# Introduction to Neuroinformatics

# Synapses I

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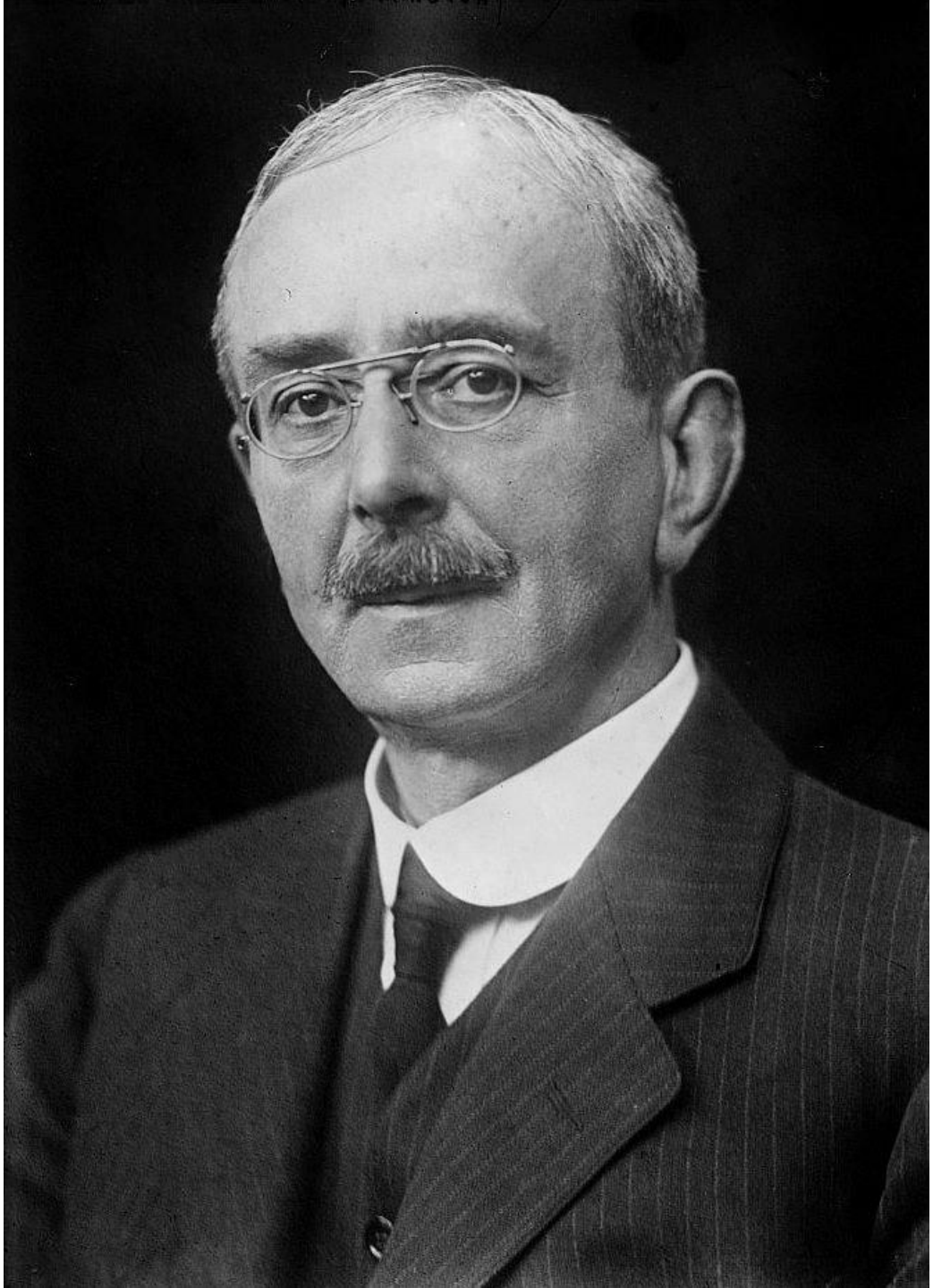
# Discovery of synaptic transmission

- Cajal's golgi staining methods suggested the presence of contacts between cells that were used for communication ~1900’s.

- Sherrington proposed the term "synapse" meaning to clasp to describe the structure, 1890’s.



C. S. Sherrington

# Cajal's drawings of golgi stain.

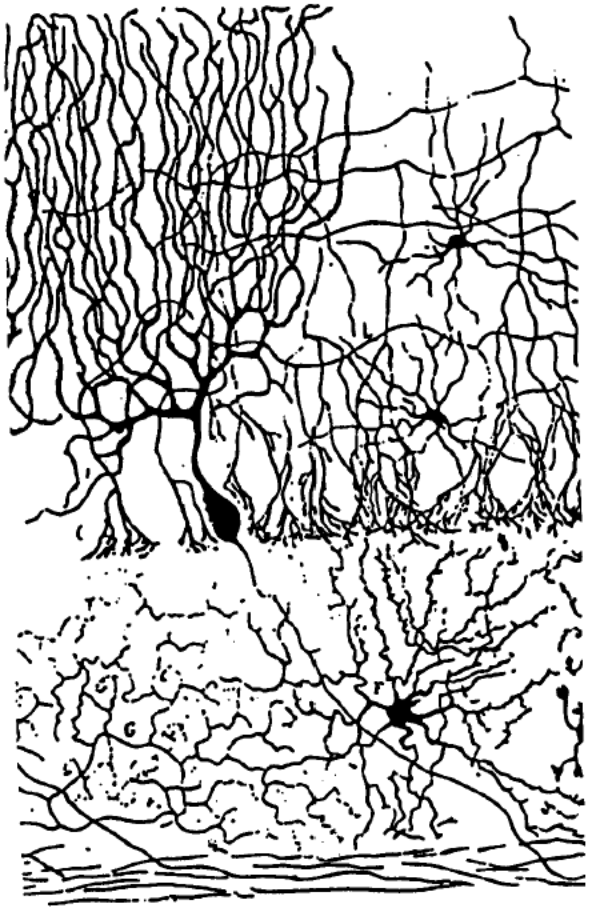


Fig. 2. *Summary view of the neuronal organization of the mammalian cerebellum, based on Golgi stains.* Note the juxtaposition of the descending fringes (the endings of basket cells) and the Purkinje cell bodies. Adapted from Ref. 5.

*TINS* Vol. 20, No. 9, 1997

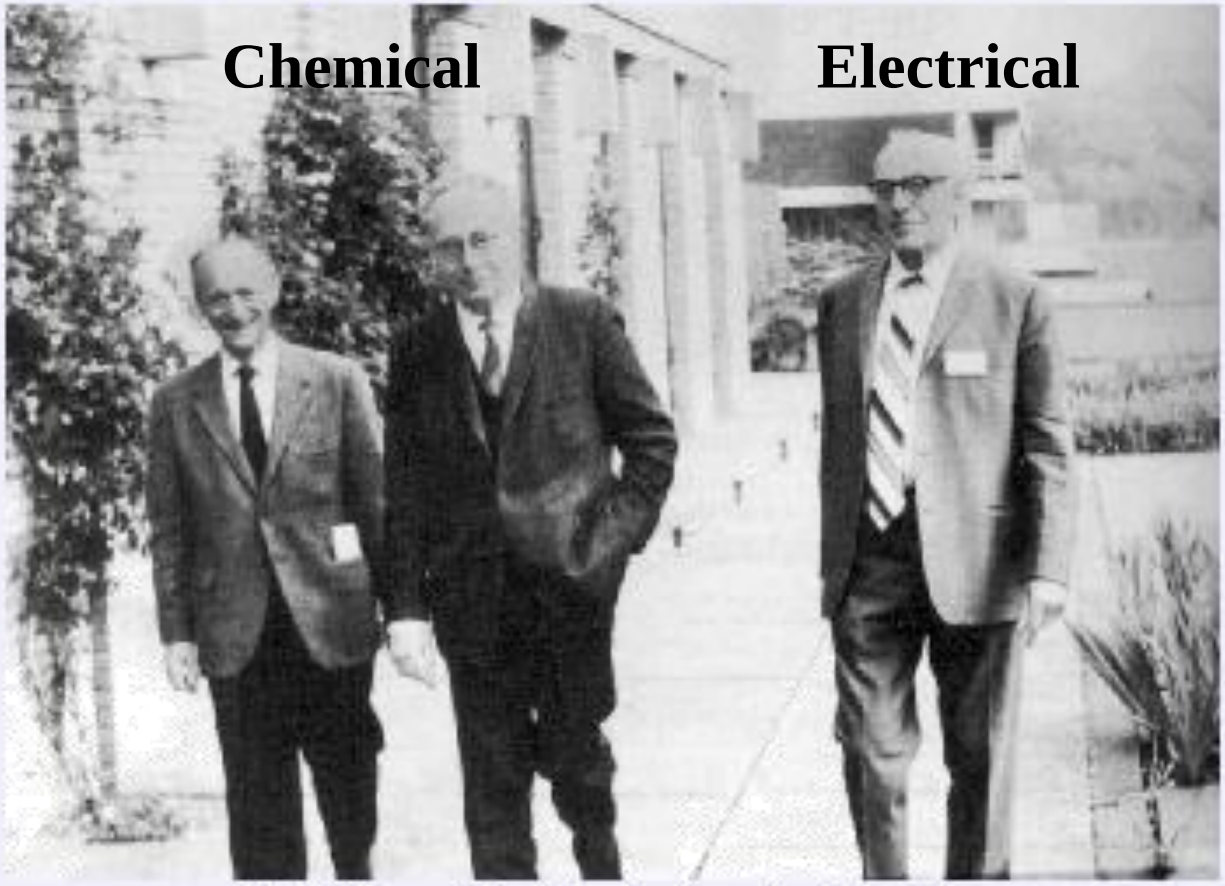
# Sherrington's insights 1890s.

'So far as our present knowledge goes, we are led to think that the tip of a twig of the arborescence is not continuous with but merely in contact with the substance of the dendrite or cell body on which it impinges. Such a special connection of one nerve cell with another might be called a synapse.'

'Such a surface might restrain diffusion, bank up osmotic pressure, restrict the movement of ions, accumulate electric charges, support a double electric layer, alter in shape and surface tension with changes in difference of potential ... or intervene as a membrane between dilute solutions of electrolytes of different concentration or colloidal suspensions with different sign of charge.'

Shepherd 1997 TINS

# Soup vs Spark Controversy about Synaptic Transmission




Kuffler, Katz vs Eccles

From Kristin Harris Lectures.
http://synapses.mcg.edu/lab/harris/lectures.htm

# Soup vs Spark

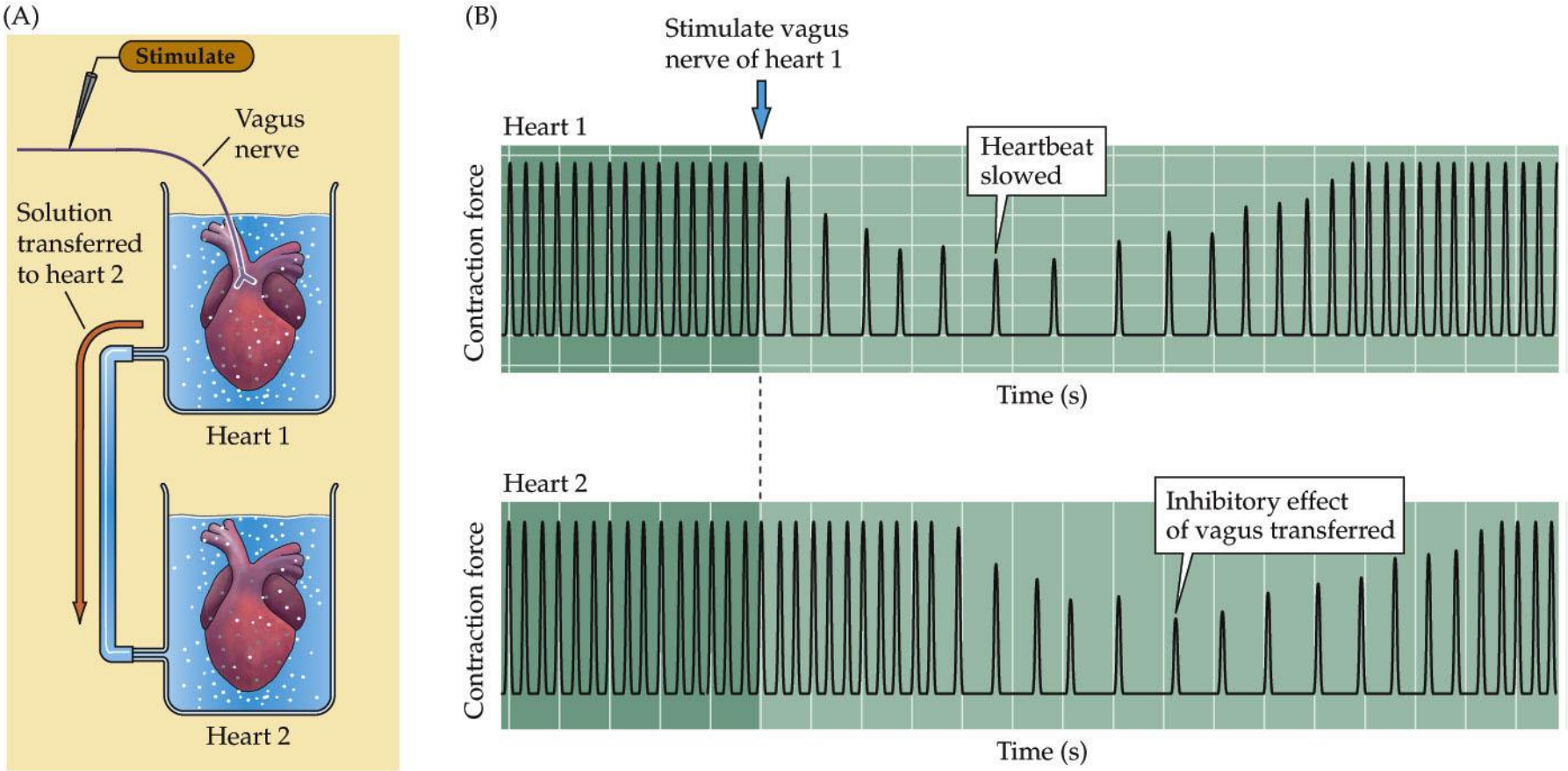
- Is Synaptic transmission mediated Chemically or by direct Electrical transfer of charge?
- Evidence for chemical transmission at the NMJ was widely accepted by Neuropharmacologists
- Some of the physiologists thought that certain aspects were too fast to be mediated chemically.

From Kristin Harris Lectures.
http://synapses.mcg.edu/lab/harris/lectures.htm

# Otto Loewi, chemical transmitter.

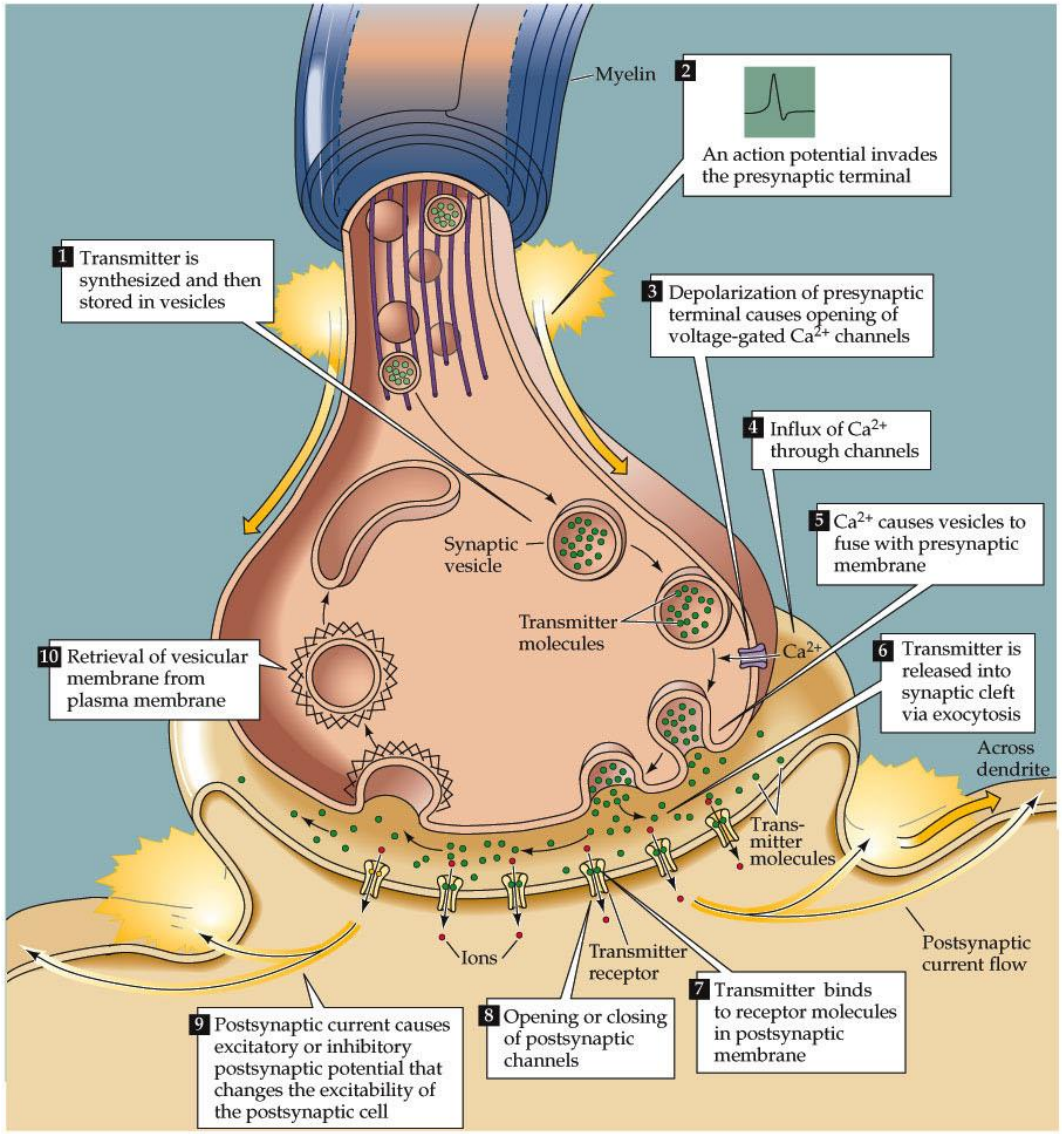
- 1936 Nobel prize for Medicine
- Showed that vagus nerve stimulation liberates a diffusible transmitter.
- Perfusate from one stimulated frog heart could be transferred to another and have an effect on beat frequency.

# An early experiment to support the neurotransmitter hypothesis




**NEUROSCIENCE, Fourth Edition, Figure 5.4**

# Chemical synapses: the predominant means of communication between neurons



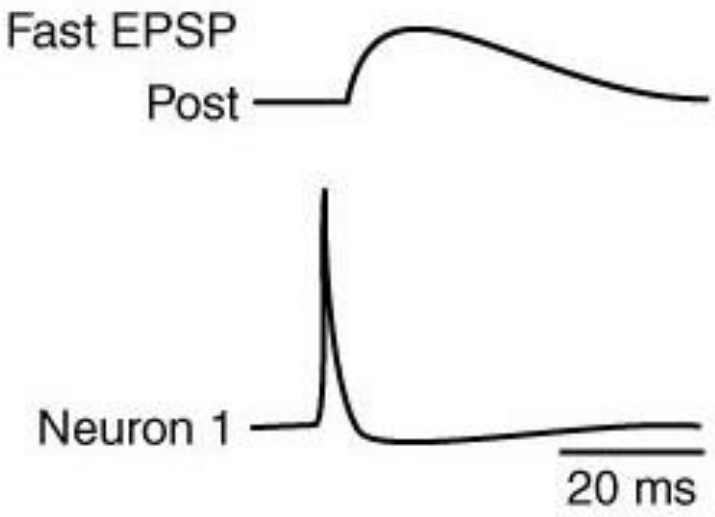

***NEUROSCIENCE, Fourth Edition,* Figure 5.3**

# Chemical Synaptic Transmission.

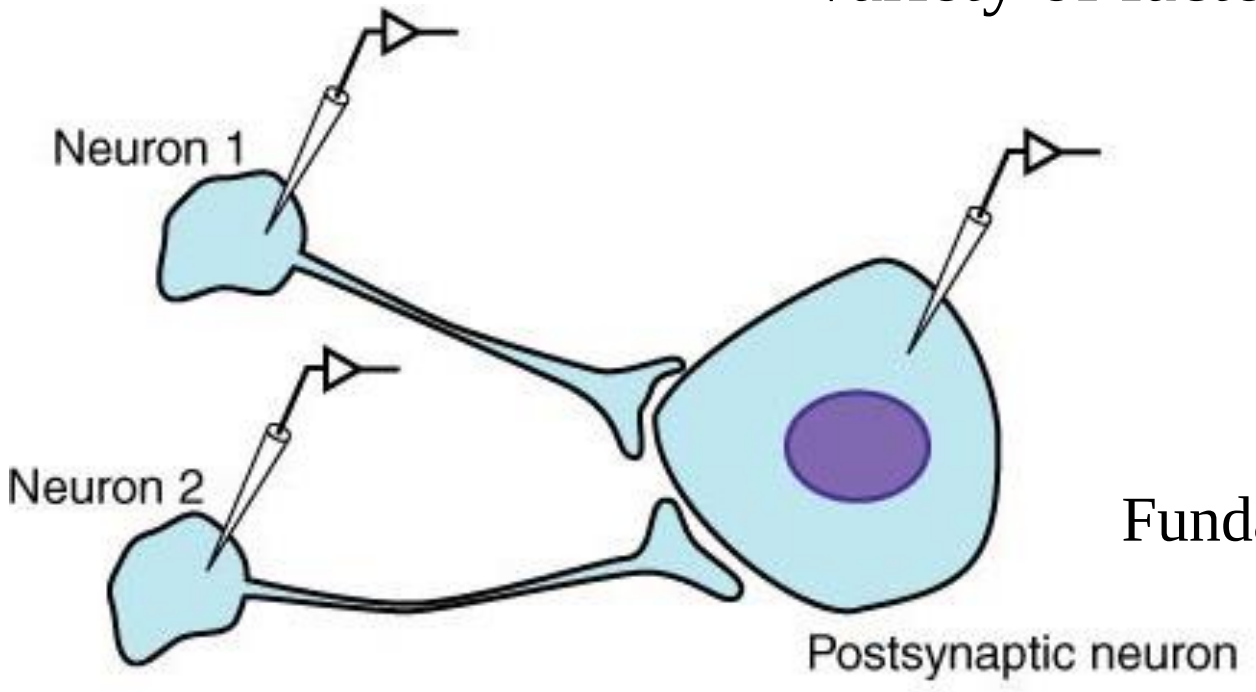
- Definition:  Communication between cells which involves the rapid release and diffusion of a substance to another cell where it binds to a receptor (at a localized site) resulting in a change in the postsynaptic cells properties.

# Chemical transmission.

- Contrary to electrical transmission multiple steps are required to release transmitter chemicals and for them to act on postsynaptic receptors, resulting in a time delay (can be as short as 0.2 msec, from Ca2+ entry to secretion).
- Directional, select localization of release machinery to presynaptic terminals and receptors to postsynaptic specializations.
- Can change sign by release of inhibitory transmitter.
- Highly modulatable as it has many steps presynaptic terminal and at the postsynaptic sites.

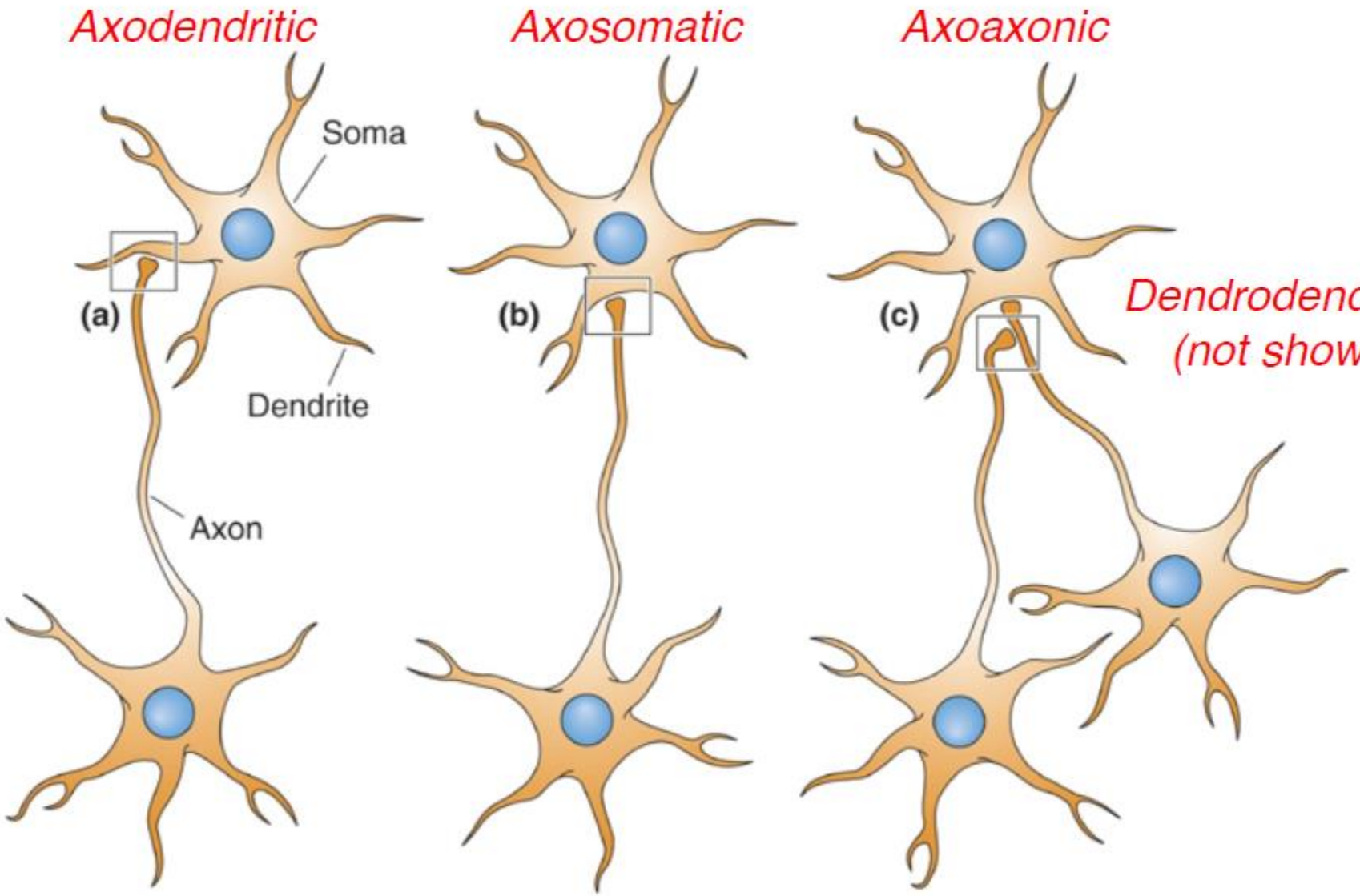



A hall mark of chemical transmission is a delay between presynaptic Ca2+ elevation and secretion. The delay can be as short as 0.2 ms, but is usually longer due to a variety of factors.




Fundamental Neuro. 2002

# Types of Synapses



# Steps to chemical synaptic transmission.

- First need to bring the presynaptic neuron to threshold at axon hillock.
- Conduction down axon, length, R*C dependent.
- Opening of voltage gated Ca channels.
- Diffusion and action of Ca at release machinery.
- Exocytosis and diffusion of transmitter in cleft.
- Activation of postsynaptic receptors.

Synaptic delays can be less than 0.2 ms from calcium entry to the beginning of secretion, but are typically longer when all steps (below) are considered.

From Sudhof 2004



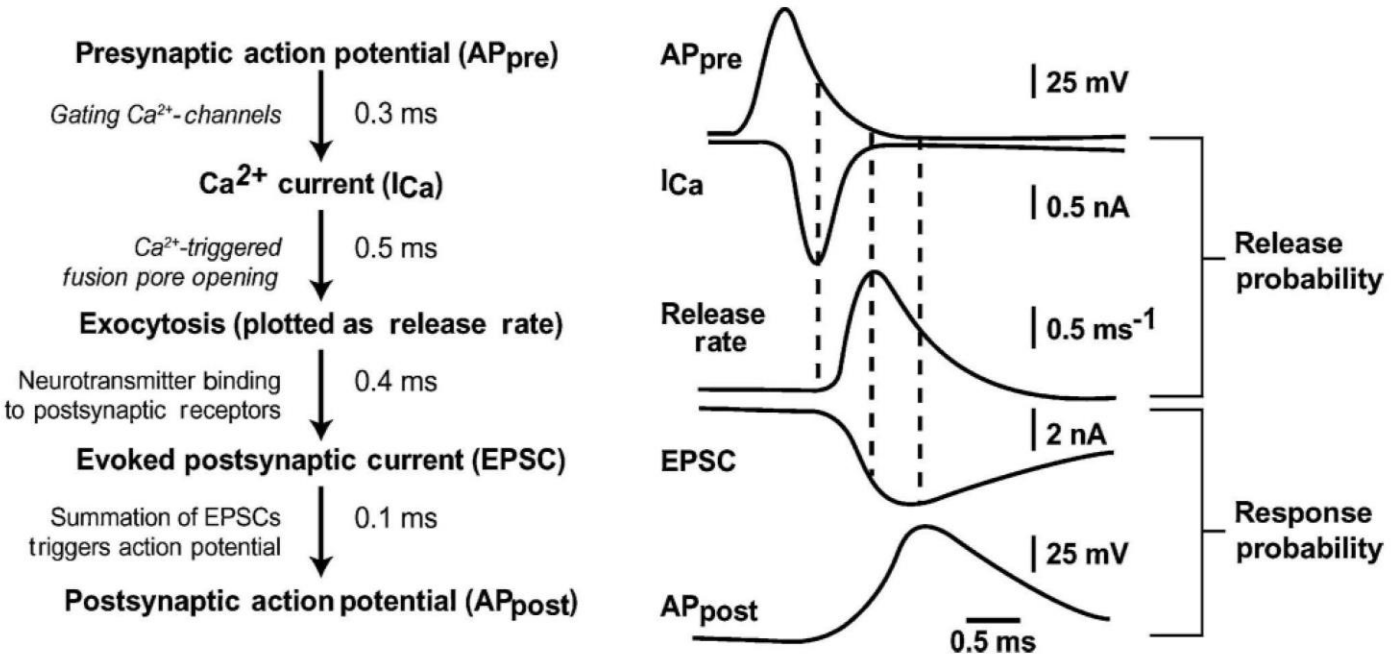
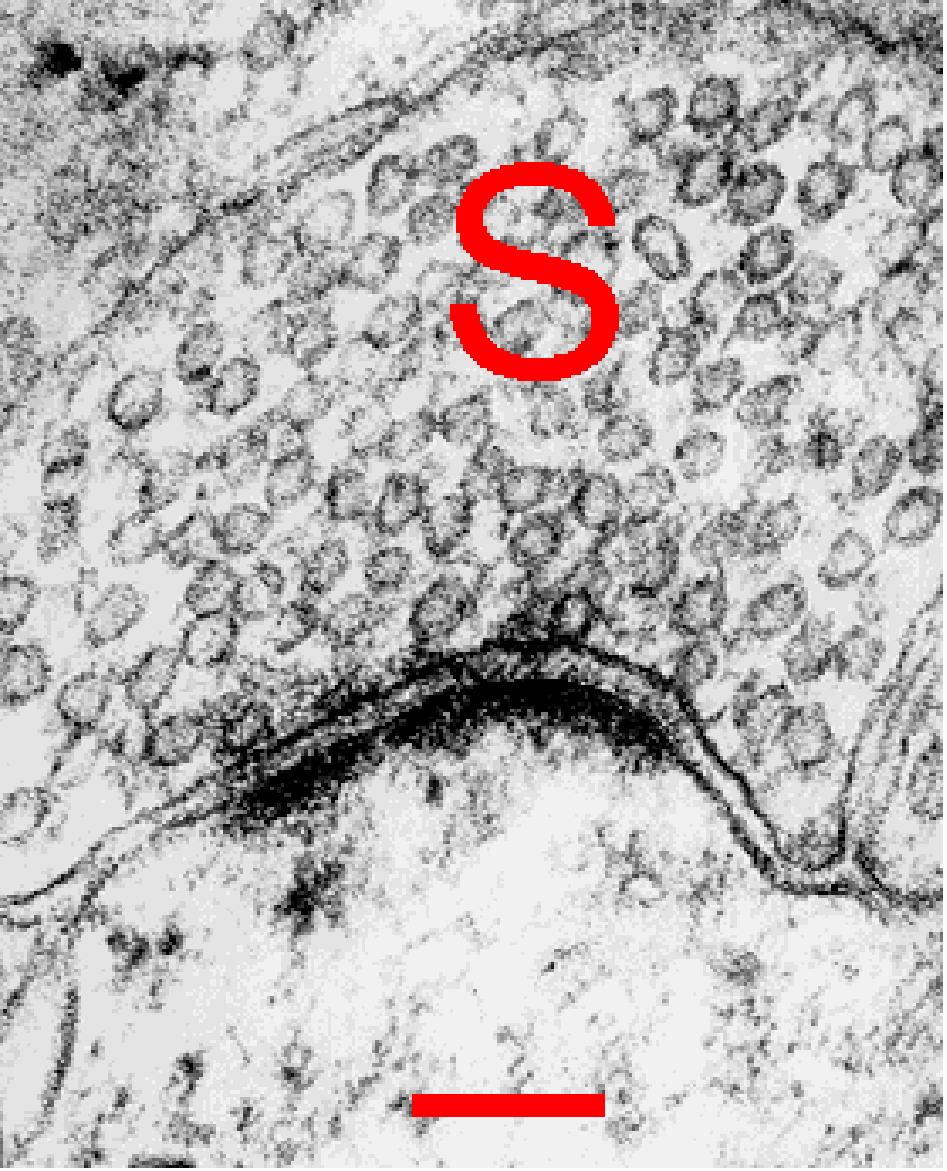
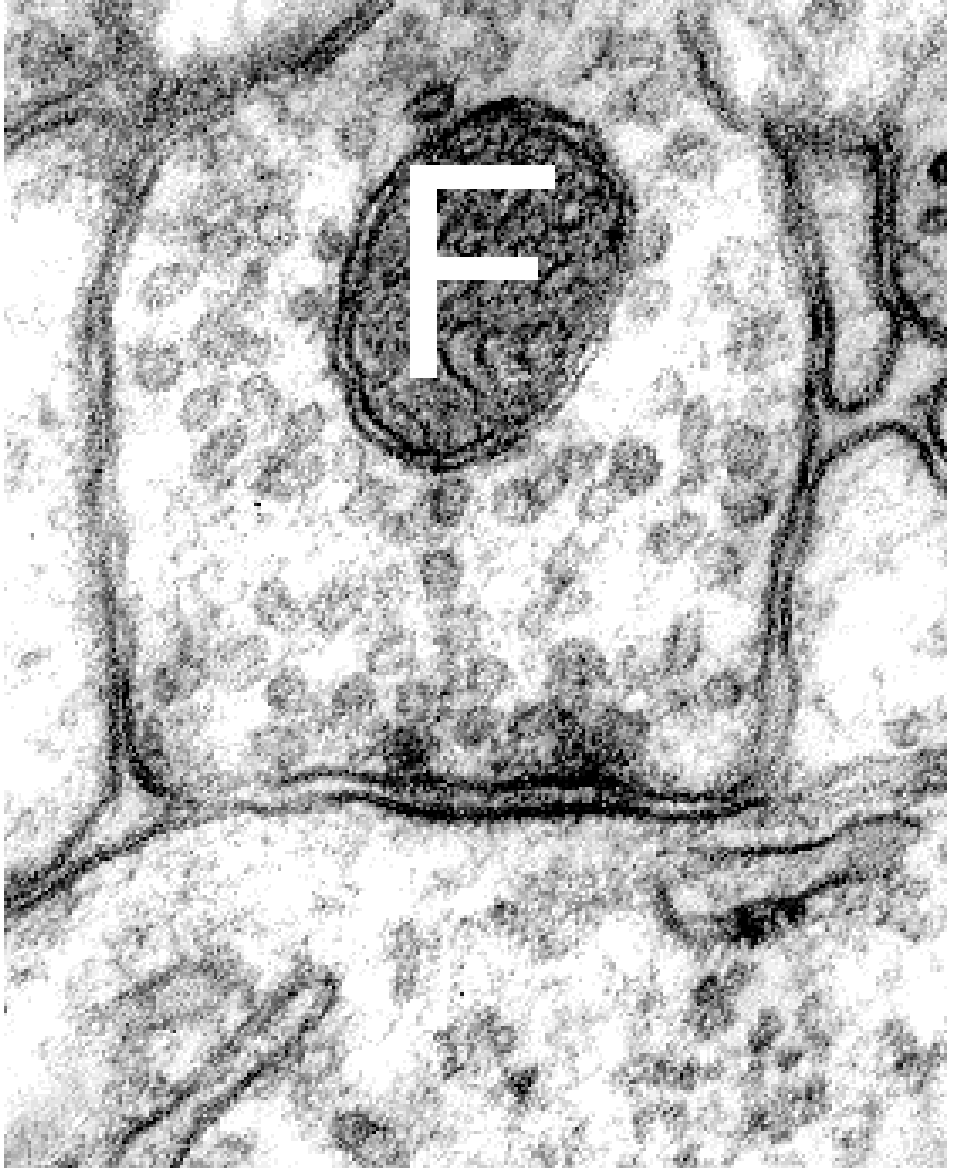



**Figure 2** Reaction sequence and timing of synaptic transmission. The principal reactions with the associated time constants are shown on the left, and traces from the corresponding reactions in the calyx of Held synapses are illustrated on the right (modified from Meinrenken et al. 2003). The time calibration bar at the bottom applies to all traces.



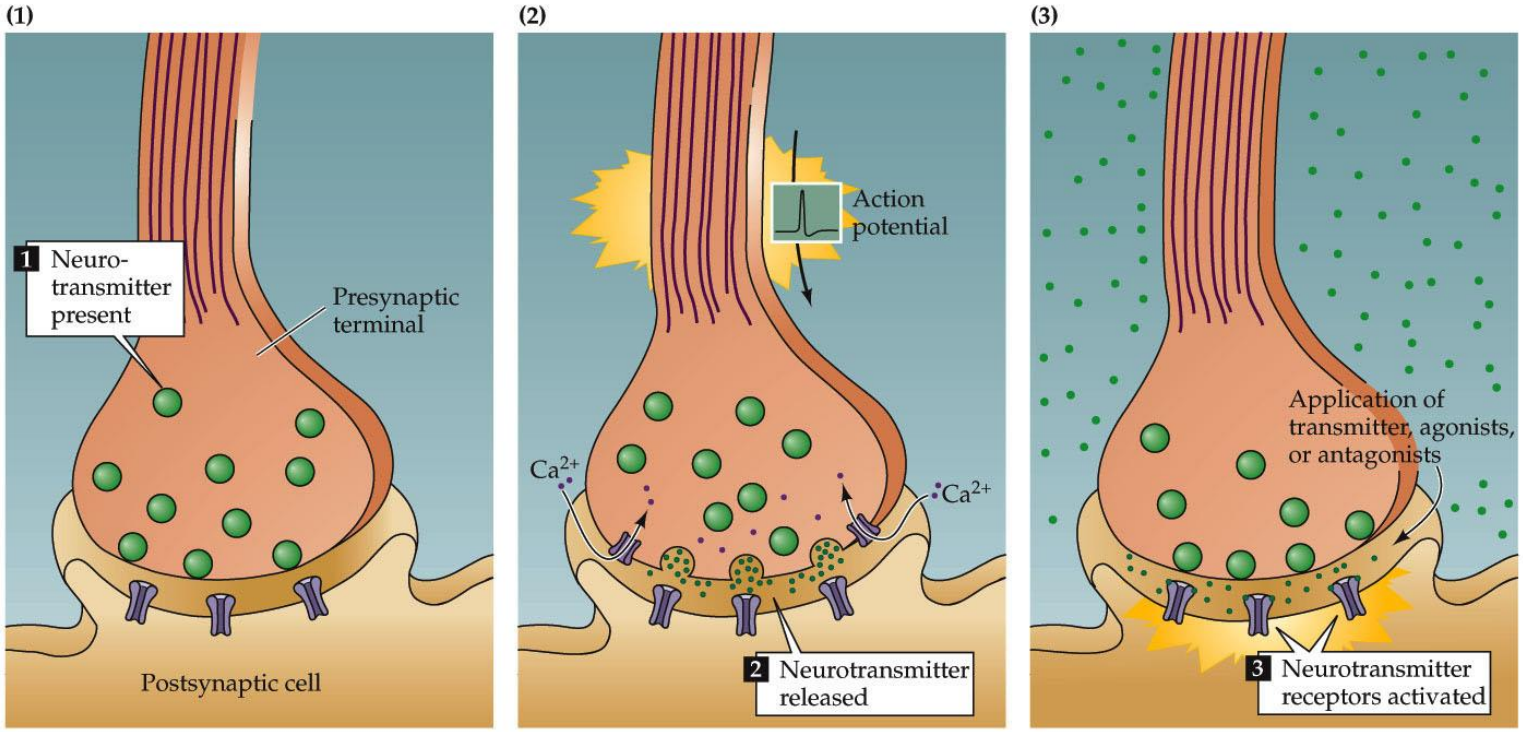

Type I Excitatory




Type II Inhibitory

# Criteria that define a neurotransmitter:

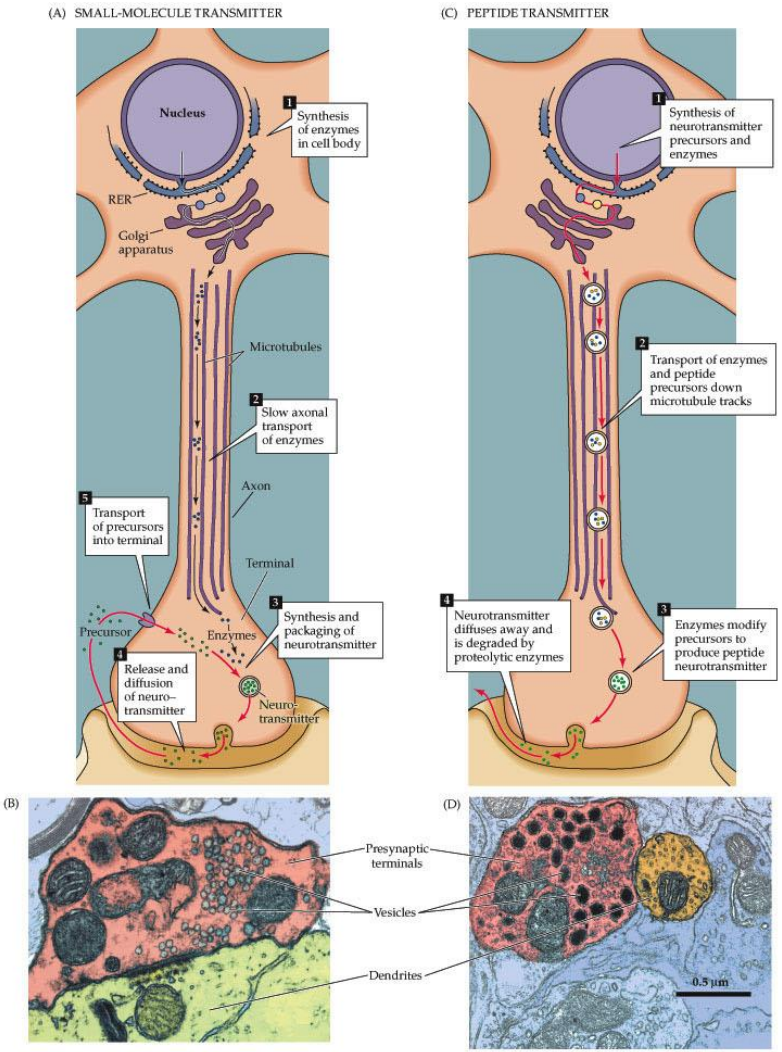
1. Must be present at presynaptic terminal
2. Must be released by depolarization, $Ca^{++}$-dependent
3. Specific receptors must be present



# Neurotransmitters may be either small molecules or peptides

## Mechanisms and sites of synthesis are different

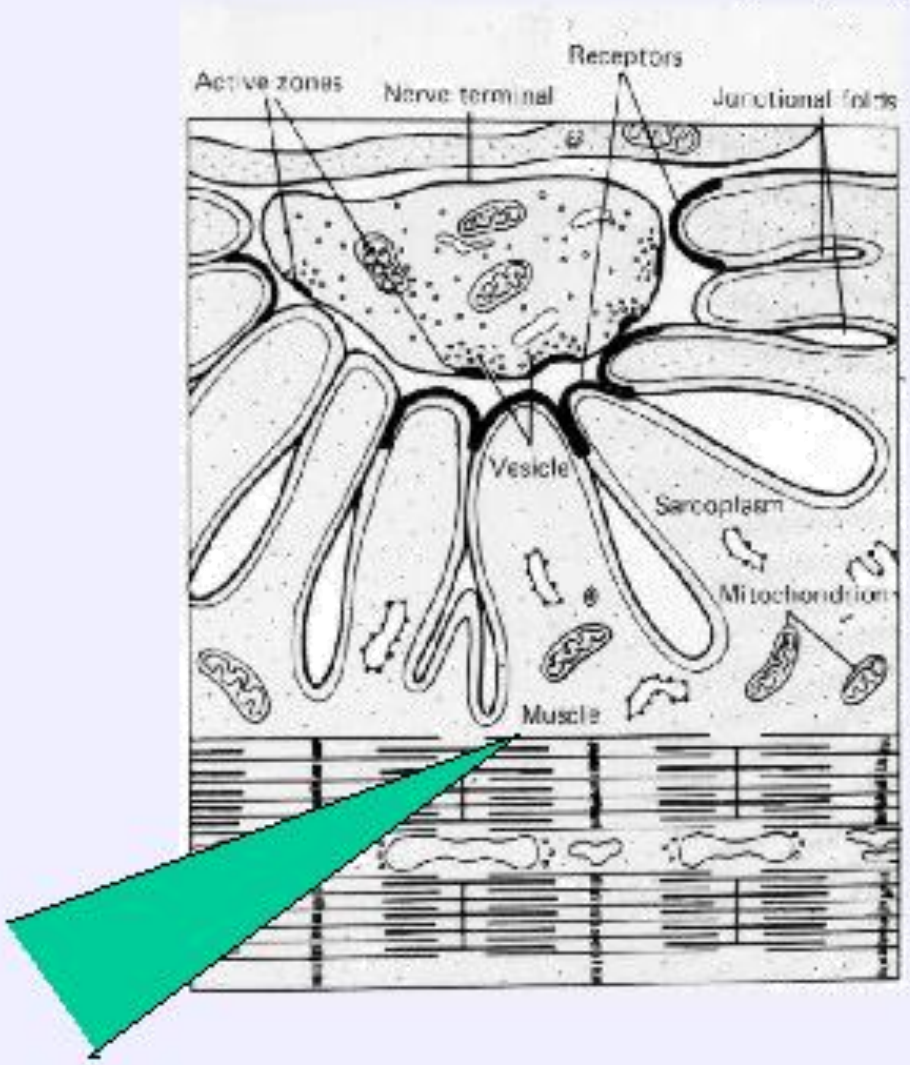
Small molecule transmitters are synthesized at terminals, packaged into small clear-core vesicles (often referred to as ‘synaptic vesicles’




Peptides, or neuropeptides are synthesized in the endoplasmic reticulum and transported to the synapse, sometimes they are processed along the way. Neuropeptides are packaged in large dense-core vesicles

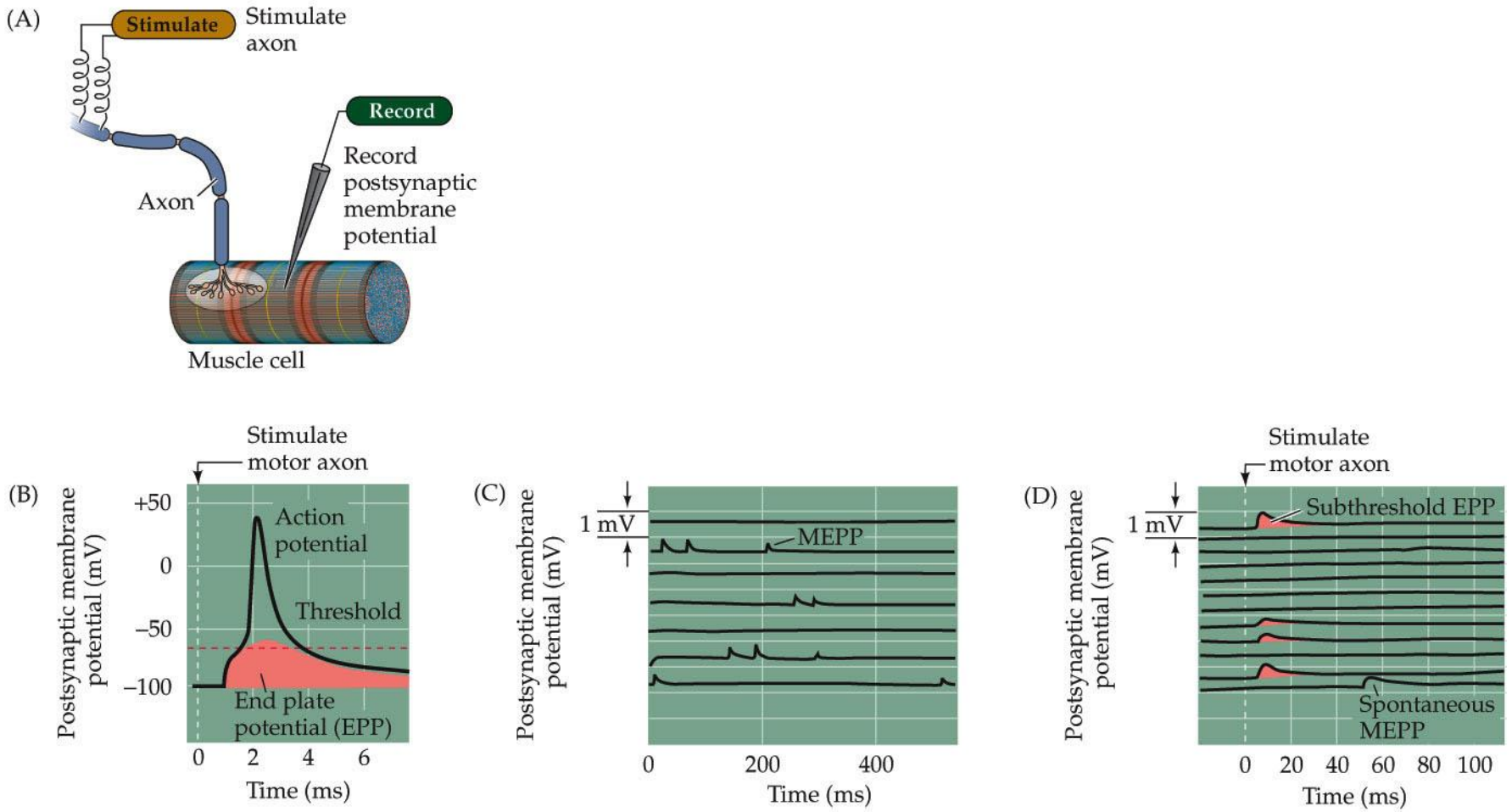
# The neuromuscular junction

NMJ recording electrode




From Kristin Harris Lectures.
http://synapses.mcg.edu/lab/harris/lectures.htm

# Neurotransmitter is released in discrete packages, or quanta



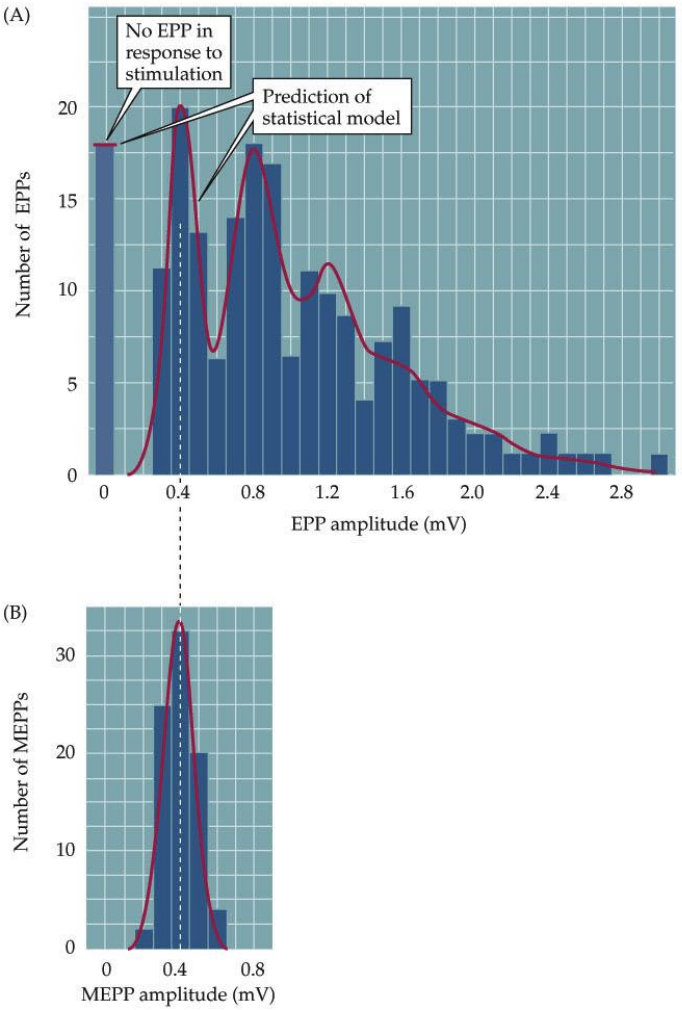

**NEUROSCIENCE, Fourth Edition, Figure 5.6**

# Standard Katz (Quantal) Model of Synaptic Transmission

- One packet of neurotransmitter = 1 quantum
- AP transiently increases in the probability of releasing NX quanta
- Several quanta are available to be released
- Each quantum gives approximately the same postsynaptic response called the "Quantal Amplitude"
- The average number of quanta released, m = np
  - where n = the number quanta available for release
  - p = their average release probability.

# Failure analysis reveals that neurons release many quanta of neurotransmitter when stimulated, that all contribute to the response

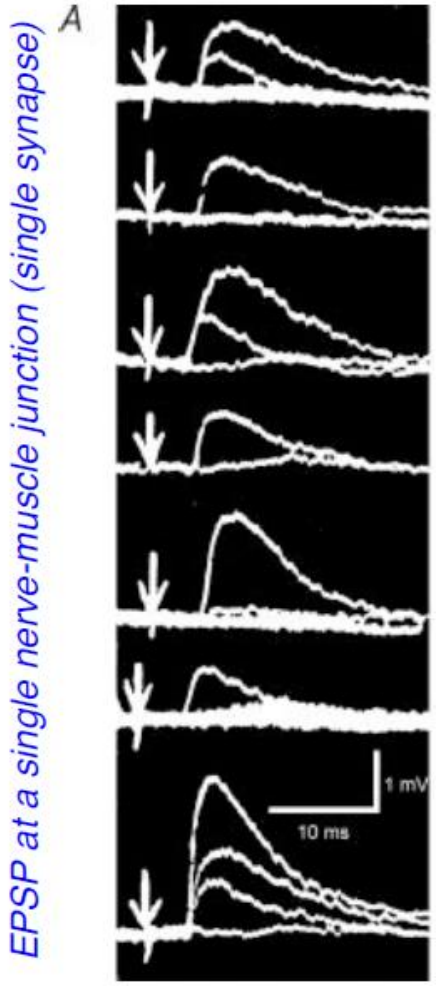
Quantal content: The number of quanta released by stimulation of the neuron




Quantal size: size of the individual quanta

**NEUROSCIENCE, Fourth Edition, Figure 5.7**

# Quantal Release of Neurotransmitters

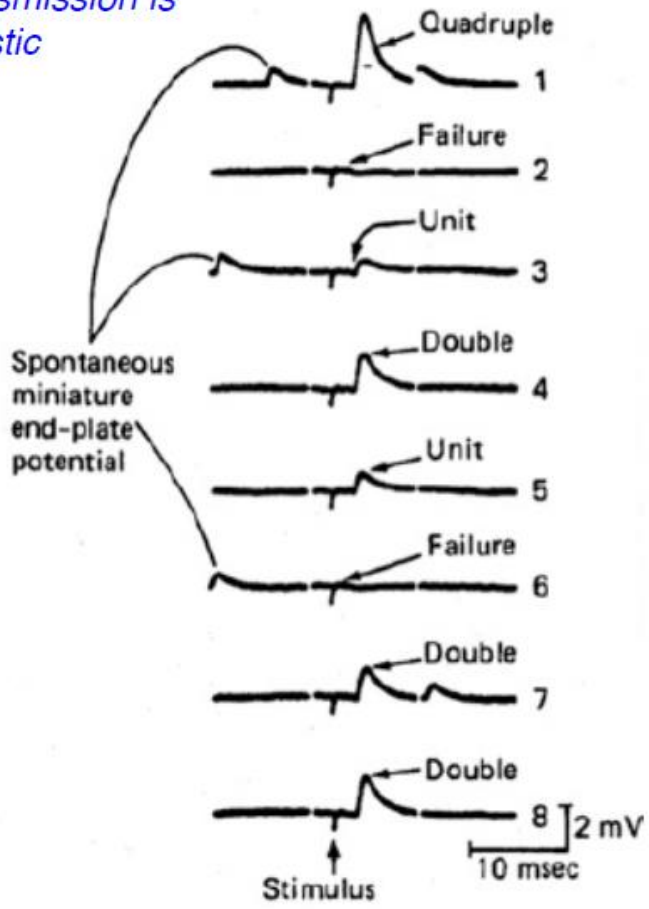



EPSP at a single nerve-muscle junction (single synapse)

Time

1. Synaptic transmission is Stochastic

Del Castillo and Katz; 1954




2. Each successful event is some product of a some unit event (or quanta)

# Quantal Release of Neurotransmitters

- If the probability of a single unit responding is *'p'*, and if each unit has an independent and equal *'p'*, then the mean number of units responding to each stimulus is given by: *'np'*
  n is the total number of available

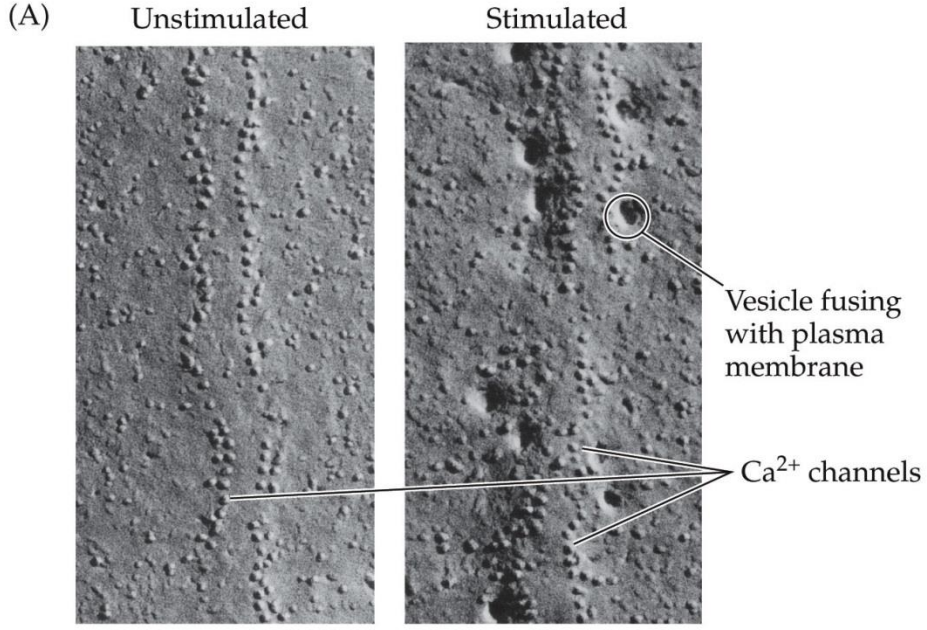
- Probability that x-units successfully contributing is given by the binomial distribution:

$$P(success = x) = \binom{n}{x} p^x (1-p)^x$$

# Quanta correspond to release of individual synaptic vesicles

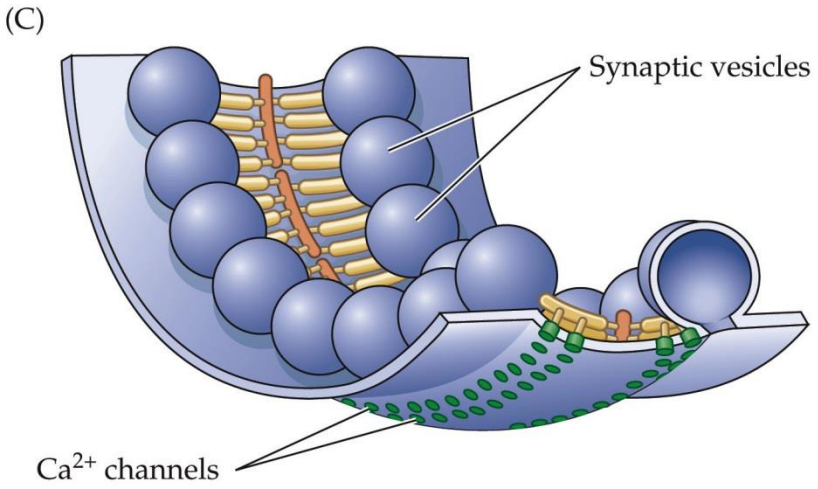
EM images and biochemistry suggest that a MEPP could be caused by a single vesicle

EM studies revealed correlation between fusion of vesicles with plasma membrane and size of postsynaptic response




NEUROSCIENCE, Fourth Edition, Figure 5.8 (Part 1)






NEUROSCIENCE, Fourth Edition, Figure 5.8 (Part 3)

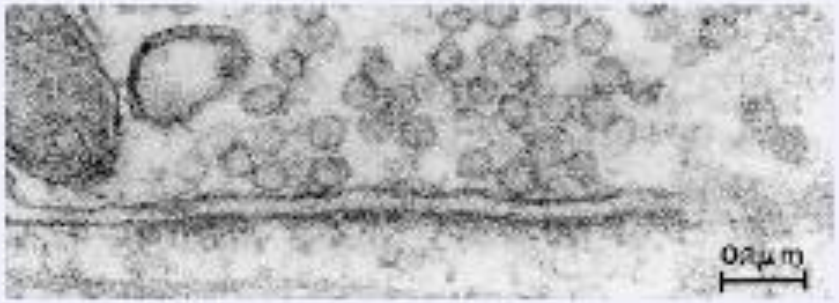
# CNS synapses and quanta.

- At CNS synapses with only a single release site, changing the probability of release (i.e. changing calcium concentration) does not effect the amplitude of the response (as only zero or one vesicle is released in theory).
- At CNS synapses with multiple release sites, changing release probability can change the postsynaptic response amplitude as more transmitter is released (graded  quantal levels).
- At the NMJ a single nerve can elicit a postsynaptic AP given multiquantal release, while at the CNS synapse (with low numbers of release sites) multiple synapses must cooperate, forces a network.

# CNS synapses and miniature release.

- Miniature release is produced in the absence of action potential stimulation.
- Thought to reflect the release of single vesicles or transmitter quanta.
- Can be stimulated by calcium entry, but may not necessarily require calcium for release.
- Commonly studied to gain insight into changes in receptors or release probability during synaptic plasticity experiments, although can be difficult to interpret.

# Docked Synaptic Vesicles

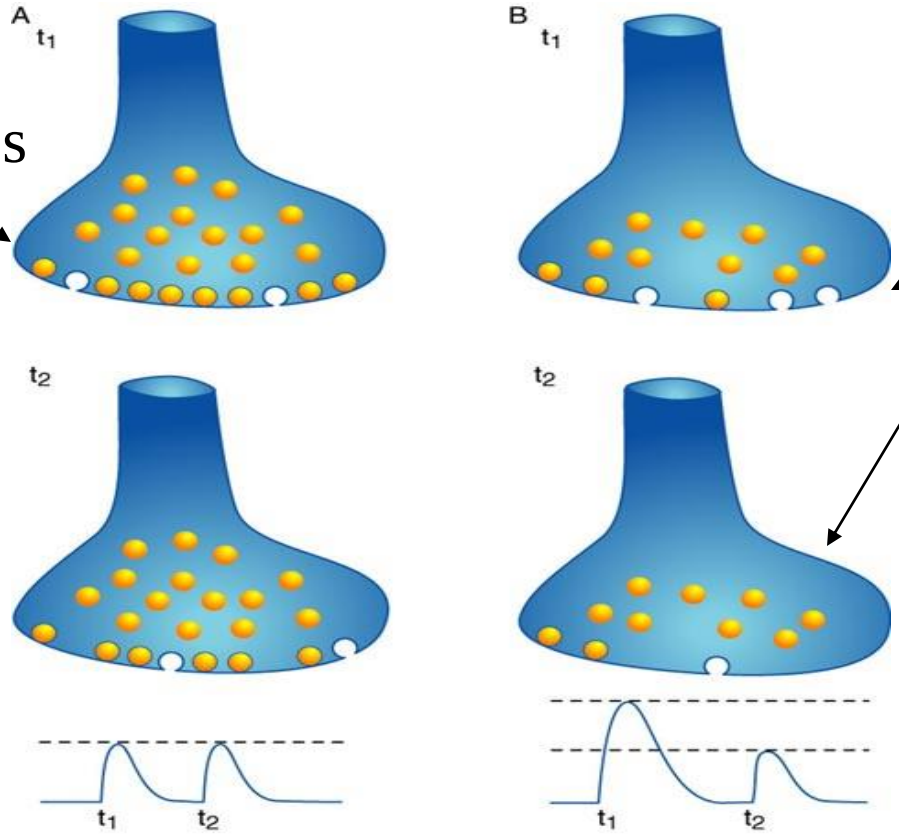



Define the number of readily releasable vesicles a synapse has available. A consequence of having of limited number is depletion at high stimulus frequency, CNS synapses may have only a small number of docked vesicles on the order of 5-10 vesicles for a hippocampal CA1 synapse (Harris and Sultan, 1995; Schikorski and Stevens, 1997).

From Kristin Harris Lectures.
http://synapses.mcg.edu/lab/harris/lectures.htm

Many vesicles in the RRP.

Few vesicles in the RRP, but Pr high undergoes depression.



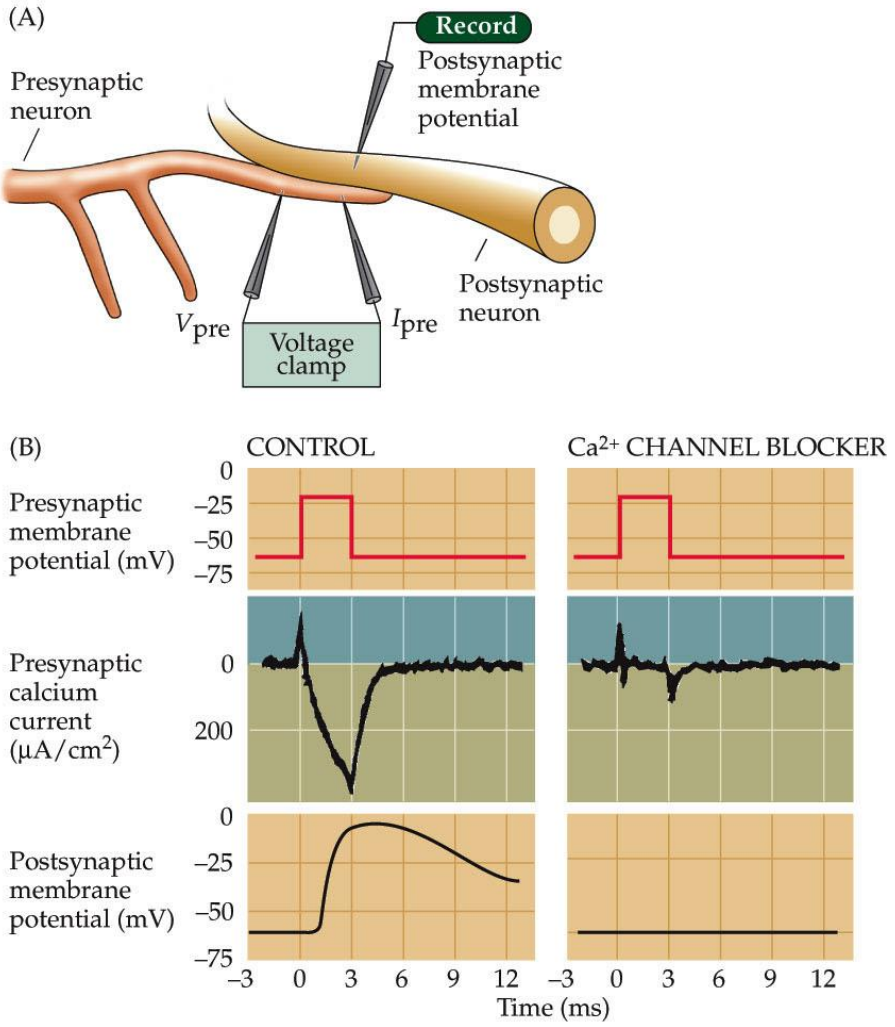

Remember depression over short timescales can also be caused by other mechanisms including desensitization and autoreceptors.



**FIGURE 10** Depletion model of synaptic depression depicting the action of two stimuli ($t_1$ and $t_2$) that arrive so closely spaced that no vesicles have been recruited to the releasable pool to replace those that fused in response to the first stimulus. (A) A synapse in which the releasable pool ($n$) is large and the probability of fusion for a given vesicle ($p$) is low shows little or no depression. Because only a small fraction of the docked, releasable vesicles fused in response to the first stimulus, the second response is comparable in amplitude. (B) A synapse in which the releasable pool ($n$) is small but the probability of fusion ($p$) is high is likely to be strongly depressing. Vesicles released by the first impulse deplete half the fusion-competent pool, leaving $n$ at $t_2$ equal to half its value at $t_1$. If $p$ has not changed at $t_2$, the second stimulus will release half as many quanta.

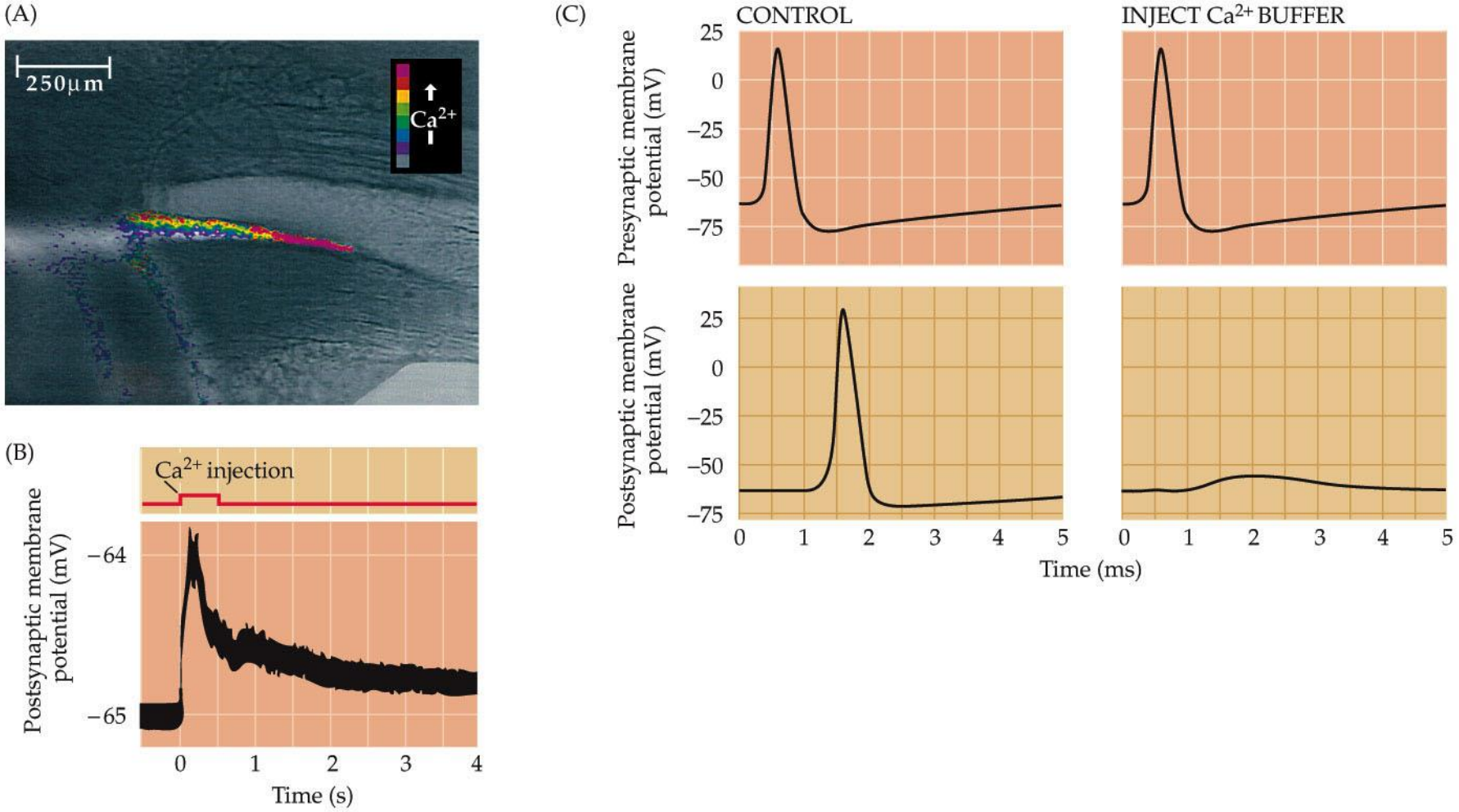
# Calcium influx is necessary for neurotransmitter release

Voltage-gated calcium channels



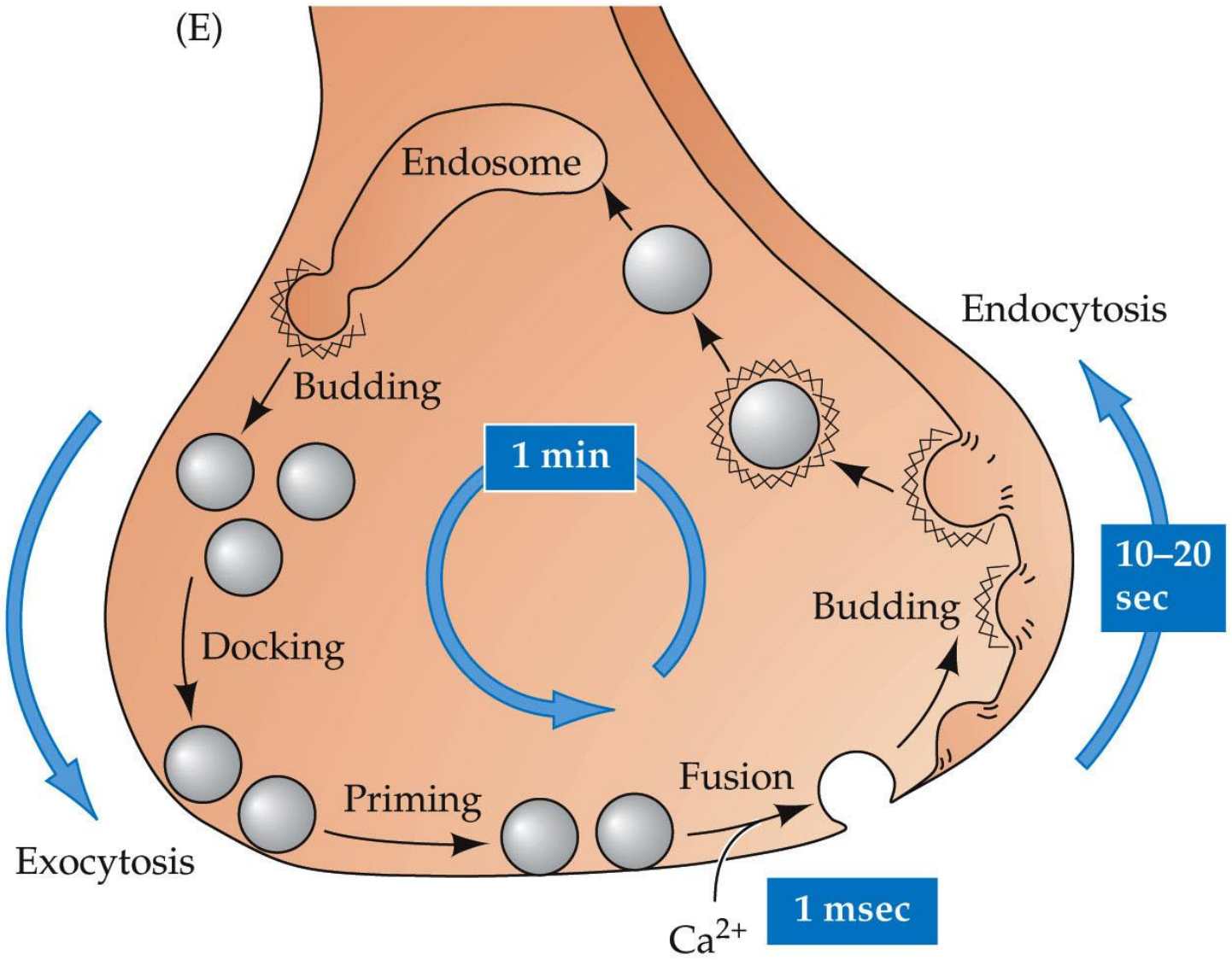

*NEUROSCIENCE, Fourth Edition,* Figure 5.10

# Calcium influx is sufficient for neurotransmitter release




**NEUROSCIENCE, Fourth Edition, Figure 5.11**

# The synaptic vesicle cycle




**NEUROSCIENCE, Fourth Edition, Figure 5.9 (Part 2)**

**Synaptic vesicle release consists of three principal steps:**

1. Docking

   Docked vesicles lie close to plasma membrane (within 30 nm)

1. Priming

   Primed vesicles can be induced to fuse with the plasma membrane by sustained depolarization, high $K^+$, elevated $Ca^{++}$, hypertonic sucrose treatment

2. Fusion

   Vesicles fuse with the plasma membrane to release transmitter. Physiologically this occurs near calcium channels, but can be induced experimentally over larger area (see 'priming'). The 'active zone' is the site of physiological release, and can sometimes be recognized as an electron-dense structure.

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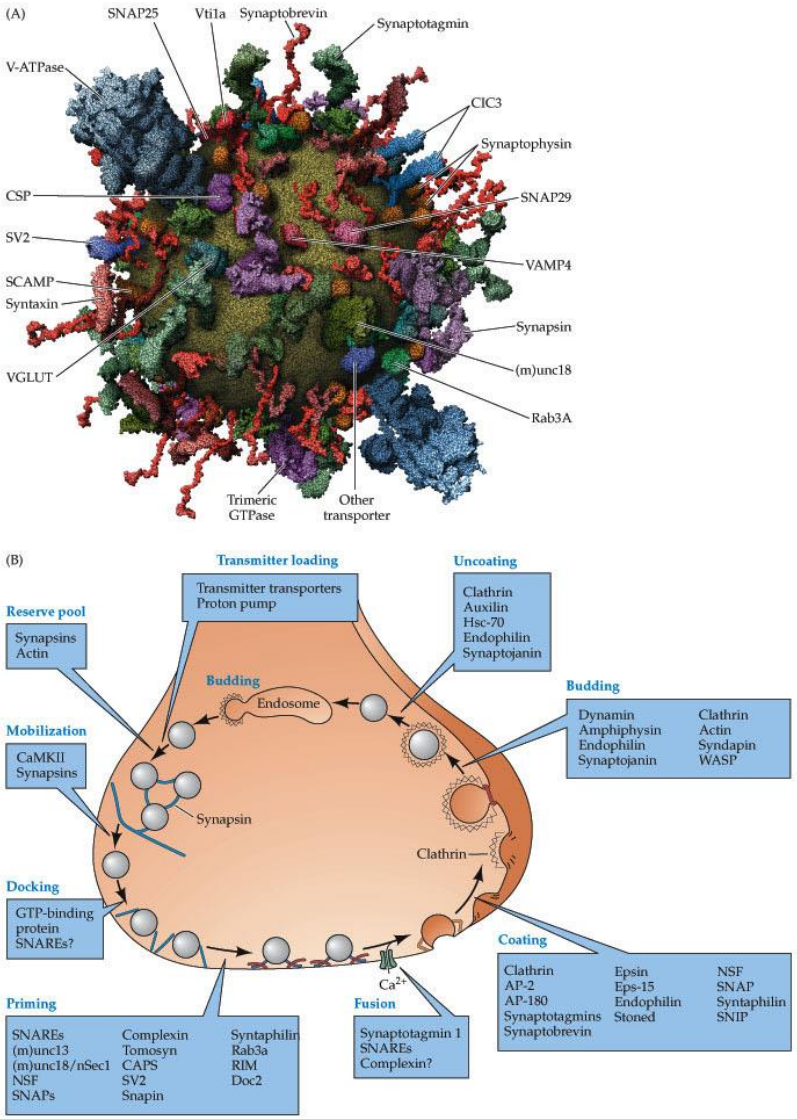
# Vesicle release requires many proteins on vesicle and plasma membrane

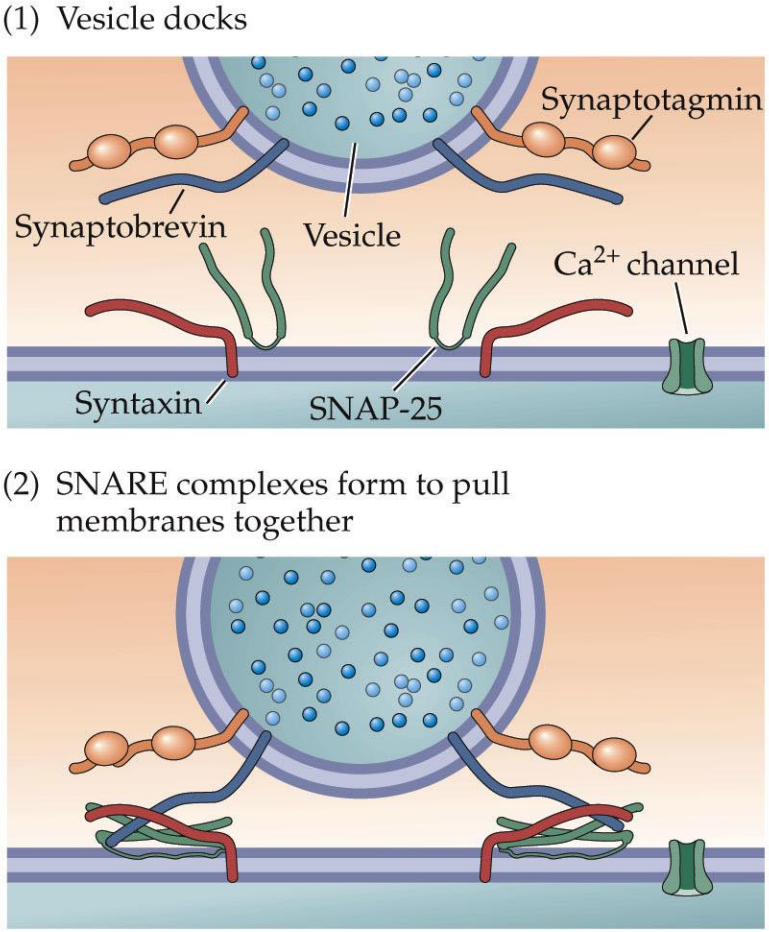



**NEUROSCIENCE, Fourth Edition, Figure 5.13**

# Priming

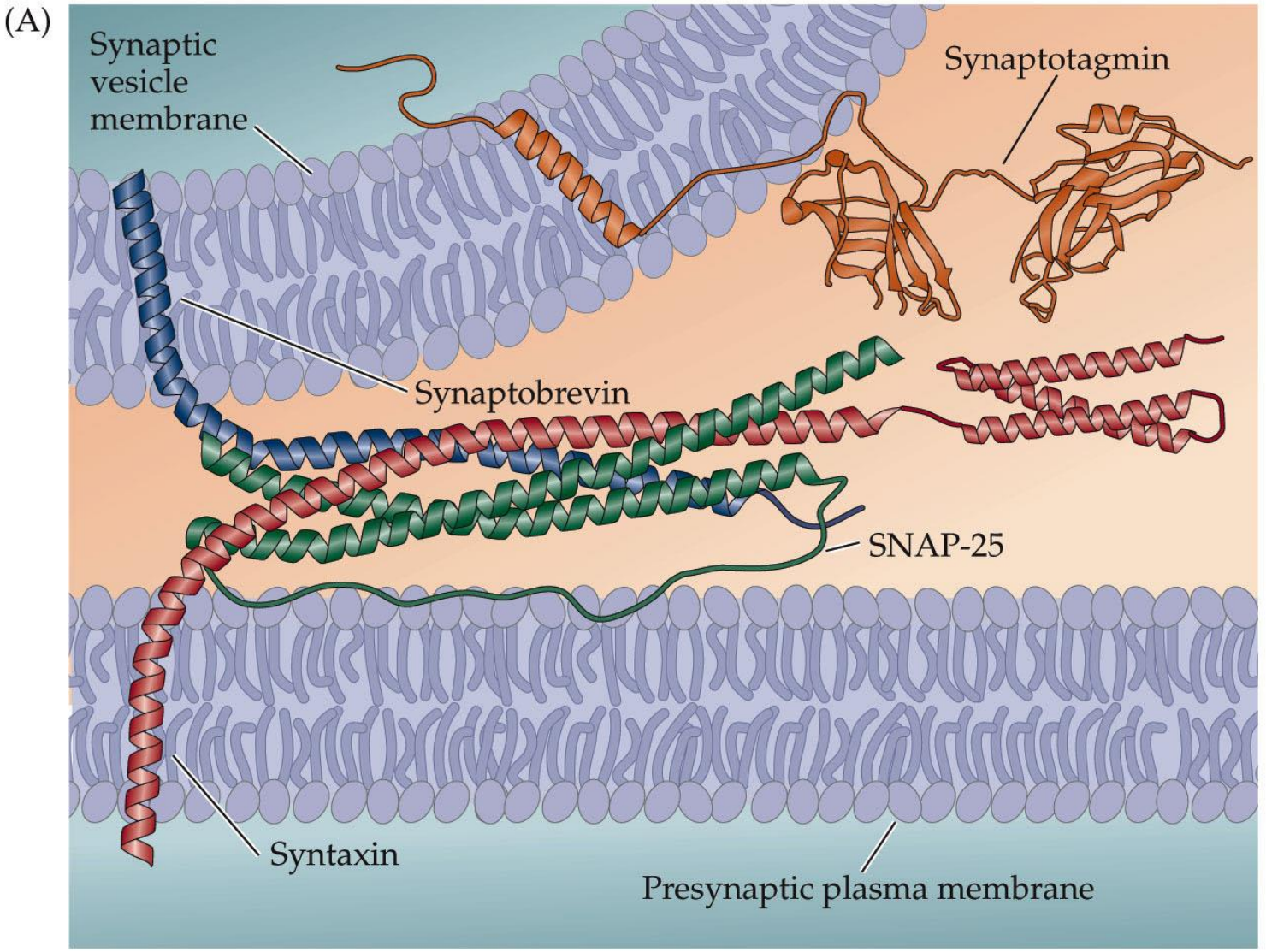
Vesicles in the reserve pool undergo priming to enter the readily-releasable pool

At a molecular level, priming corresponds to the assembly of the SNARE complex



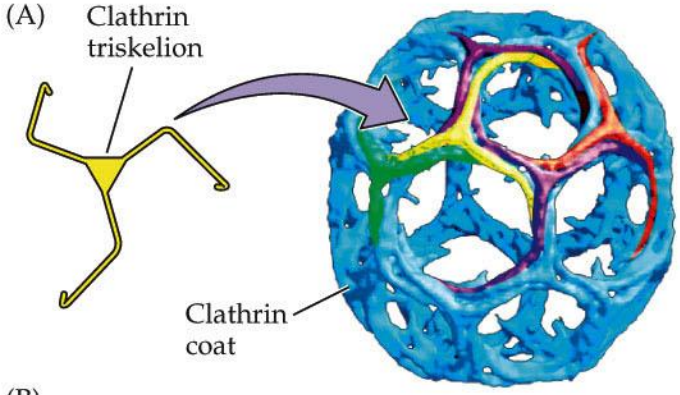

***NEUROSCIENCE, Fourth Edition,* Figure 5.14 (Part 2)**

# The SNARE complex

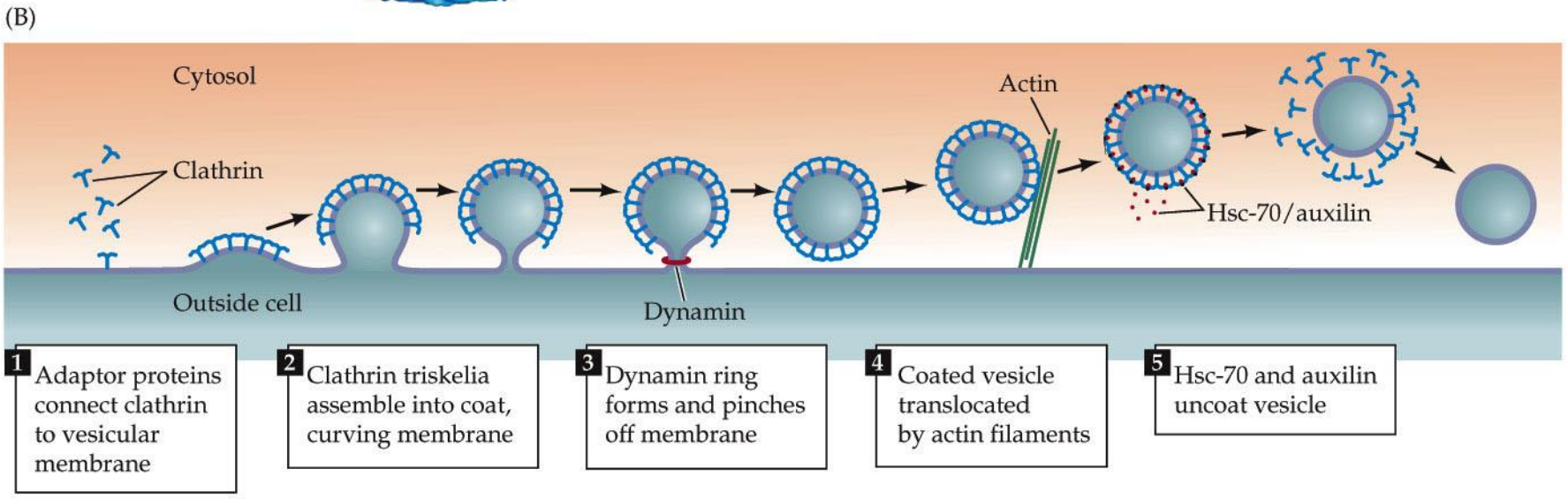



***NEUROSCIENCE, Fourth Edition,* Figure 5.14 (Part 1)**

# Endocytosis retrieves synaptic vesicle membrane and protein from the plasma membrane following fusion




The ATP-ase NSF disassembles the SNARE complex




**NEUROSCIENCE, Fourth Edition, Figure 5.15**