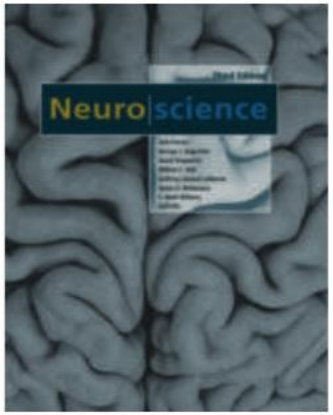
Synaptic Transmission

It Is All About Communication...

Topics I	Topics II
Introduction & Electrochemical Gradients	Synaptic Transmission
Passive Membrane Properties	Electrophysiology Techniques
Action Potentials	Basic Circuits (Spinal Cord)
Voltage-Gated Ion Channels	Sensory Systems Overview
Ligand-Gated Ion Channels	Synaptic Plasticity

Study Material

- NEUROSCIENCE Third Edition
  - Dale Purves
- Chapter 5



THE COVER
Dorsal view of the human brain.
(Courtesy of S. Mark Williams.)

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Aims for this Lecture

- Understand synaptic transmission as a fast secretory process at a specialized contact .
- Understand the stochastic nature of vesicular release.
- Know the importance of presynaptic calcium influx in synaptic release.

Recapitulation L5

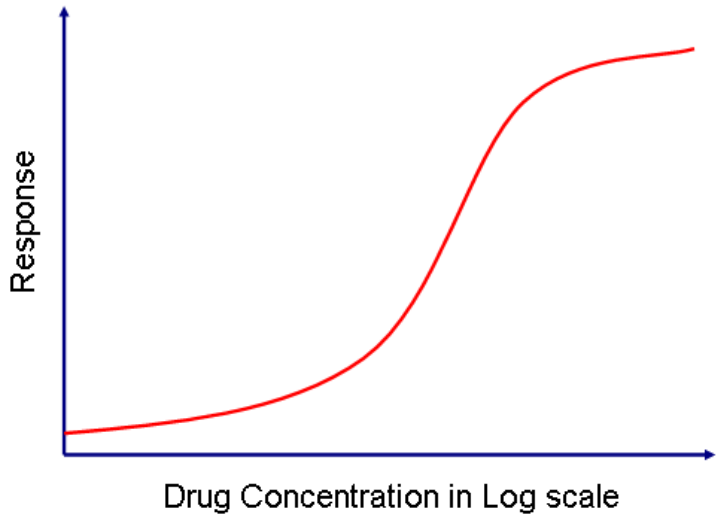
- Ligand-gated ion channels are crucial to translate chemical signals into electrical ones.
- They form families of related channels with two large groups (NAChR GABA …) and (Glutamate) with 5 and 4 subunits.
- Excitatory receptors typically are Na and K permeable and inhibitory ones typically form Cl pores.

Recapitulation L5

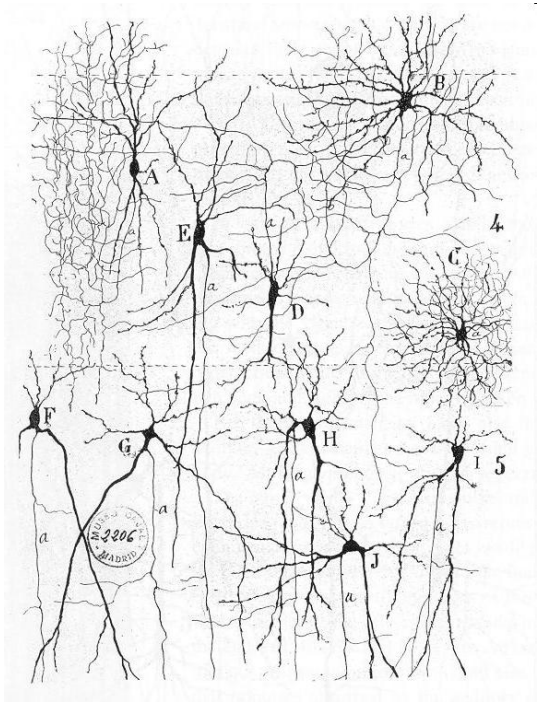
- Agonists are ligands that activate a receptor system.
- Antagonists hinder this activation, but do not affect the activity in the absence of agonist.
- Competitive antagonists shift the dose-response curve to the right.
- Non-competitive antagonists reduce the maximal obtainable effect.

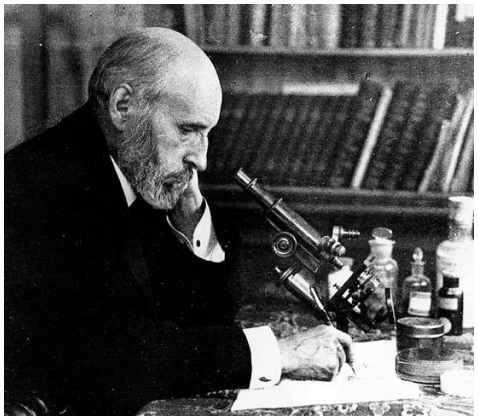
Recapitulation L5

- The effect of a pharmacological agent (often normalized to maximum) plotted against the concentration of that substance.
- For the concentration usually a logarithmic scale is used.



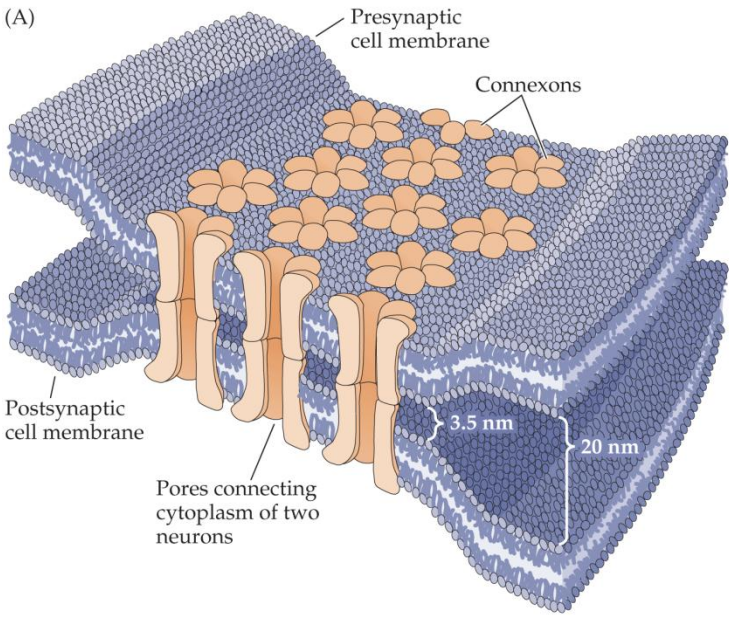
The ‘Cell-Hypothesis’

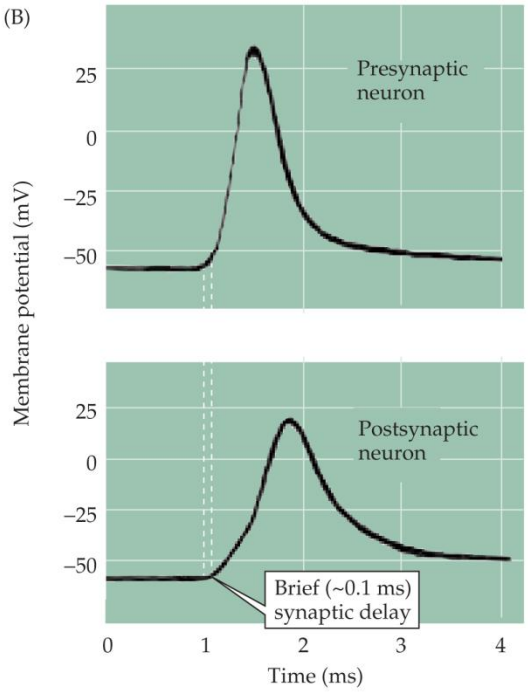




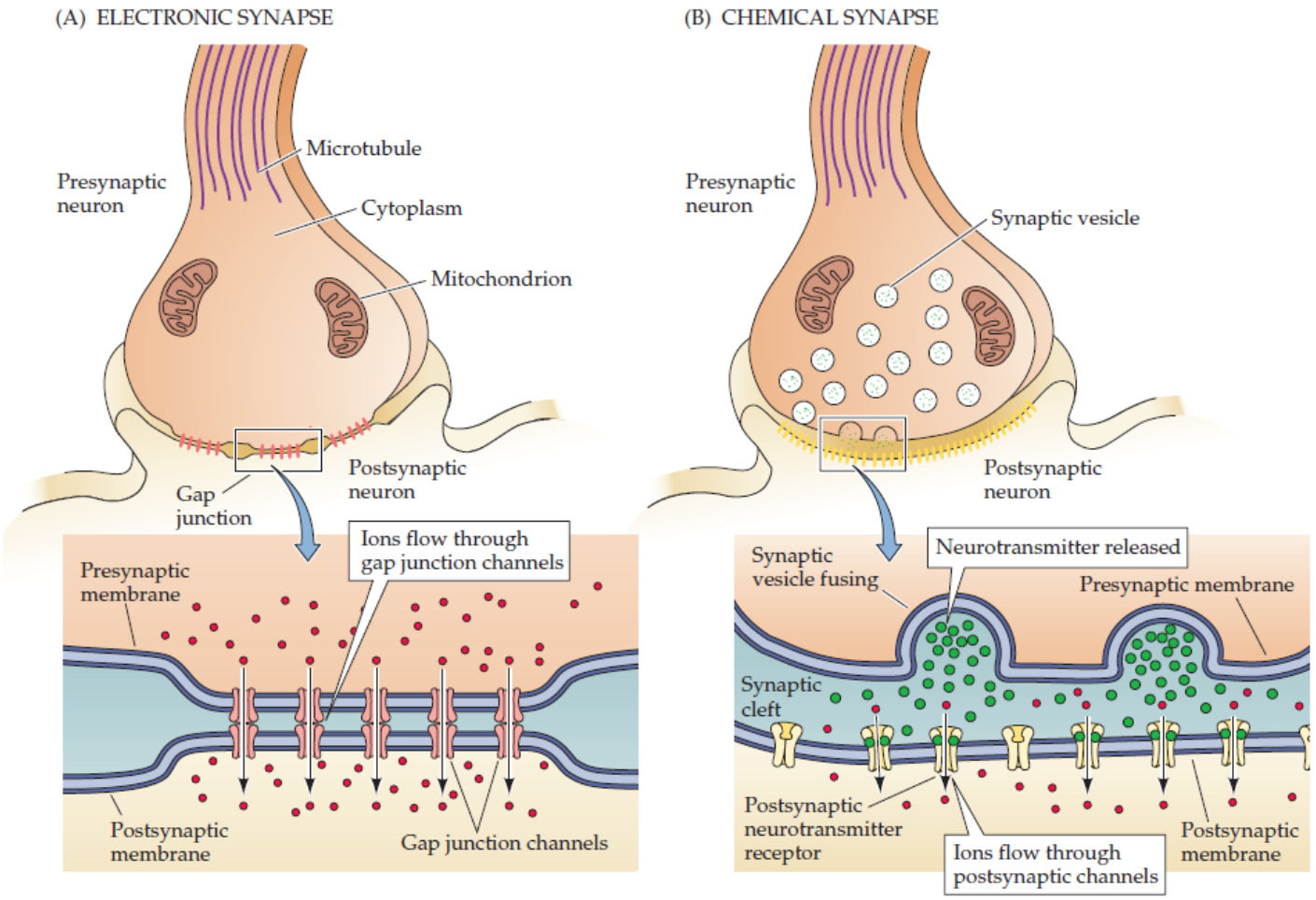
- After the introduction of the silver impregnation method by Camillo Golgi, Santiago Ramon y Cajal uses it on the central nervous system and makes a series of groundbraking discoveries.
- Chief among them the insight that the CNS is made up of individual neurons – who need to somehow communicate...

Electrical Synapses





Two Types of Synapses

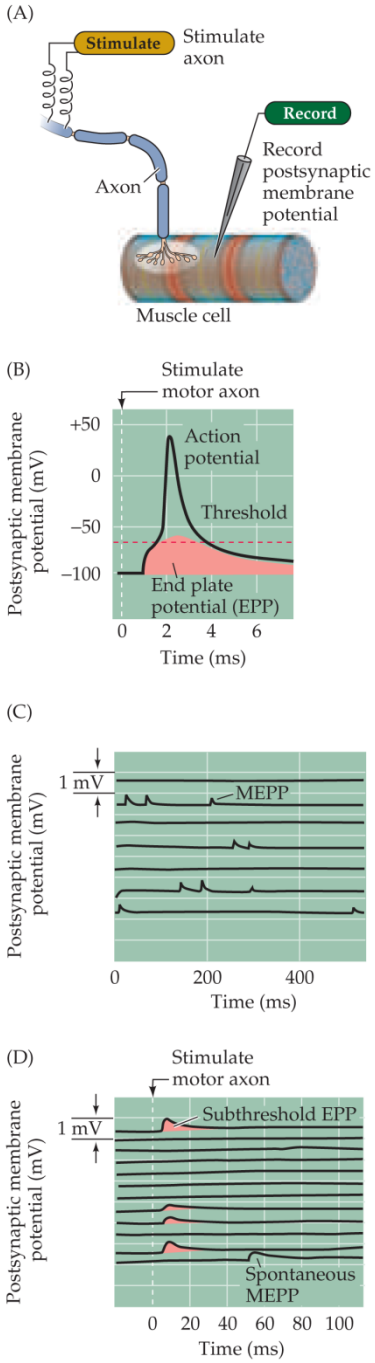


John Eccles

- The effects described by Otto Loewi occur with a delay of several hundreds of milliseconds – clearly too slow for effects (such as spinal reflexes) that occur in the millisecond range.
- Until the mid 1950 Sir John Eccles was of the opinion that synapses were purely electrical.
- The discovery of fast direct hyperpolarizing inhibition by him led the way to discovery of the fast chemical synapse..... and to his Nobel prize.

Soup vs Spark Controversy about Synaptic Transmission

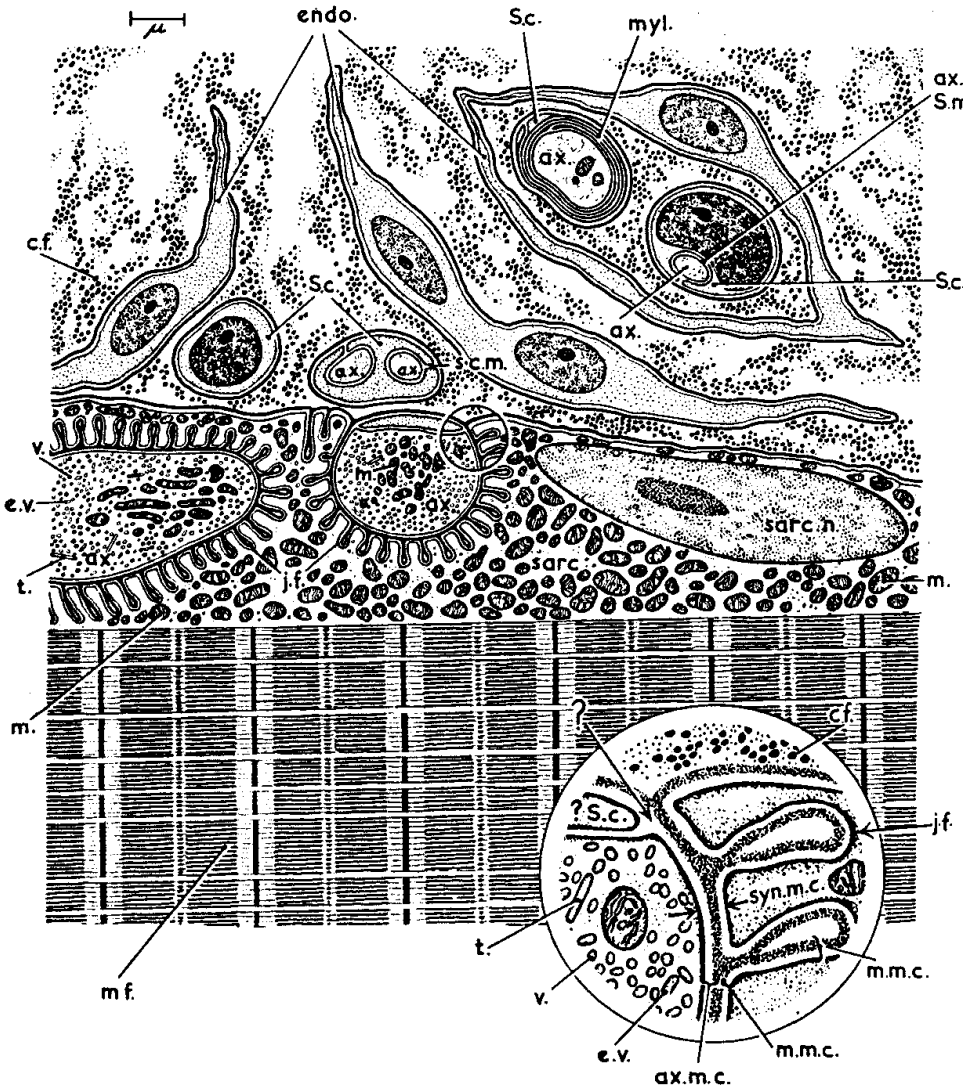
Kuffler, Katz vs Eccles



Neuromuscular Endplate

- Due to its size and accessability the most important preparation for the early study of synaptic transmission.
- Causes the excitation and thereby contraction of striped muscle fibers after firing of the motor nerve.
- Large synapse with a high safety factor – not typical for CNS synapses.
- The first functional studies coincided with the first electron microscopic images of their structure.

Neuromuscular Endplate



One of the first depictions after EM pictures

THE ULTRASTRUCTURE OF A REPTILIAN MYONEURAL JUNCTION*‡

By J. DAVID ROBERTSON,§ M.D.

(*From the Department of Pathology and Oncology, University of Kansas School of Medicine, Kansas City, Kansas*)

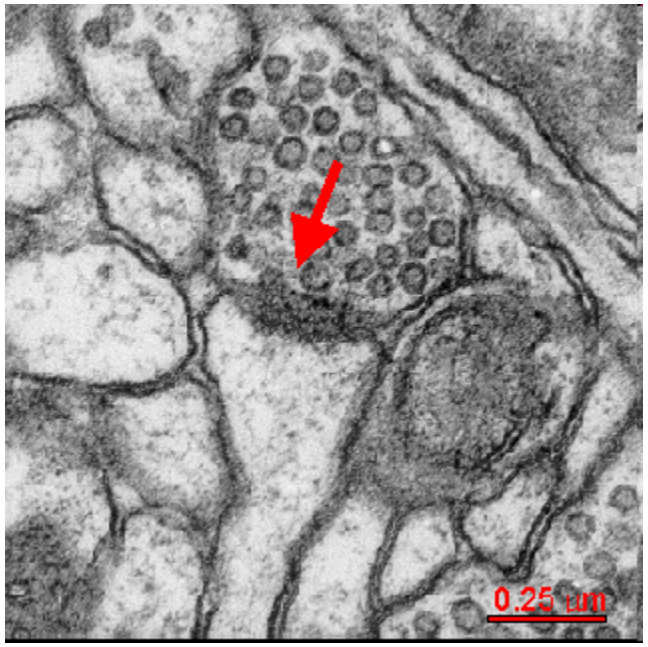
PLATES 91 TO 96

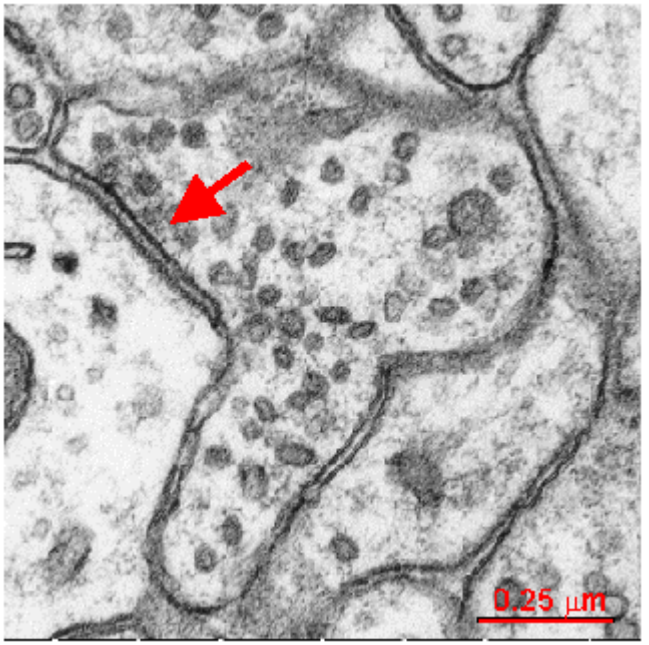
(Received for publication, January 30, 1956)

TEXT-FIG. 1. An interpretative diagram of a myoneural junction in *Anolis*. The double surface membrane complexes of the Schwann cells (*S.c.*), muscle fiber, and endoneurial sheath cells (*endo.*) are shown. The manner in which the muscle surface complex is thrown into the junctional folds of the subneural apparatus is indicated. The five layers of the compound synaptic membrane complex which separates terminal axoplasm from sarcoplasm may be seen. The main features of terminal axoplasm and sarcoplasm are included. The continuities of the synaptic, muscle, and ?Schwann cell surface complexes shown in the diagram represent in part interpretations rather than direct observations. Furthermore, the inclusion of the surface connecting membranes (mesaxons) in the juxtaterminal nerve fibers is partly interpretative.

The region marked by the circle is enlarged to show more detail. The continuities between the membrane structures in the region of ?arrow is interpretative. The five layers of the compound synaptic membrane complex shown between the arrows *syn.m.c.* are discussed in the text. X ~ 10,000. Inset X ~ 60,000.

Two Types of CNS Synapses





Gray Type I
CommonHäufig
On spinesAn Spines
Narrow gap
Round vesicles

Gray Type II
Rarer
On dendritic shaft and somata
Wider gap
Oval vesicles

Vesicle Cycle

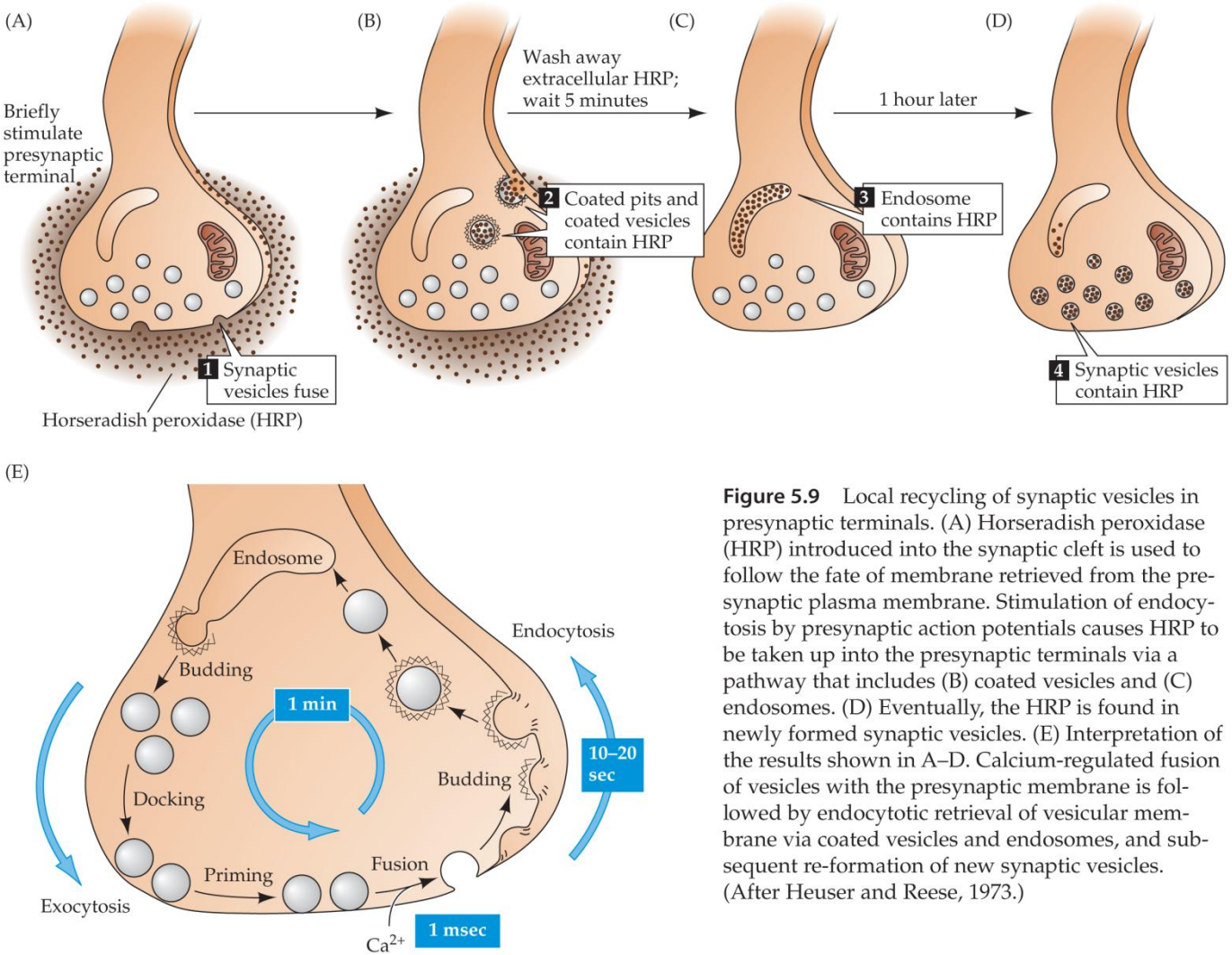
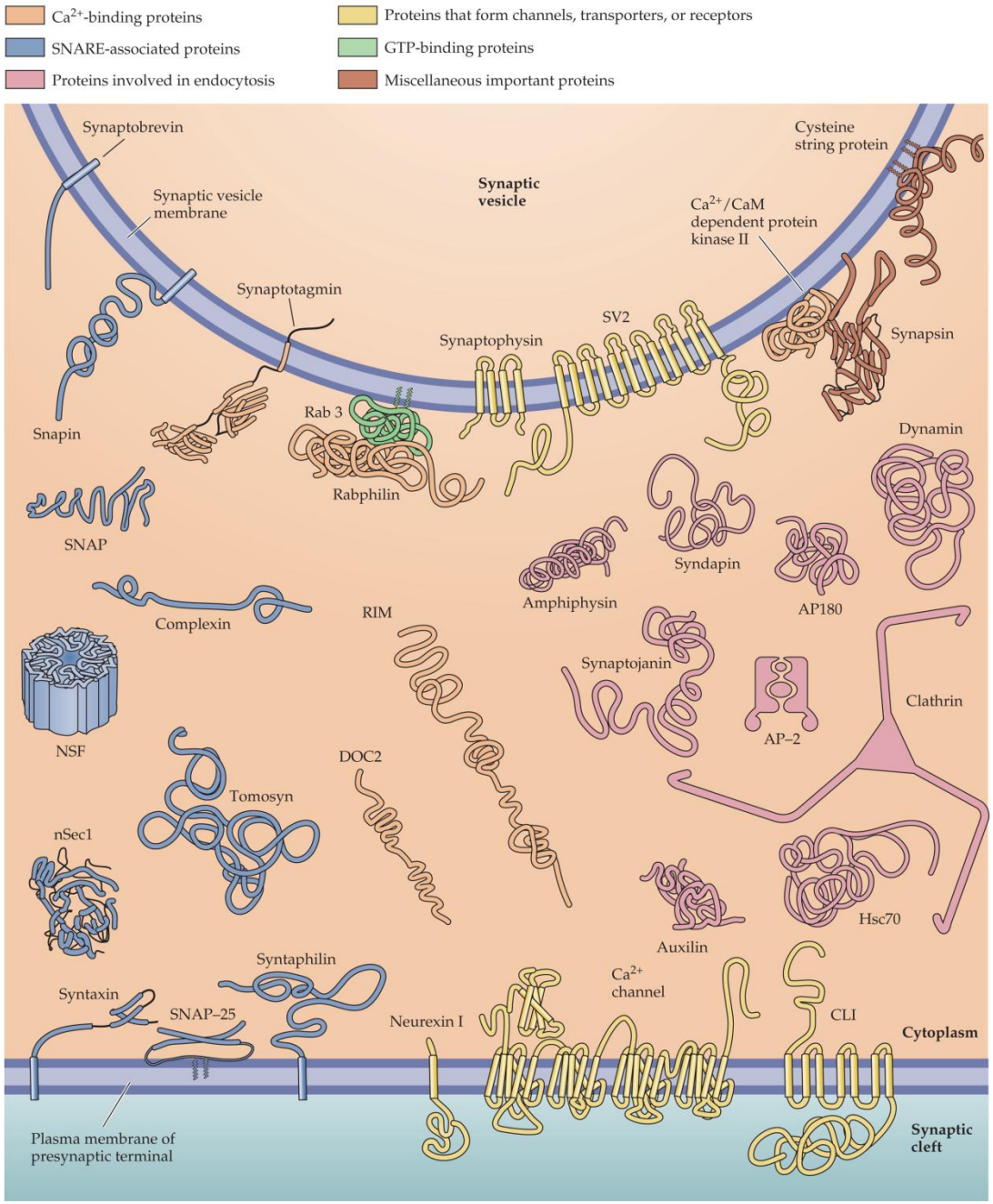


Figure 5.9 Local recycling of synaptic vesicles in presynaptic terminals. (A) Horseradish peroxidase (HRP) introduced into the synaptic cleft is used to follow the fate of membrane retrieved from the presynaptic plasma membrane. Stimulation of endocytosis by presynaptic action potentials causes HRP to be taken up into the presynaptic terminals via a pathway that includes (B) coated vesicles and (C) endosomes. (D) Eventually, the HRP is found in newly formed synaptic vesicles. (E) Interpretation of the results shown in A–D. Calcium-regulated fusion of vesicles with the presynaptic membrane is followed by endocytotic retrieval of vesicular membrane via coated vesicles and endosomes, and subsequent re-formation of new synaptic vesicles. (After Heuser and Reese, 1973.)

Synapses are far from the somata of neurons. They need a high degree of autonomy and have to use ressources carefully. Proteins need to be efficiently recycled.

The Presynaptic Machinery



The Machinery and Release

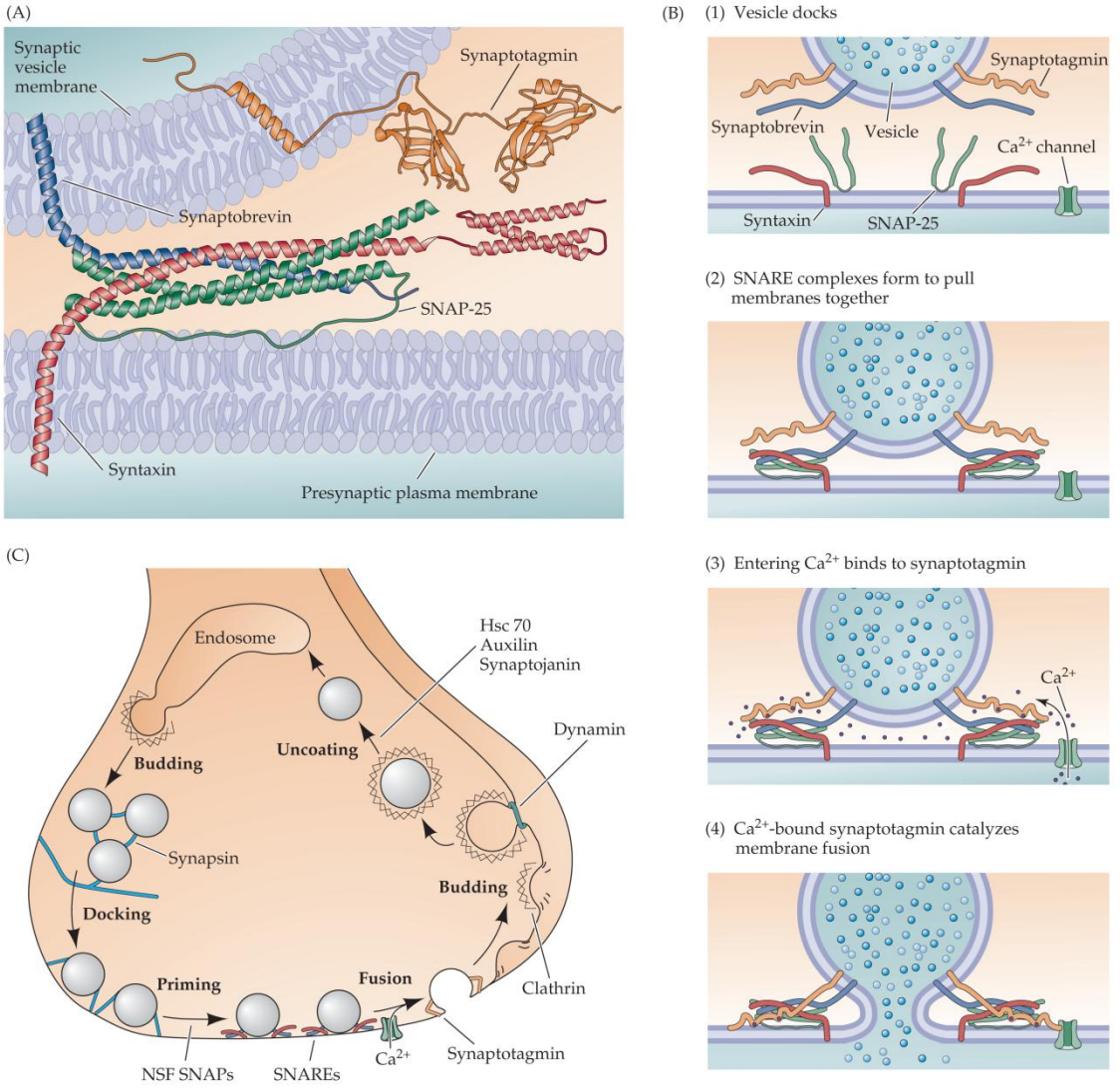
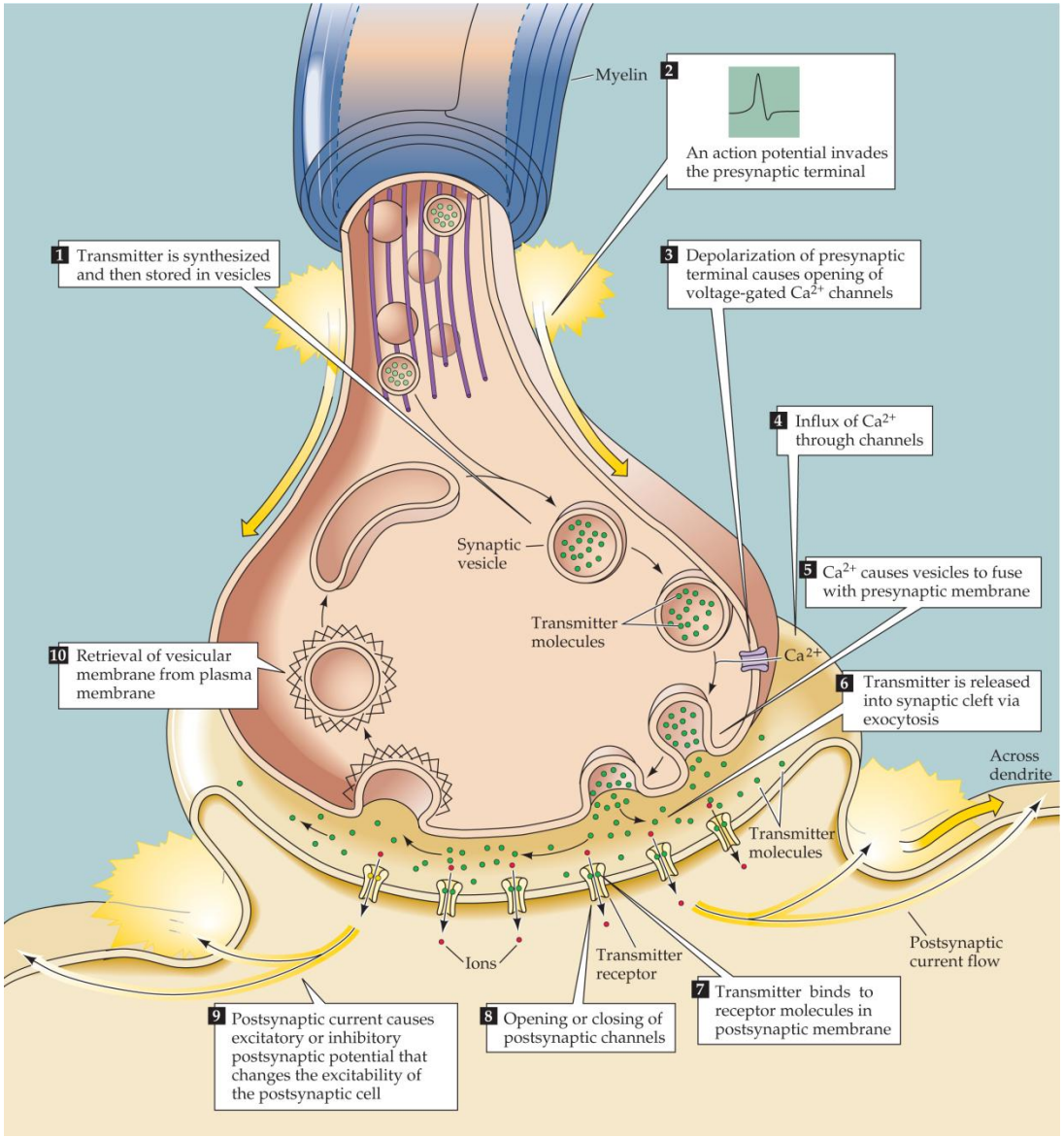
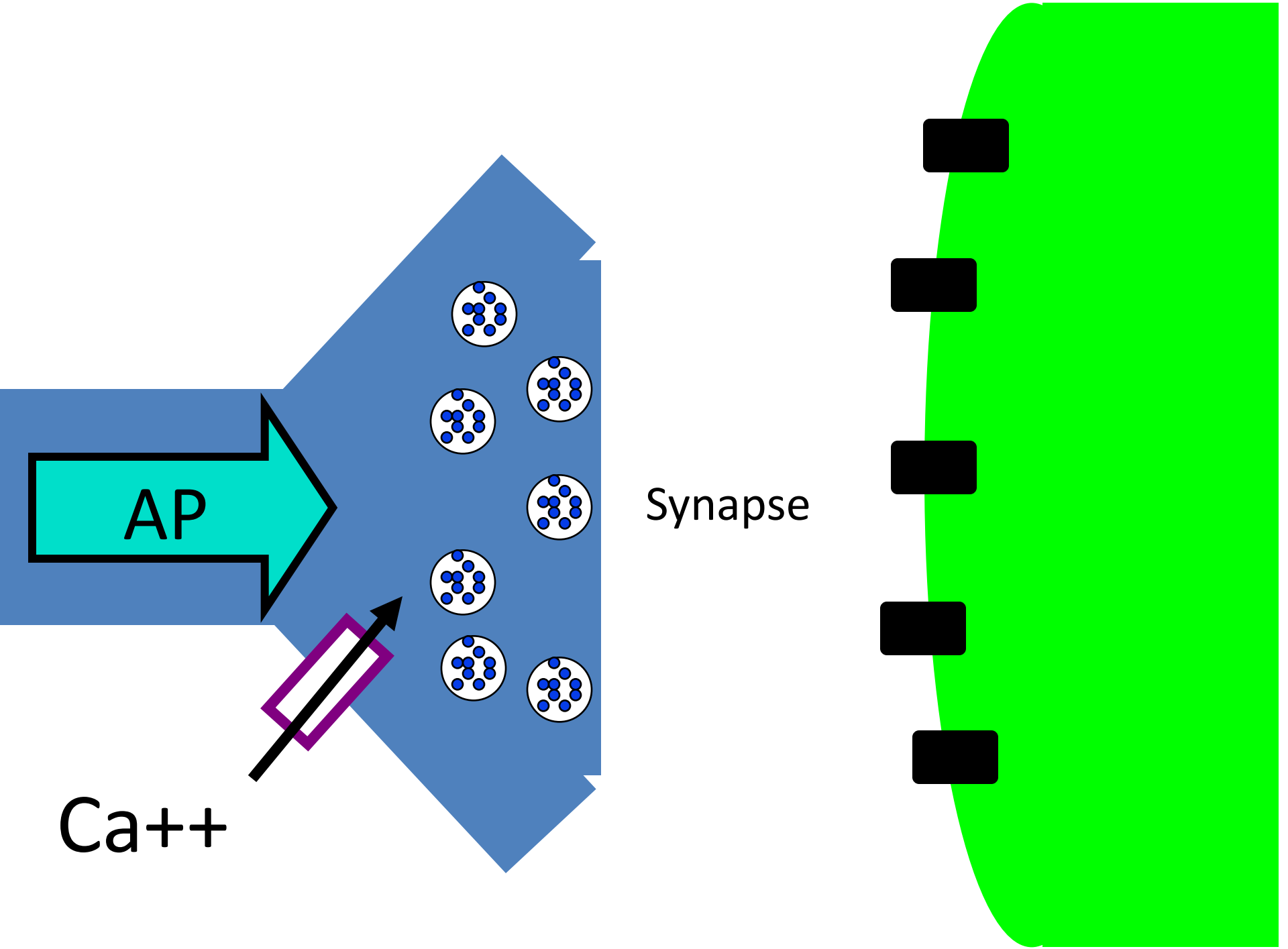
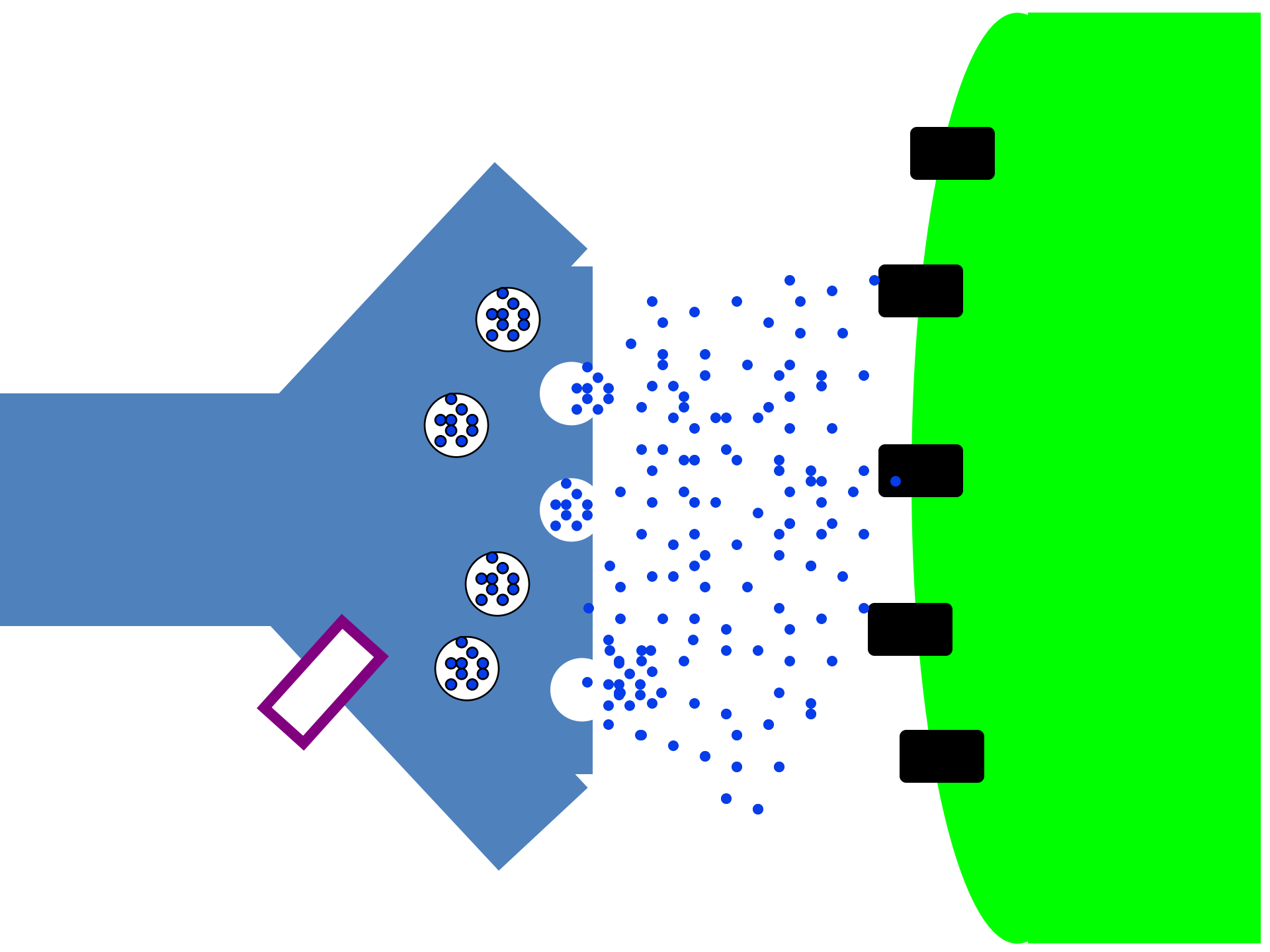


Figure 5.14 Molecular mechanisms of neurotransmitter release. (A) Structure of the SNARE complex. The vesicular SNARE, synaptobrevin (blue), forms a helical complex with the plasma membrane SNAREs syntaxin (red) and SNAP-25 (green). Also shown is the structure of synaptotagmin, a vesicular Ca^{2+}-binding protein. (B) A model for Ca^{2+}-triggered vesicle fusion. SNARE proteins on the synaptic vesicle and plasma membranes form a complex (as in A) that brings together the two membranes. Ca^{2+} then binds to synaptotagmin, causing the cytoplasmic region of this protein to insert into the plasma membrane, bind to SNAREs and catalyze membrane fusion. (C) Roles of presynaptic proteins in synaptic vesicle cycling. (D) Individual clathrin triskelia (left) assemble together to form membrane coats (right) involved in membrane budding during endocytosis. (A after Sutton et al., 1998; C after Sudhof, 1995; D after Marsh and McMahon, 2001.)

Chemical Synapses




AP
Synapse
Ca++



Calcium Is Needed for Release

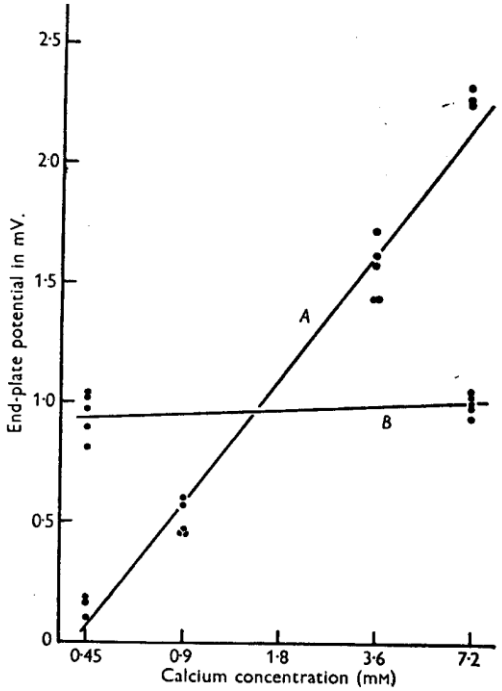


Fig. 3. *A*. Ordinates: amplitude of the end-plate potential in relative units with their amplitude in Ringer's solution (1·8 mM. calcium) taken as unity. Abscissae: calcium concentration in mM. plotted logarithmically. *B*. Ordinates: amplitude of the depolarization in relative units. Its amplitude in Ringer's solution is taken as unity. Abscissae: same as for *A*.

J. Physiol. (1952) 116, 507–515

THE EFFECT OF CALCIUM IONS ON THE MOTOR END-PLATE POTENTIALS

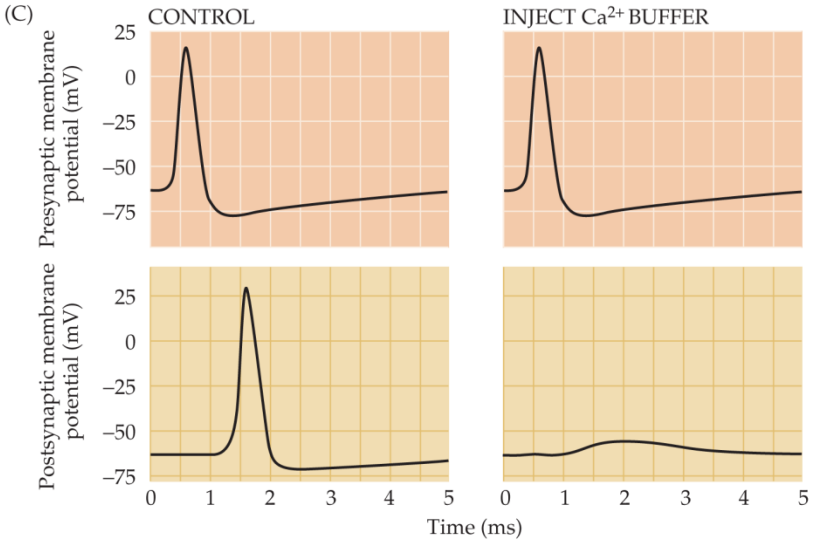
By J. del CASTILLO and L. STARK

From the Department of Physiology, University College, London

(*Received* 2 *November* 1951)

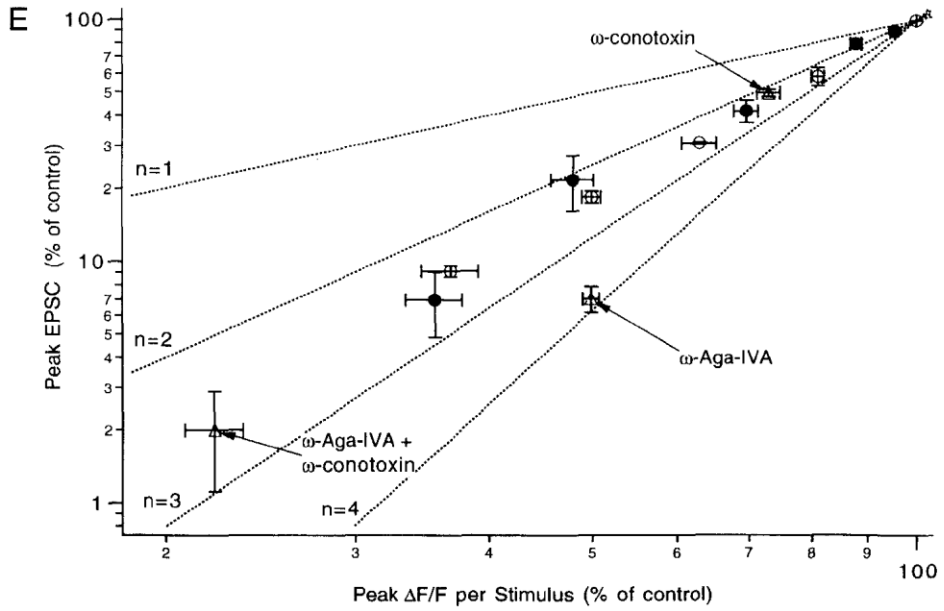
Line (A) describes the synaptic response as a function of increasing extracellular calcium ion concentration (log scale). Line B describes just the response of the muscle fiber to the direct application of the transmitter.

Synaptic release strongly depends on calcium influx.



The ‚Power-Law‘

Die verschiedenen Toxine blockieren Calcium Kanäle



Neuron, Vol. 15, 675-688, September, 1995
Calcium Control of Transmitter Release
at a Cerebellar Synapse
I. M. Mintz,* B. L. Sabatini,
and W. G. Regehr

The potency is around 3 in these experiments. Doubling the caclium influx increases release by a factor of eight.

On a log-log plot the slope of a line shows the exponent of a power low relationship.

$$y \sim x^n$$

$$\log y \sim n \cdot \log x$$

Release is ‘Quantal’

J. Physiol. (1952), 117, 109–128

SPONTANEOUS SUBTHRESHOLD ACTIVITY AT MOTOR NERVE ENDINGS

By P. FATT and B. KATZ

From the Biophysics and Physiology Departments, University College, London

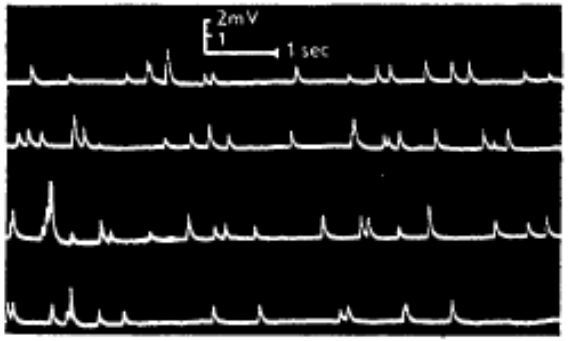


Fig. 2. Example of miniature e.p.p.'s in a muscle treated with 10^{-6} prostigmine bromide.

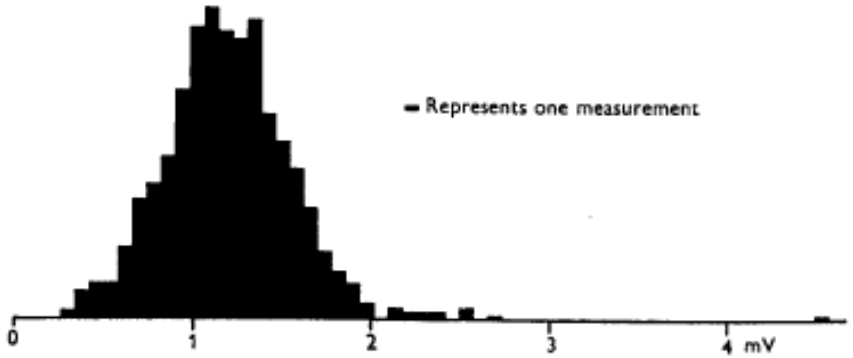


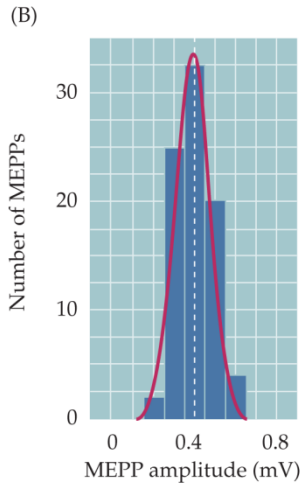
Fig. 13. Distribution of amplitudes. Muscle treated with prostigmine. Same 800 miniature potentials as used in Figs. 11 and 12.

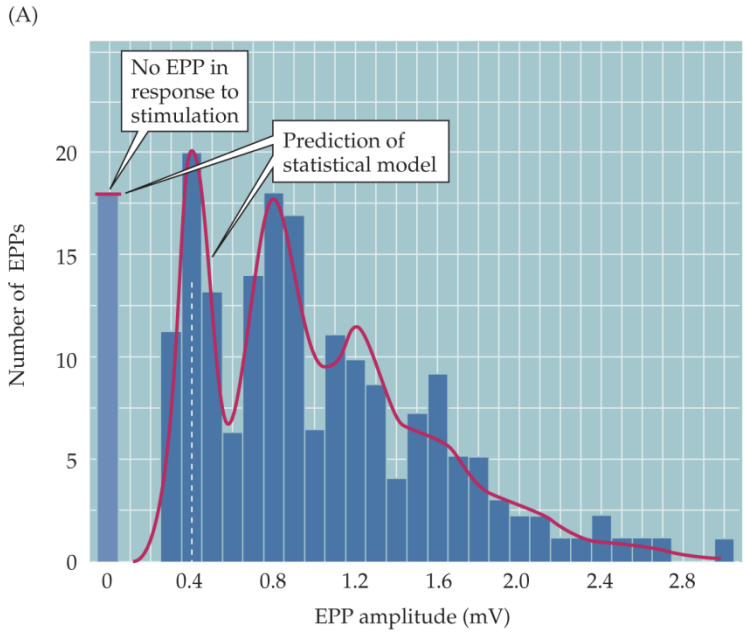
Synapses are never completely silent!

Tiny miniature signals can be measured even if the nerve is not firing any action potentials.

At the neuromuscular endplate these are called ‘miniature endplate potential (mepp)‘. At CNS Synapses these signals are called ‘miniature excitatory postsynaptic potential (mEPSP)’ or miniature inhibitory postsynaptic potential (mIPSP)’.

Quanta and Vesicles





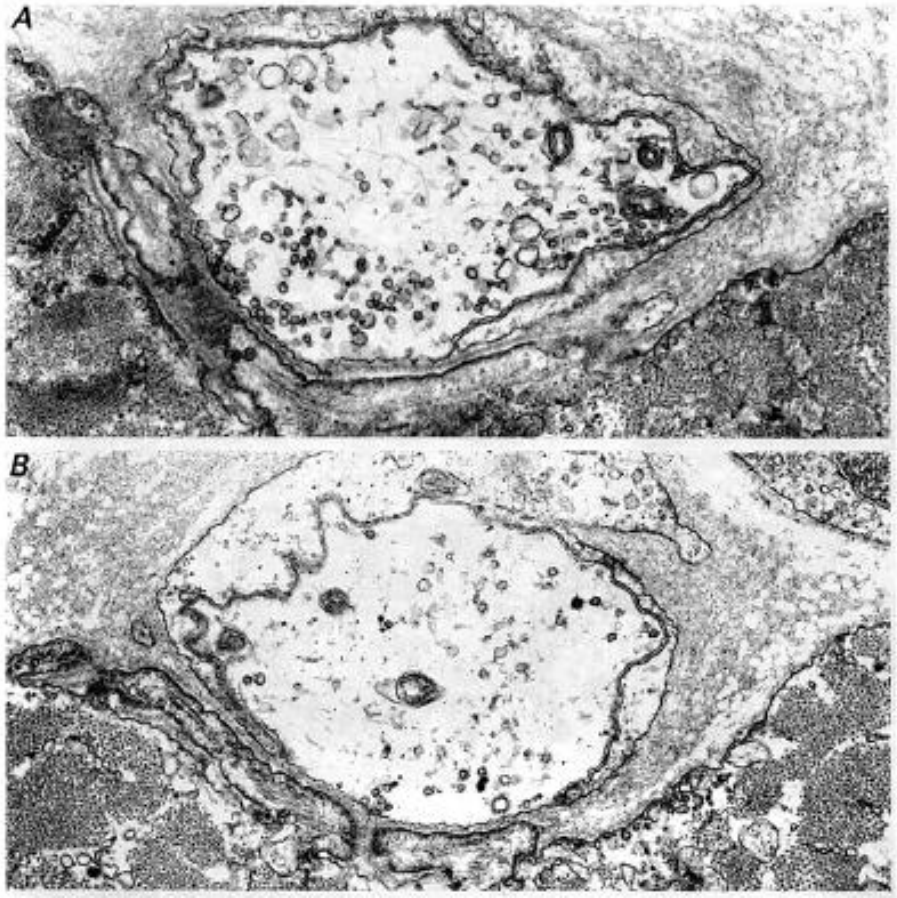
Latrodectus (Schwarze Witwe) Spinnen - α-latrotoxin

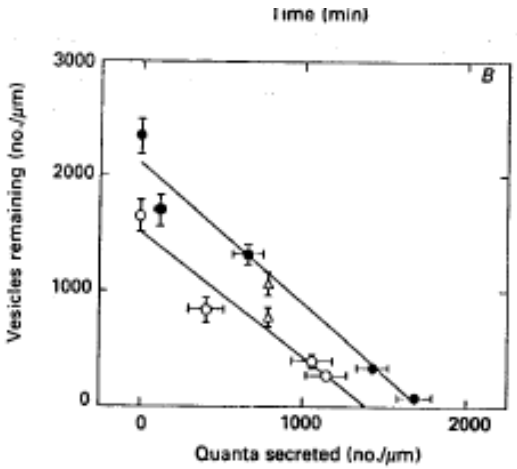
Quanta and Vesicles

Journal of Physiology (1990), **425**, *pp.* 501–526
With 10 figures
Printed in Great Britain

CORRELATION BETWEEN QUANTAL SECRETION AND VESICLE LOSS AT THE FROG NEUROMUSCULAR JUNCTION

BY W. P. HURLBUT*, N. IEZZI, R. FESCE AND THE LATE B. CECCARELLI

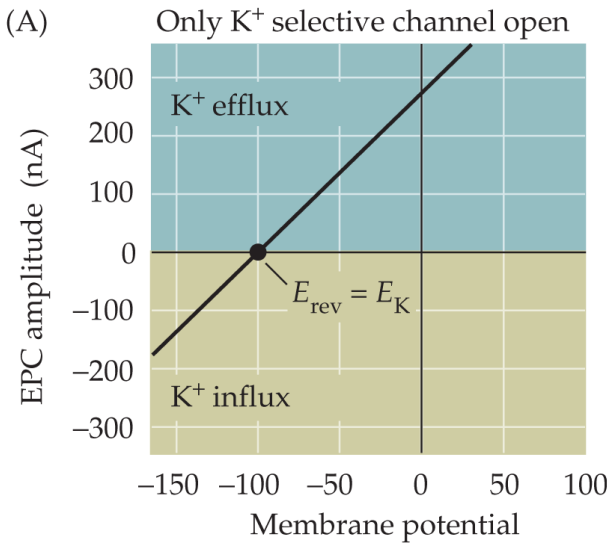


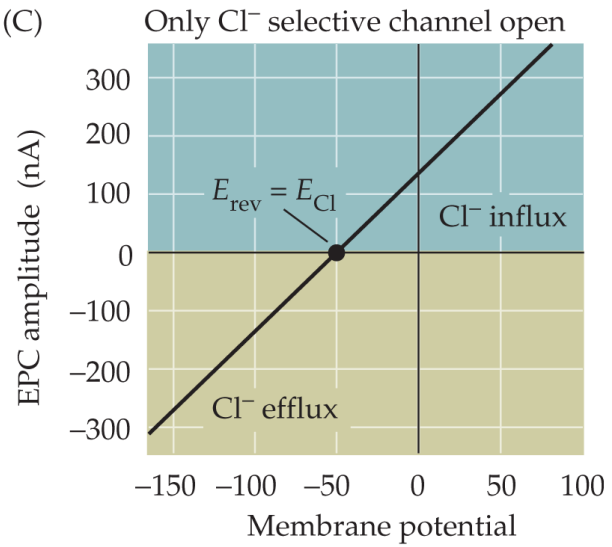


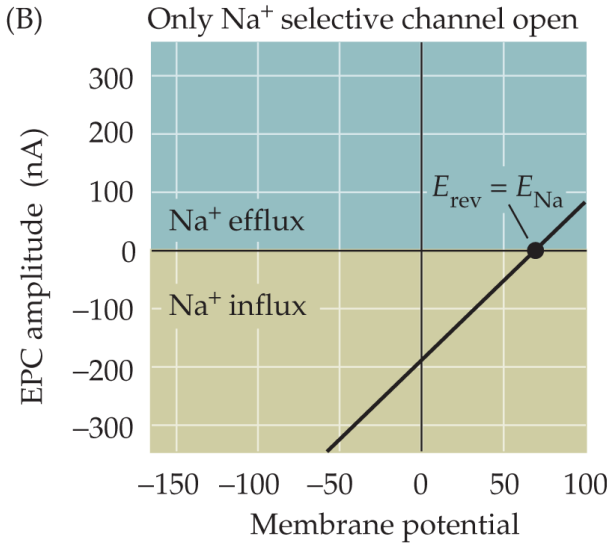
With α-Latrotoxin vesicles are very efficiently released.
The number of miniature events negatively correlates with the number of vesicles left.

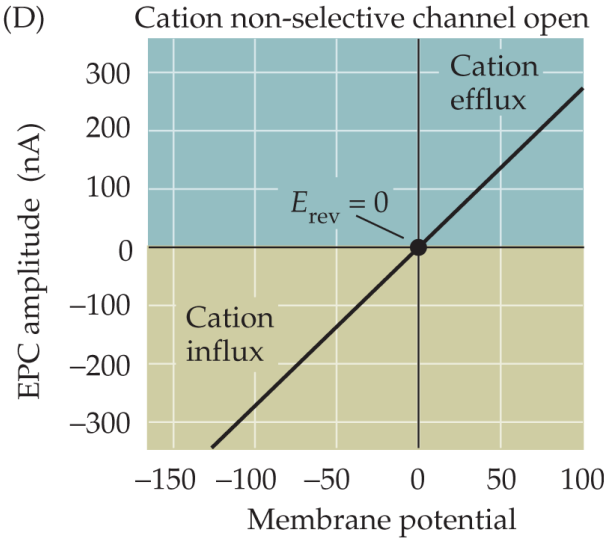
Only valid if recycling of vesicles is blocked.

Postsynaptic Receptors

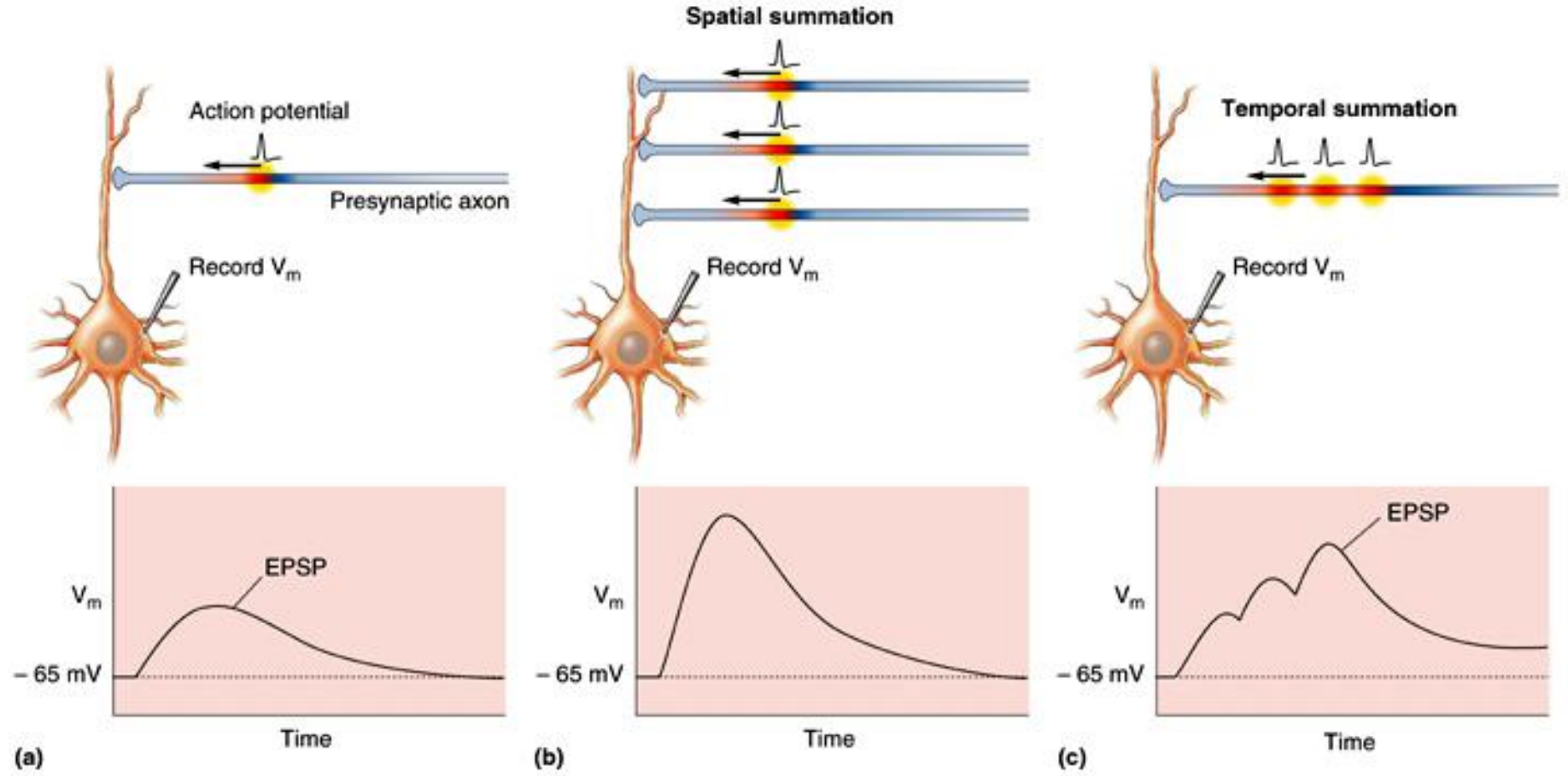








Summation



Summation-Inhibition

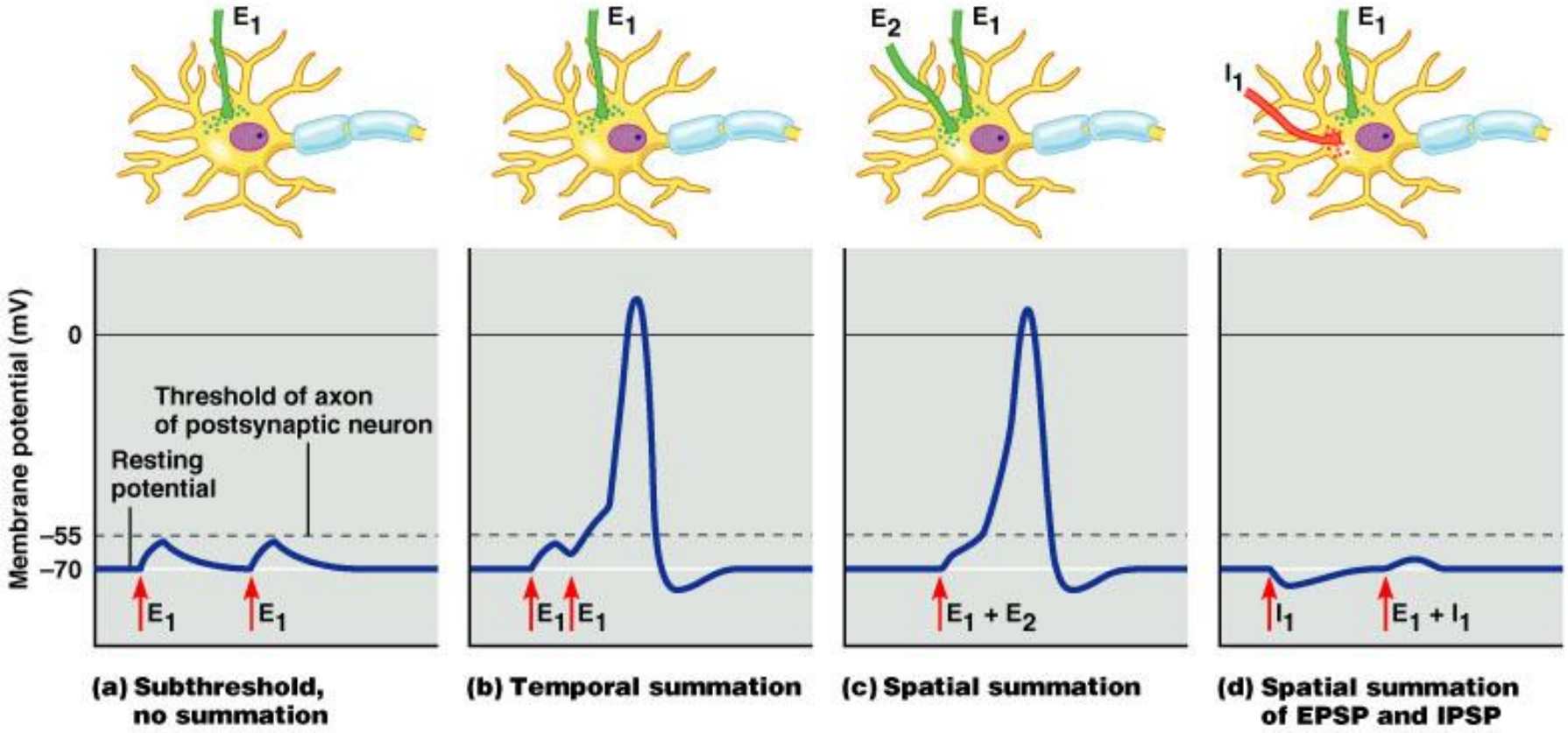


Figure 11.21