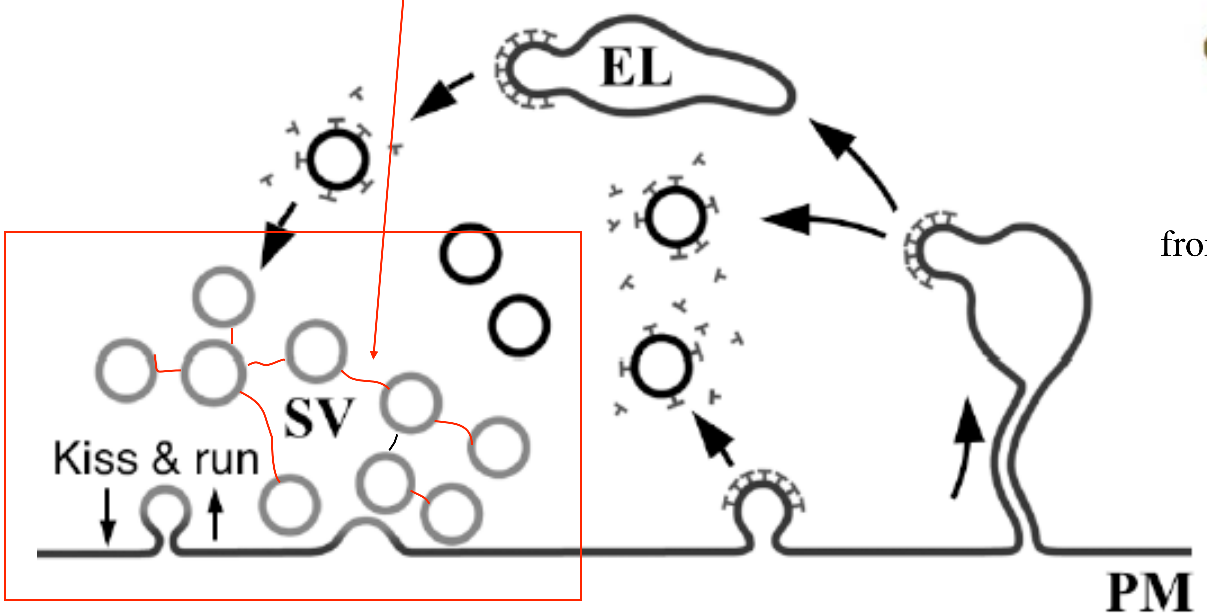
Black = extracellular tracer added during previous stimulation

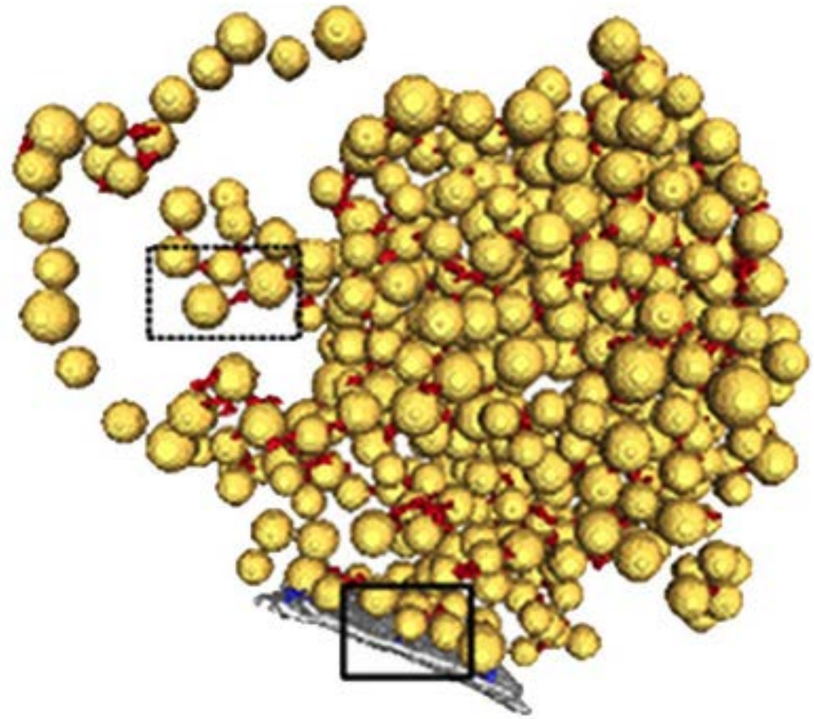
Neurotransmitter loading



Steps in vesicle recycling

Vesicle clustering:
Cytoskeletal elements cross-link vesicles to each other



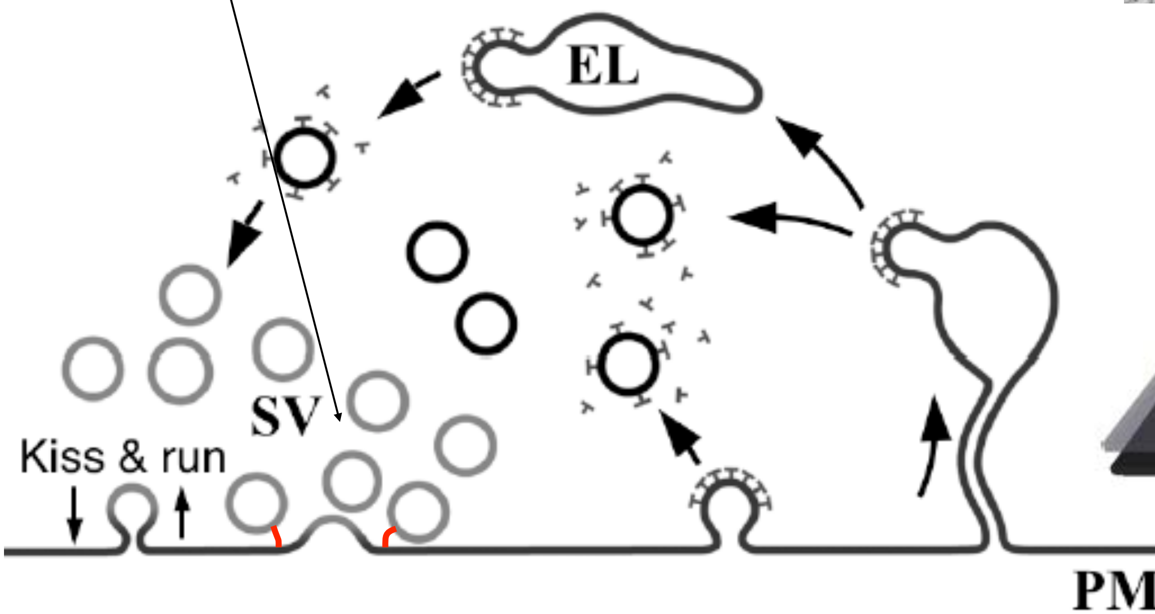


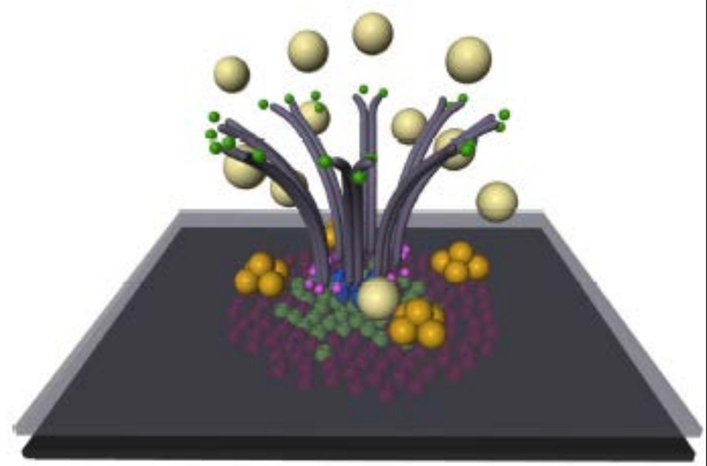
from Fernandez-Busnadiego et al.

Steps in vesicle recycling

Striking example of tethering structure

Vesicle tethering

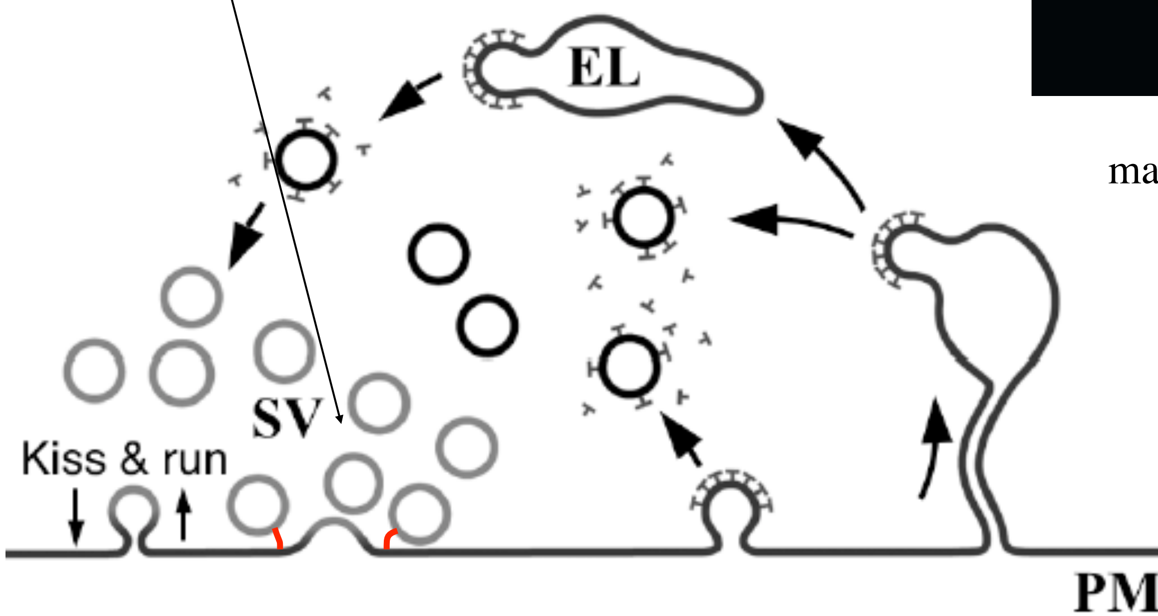


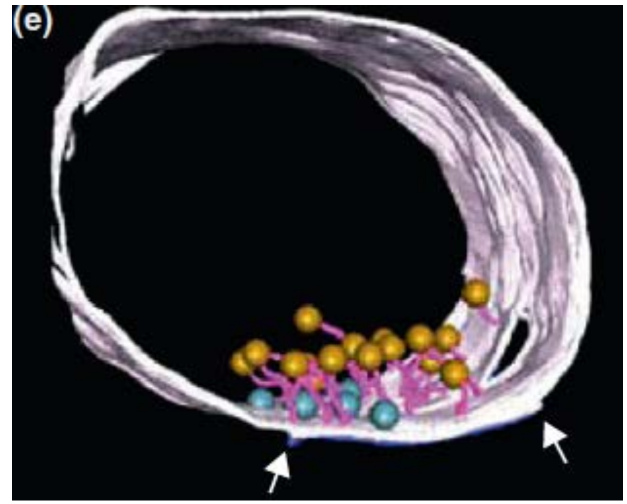


Drosophila NMJ
cross-section

Steps in vesicle recycling

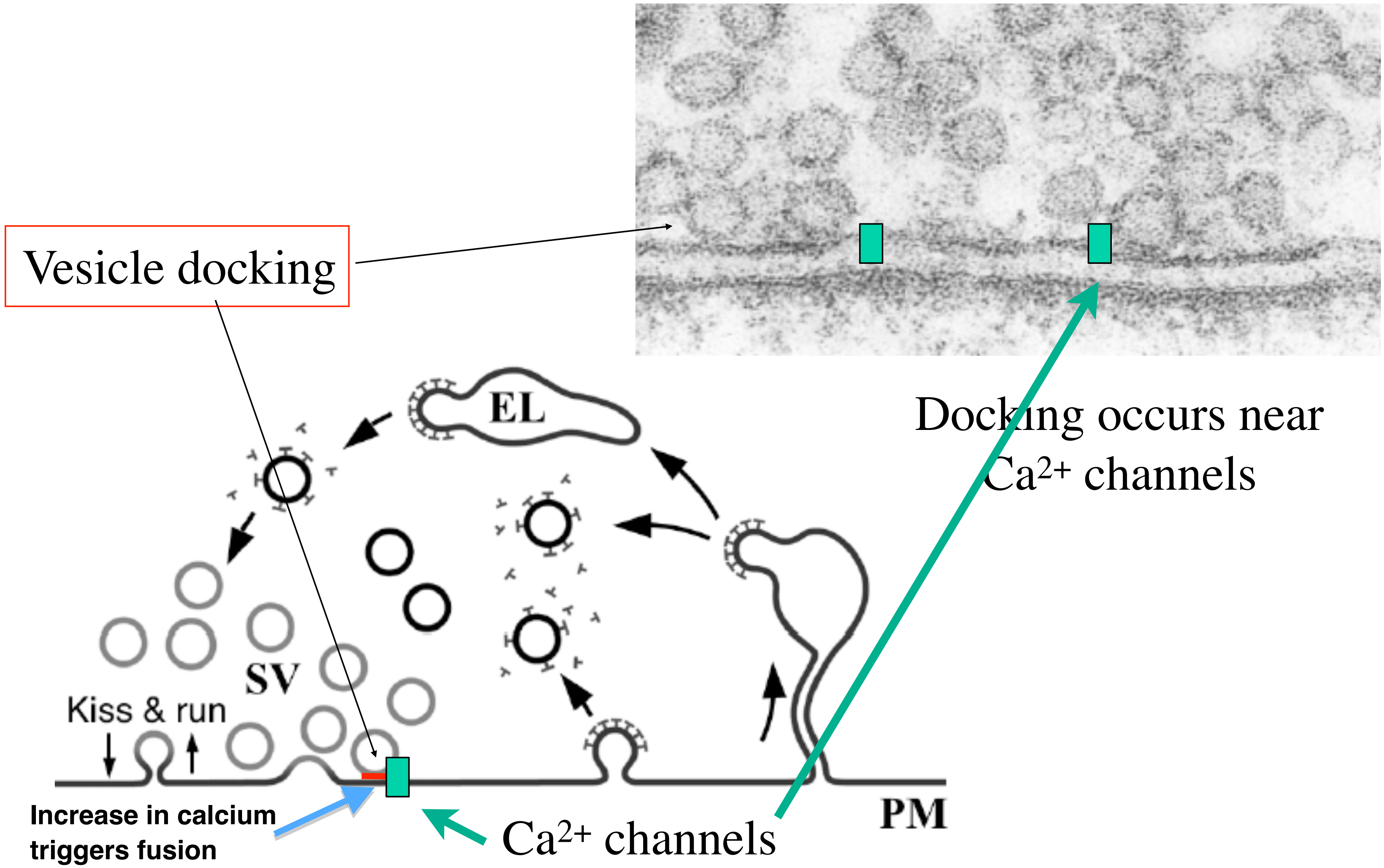
Vesicle tethering





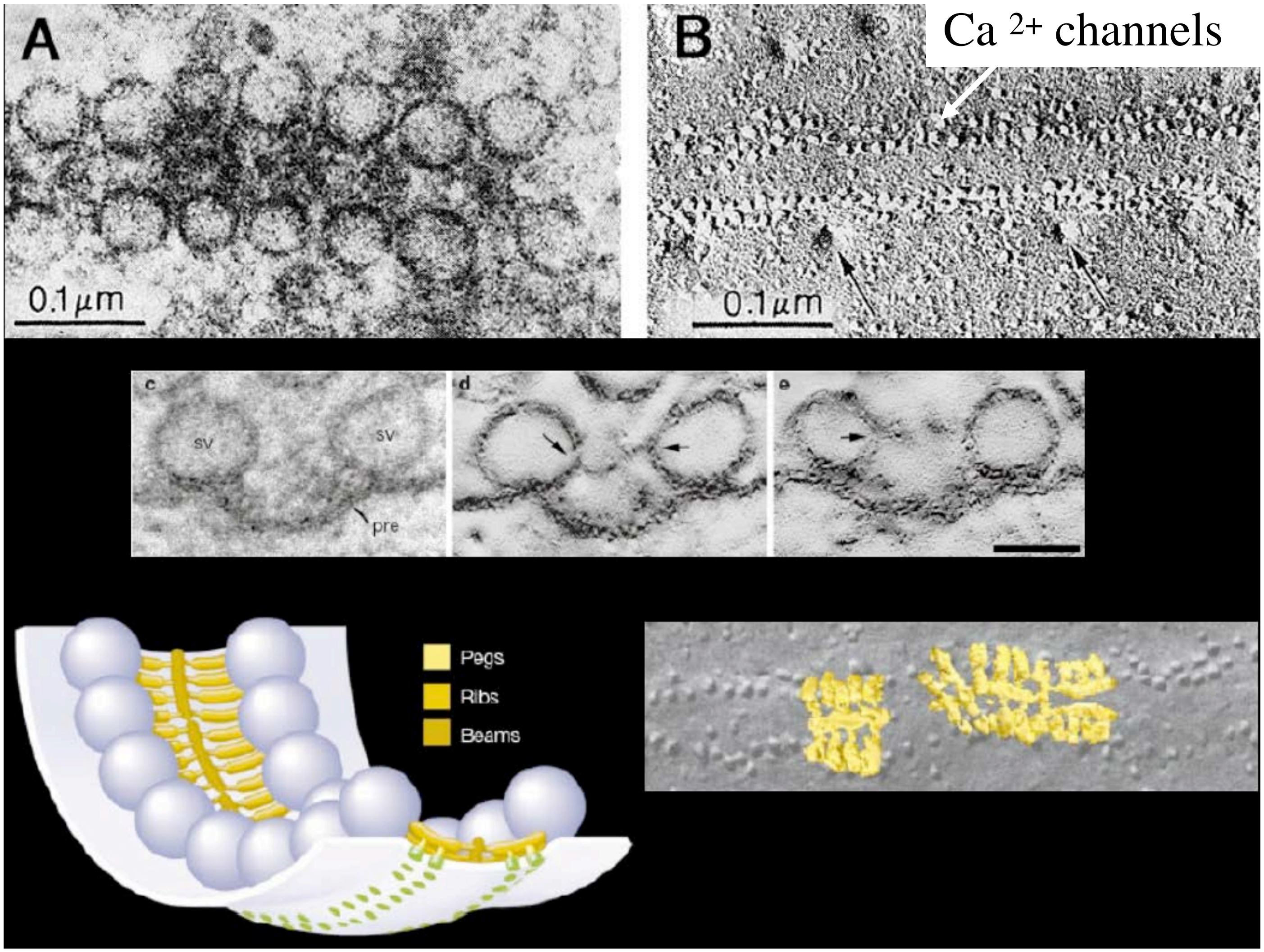
mammalian central synapse
EM tomography

Steps in vesicle recycling



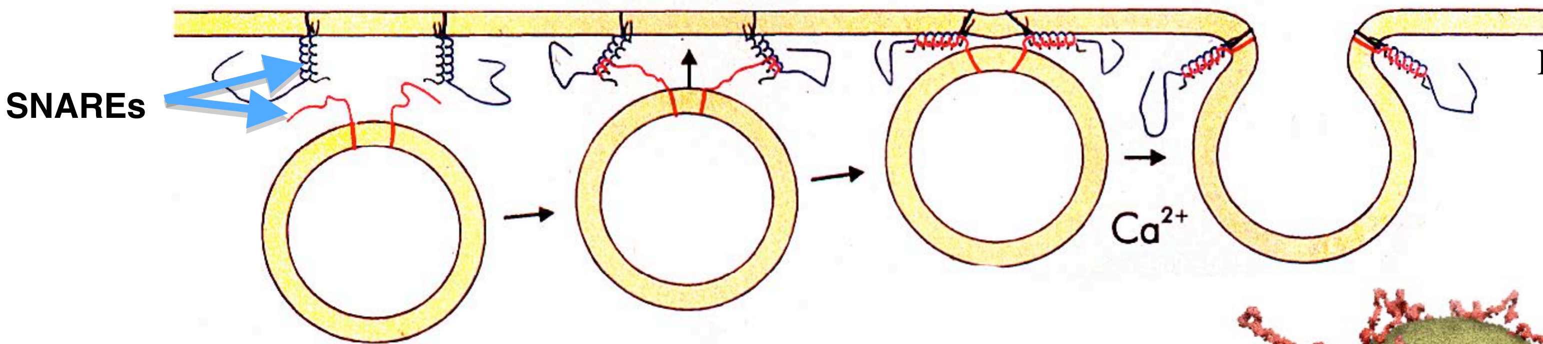
Frog neuromuscular junction

Frog neuromuscular junction

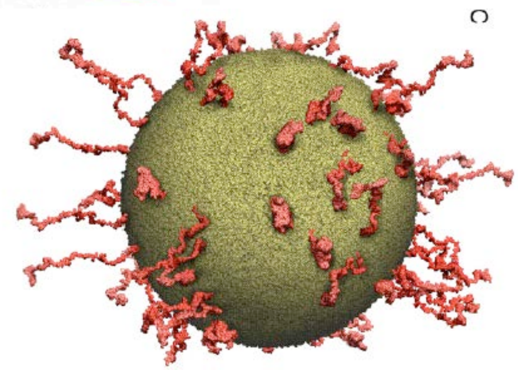


From Heuser's lab and McMahan's lab

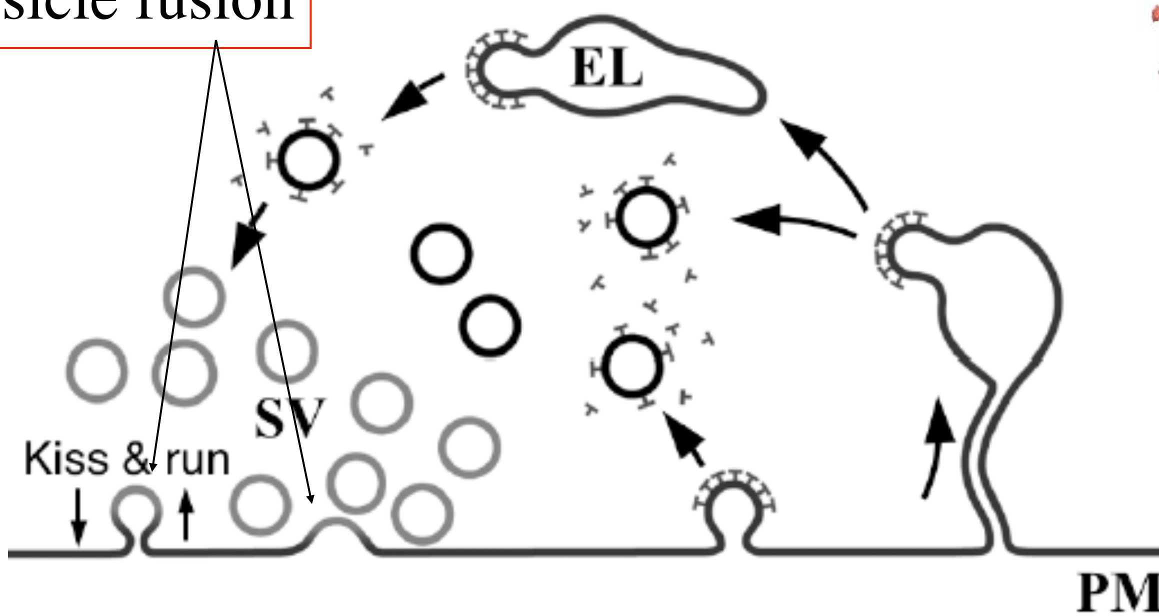
Steps in vesicle recycling



From R. Jahn



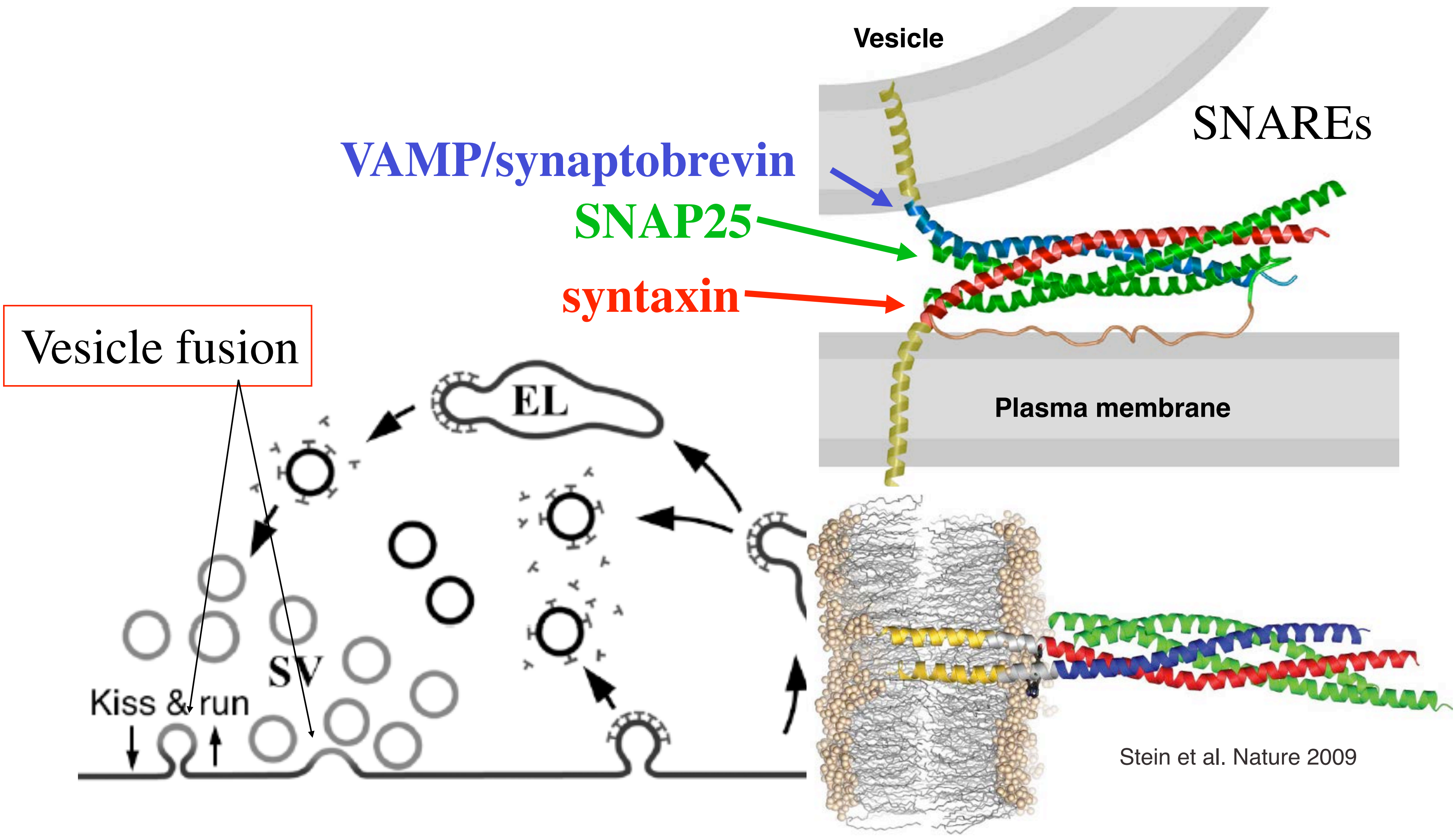
Vesicle fusion



SNAREs: critical players in membrane fusion

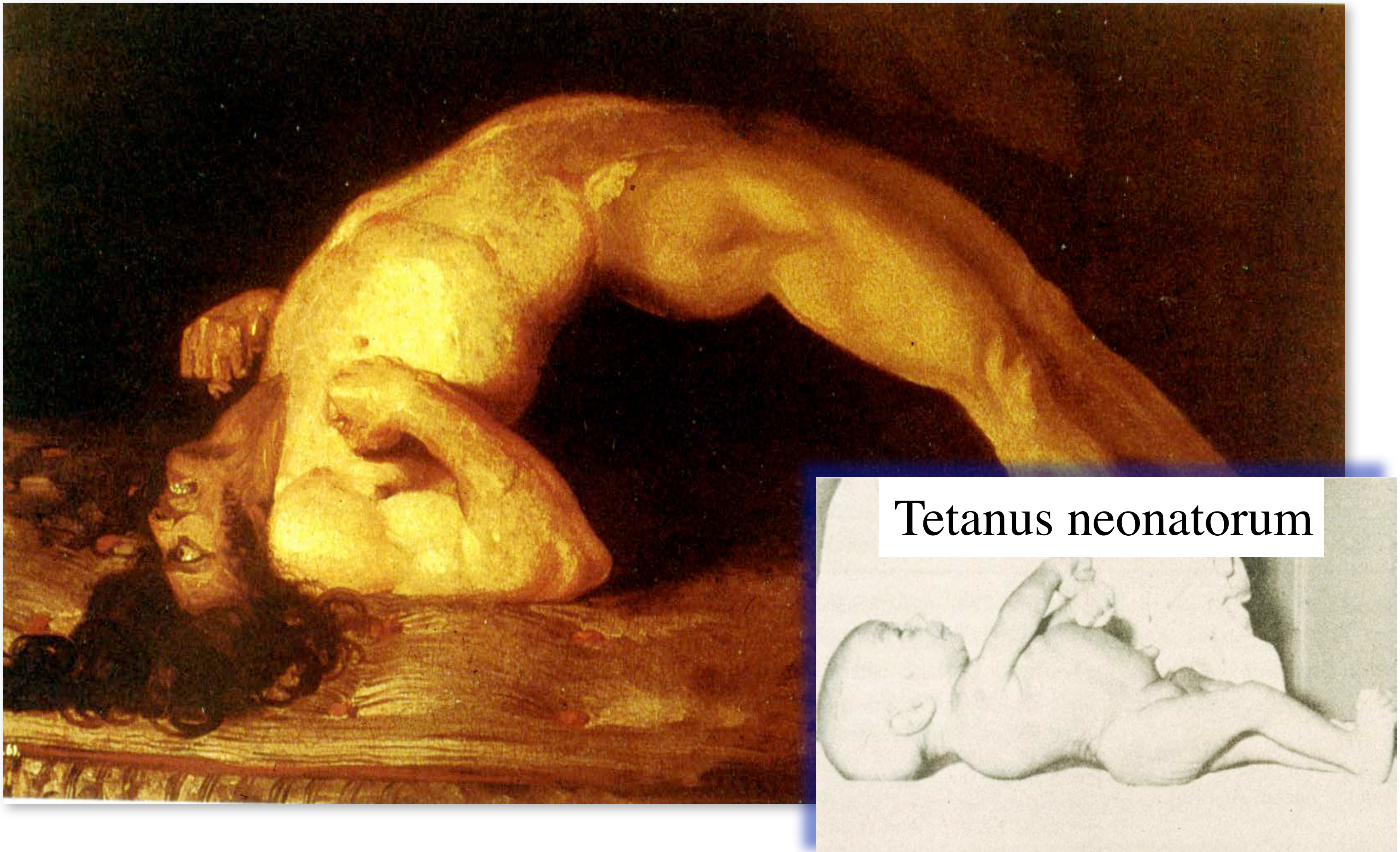
Sollner... and J.Rothman, Nature 1993

Steps in vesicle recycling



Tetanus toxin cause prolonged contraction of muscle. Blocks synaptic vesicle fusion in neurons that inhibit the activity of motor neurons.

TETANUS



Botulism toxin inhibits muscle contraction. Blocks fusion of synaptic vesicles at NMJ in motor neurons.

BOTULISM

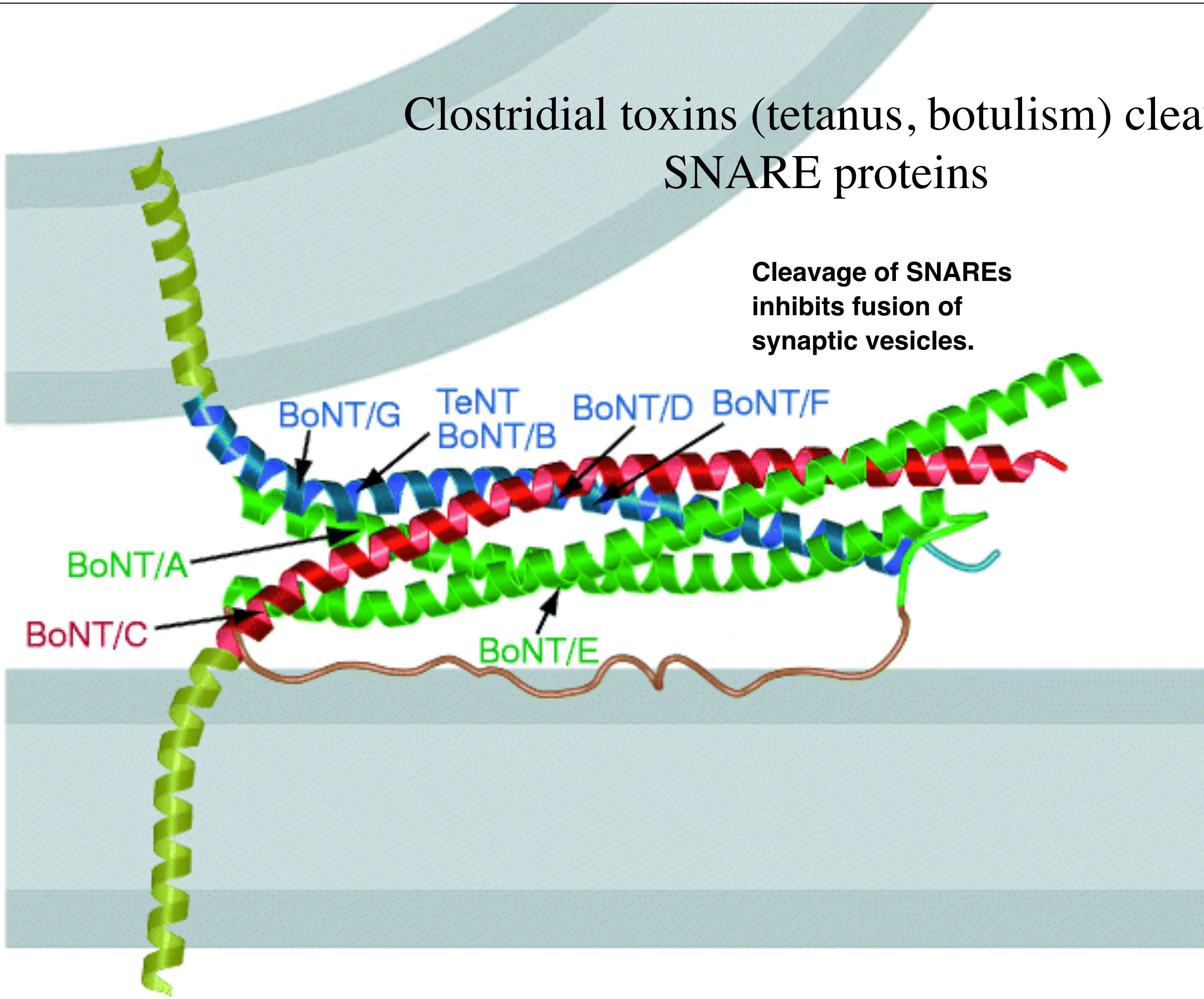
Botox

Therapeutic uses

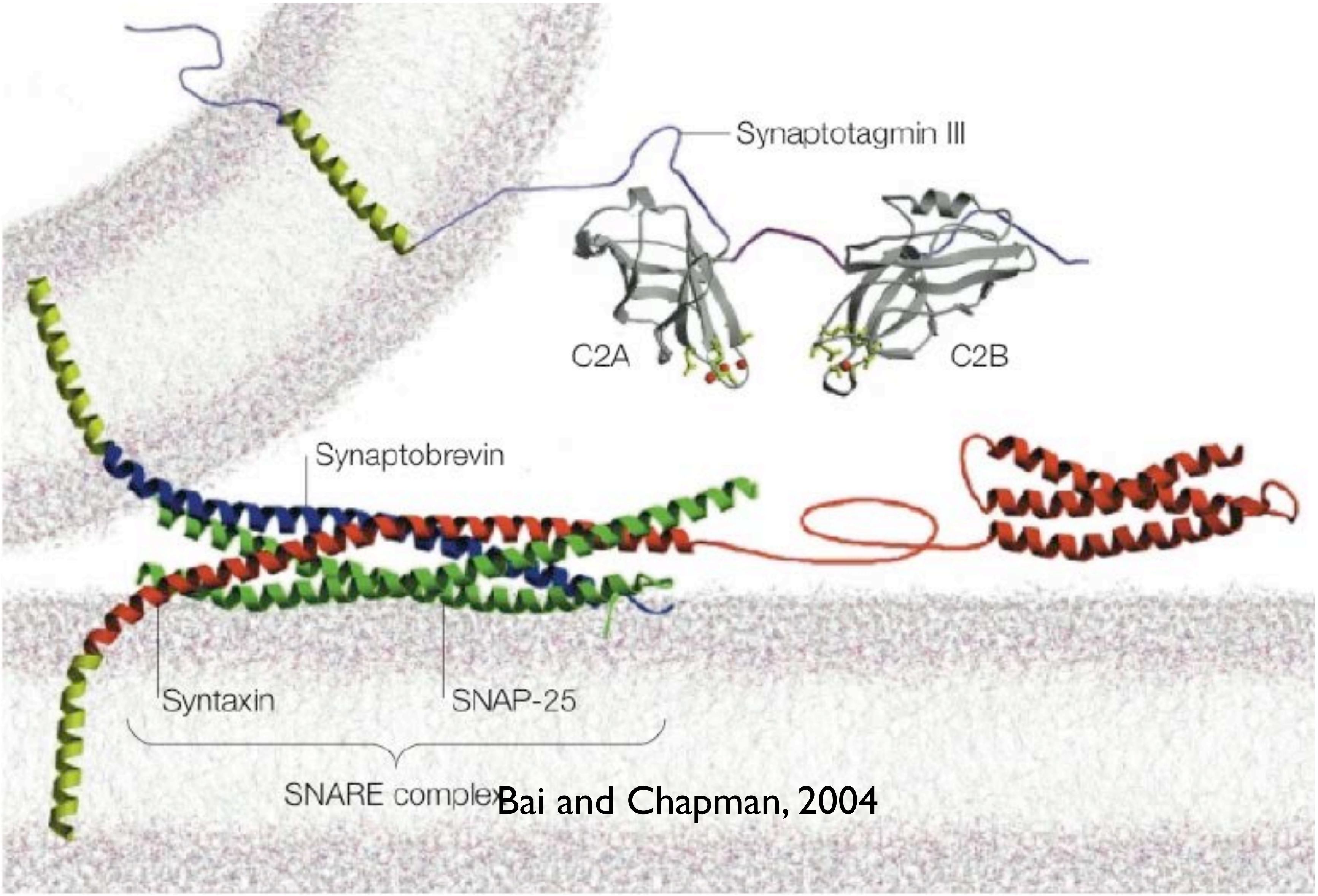
Cosmetic uses

Clostridial toxins (tetanus, botulism) cleave SNARE proteins

Cleavage of SNAREs inhibits fusion of synaptic vesicles.



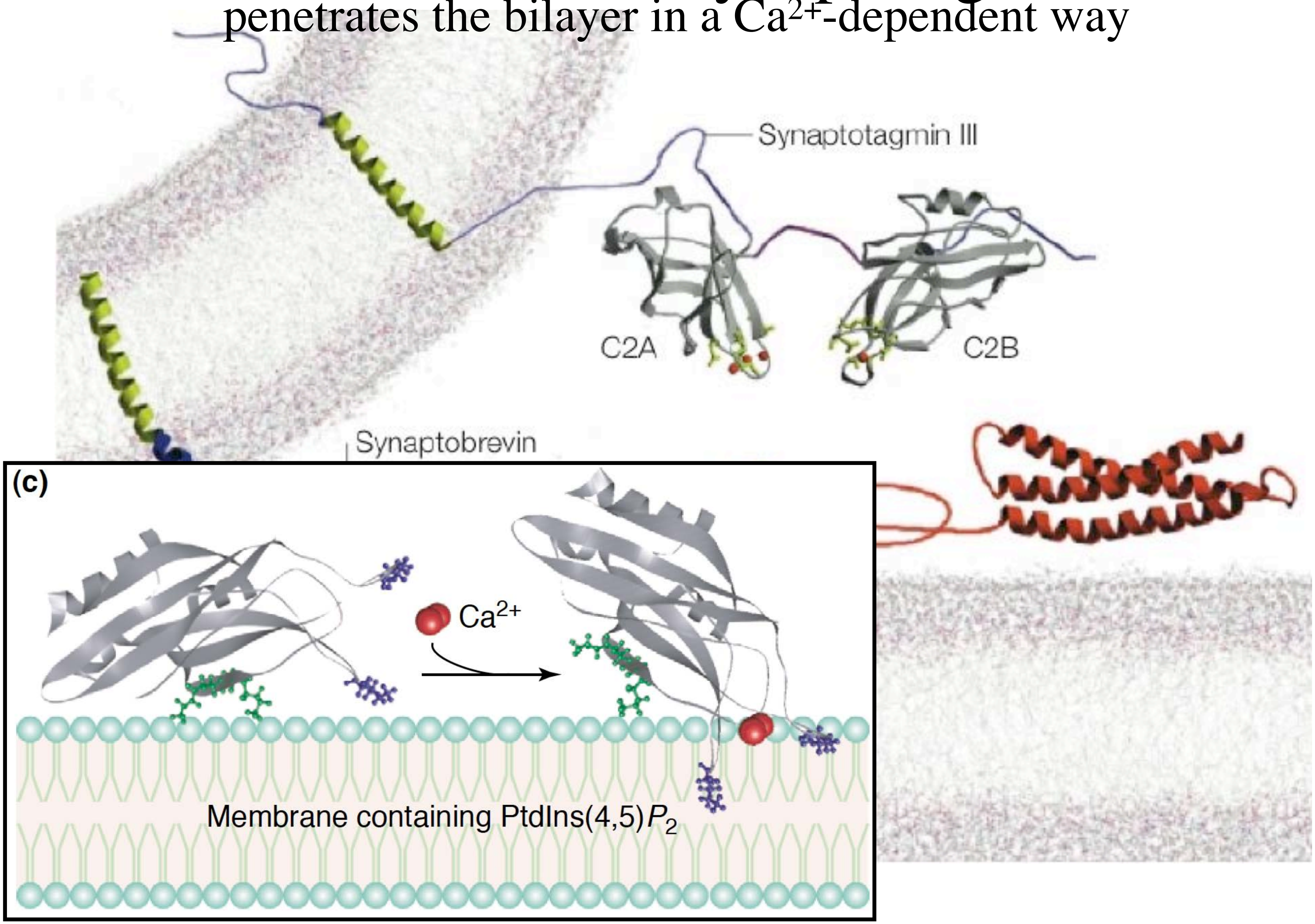
A Ca $^{2+}$ sensor: synaptotagmin



Bai and Chapman, 2004

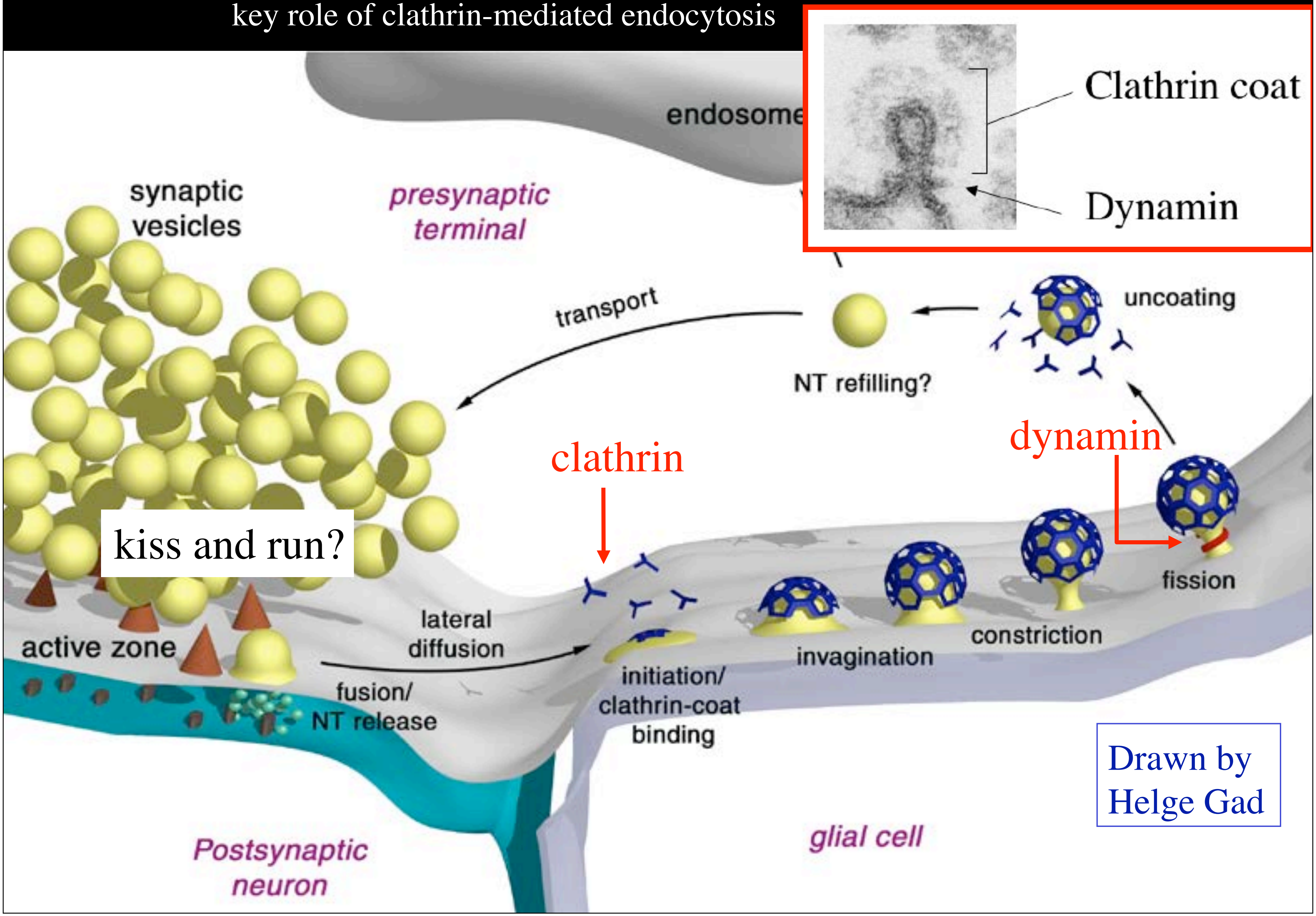
A Ca $^{2+}$ sensor: synaptotagmin

penetrates the bilayer in a Ca^{2+}-dependent way



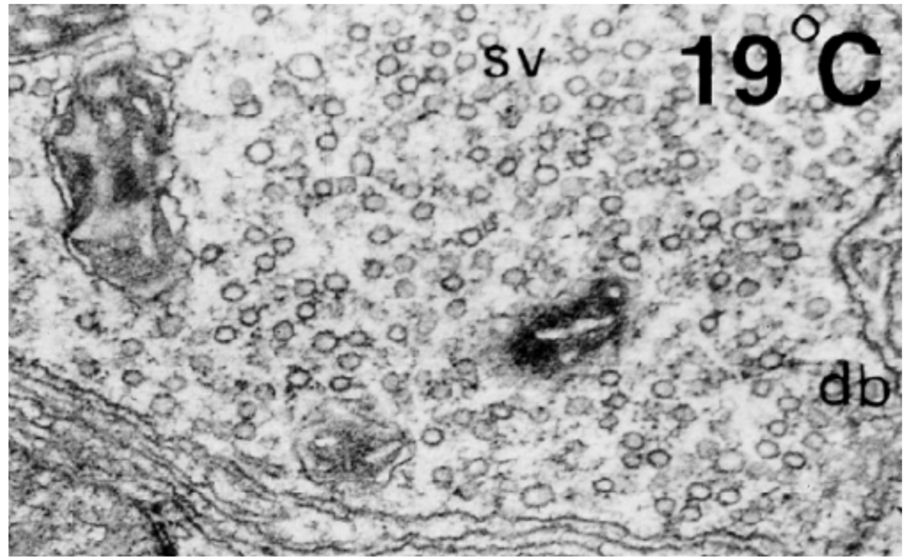
Riformation of synaptic vesicles after exocytosis

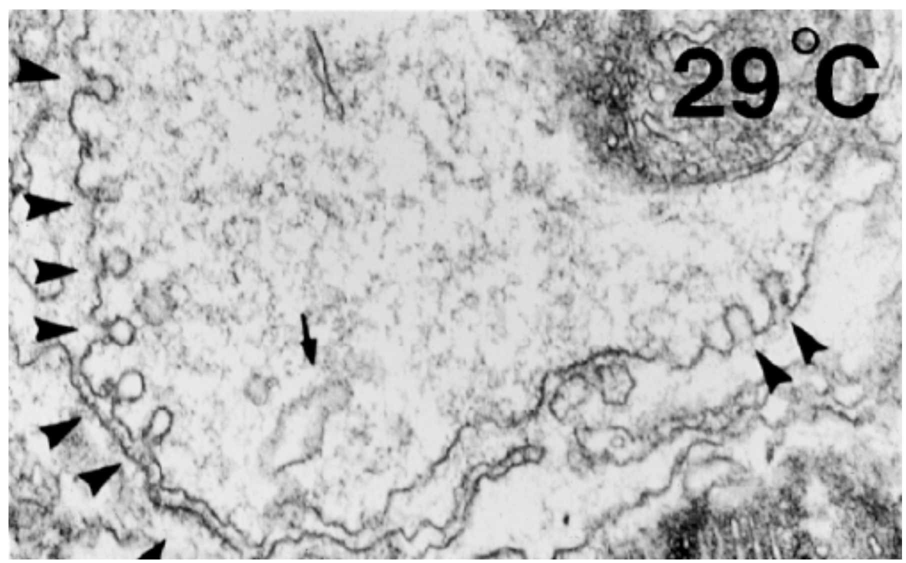
key role of clathrin-mediated endocytosis

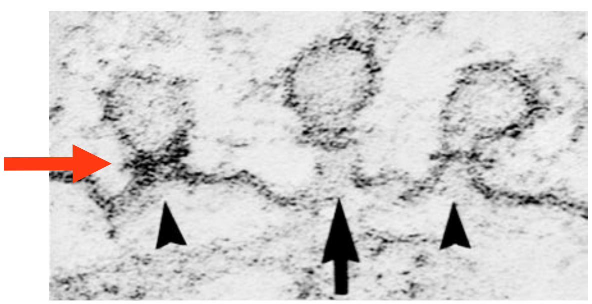


shibire Mutation of Drosophila due to a mutation in the dynamin gene

Movie by Bin Zhang



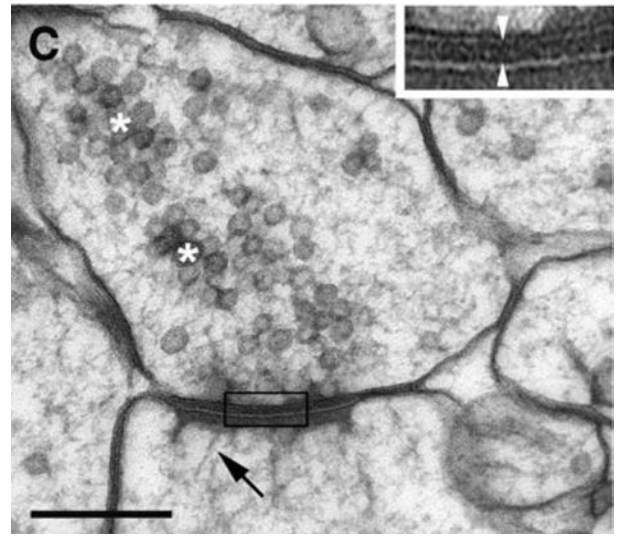


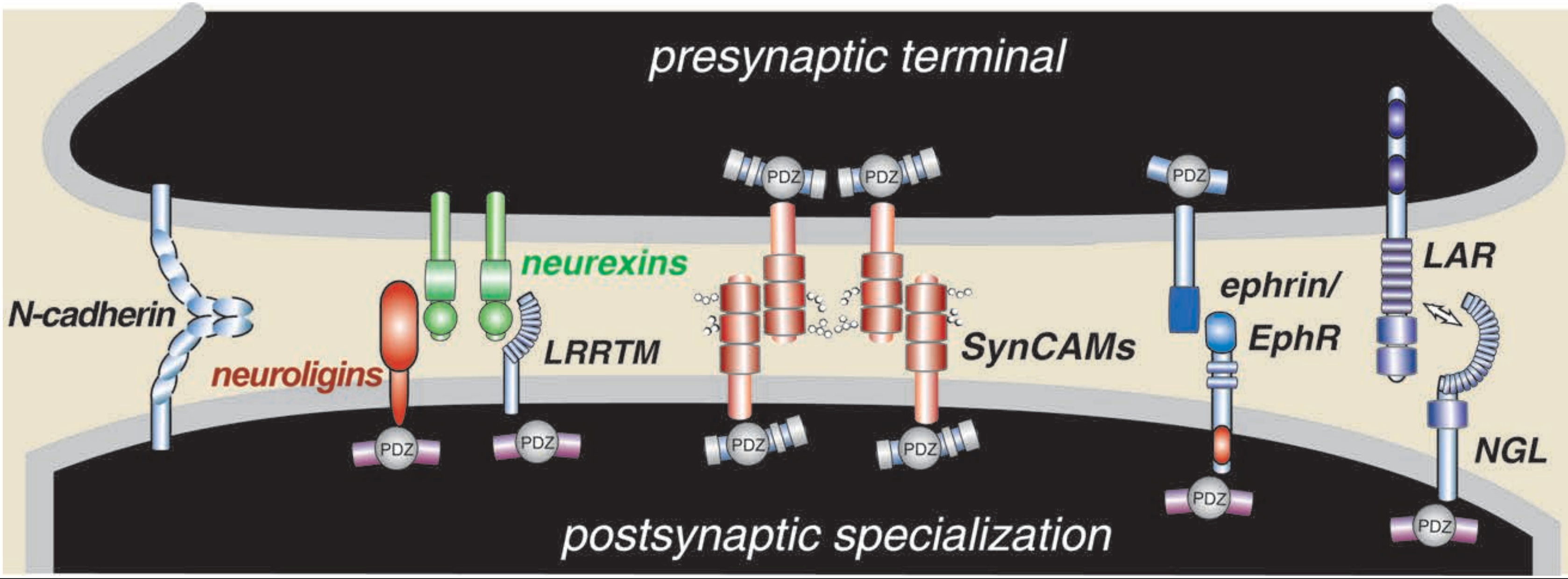


Koenig and Ikeda, 1989

The synaptic cleft

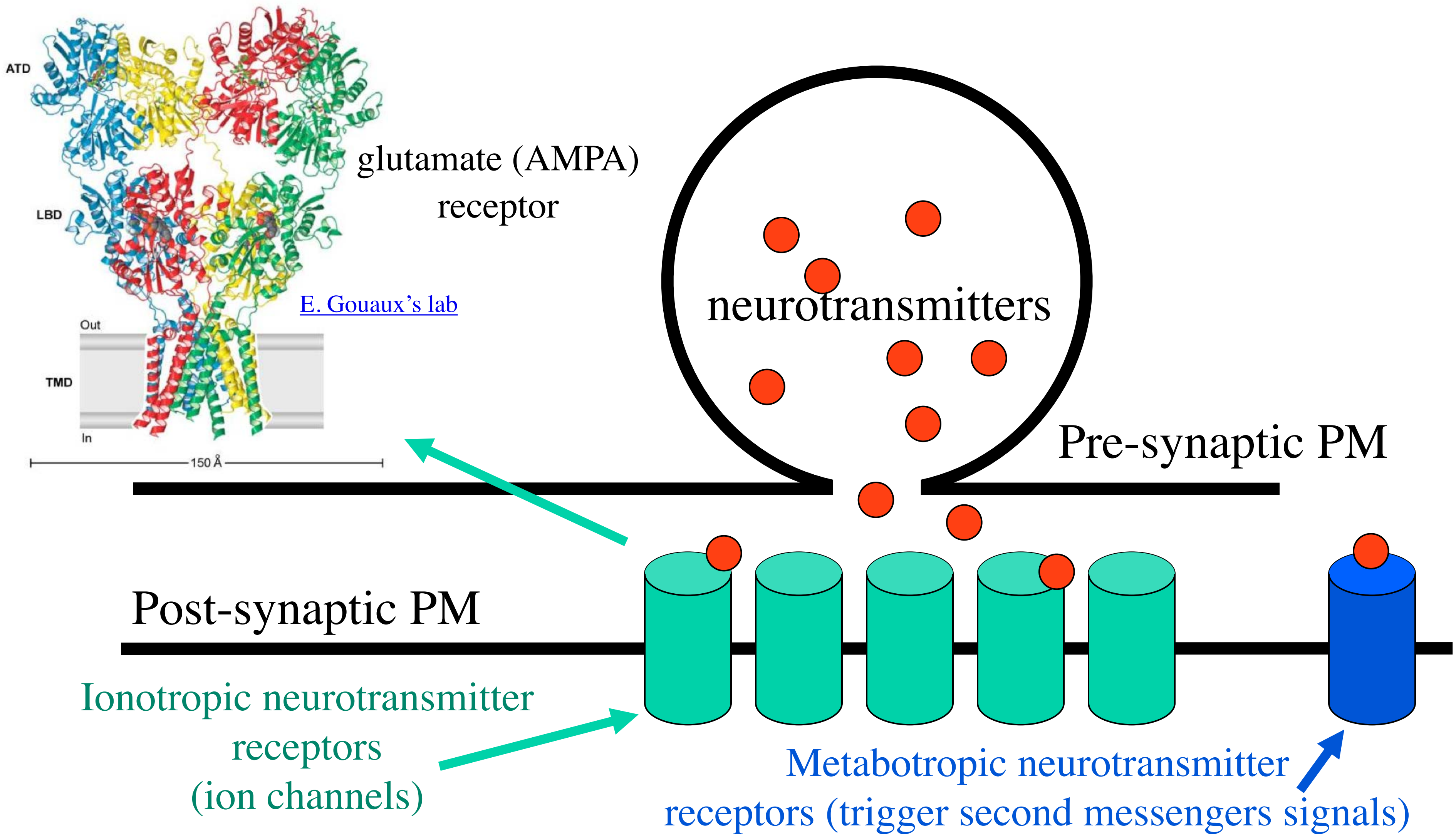
synapse adhesion molecules



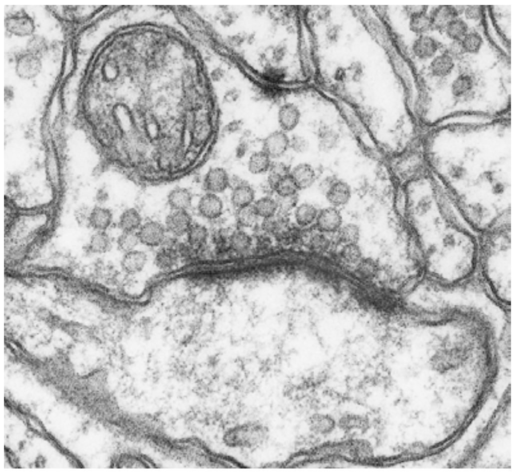


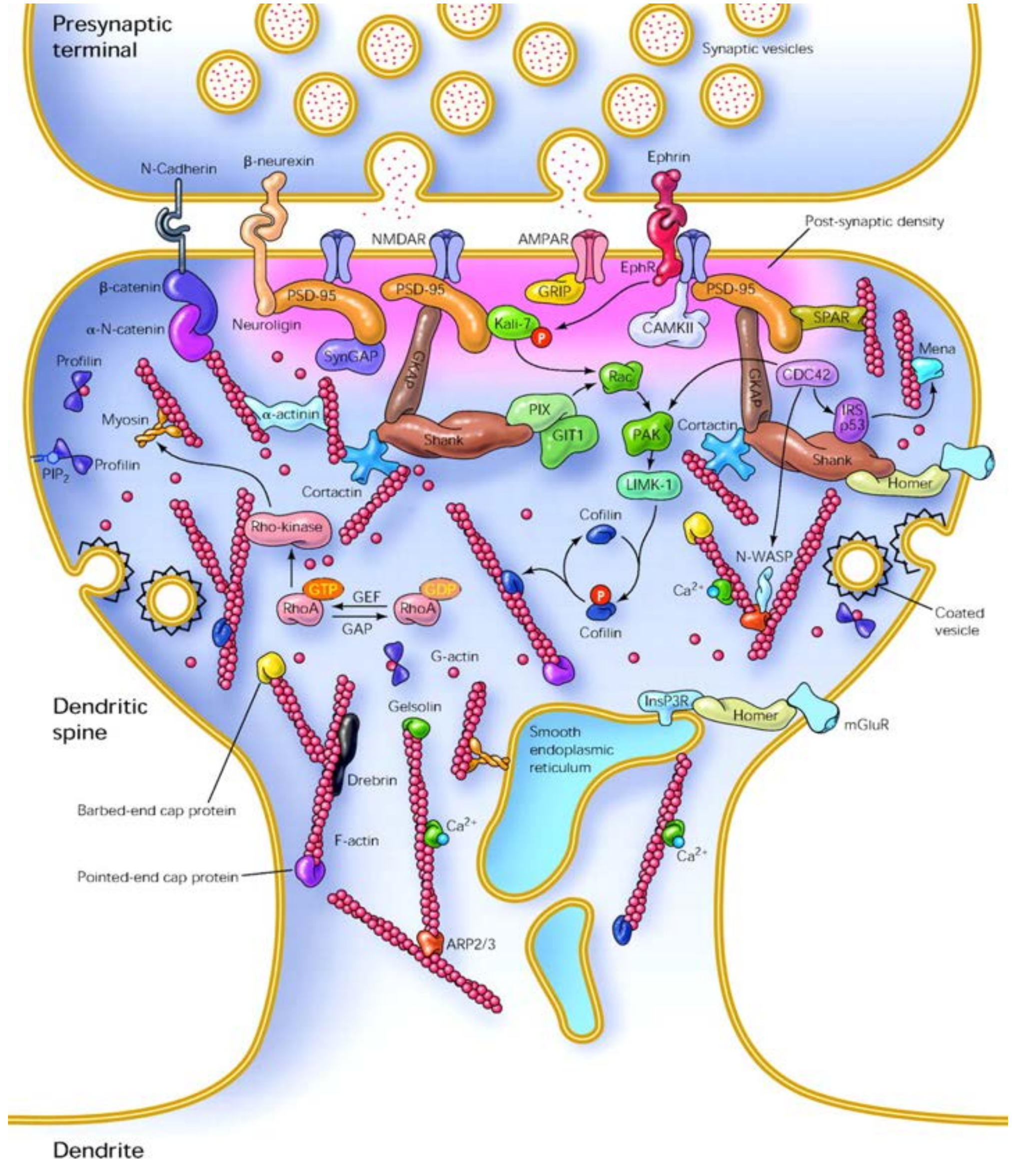
Post-synaptic plasma membrane

neurotransmitter receptors



Post-synaptic compartment
(dendritic spine)

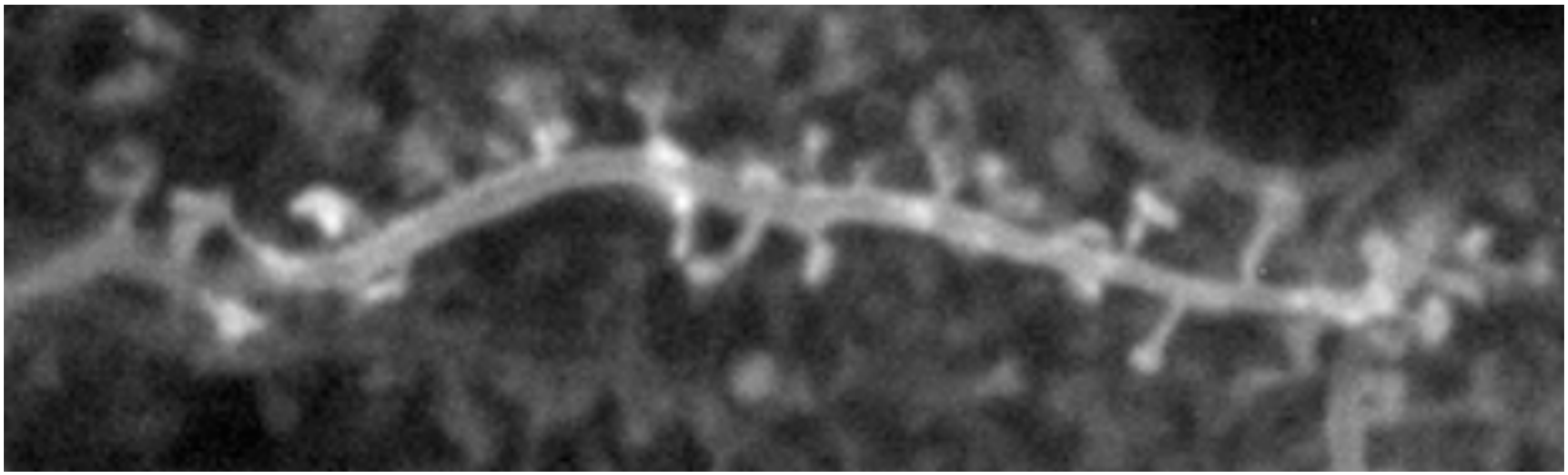




A complex molecular network in dendritic spines:
+ Clustering and traffic of receptors
+ Control of their properties
+ Structural role in spine shape and size

Synapses are dynamics

dendritic spines



(GFP-ACTIN)

From A. Matus

Optogenetics

Use of light to monitor and to trigger synaptic activity

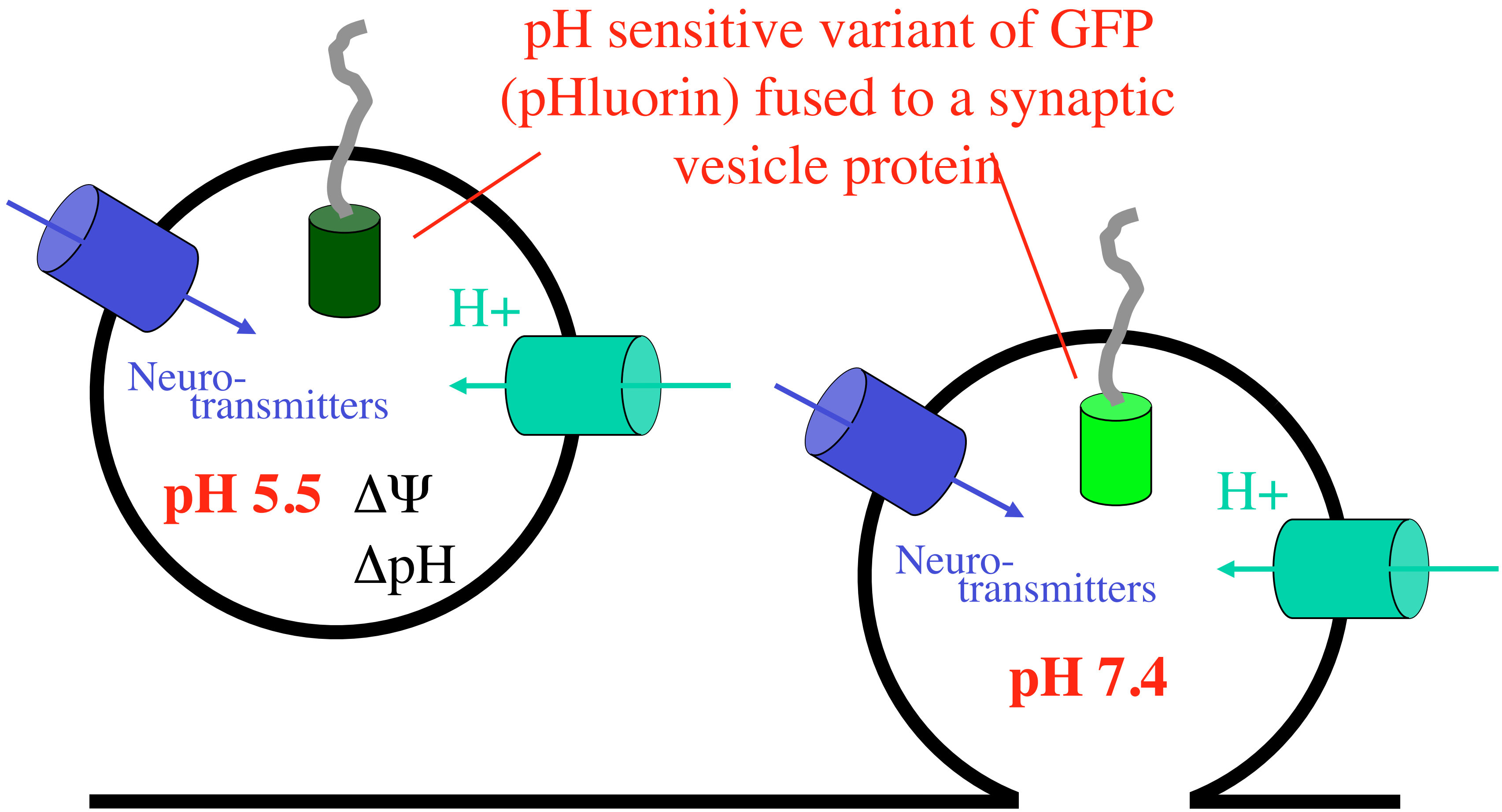
Optogenetics in Neural Systems

Ofer Yizhar,[1] Lief E. Fenno,[1] Thomas J. Davidson,[1] Murtaza Mogri,[1] and Karl Deisseroth[1,2,3,4,*]

Neuron *71*, July 14, 2011 ©2011

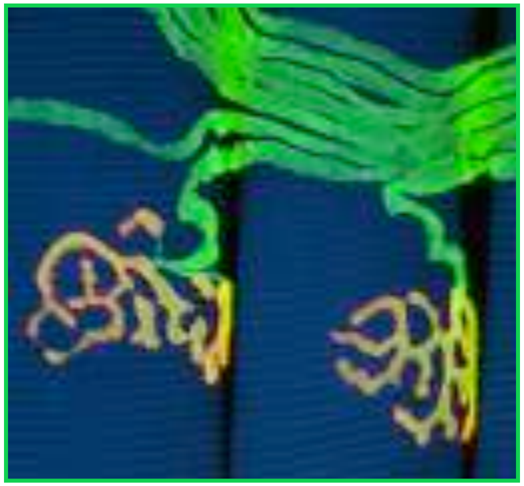
Imaging synaptic transmission

(synaptic vesicle exocytosis)



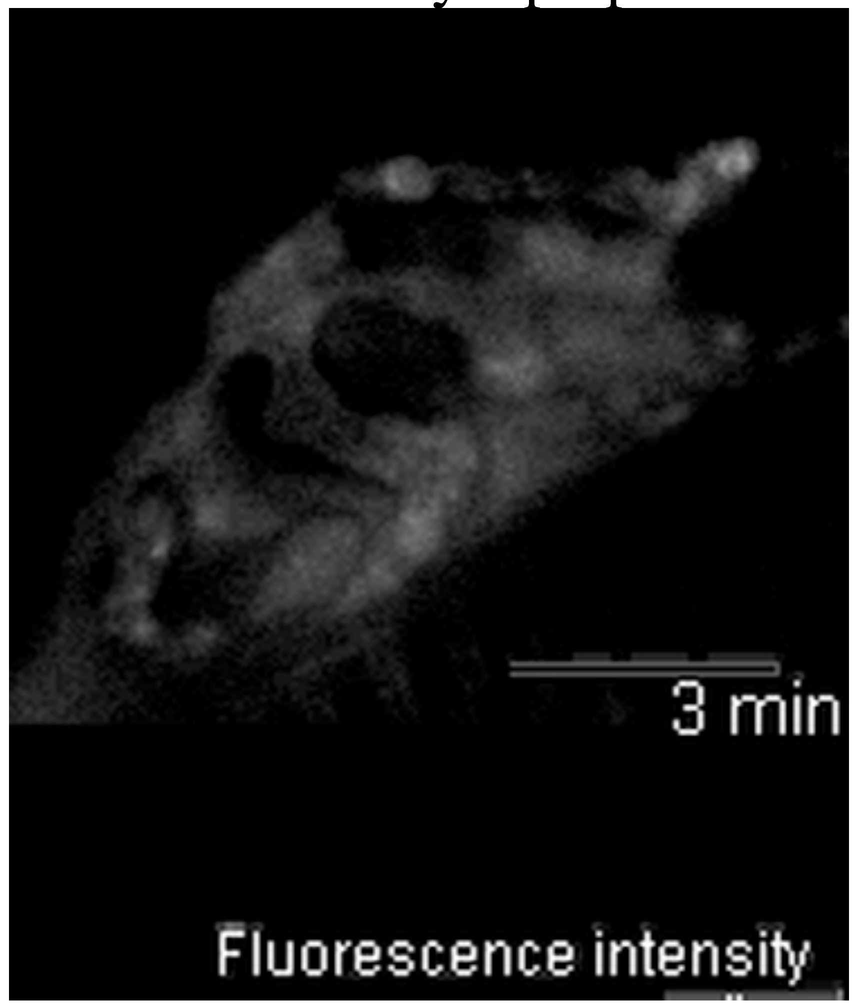
Imaging synaptic transmission

(synaptic vesicle exocytosis)



Mammalian
neuromuscular junction

synaptopHluorin



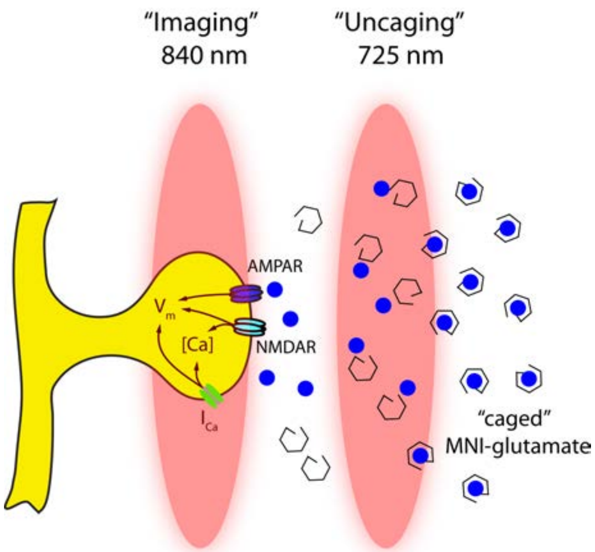
movie

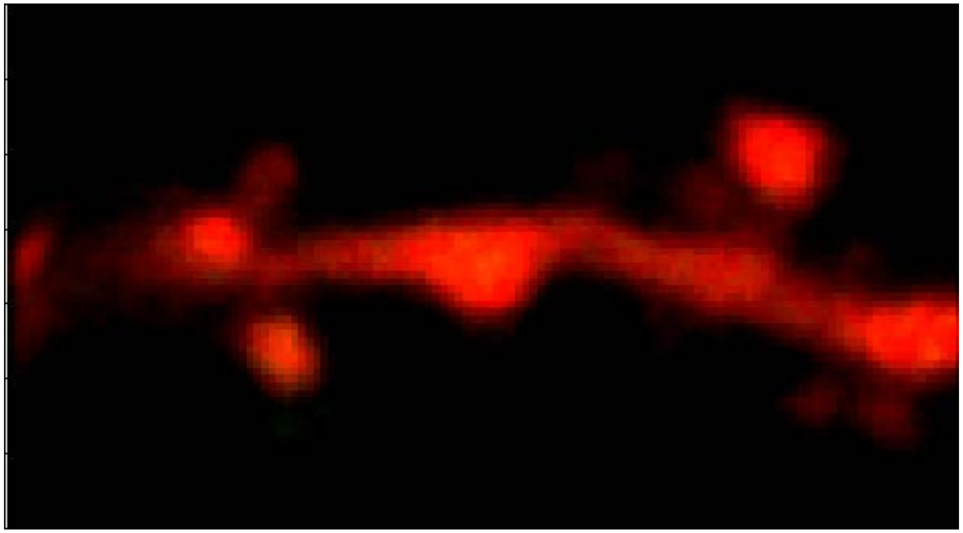
From Bill Betz

Imaging synaptic transmission

(postsynaptic action of glutamate)

Simultaneous 2-photon Calcium Imaging and Focal Glutamate Uncagingin Living Brain Slices



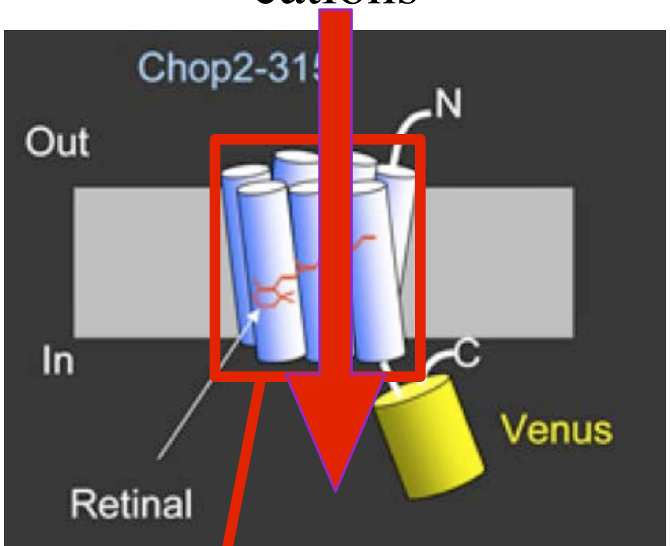


Mike Higley (Yale CNNR)

Neuron, filled with the Ca-insensitive red fluorophore Alexa-594 and the Ca indicator Fluo-5F

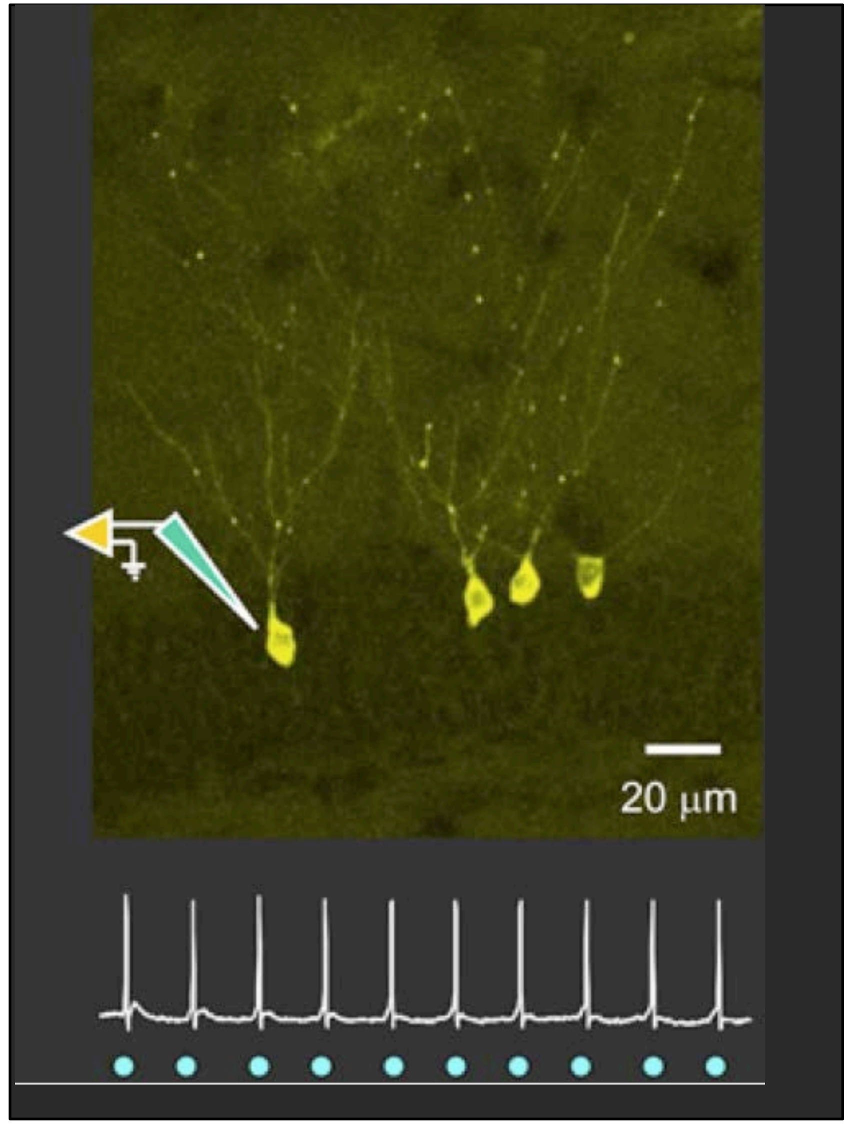
Optogenetics

use of light and genetically encoded probes to examine and manipulate synaptic function



channelrhodopsin
cation channel controlled by light
from alga *Chlamydomonas reinhardtii*

halorhodopsin: Cl^- pump
(inhibitory) controlled by light
da archibatteri



sendaibrain.org/kyoten/images/yawo_photo02.jpg

Photostimulation in living organisms

Espression of channelrhodopsin *in vivo*

channelrhodopsin in inhibitory motor neurons

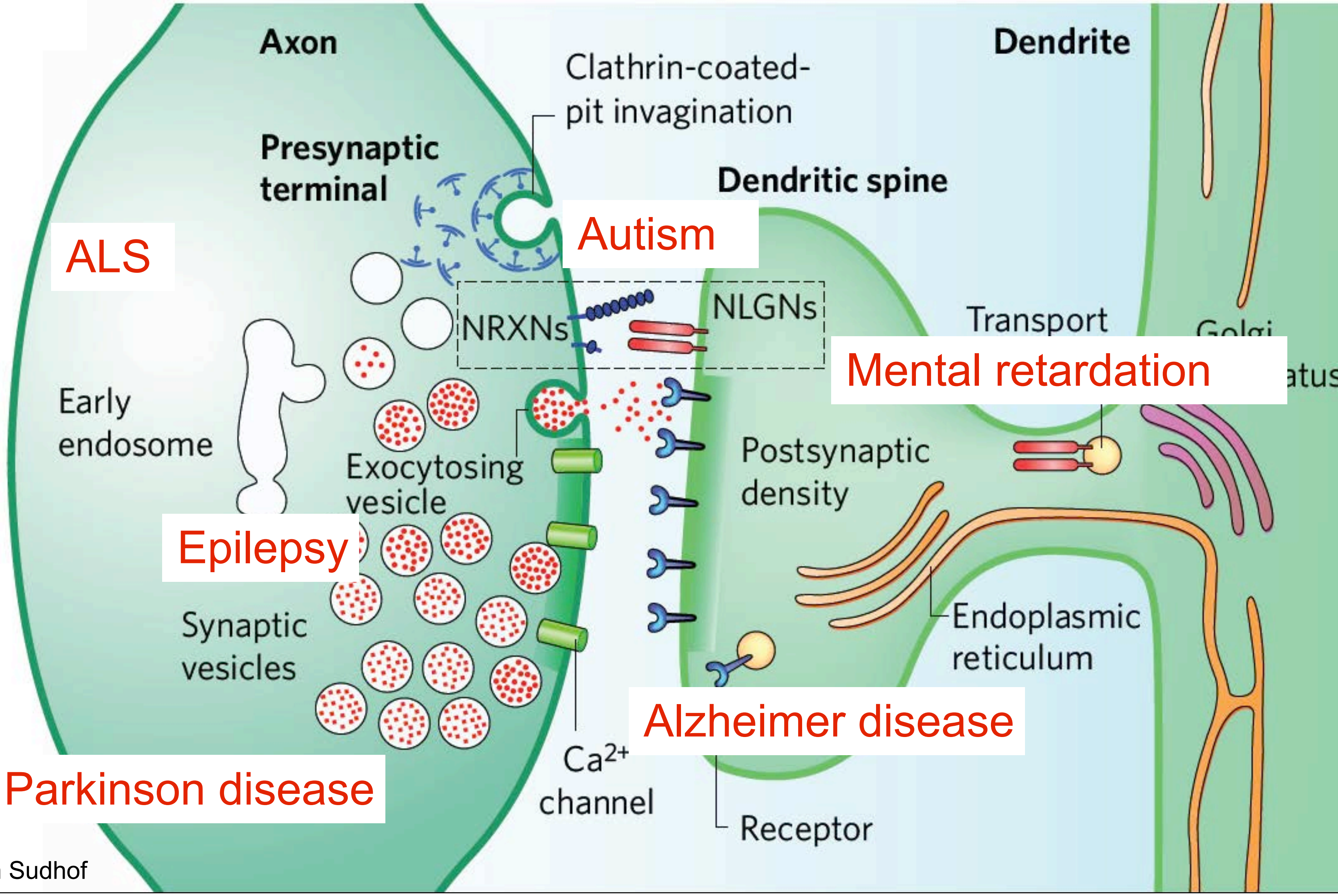
Liewald et al. Gottshalk lab
Nature Methods 2008

Channelrhodopsin expression in cortical neurons

(five light pulses, 20 Hz, 1 ms duration

Hubel et al. (Svoboda lab), Nature 2008

Synapses and neurological & psychiatric diseases



From Sudhof