Synaptic Transmission

N500, 30 Aug., 2015

- Otto Loewi’s experiments
- Bernard Katz’s experiments
- Quantal analysis
- Synaptic transmission
- Synaptic reversal potentials
- Gap junctions

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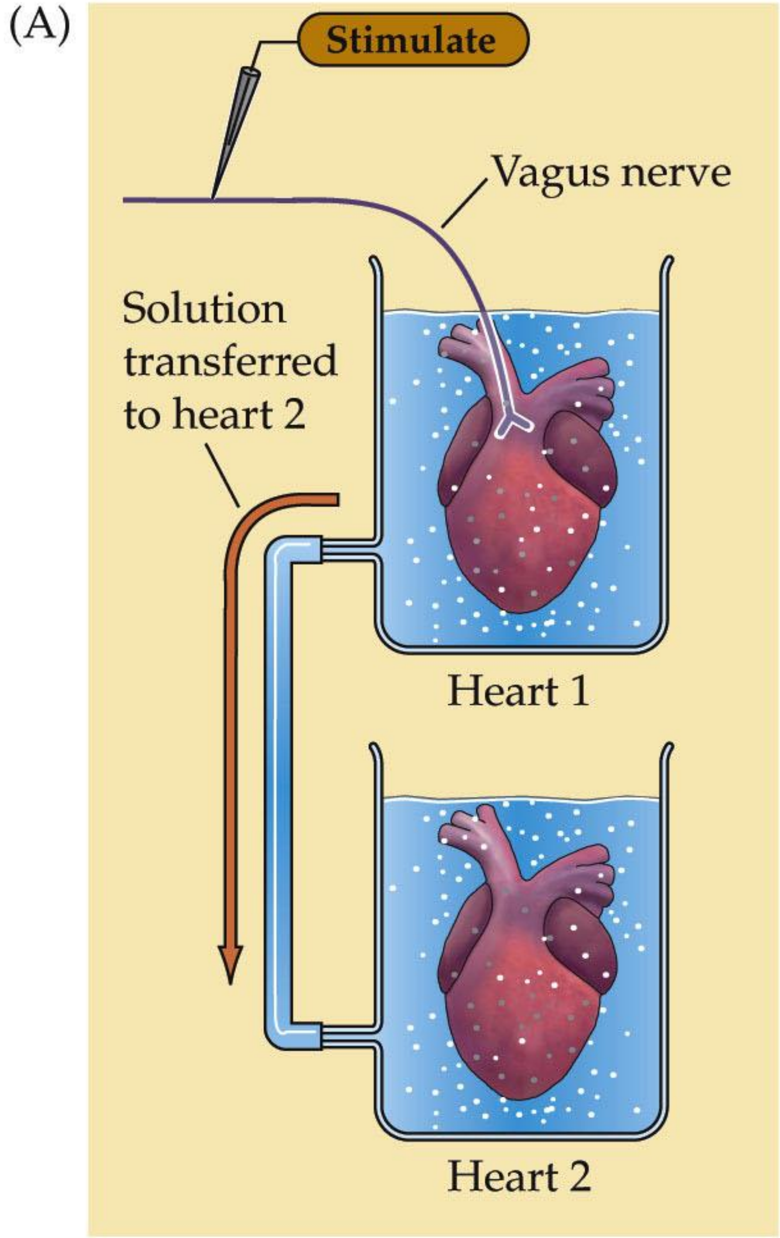
Otto Loewi 1873 - 1961

Is transmission chemical?

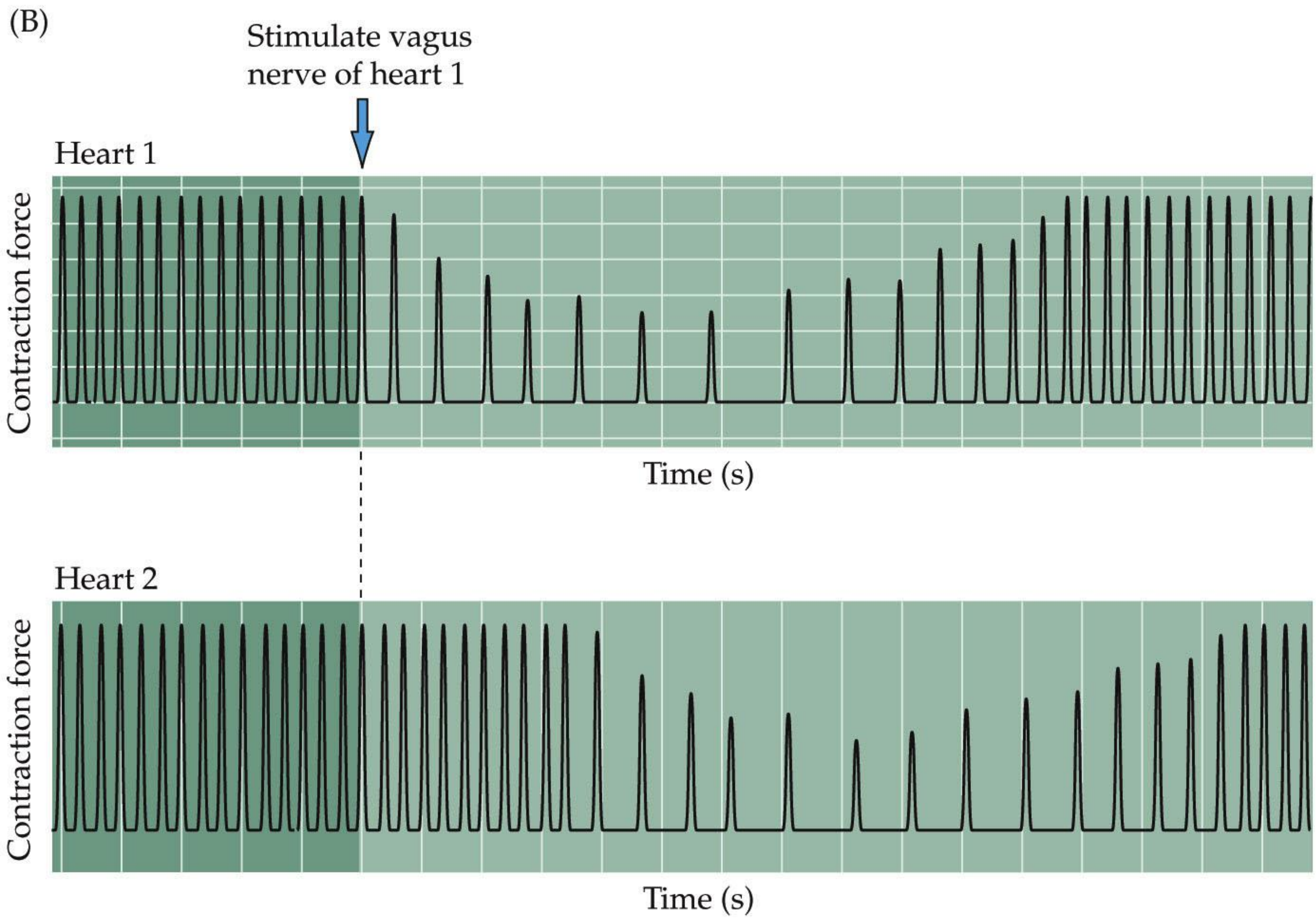
If so, how could this be tested?

Figure 5.4 Loewi's experiment demonstrating chemical neurotransmission (Part 1)



NEUROSCIENCE, Fourth Edition, Figure 5.4 (Part 1)

Figure 5.4 Loewi's experiment demonstrating chemical neurotransmission (Part 2)



NEUROSCIENCE, Fourth Edition, Figure 5.4 (Part 2)

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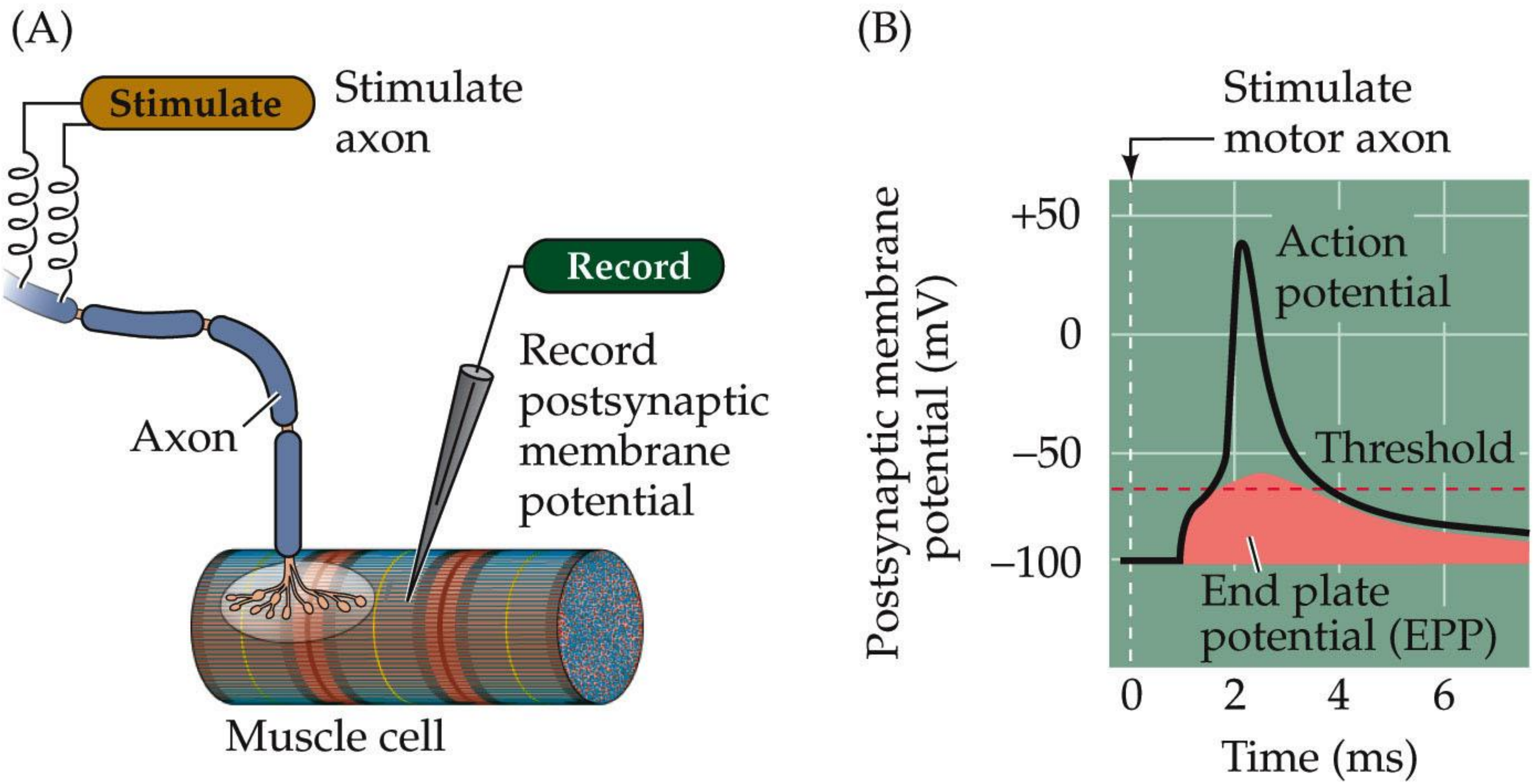
- Gap junctions

Bernard Katz 1911 - 2003

How is chemical transmission accomplished?

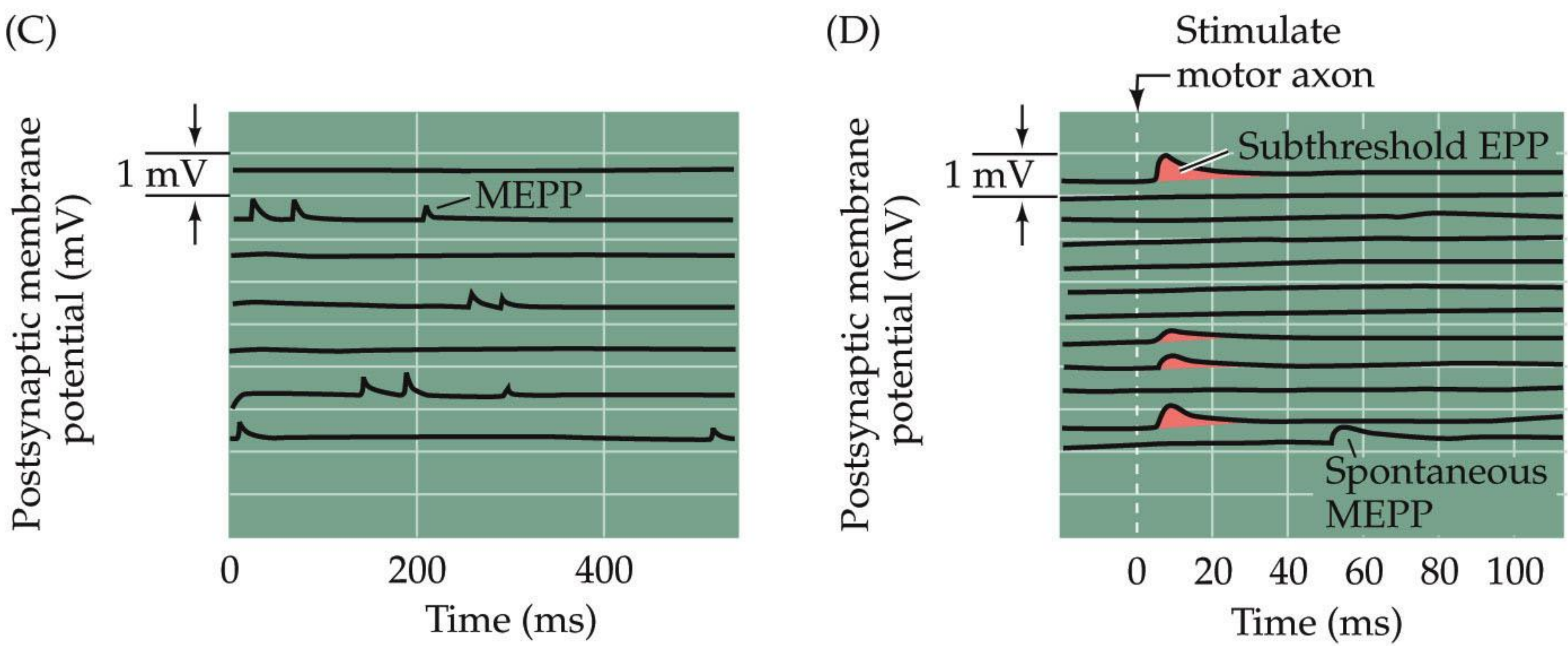
Are there packets of transmitter molecules?

Figure 5.6 Synaptic transmission at the neuromuscular junction (Part 1)

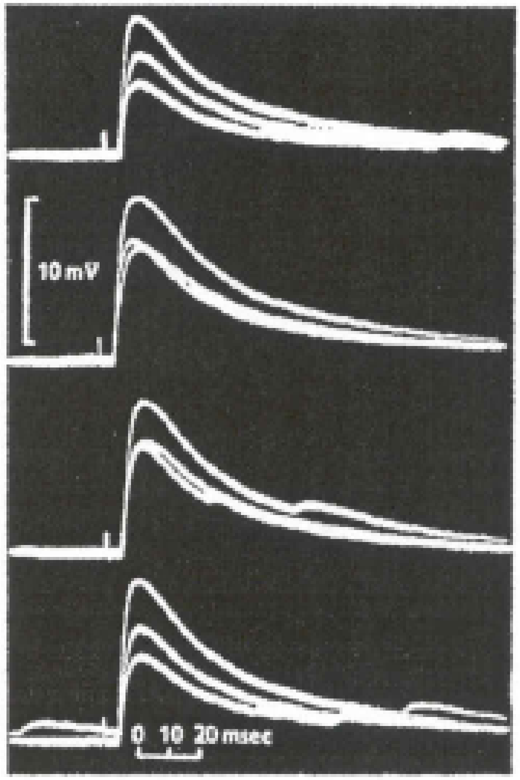


***NEUROSCIENCE*, *Fourth Edition*, Figure 5.6 (Part 1)**

Figure 5.6 Synaptic transmission at the neuromuscular junction (Part 2)

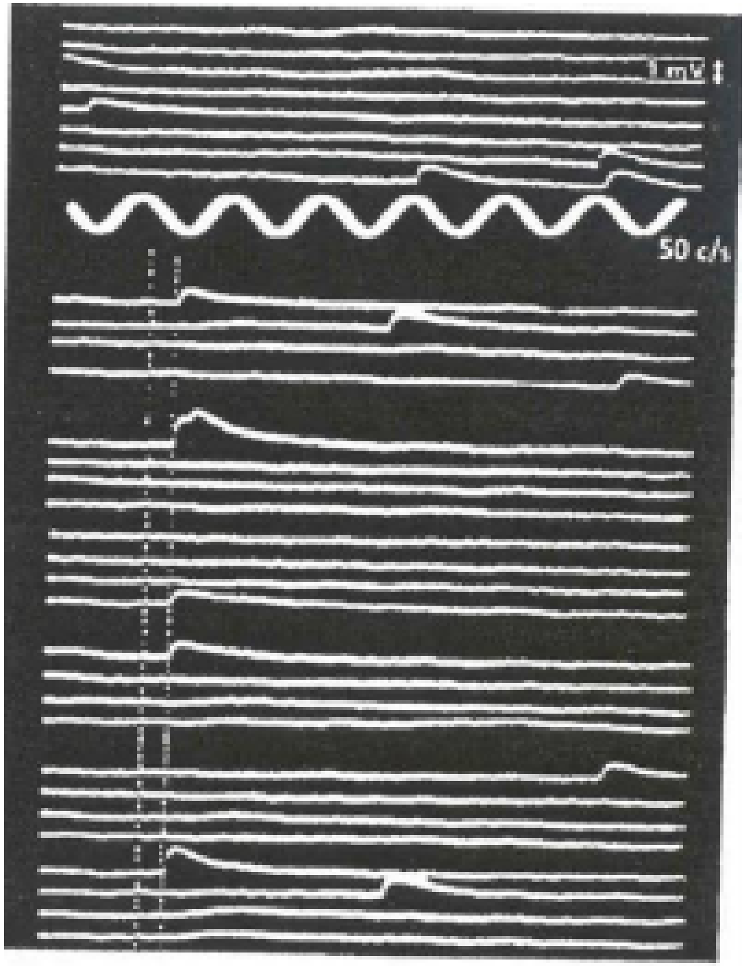


Endplate potentials in normal Ca^{2+}, elevated (10 mM) Mg^{2+}



- Responses now smaller, subthreshold
- Varied amplitude of evoked response apparent
- Occasional spontaneous waveforms (less varied)

Endplate potentials in low Ca^{2+} (0.9 mM), elevated (10 mM) Mg^{2+}



- Persistence of spontaneous “miniature” EPPs (mEPPs)
- Smaller average evoked EPP, with emergence of transmission failures
- Smallest EPPs were similar in amplitude to mEPPs.

Katz's "quantal hypothesis"

1. The quantum of transmitter underlying the smallest nerve-evoked EPP and the spontaneous MEPP are one and the same;

2. The release of each quantum of neurotransmitter is independent of the release of other quanta and occurs with a very low statistical probability (i.e. random);

3. The evoked EPP is caused by the synchronous release of several quanta, due to a transient and large increase in the probability of release of individual quanta.

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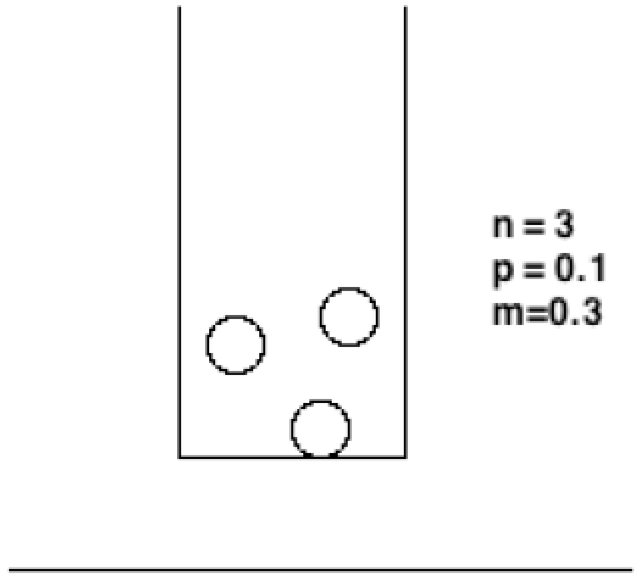
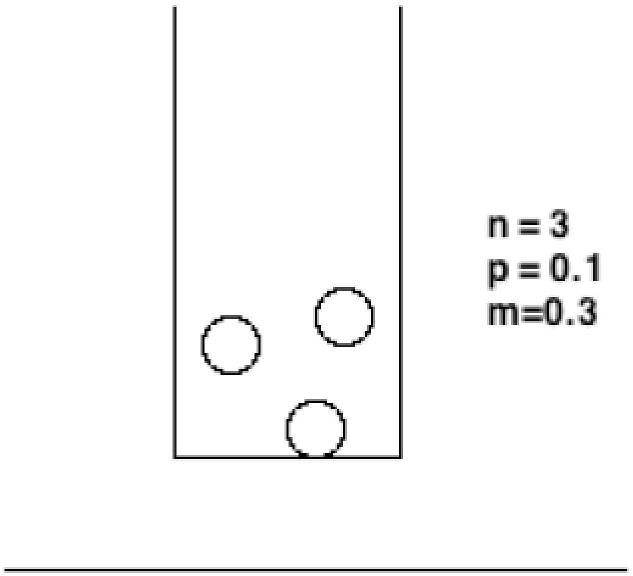
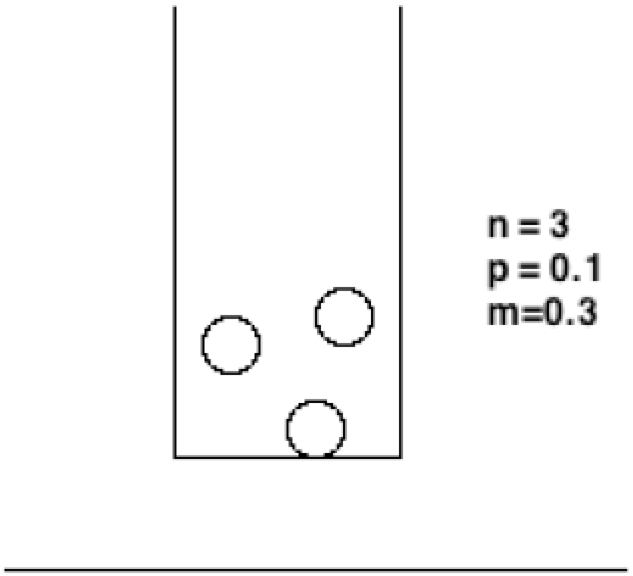
quantal content = m = n * p



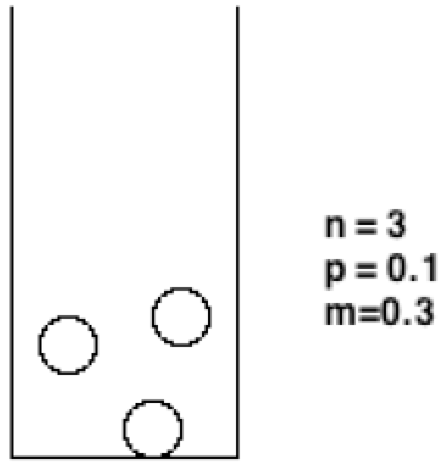


$$P(3) = p.p.p = p^3 \quad (= 0.001)$$



$$P(3) = p.p.p = p^3 \quad (= 0.001)$$

$$P(0) = (1\text{-}p).(1\text{-}p).(1\text{-}\ p) = q.q.q = q^3 \quad (= 0.729)$$



$$P(3) = p.p.p = p^3 \quad (= 0.001)$$

$$P(0) = (1\text{-}p).(1\text{-}p).(1\text{-}\ p) = q.q.q = q^3 \quad (= 0.729)$$

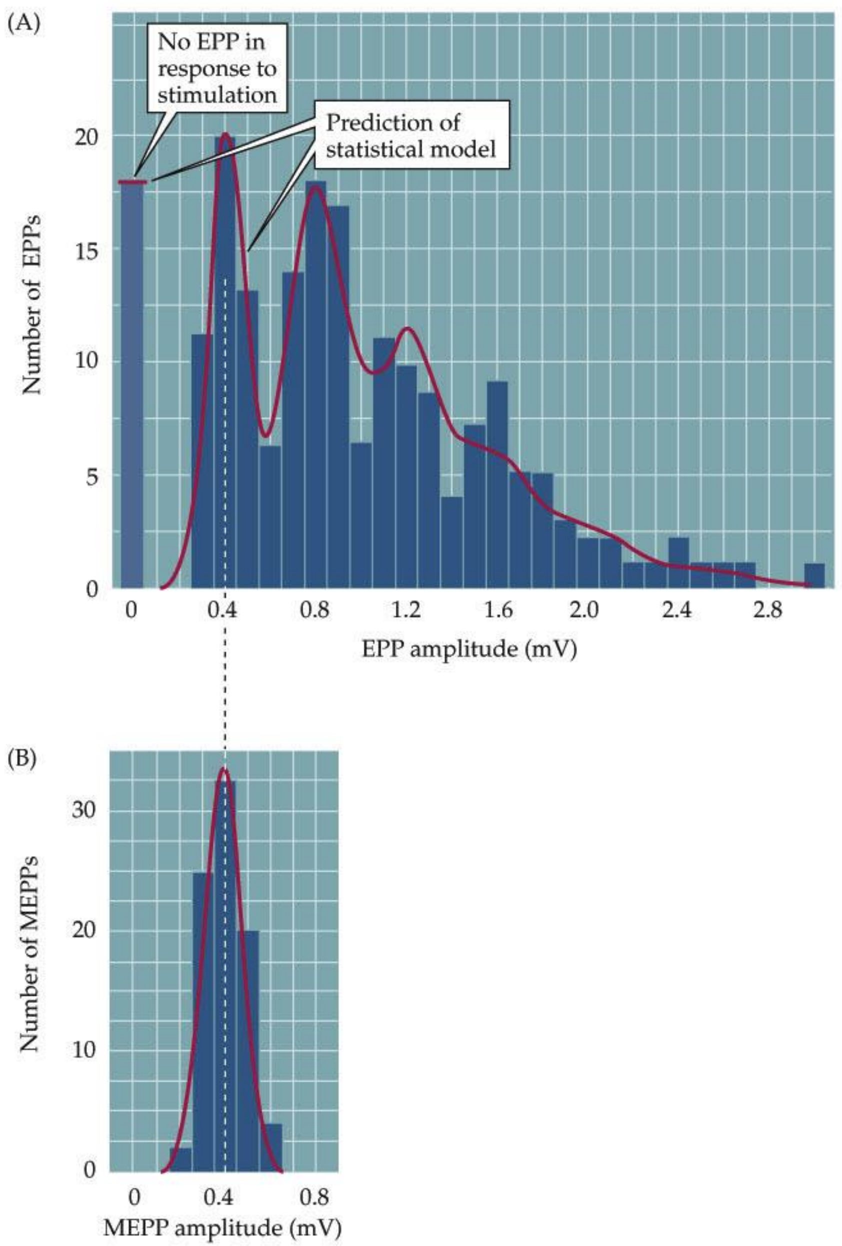
$$P(0) = (1-p).(1-p).(1-p) = q.q.q = q^3 \quad (= 0.729)$$

$$P(1) = p.q.q + p.q.q + p.q.q = 3\,p.q^2 \quad (= 0.243)$$

$$P(2) = p.p.q + p.p.q + p.p.q = 3\,p^2.q \; (=0.027)$$

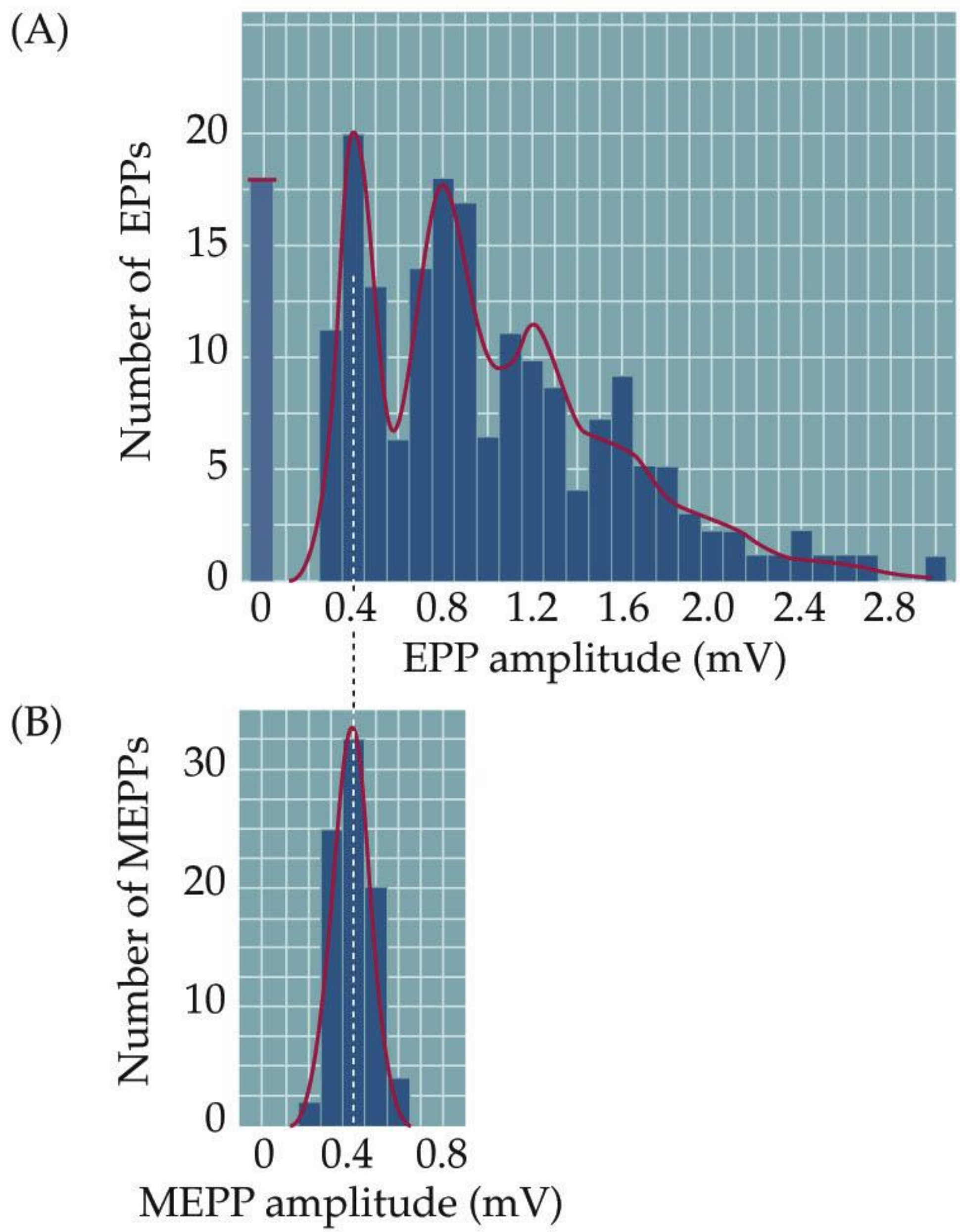
$$P(3) = p.p.p = p^3 \quad (= 0.001)$$

Figure 5.7 Quantized distribution of EPP amplitudes evoked in a low Ca^{2+} solution



NEUROSCIENCE, Fourth Edition, Figure 5.7

Figure 5.7 Quantized distribution of EPP amplitudes evoked in a low Ca^{2+} solution



NEUROSCIENCE, Fourth Edition, Figure 5.7

Quantal hypothesis (part 1)

- mEPP represents quantal unit
- Evoked EPPs represent integer multiples of this quantal unit.
- If so, mean number of quanta released equals mean EPP/mean mEPP
- $m_d = V_{avg}/q_{avg}$
  - m avg. # quanta released by AP, or *quantal content*
  - V_{avg} is avg. EPP
  - q is quantal size (avg)
- This is the direct method of calculating quantal content (m).

Quantal hypothesis (part 2)

- Failures and variability in EPP amplitude implied *probabilistic* nature of transmission
- Statistical models might be applied to quantitatively describe transmission
- Katz et al. considered models in which there were **n** quanta available for release with probability **p**.
- One special case that accounts for situations where **n** is very large, **p** very small: Poisson statistics.

1^{st} test of Poisson model: method of failures

$$P(x) = \frac{m^x e^{-m}}{x!}$$

When x = 0

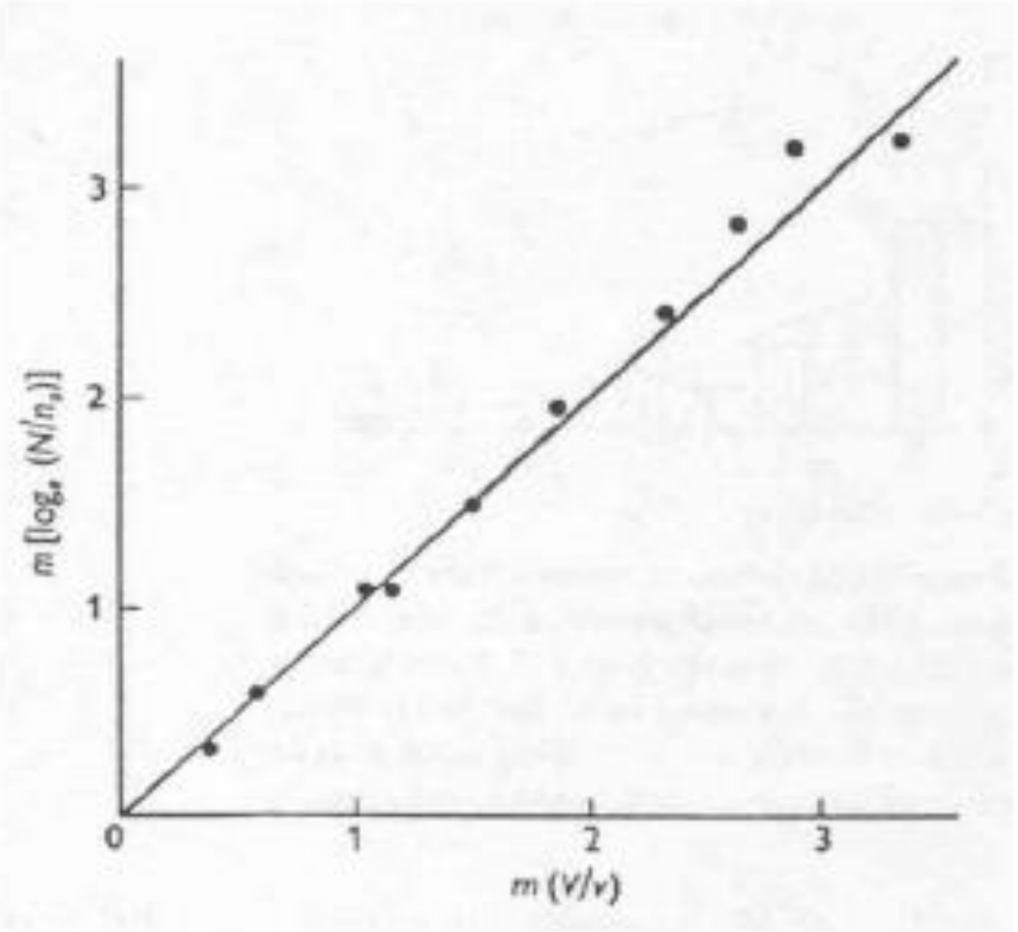
$$m_f = \ln\left(\frac{N}{N_0}\right)$$

N = # trials,

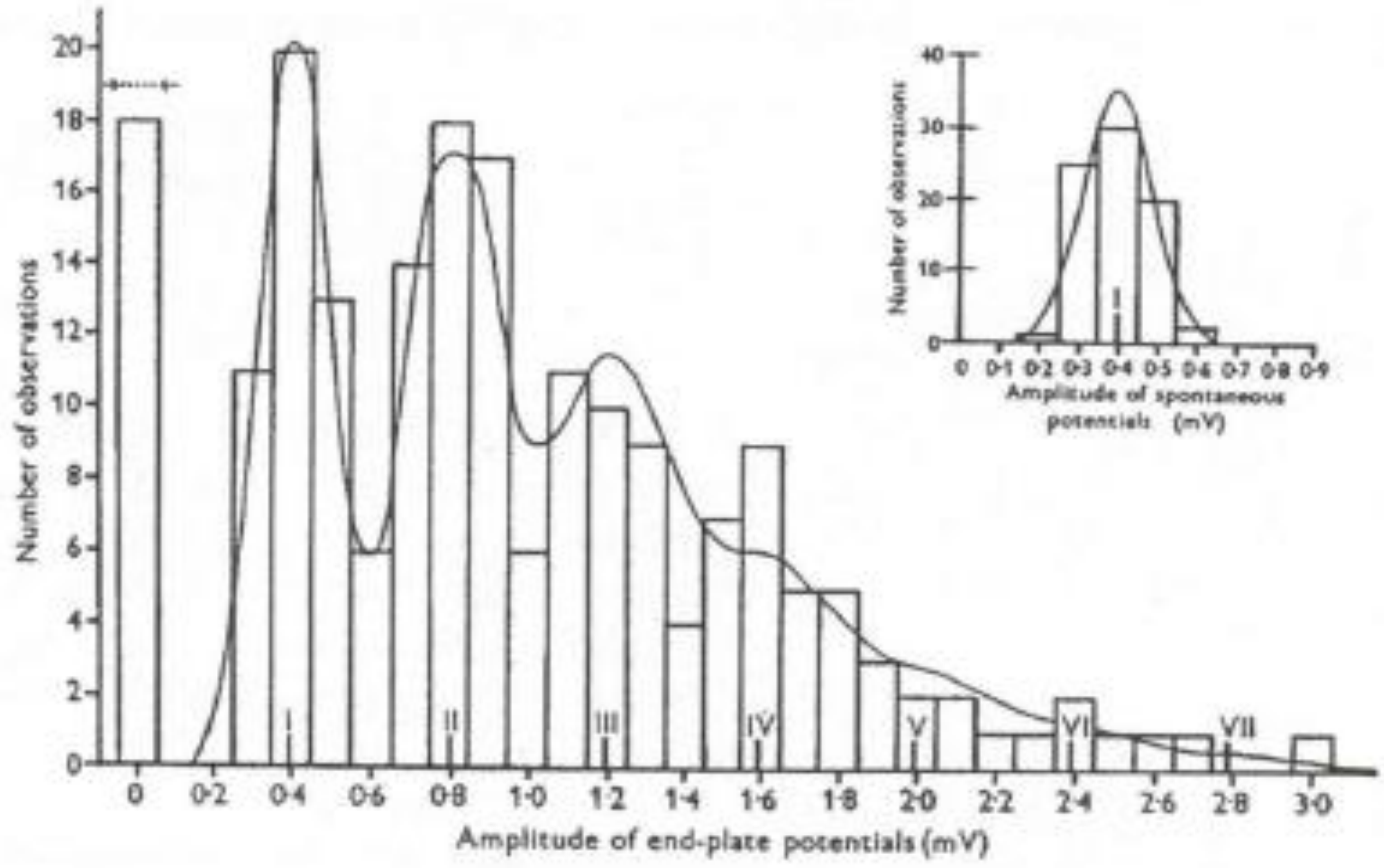
N_o= # trials where failure occurred

Prediction: $m_f = m_d$

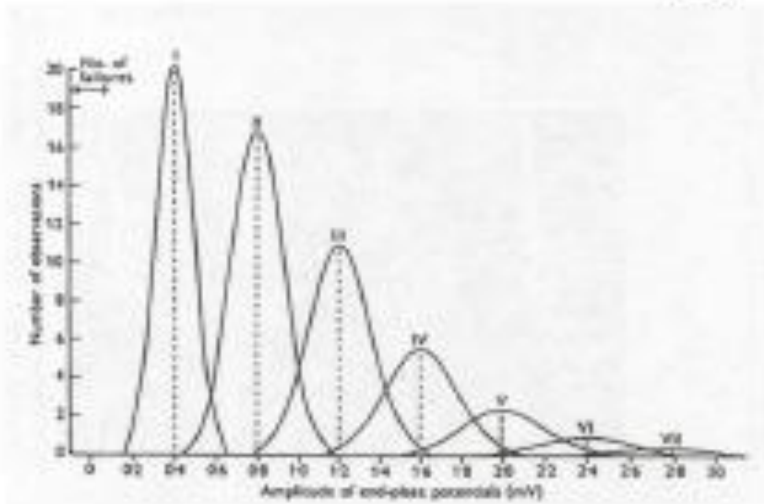
Correspondence between m_f and m_d



2nd test of Poisson model: histogram fitting



Histogram fitting



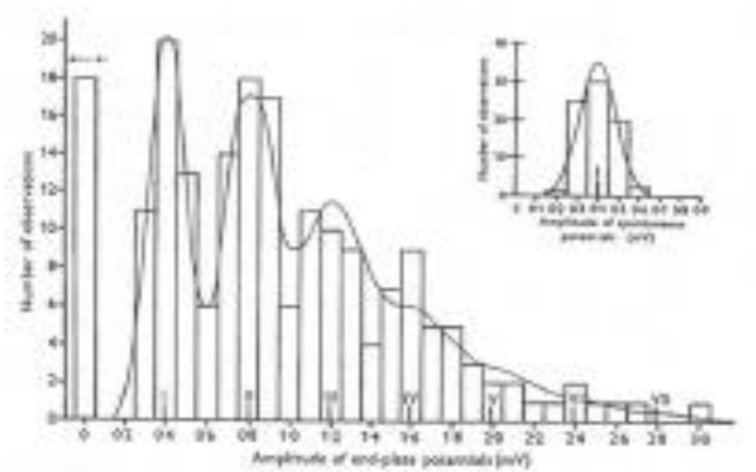
Predictions of Poisson model

$$N_0 = N e^{-m}$$

$$N_1 = (m e^{-m})N = mN_0$$

$$N_2 = \frac{m^2 e^{-m}}{2} N = \frac{m}{2} N_1$$

$$N_3 = \frac{m^3 e^{-m}}{6} N = \frac{m}{3} N_2$$



Observations (bars)

Sum of predictions (line)

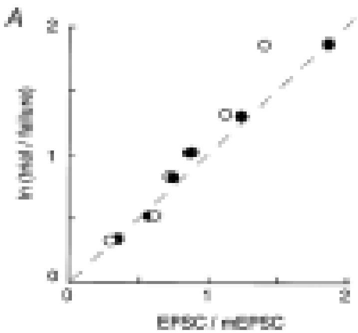
A final test Poisson model: coefficient of variation

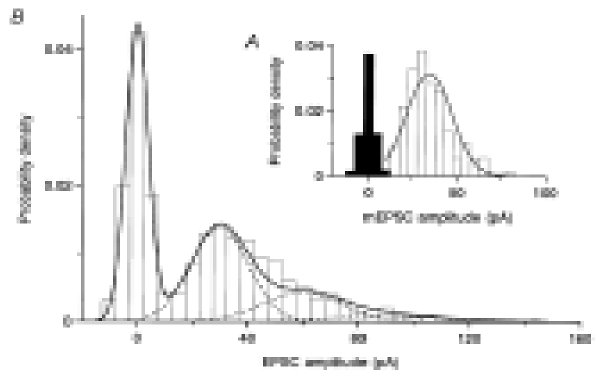
- For Poisson distribution mean = variance
- $A = \sigma_a^2$; $m = \sigma_m^2$
  - A = amplitude of evoked response
  - m = quantal content
  - σ^2 = variance

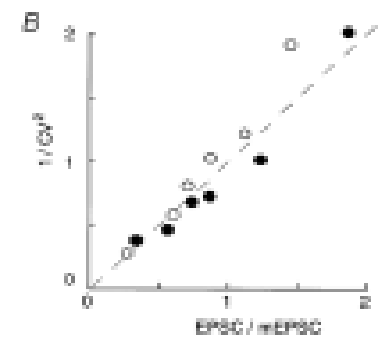
$$CV = \frac{\sigma}{m} = \frac{1}{\sigma} = \frac{1}{\sqrt{m}}$$

- $m = 1/CV^2$
- Prediction $1/CV^2 = m_d$
- Castillo and Katz found that this prediction also was met

Transmitter release obeys Poisson statistics at a central synapse







Sahara and Takahashi (2001) J Physiol 536: 189

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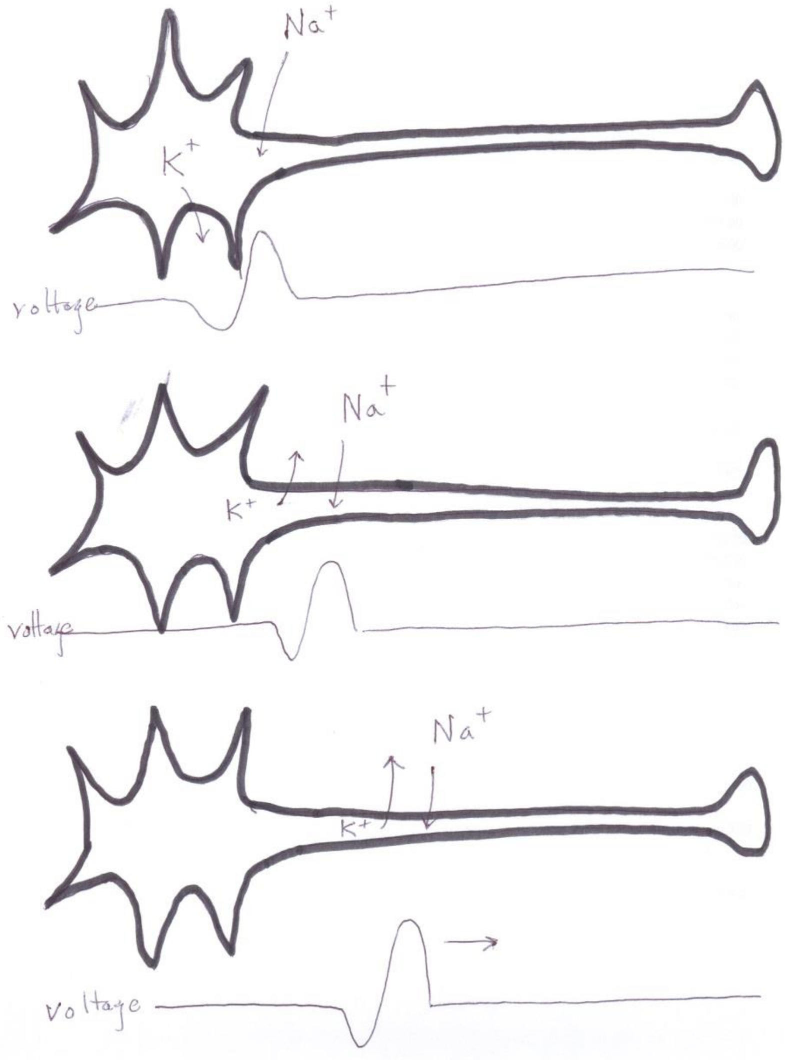
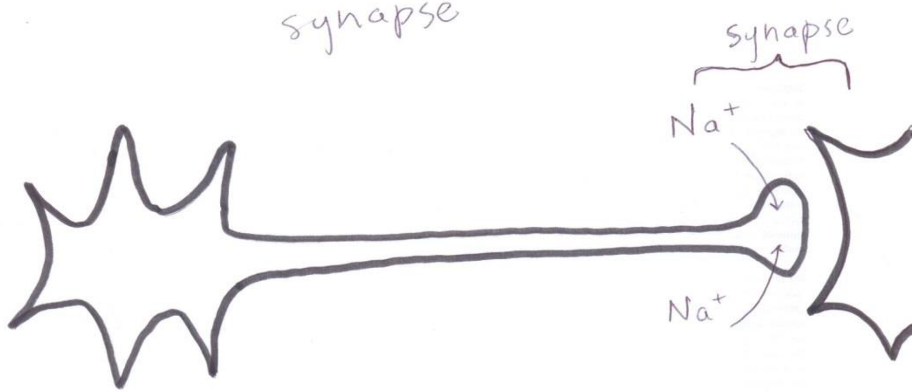
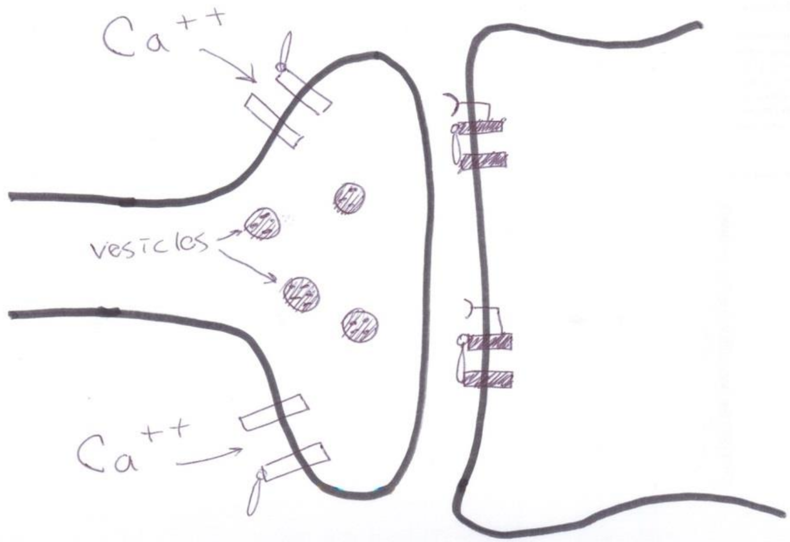
How voltage pulses travel

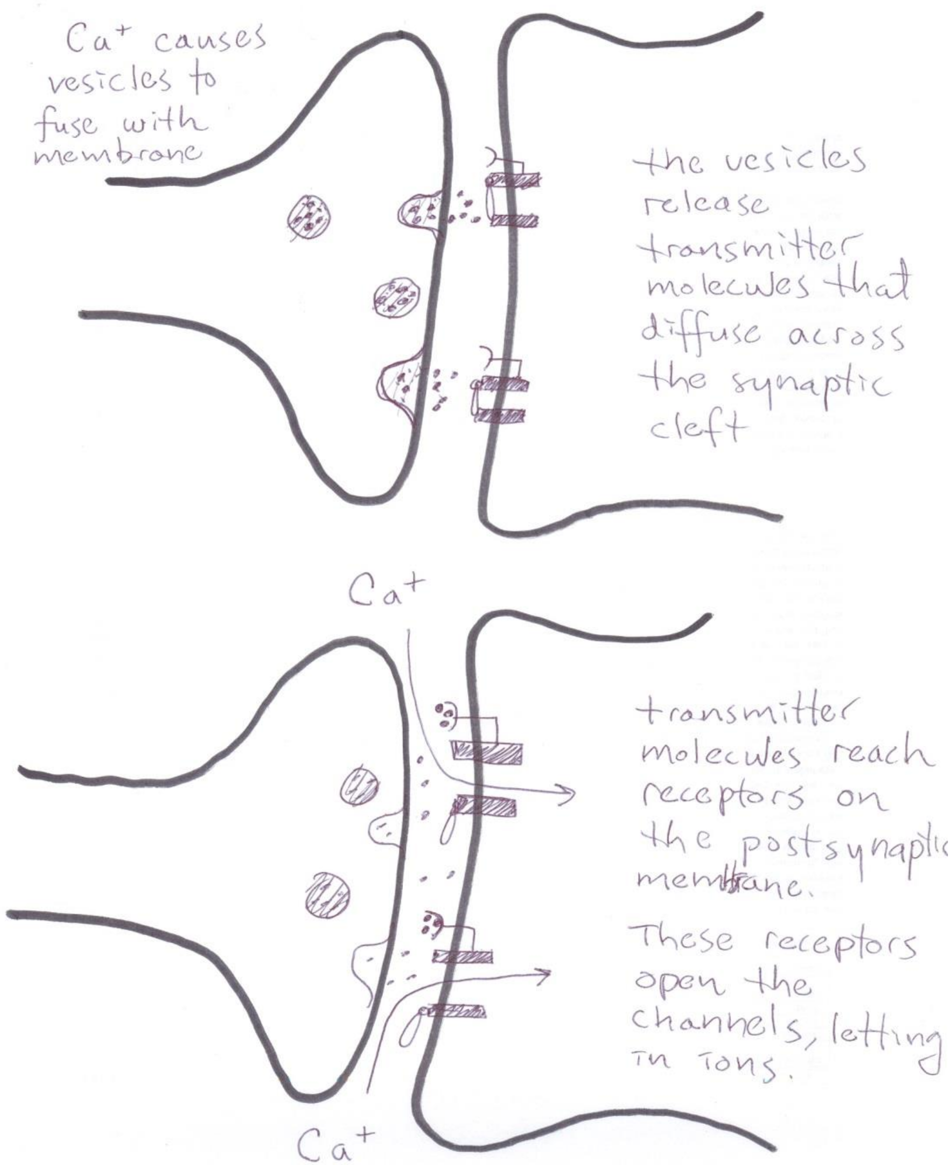


How a pulse travels across a synapse



voltage-gated channels open, letting in Ca^{++}




Ca+ causes vesicles to fuse with membrane
the vesicles release transmitter molecules that diffuse across the synaptic cleft
Ca+
transmitter molecules reach receptors on the postsynaptic membrane.
These receptors open the channels, letting in ions.
Ca+

Synapses

- Two major types of synapses
  - Electrical
  - Chemical
- Chemical Synapses
  - Specialized neuroanatomy to support it.
  - Typical synapse in mammalian brain is very small (< 1 um^2)
  - Neurons have large numbers of synapses: 5-10 K for small neurons, as many as 100 K for large neurons.
  - Axons branch, taper, and form synaptic boutons: presynaptic terminals, postsynaptic density, synaptic cleft which separates them (20-40 nm)
- Neurotransmitter release
  - Ca^{2+}-dependent release of packets of neurotransmitter, packaged into vesicles.
- Two categories of chemical synaptic transmission
  - Ionotropic: fast, local channel-mediated changes in membrane potential (EPSPs, IPSPs)
  - Metabotropic: slow, G-protein- and second-messenger- mediated changes

Overview of Synaptic Transmission

- FIGURE 12.1. Overview of synaptic transmission mechanisms. Gap junctions (left) directly couple the presynaptic and postsynaptic membrane potentials. Ionotropic receptors open ion-selective channels that can modify the postsynaptic membrane potential as well as pass calcium ions, which play an important role in intracellular second messenger pathways. G-protein coupled receptors, also called metabotropic receptors, can directly affect the properties of ion channels such as K^+ or Ca^{2+} channels. They can also cause calcium to be released from internal stores through activation of phospholipase C(PLC) and generation of inositol1,4,5-triphosphate (IP3). In addition, diacylglycerol (DAG) can activate protein kinase C (PKC) which in turn affects the function of K^+ and Ca^{2+} channels. Finally, protein kinase A (PKA) can affect the function of Ca^{2+} channels following activation by adenylyl cyclase and cyclic AMP (cAMP). Intracellular calcium can in turn activate calmodulin and a range of calmodulin-dependent enzymes.

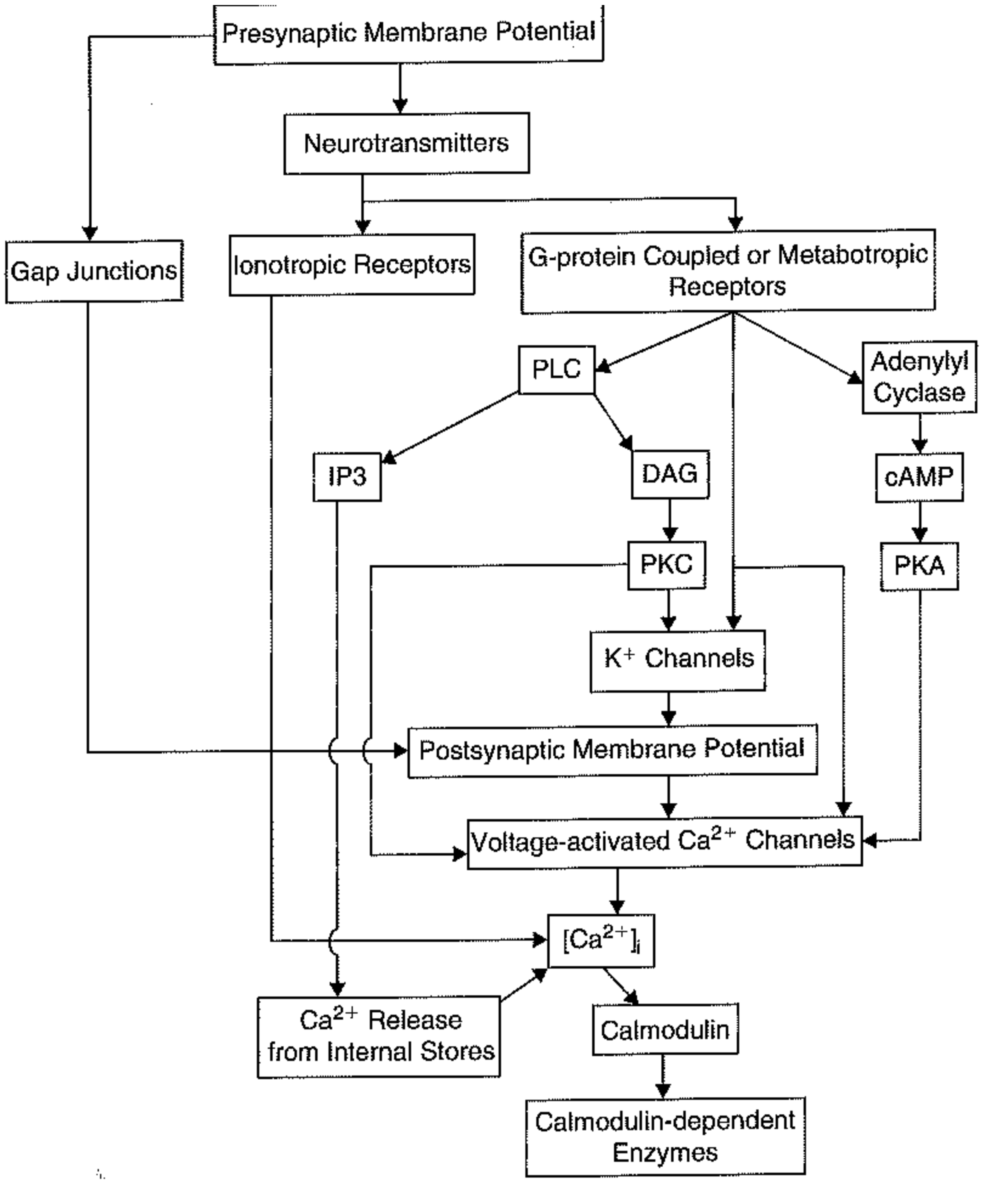
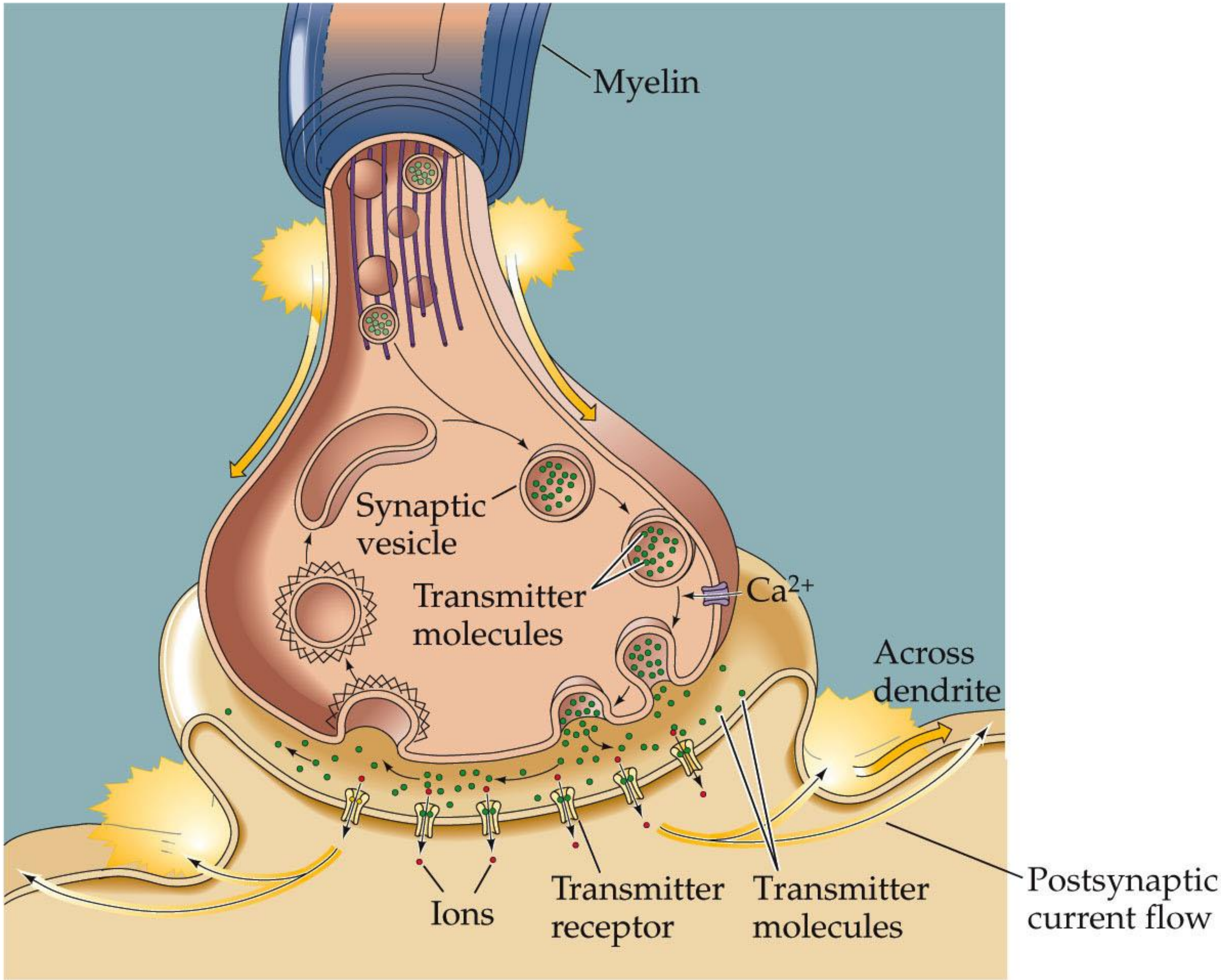
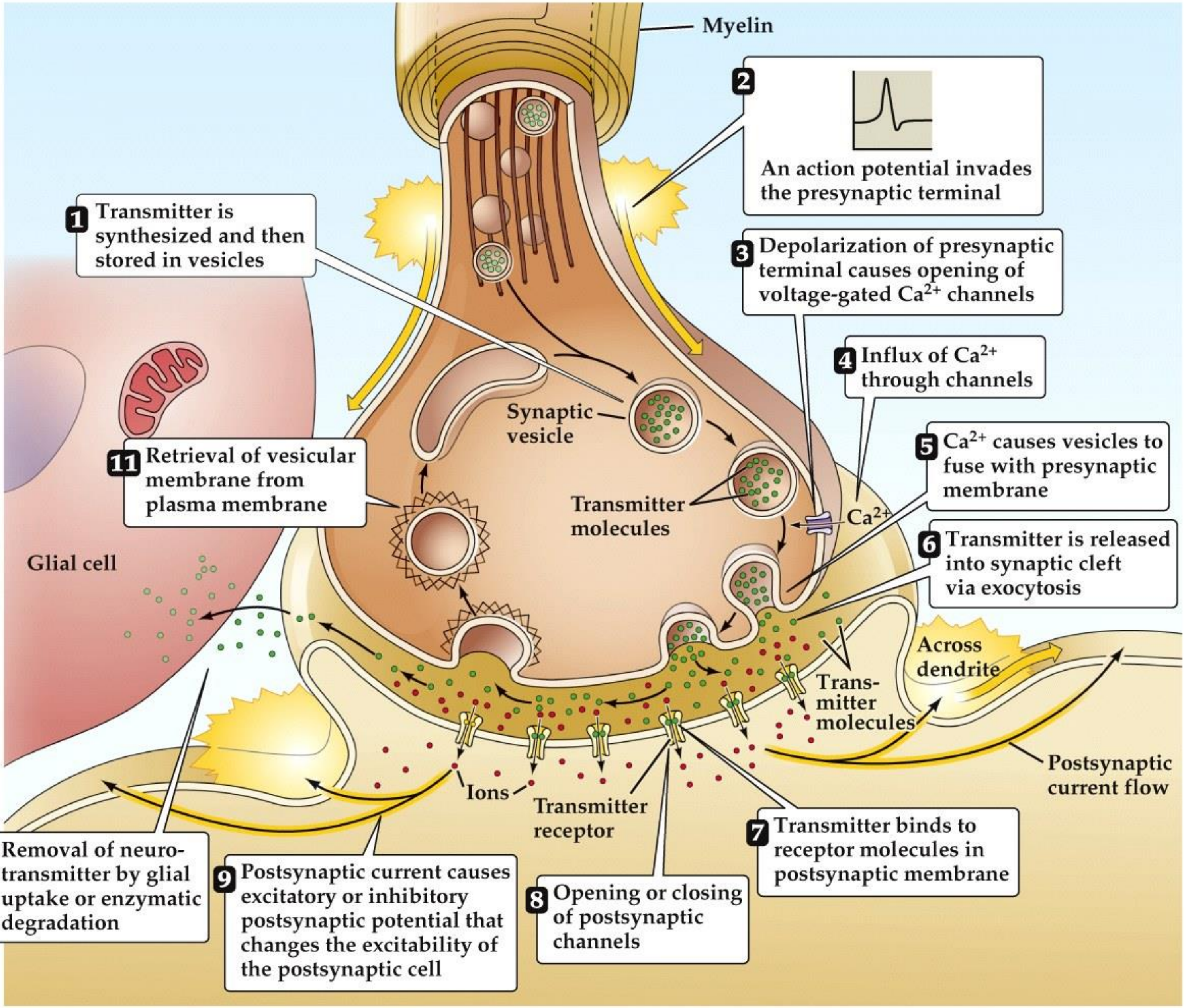


Figure 5.3 Sequence of events involved in transmission at a typical chemical synapse



NEUROSCIENCE, Fourth Edition, Figure 5.3

Figure 5.3 Sequence of events involved in transmission at a typical chemical synapse



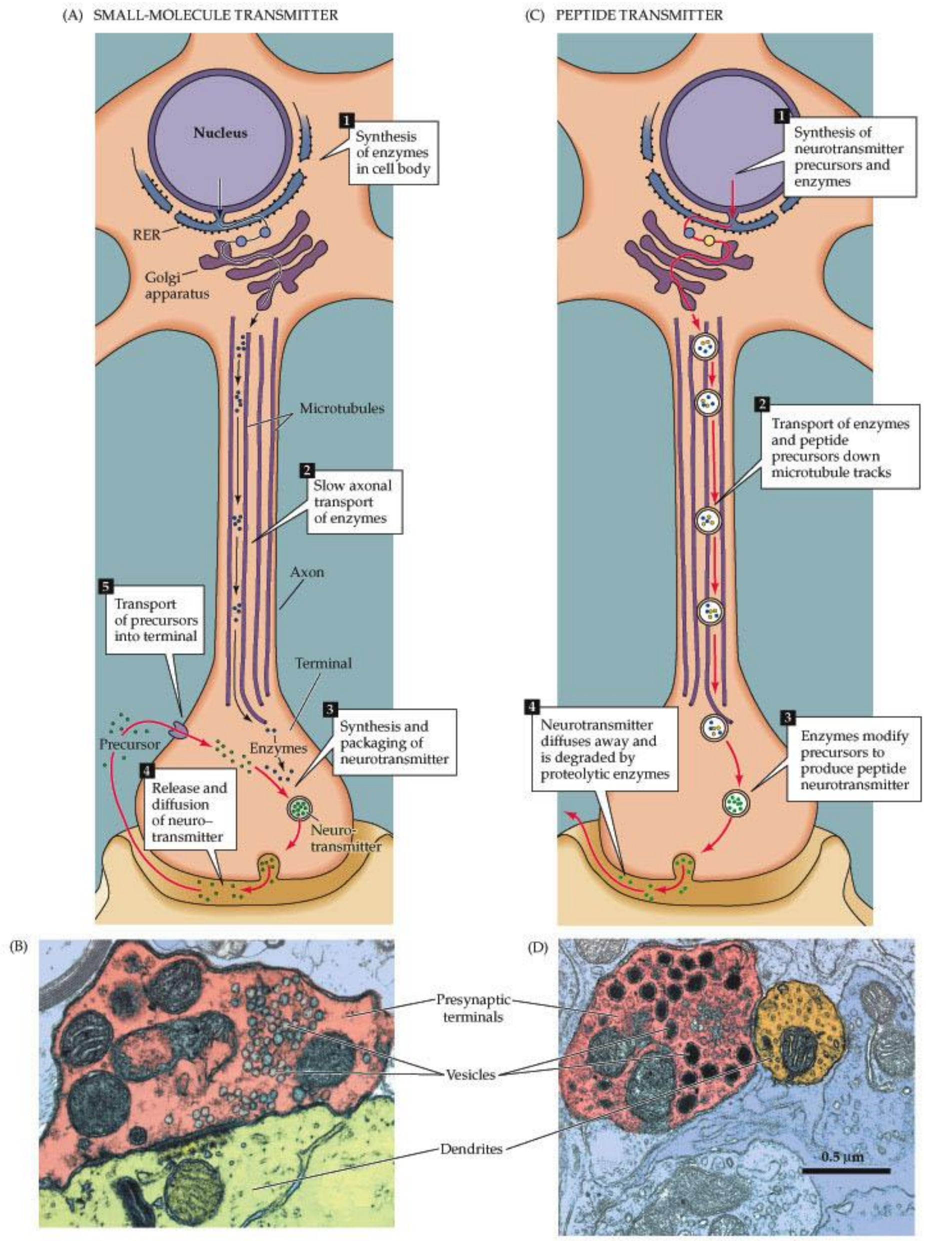
NEUROSCIENCE 5e, **Figure 5.3**

Benefits of chemical transmission

- Amplification
- Sign inversion
- Graded vs. all-or-none
- Varied temporal duration
- Multiple receptors with distinct properties
- Malleability/plasticity

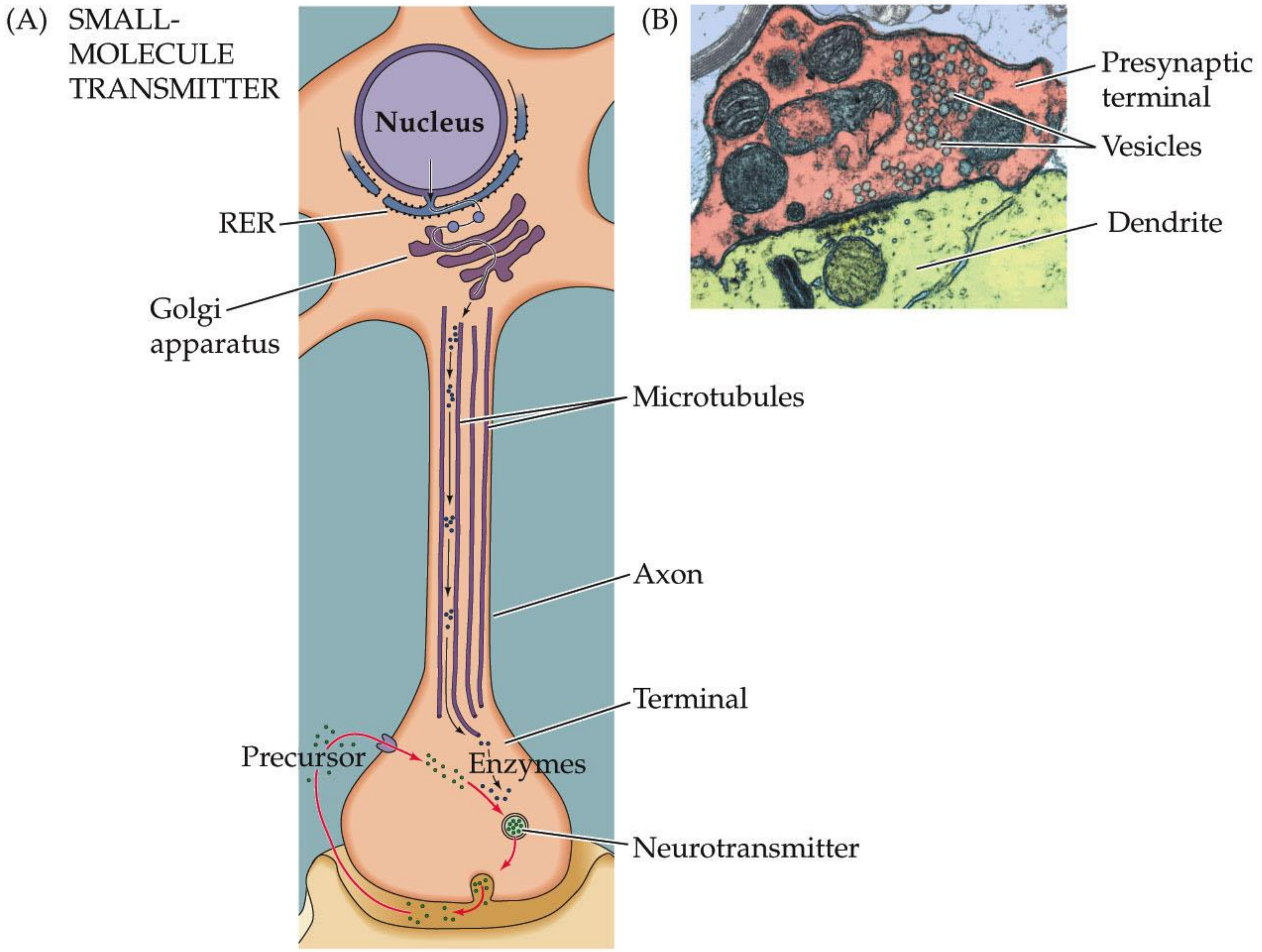
- Steps in neurotransmission
- Vesicle loading, docking, priming
- Action potential invasion
- Ca^{2+} channel opening, Ca^{2+} influx
- Exocytosis
- Postsynaptic membrane potential change
- Membrane reuptake (endocytosis)

Figure 5.5 Metabolism of small-molecule and peptide transmitters



NEUROSCIENCE, Fourth Edition, Figure 5.5

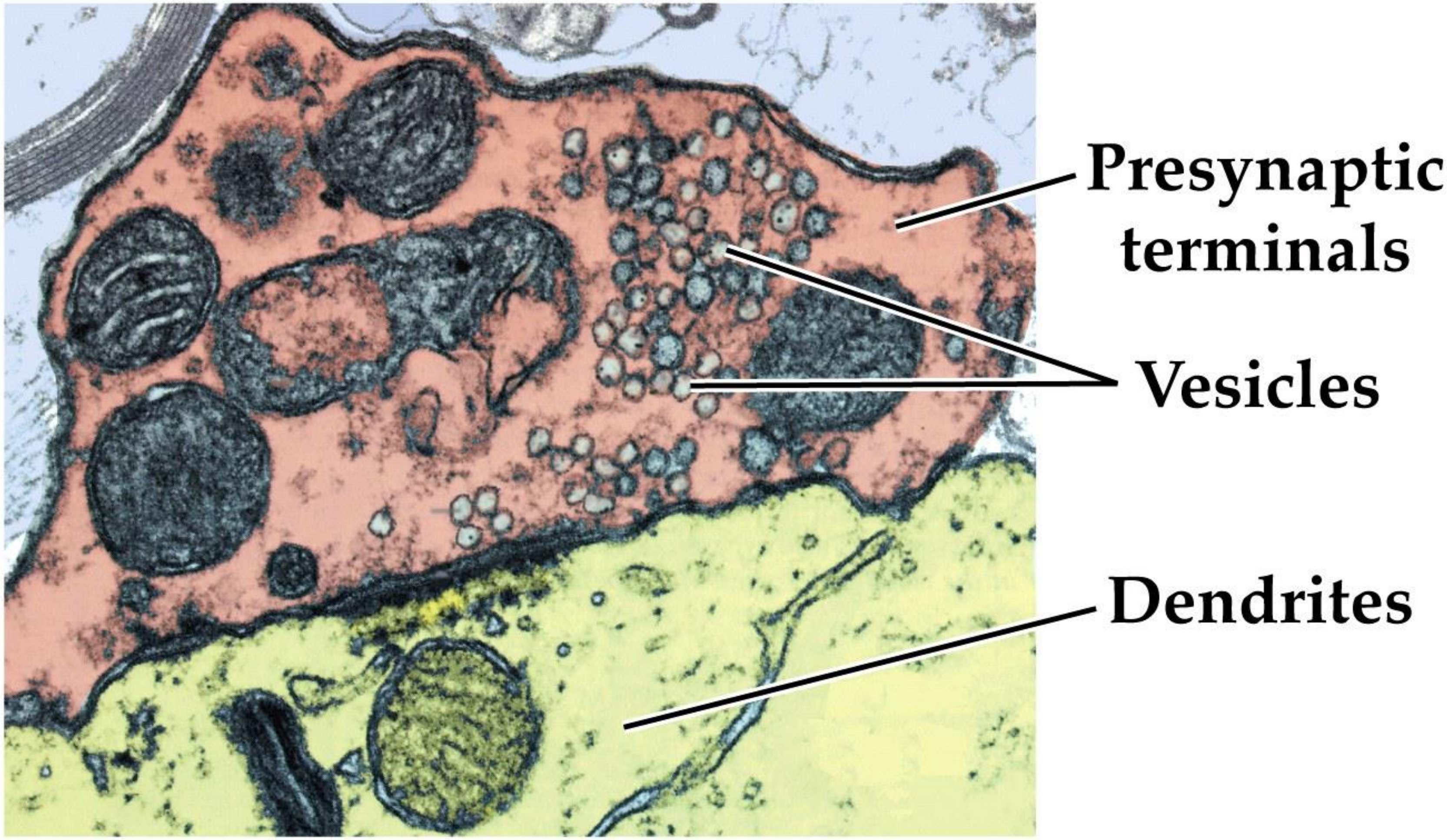
Figure 5.5 Metabolism of small-molecule and peptide transmitters (Part 1)



NEUROSCIENCE, Fourth Edition, Figure 5.5 (Part 1)

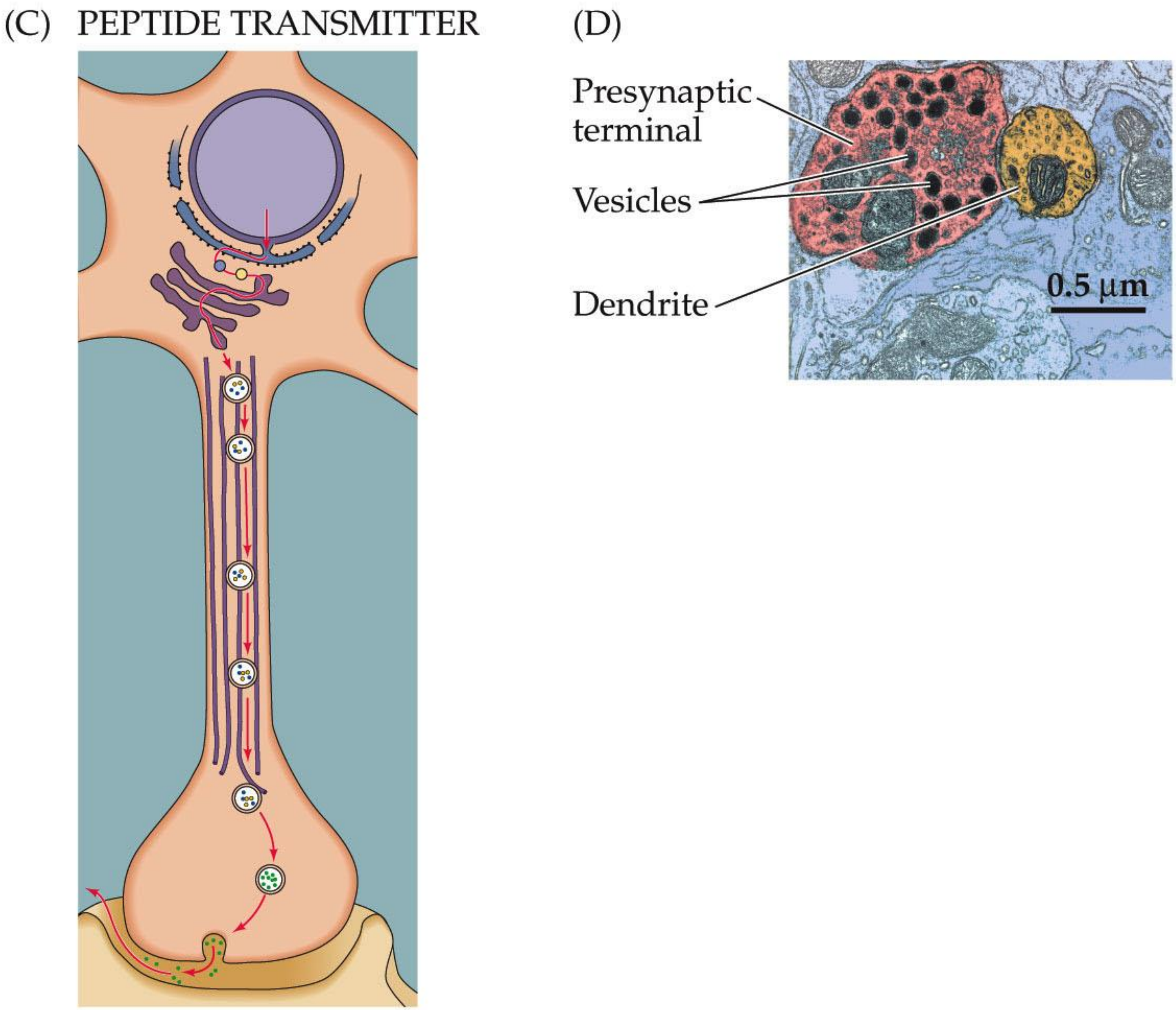
Figure 5.5 Metabolism of small-molecule and peptide transmitters (Part 2)

(B)



NEUROSCIENCE 5e, Figure 5.5 (Part 2)

Figure 5.5 Metabolism of small-molecule and peptide transmitters (Part 2)



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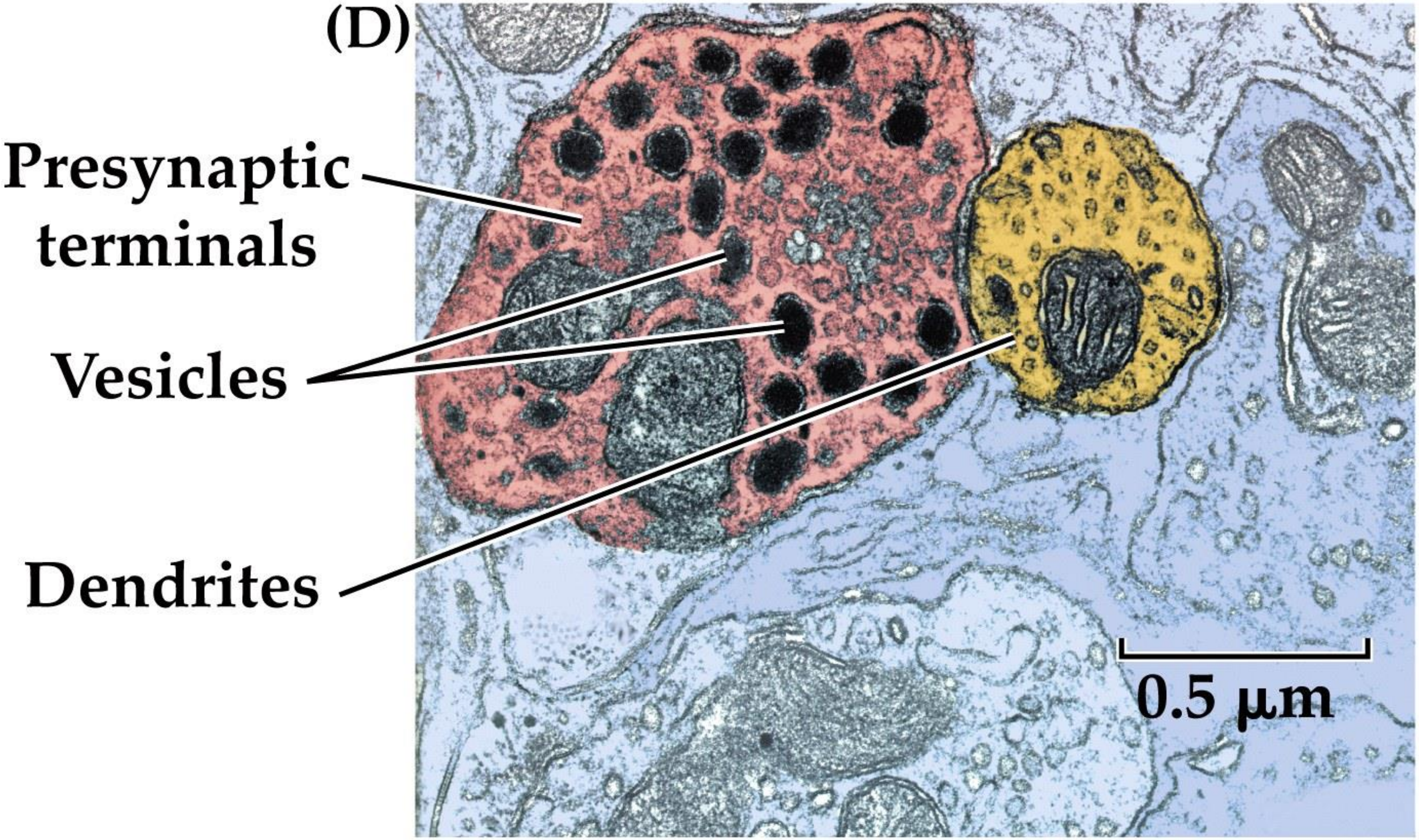
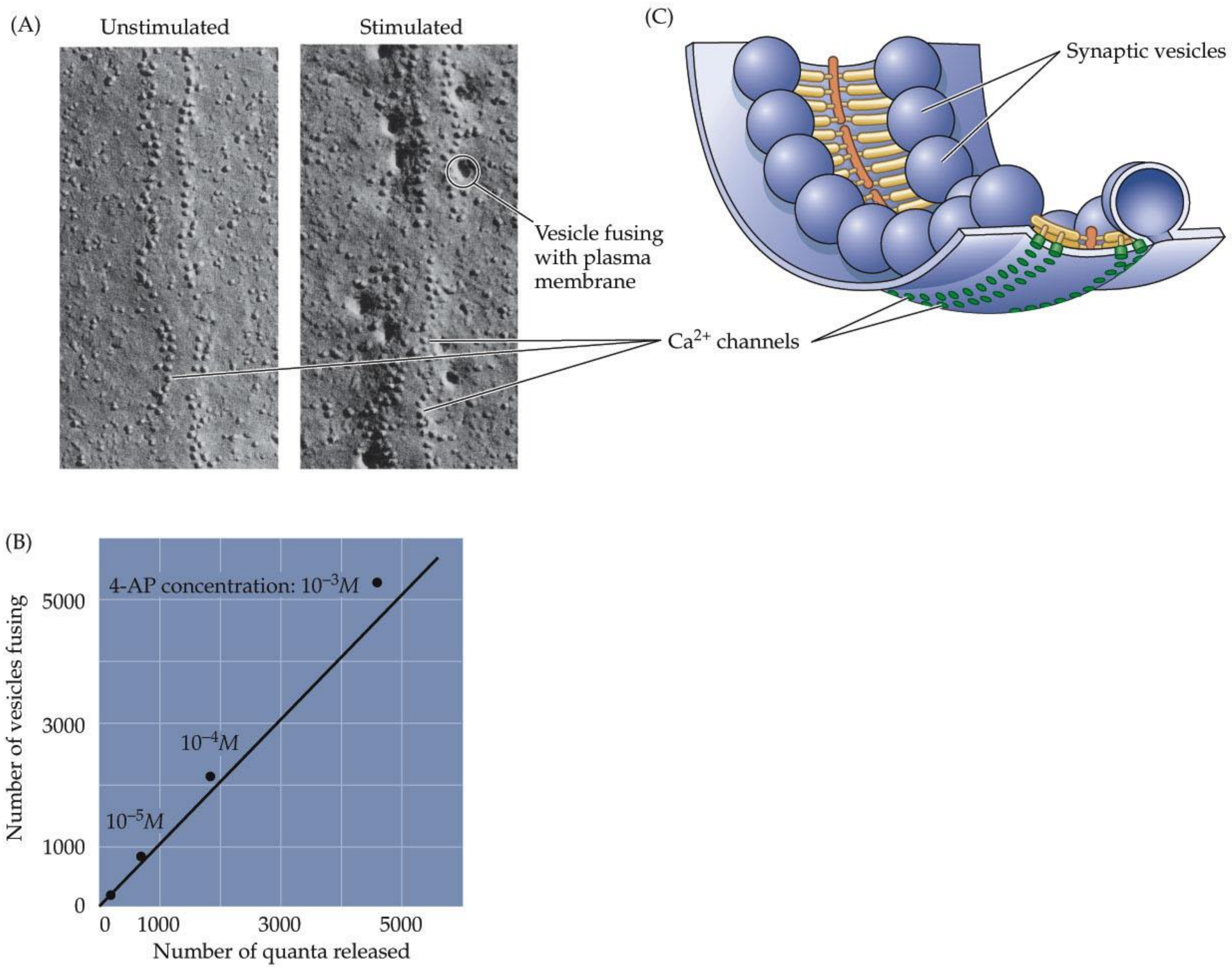


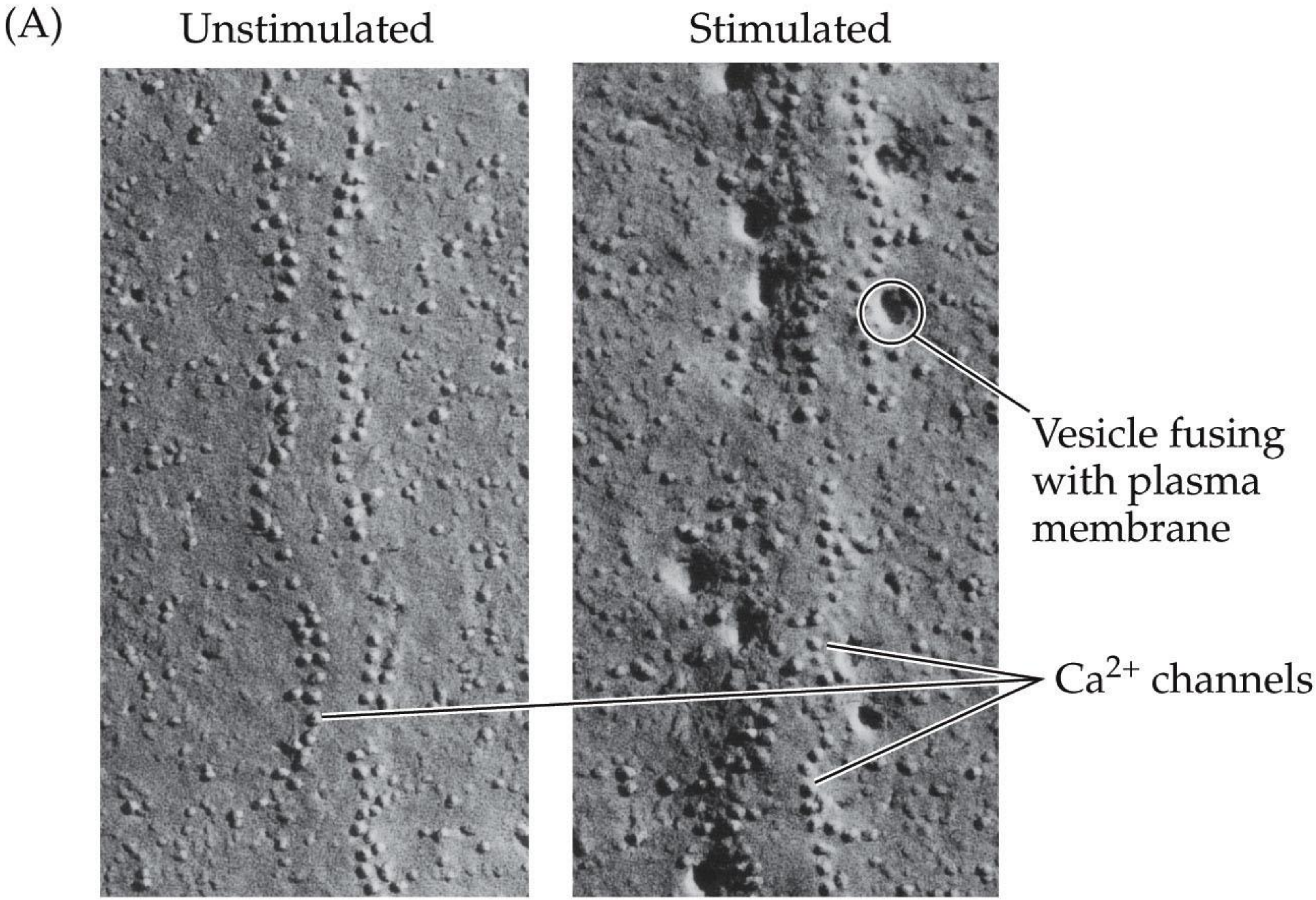
NEUROSCIENCE 5e, Figure 5.5 (Part 4)

Figure 5.8 Relationship of synaptic vesicle exocytosis and quantal transmitter release



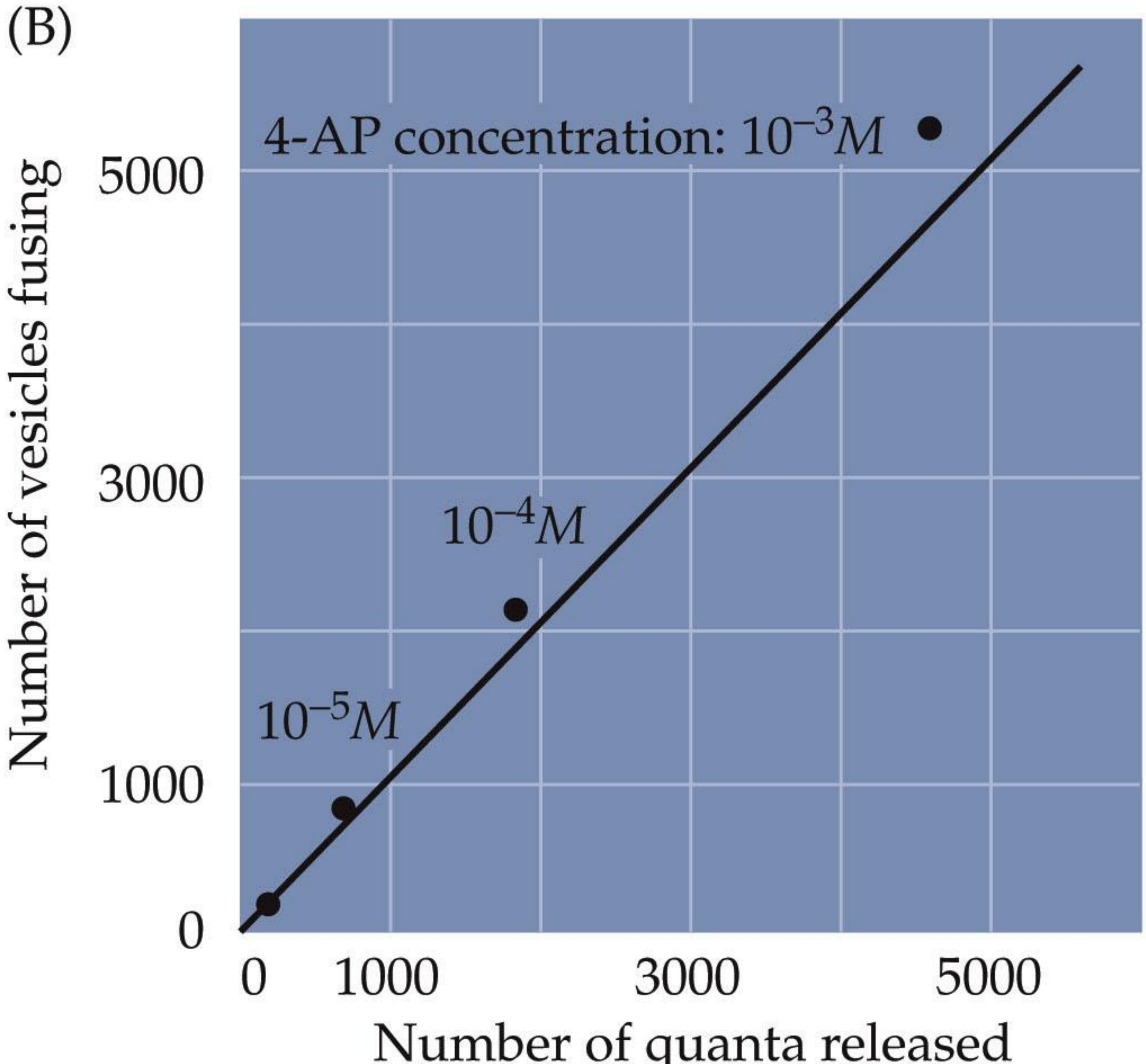
NEUROSCIENCE, Fourth Edition, Figure 5.8

Figure 5.8 Relationship of synaptic vesicle exocytosis and quantal transmitter release (Part 1)



NEUROSCIENCE, Fourth Edition, Figure 5.8 (Part 1)

Figure 5.8 Relationship of synaptic vesicle exocytosis and quantal transmitter release (Part 2)



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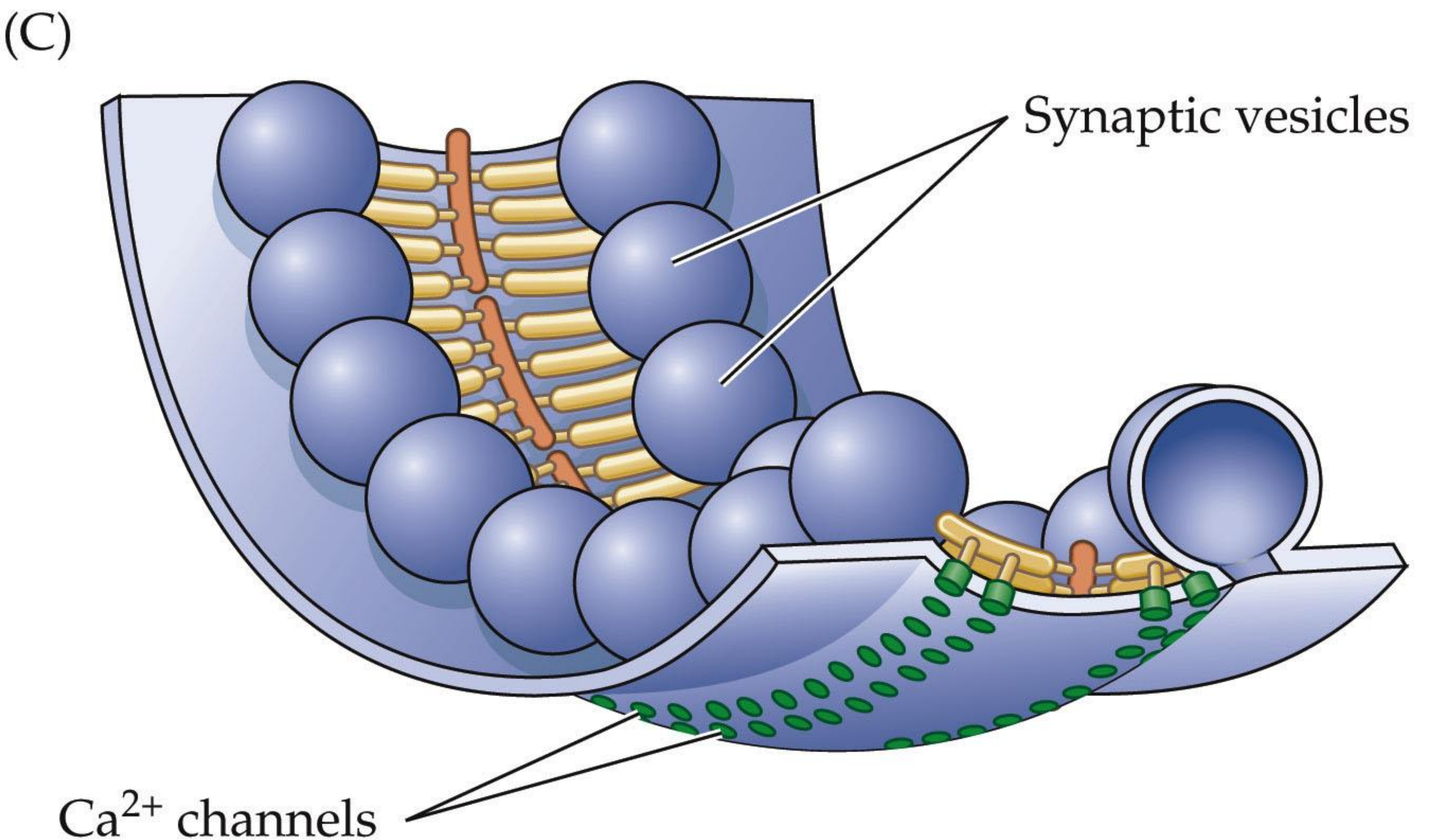
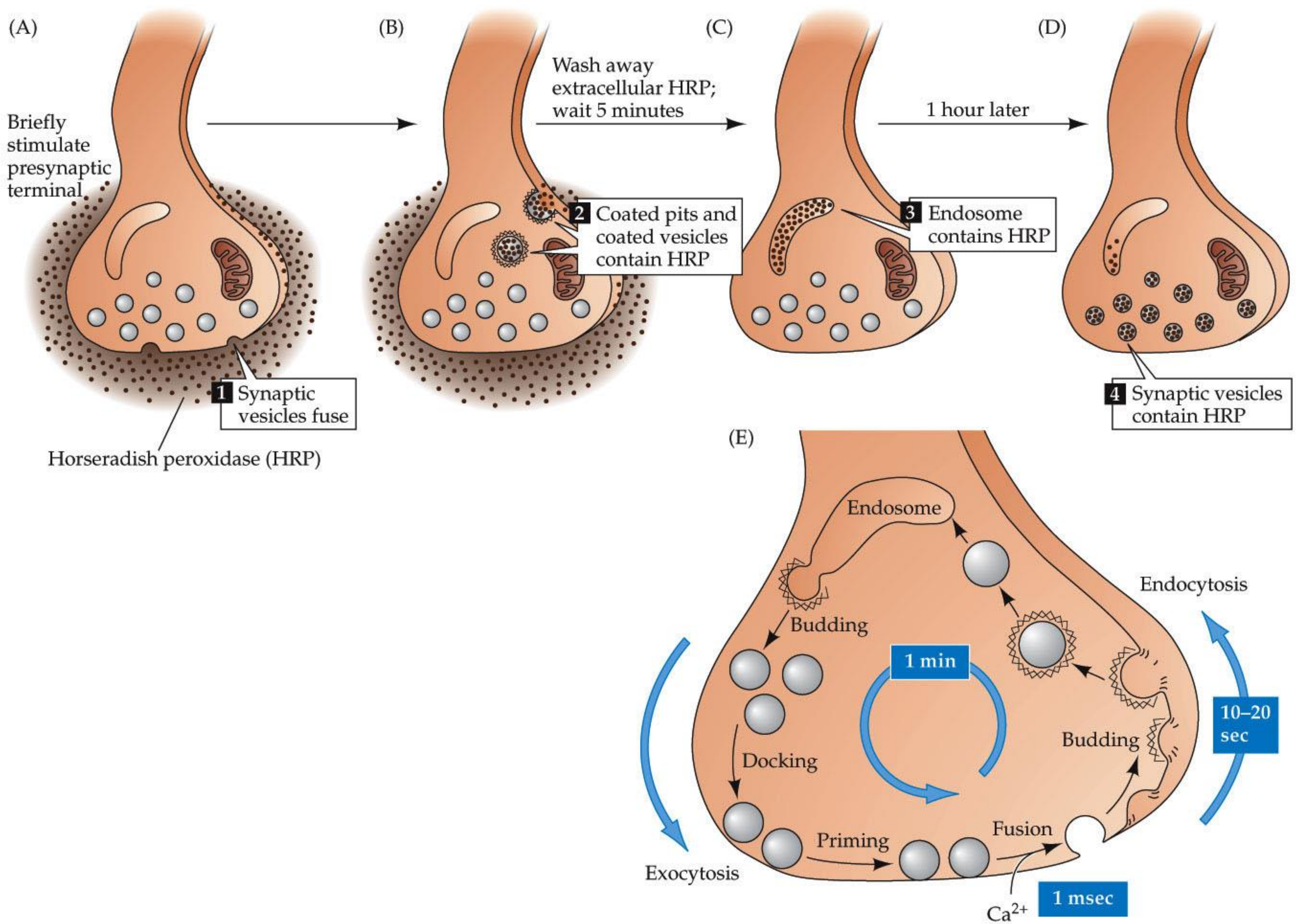
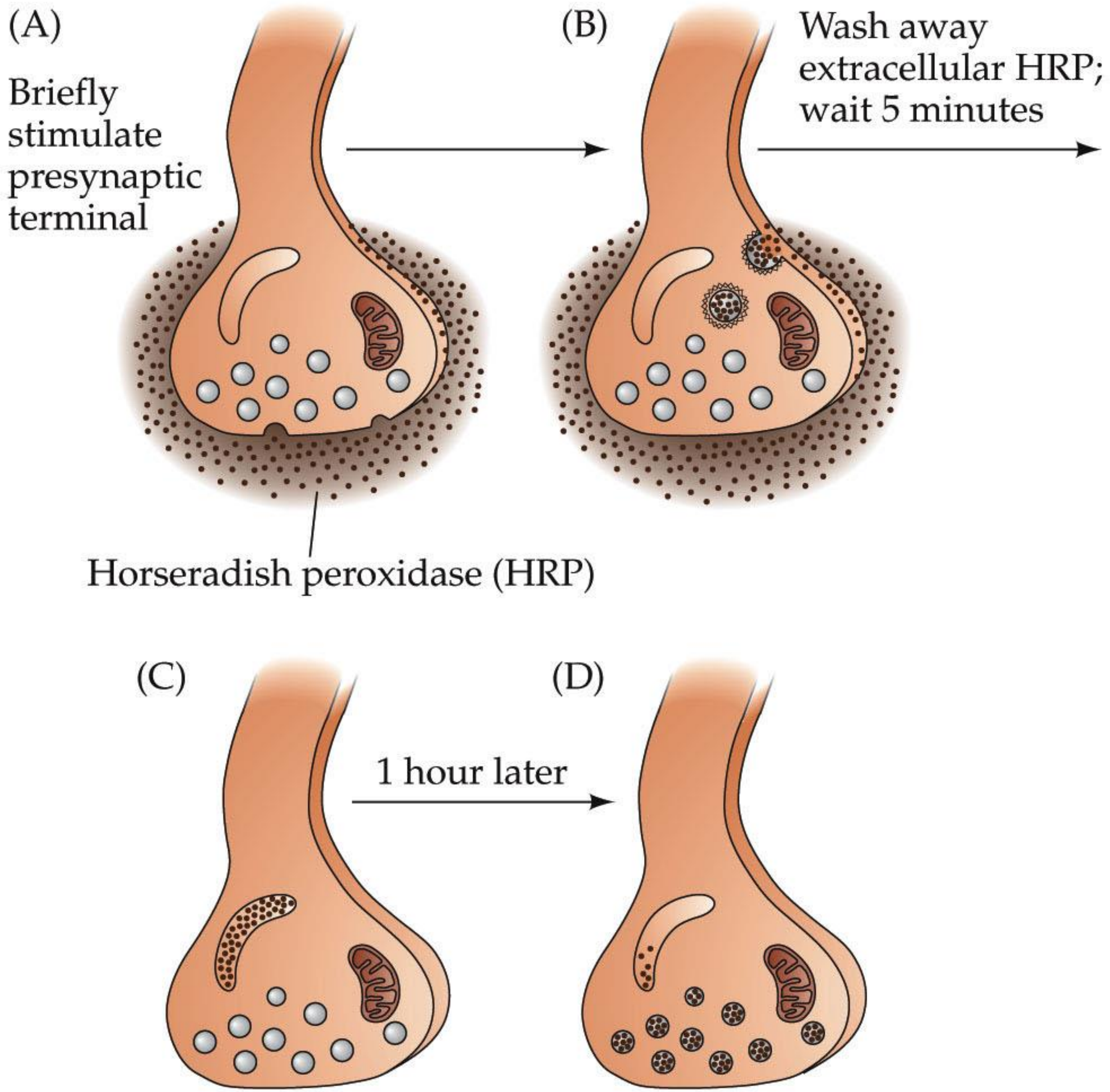

(C)
Synaptic vesicles
Ca2+ channels

Figure 5.9 Local recycling of synaptic vesicles in presynaptic terminals



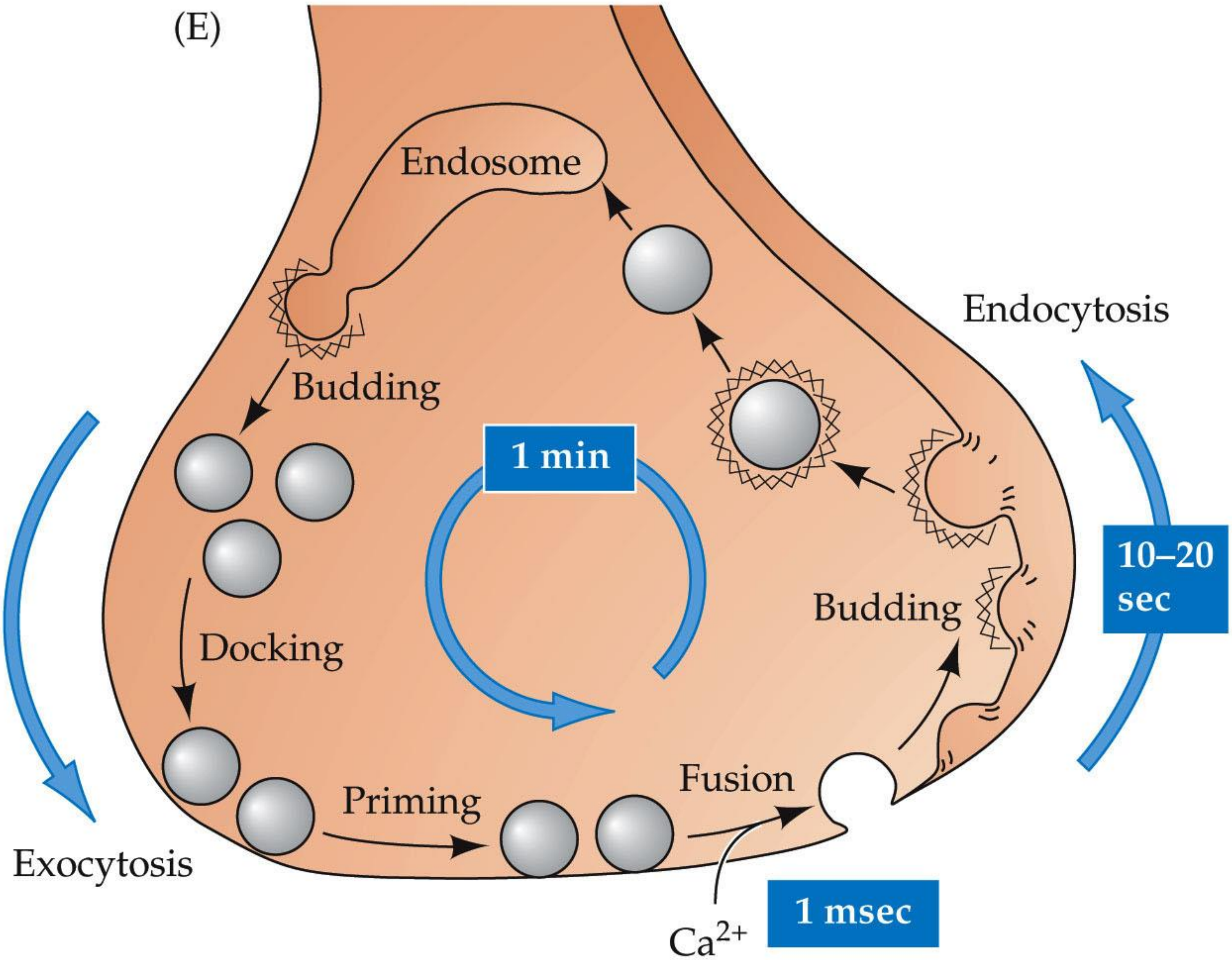
NEUROSCIENCE, *Fourth Edition*, Figure 5.9

Figure 5.9 Local recycling of synaptic vesicles in presynaptic terminals (Part 1)



***NEUROSCIENCE*, *Fourth Edition*, Figure 5.9 (Part 1)**

Figure 5.9 Local recycling of synaptic vesicles in presynaptic terminals (Part 2)



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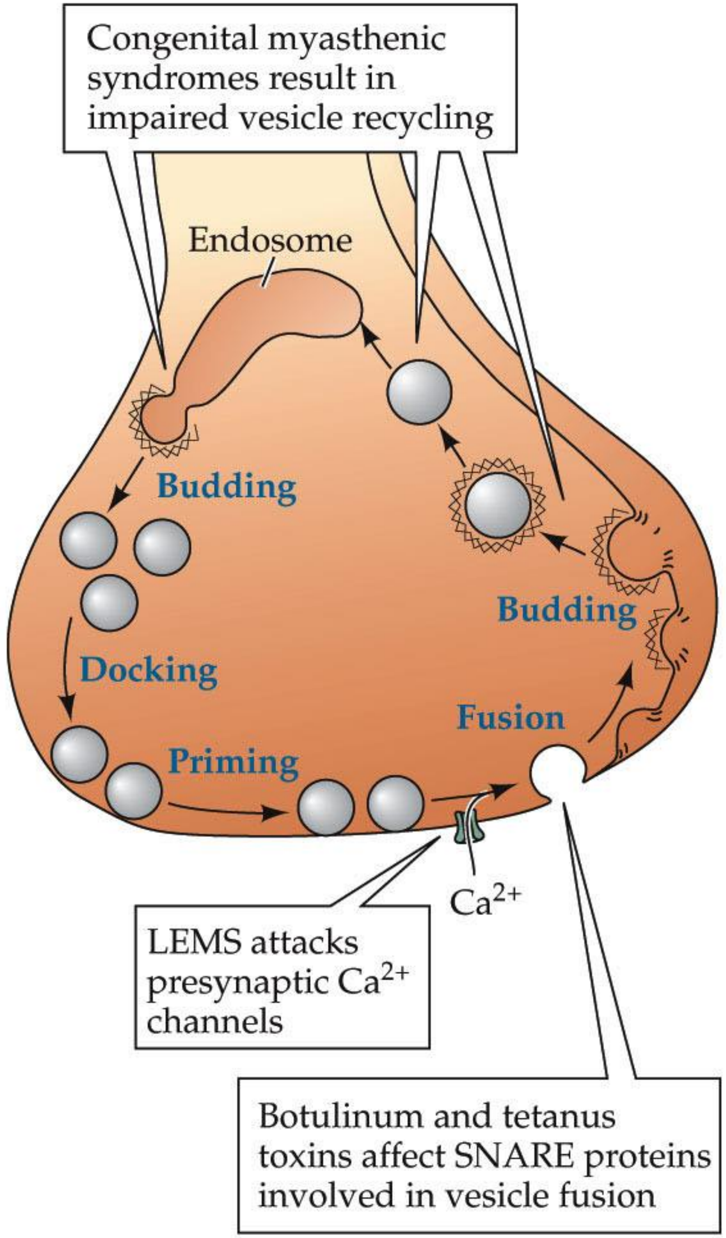
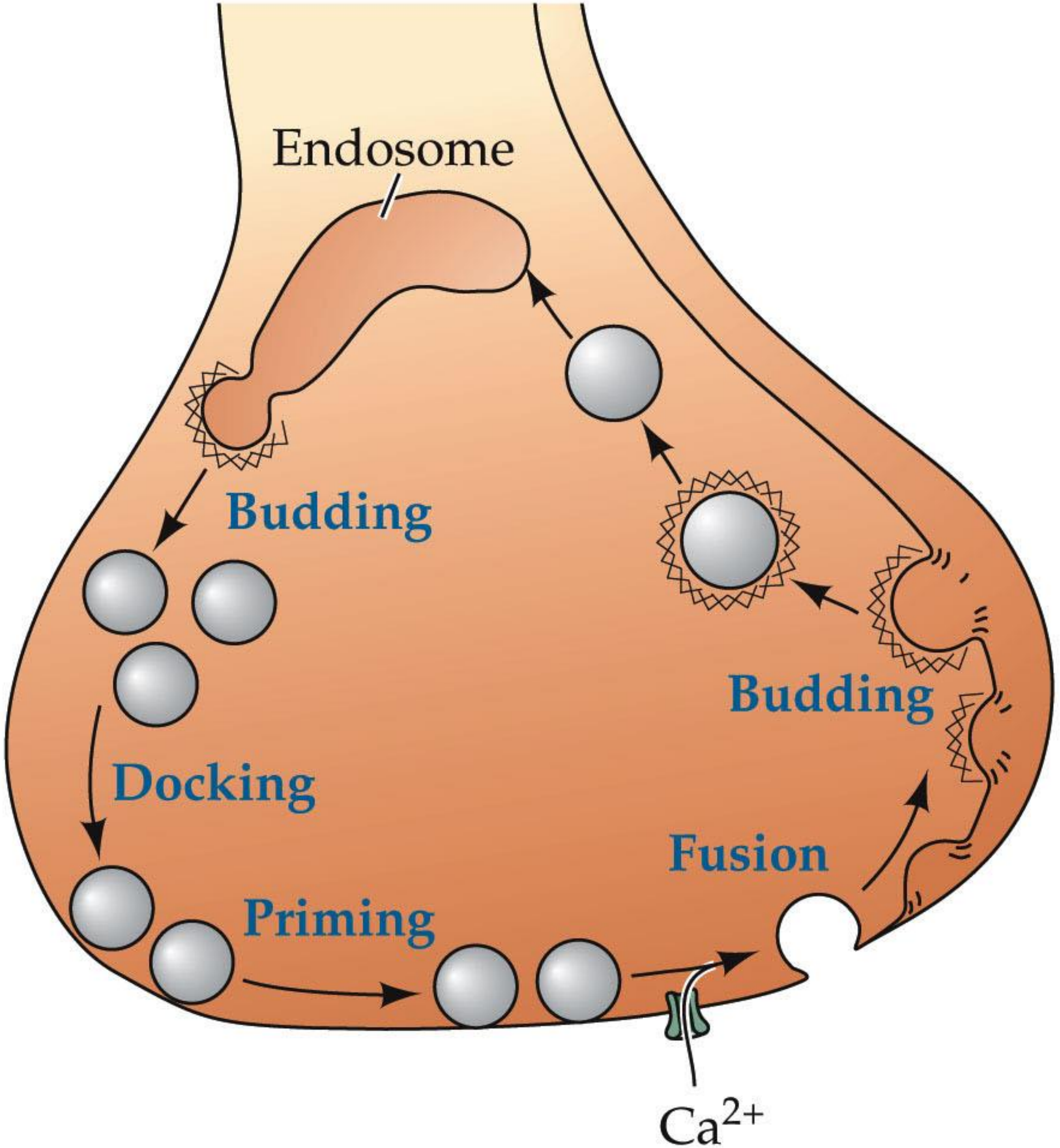
Box 5B Diseases That Affect the Presynaptic Terminal



NEUROSCIENCE, Fourth Edition, Box 5B

Box 5B Diseases That Affect the Presynaptic Terminal



NEUROSCIENCE, Fourth Edition, Box 5B

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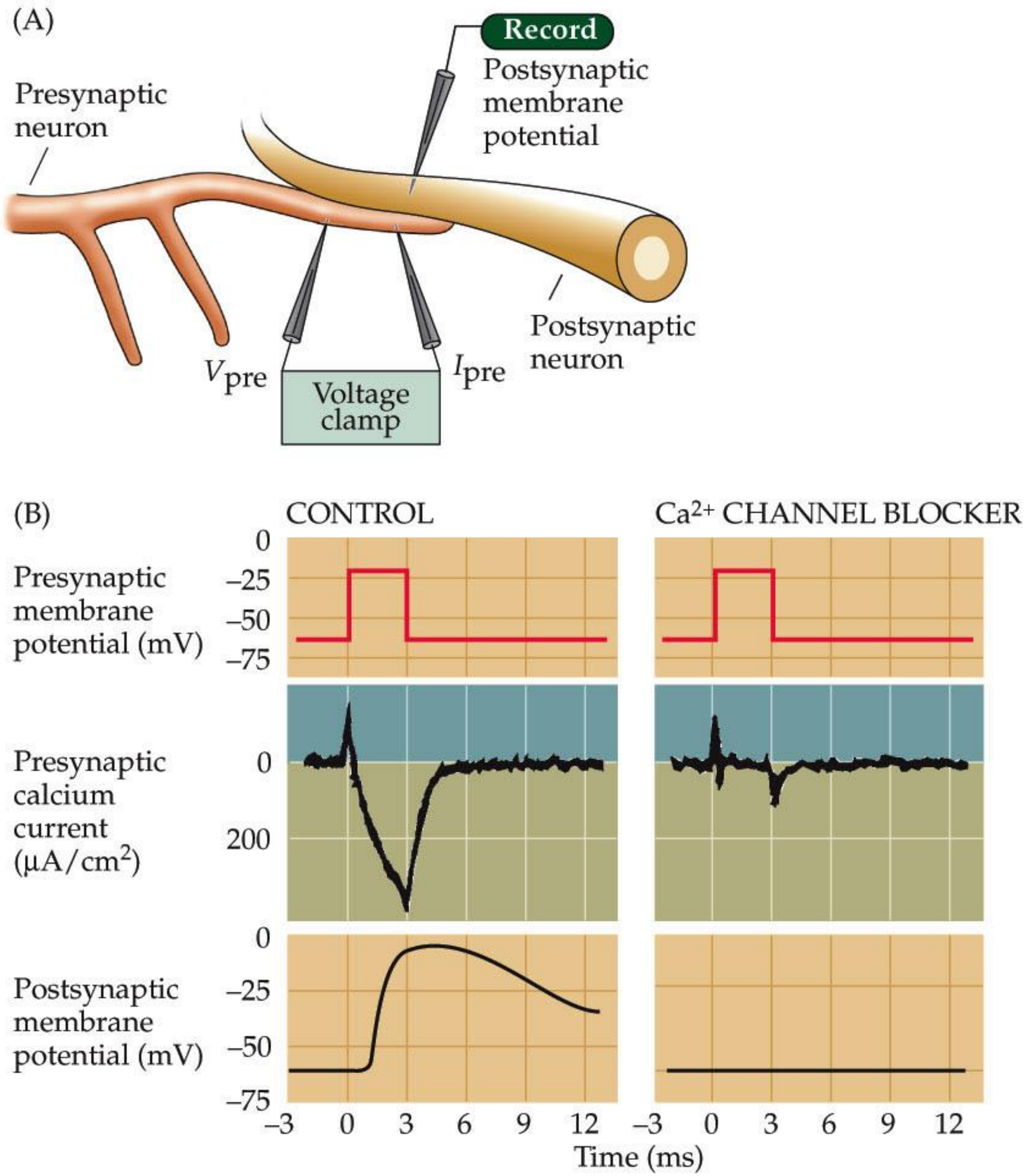
Figure 5.10 Ca^{2+} entry through the specific voltage-dependent calcium channels in the presynaptic terminals causes transmitter release



NEUROSCIENCE, Fourth Edition, Figure 5.10

Figure 5.10 Ca^{2+} entry through the specific voltage-dependent calcium channels in the presynaptic terminals causes transmitter release (Part 1)

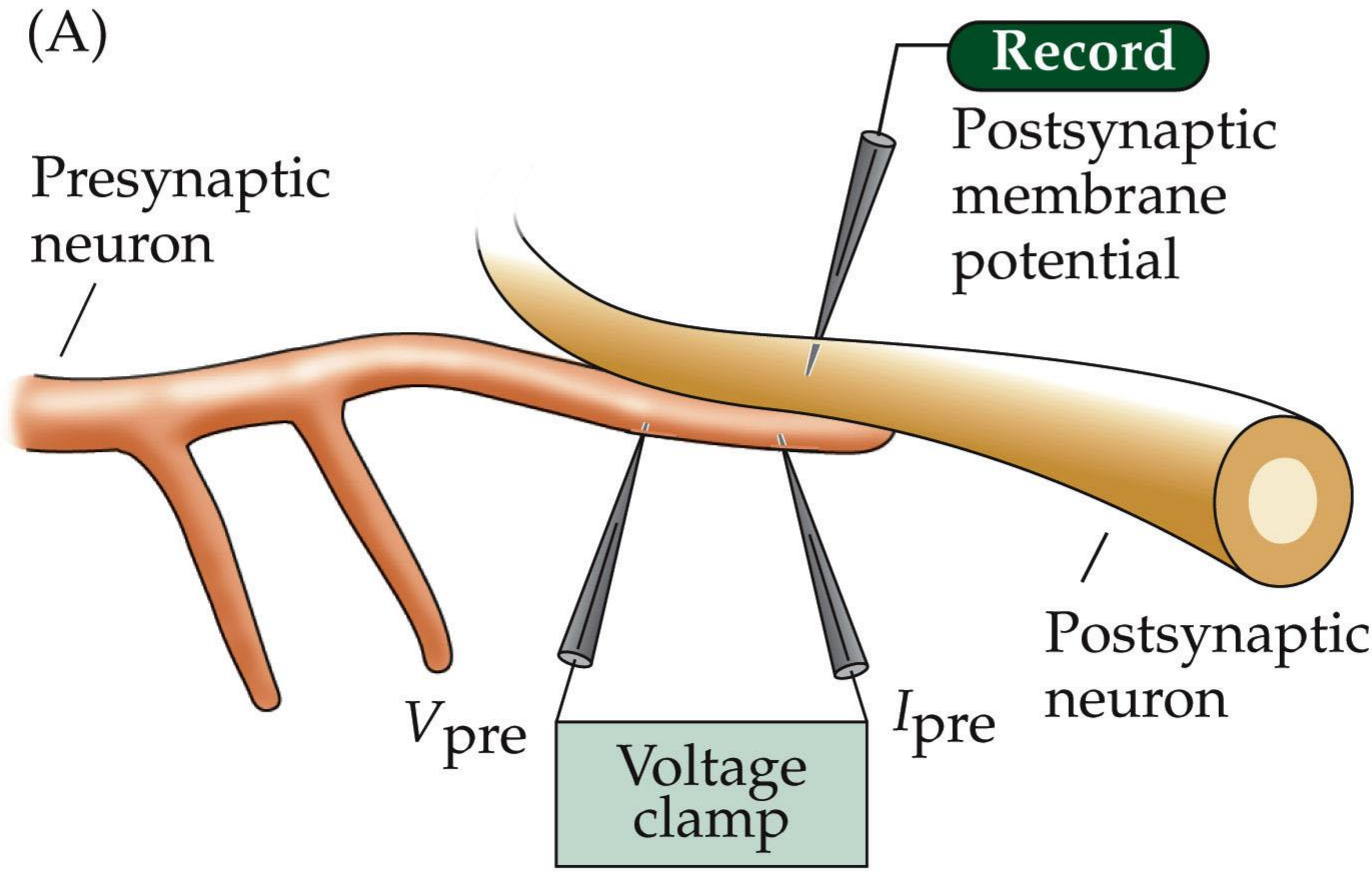
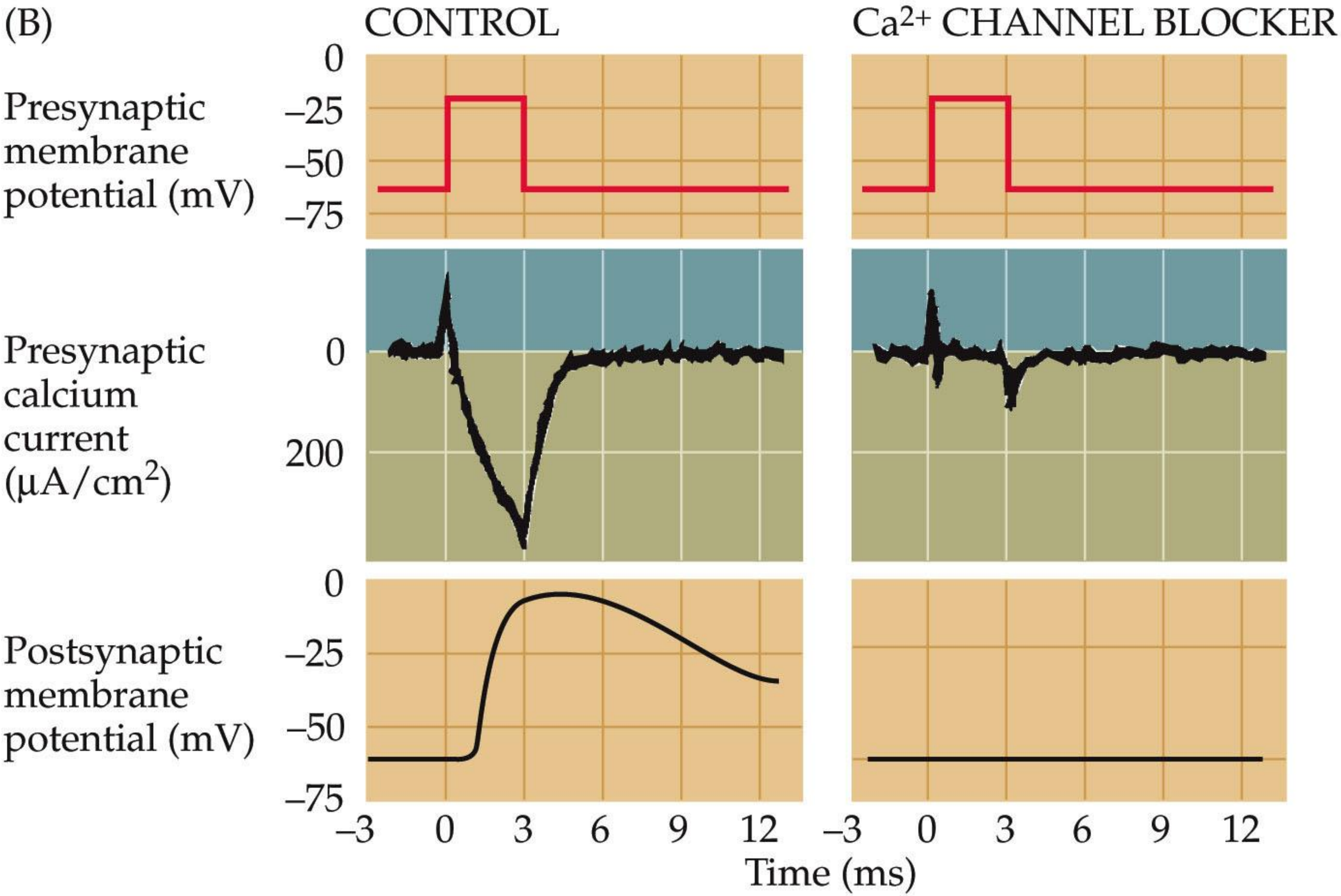


Figure 5.10 Ca^{2+} entry through the specific voltage-dependent calcium channels in the presynaptic terminals causes transmitter release (Part 2)



NEUROSCIENCE, Fourth Edition, Figure 5.10 (Part 2)

Figure 5.11 Evidence that a rise in presynaptic Ca^{2+} concentration triggers transmitter release from presynaptic terminals

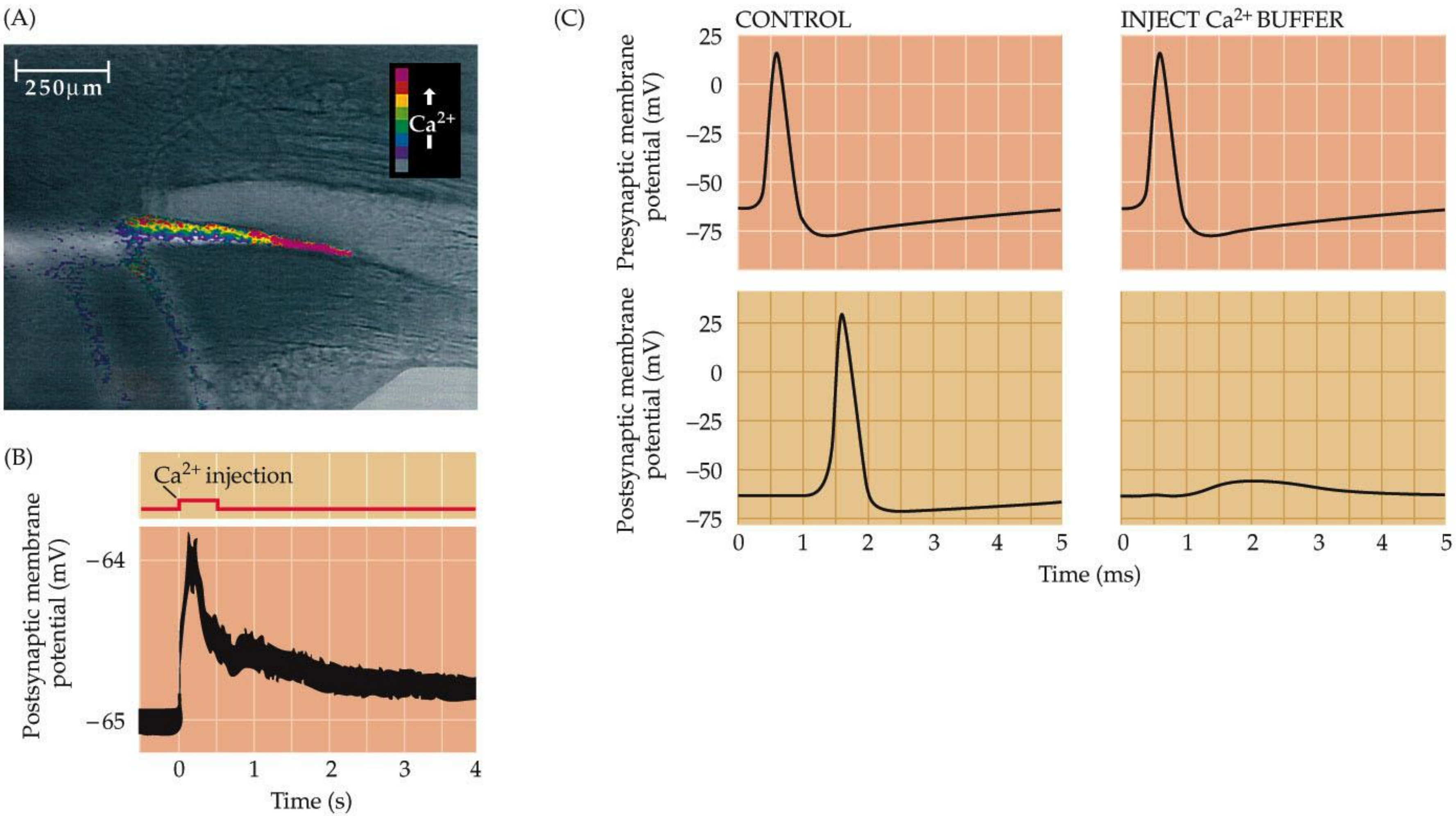


Figure 5.11 Evidence that a rise in presynaptic Ca^{2+} concentration triggers transmitter release from presynaptic terminals (Part 1)

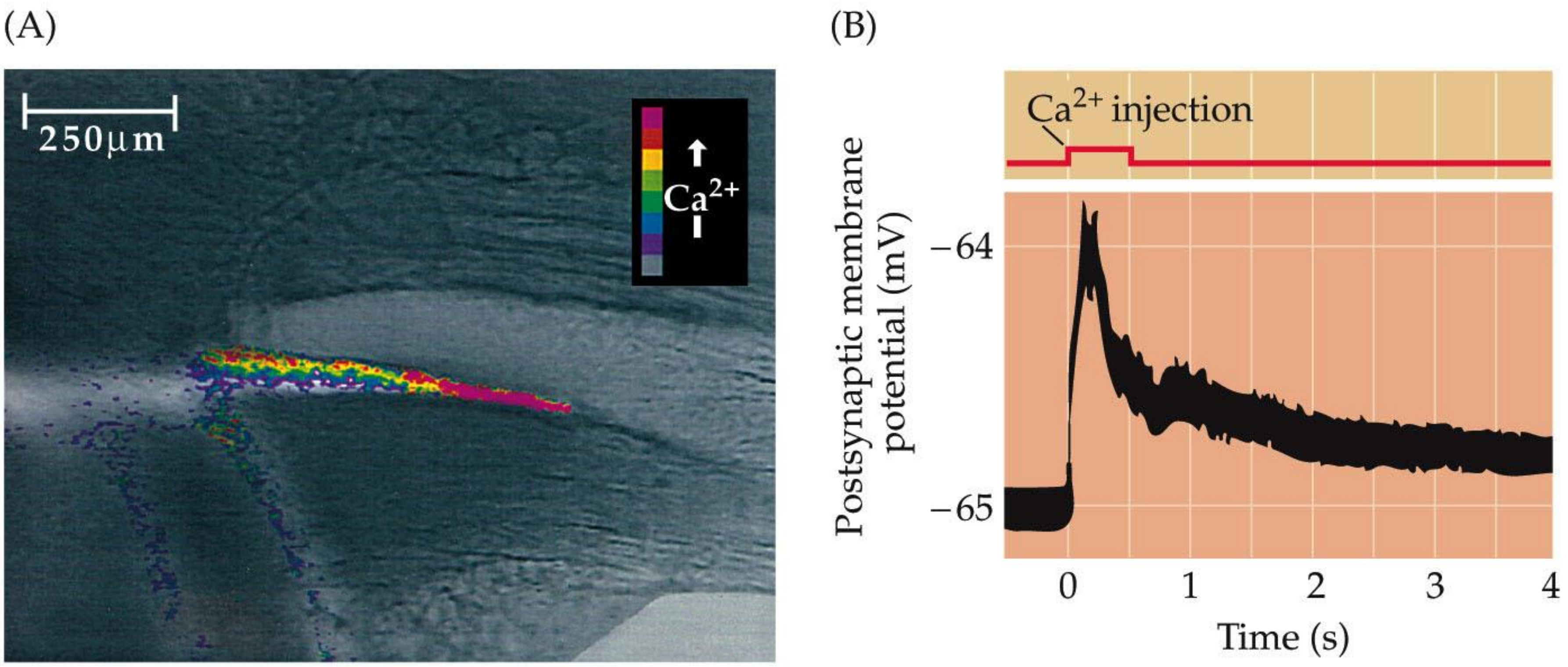
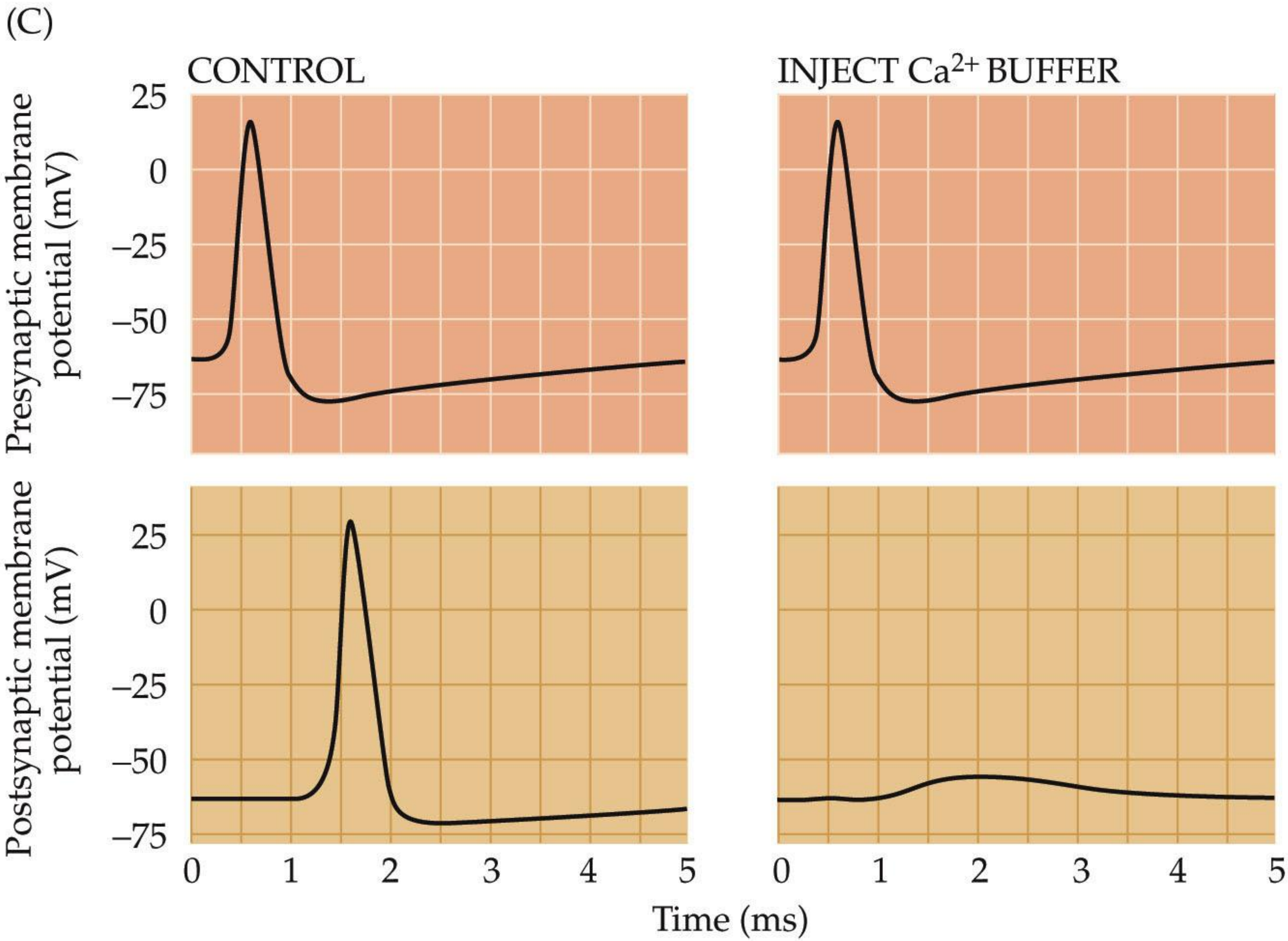
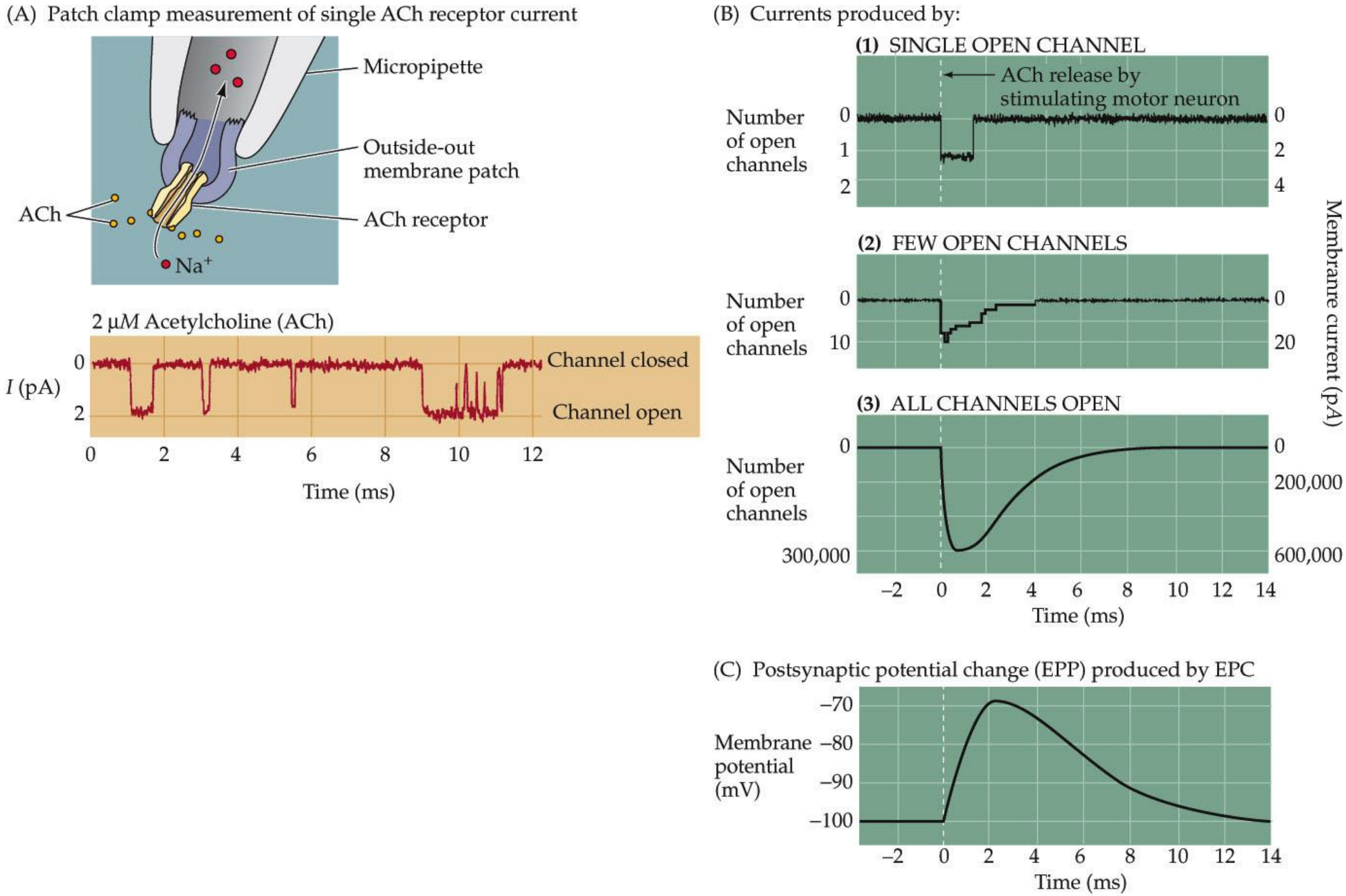


Figure 5.11 Evidence that a rise in presynaptic Ca^{2+} concentration triggers transmitter release from presynaptic terminals (Part 2)

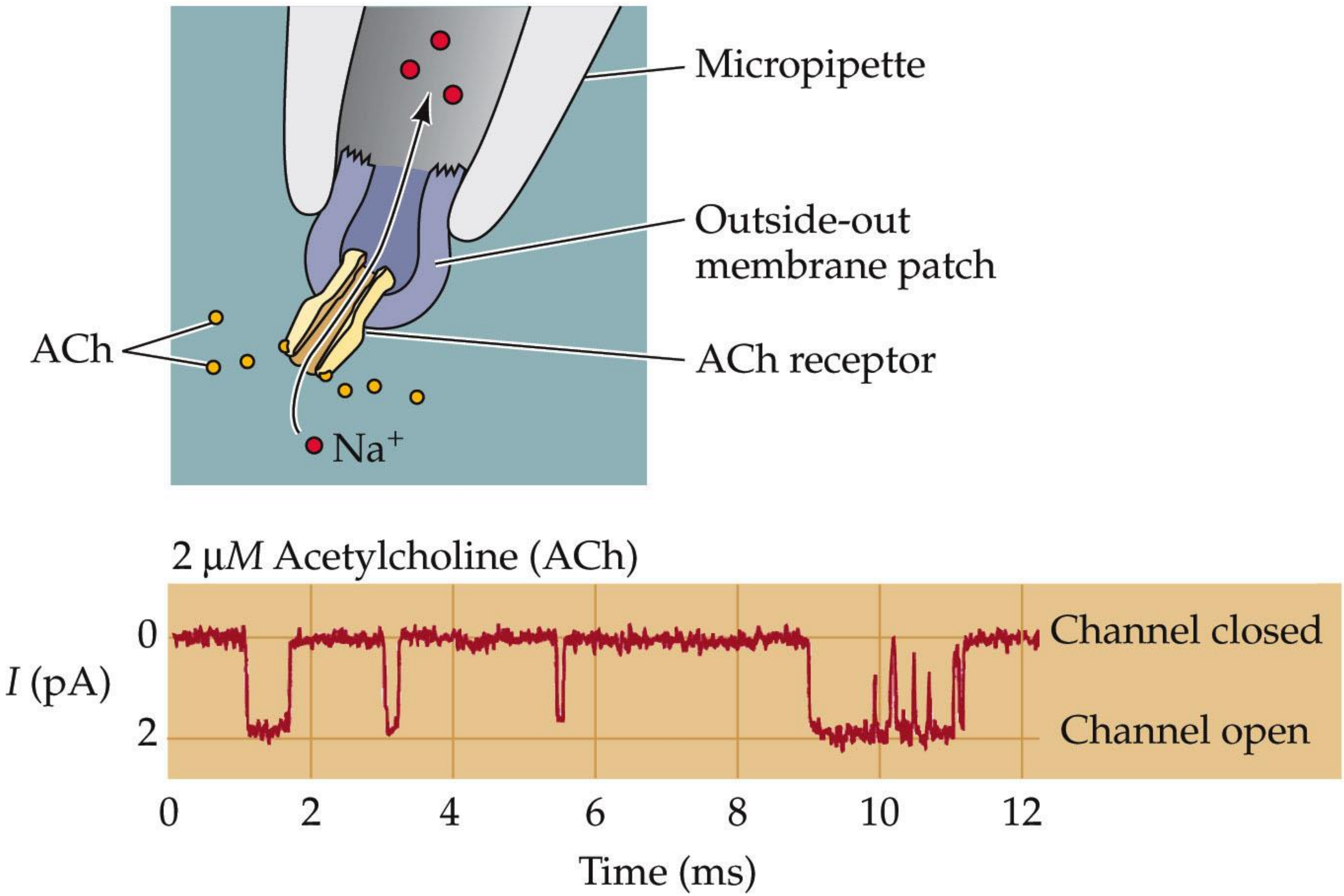


NEUROSCIENCE, Fourth Edition, Figure 5.11 (Part 2)

Figure 5.16 Activation of ACh receptors at neuromuscular synapses

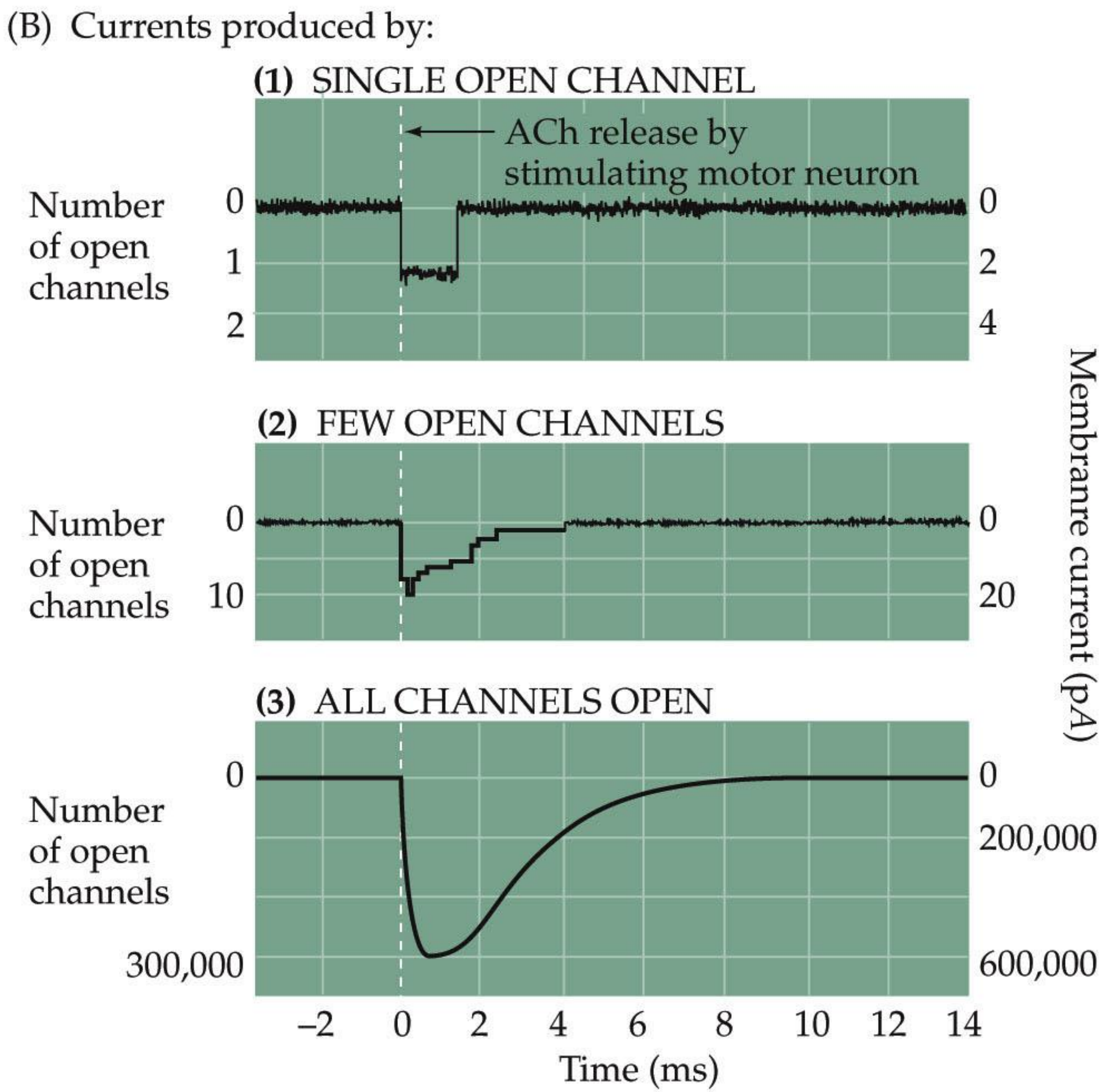


(A) Patch clamp measurement of single ACh receptor current



***NEUROSCIENCE*, *Fourth Edition*, Figure 5.16 (Part 1)**

Figure 5.16 Activation of ACh receptors at neuromuscular synapses (Part 2)



NEUROSCIENCE, Fourth Edition, Figure 5.16 (Part 2)

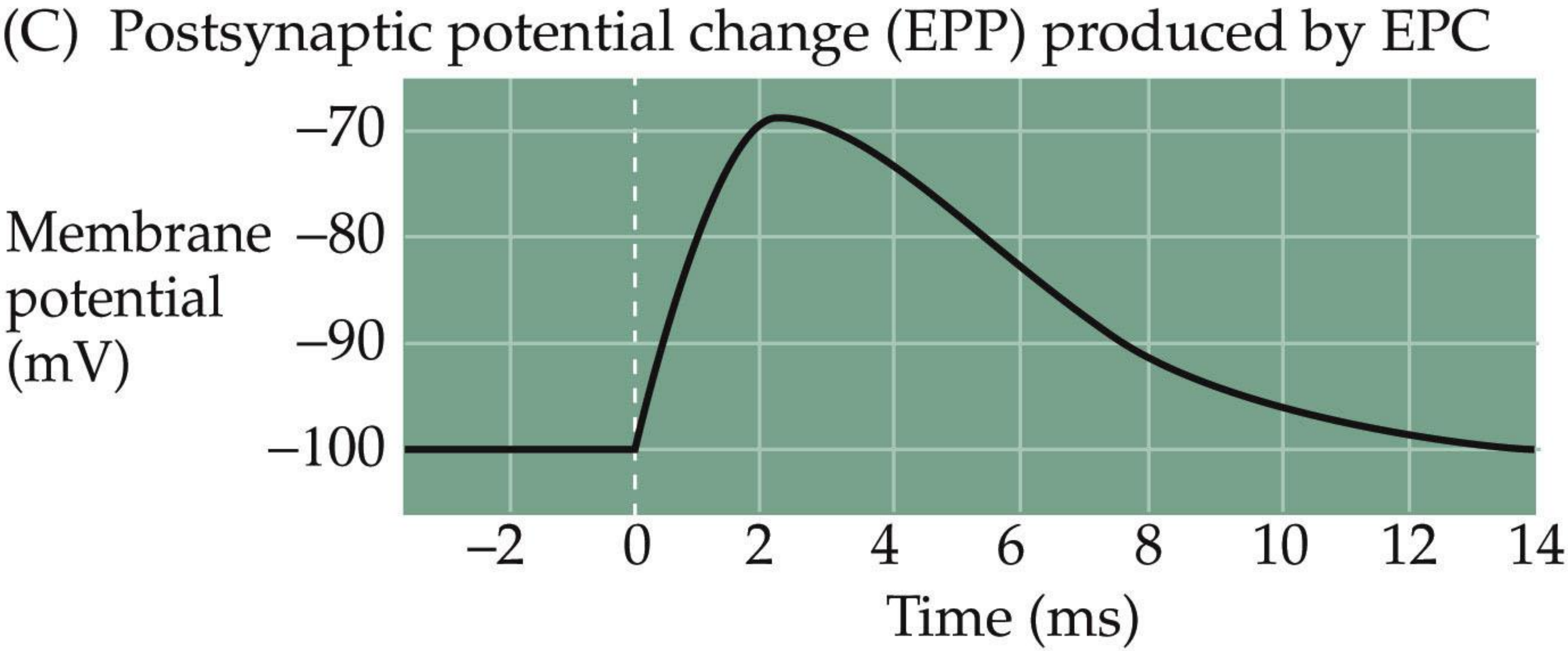
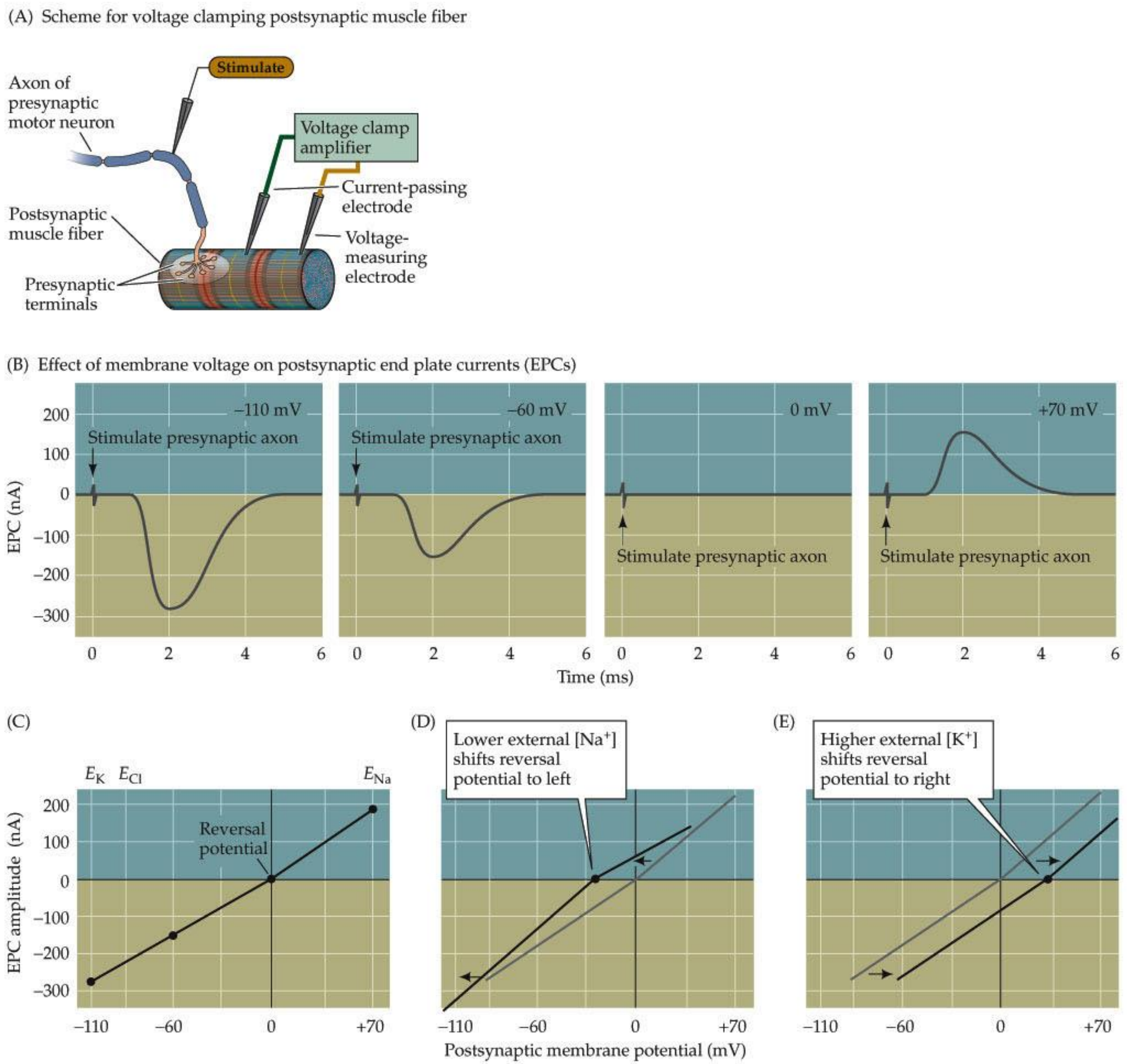

(C) Postsynaptic potential change (EPP) produced by EPC
Membrane potential (mV)
–70
–80
–90
–100
–2
0
2
4
6
8
10
12
14
Time (ms)

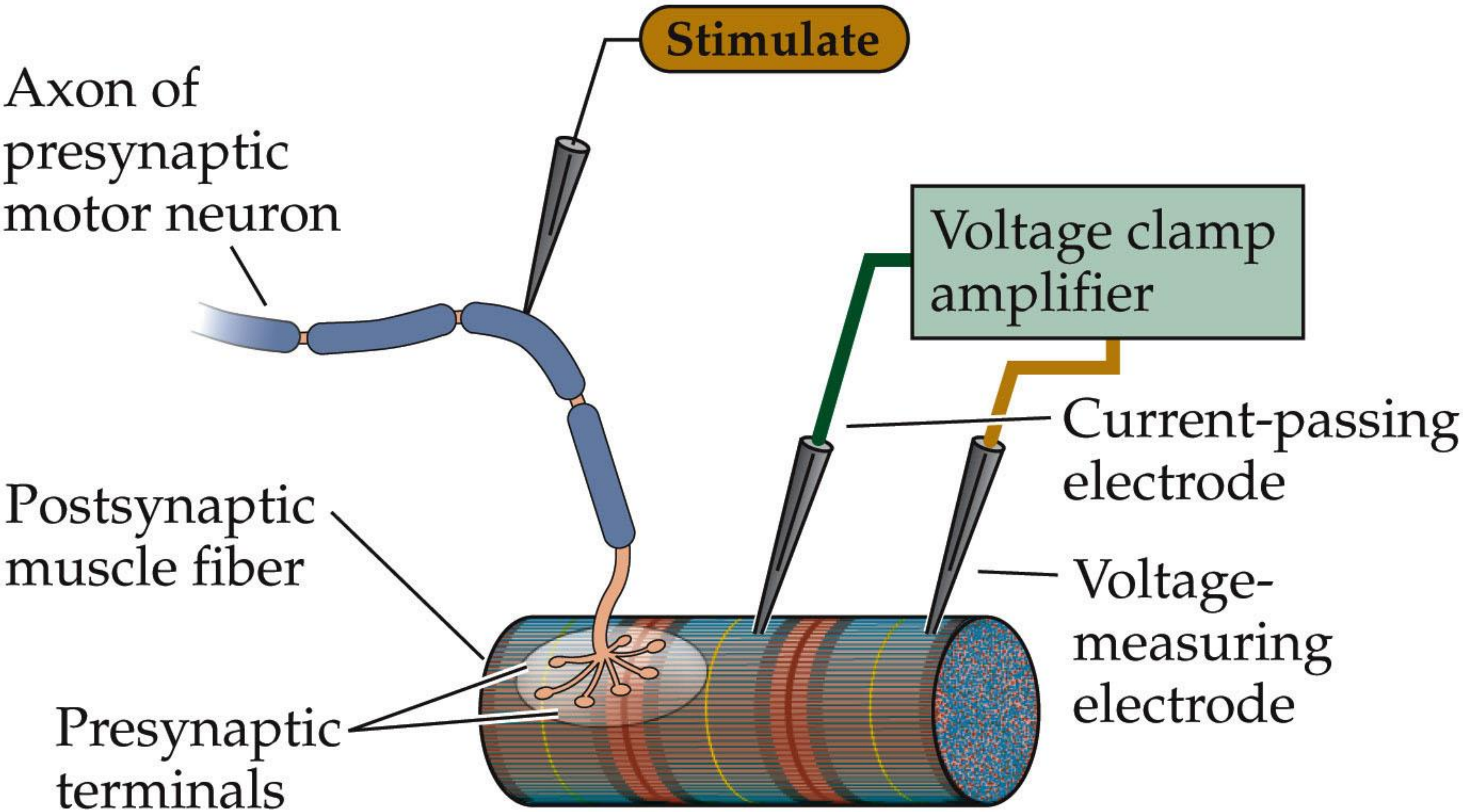
Figure 5.17 The influence of the postsynaptic membrane potential on end plate currents



NEUROSCIENCE, Fourth Edition, Figure 5.17

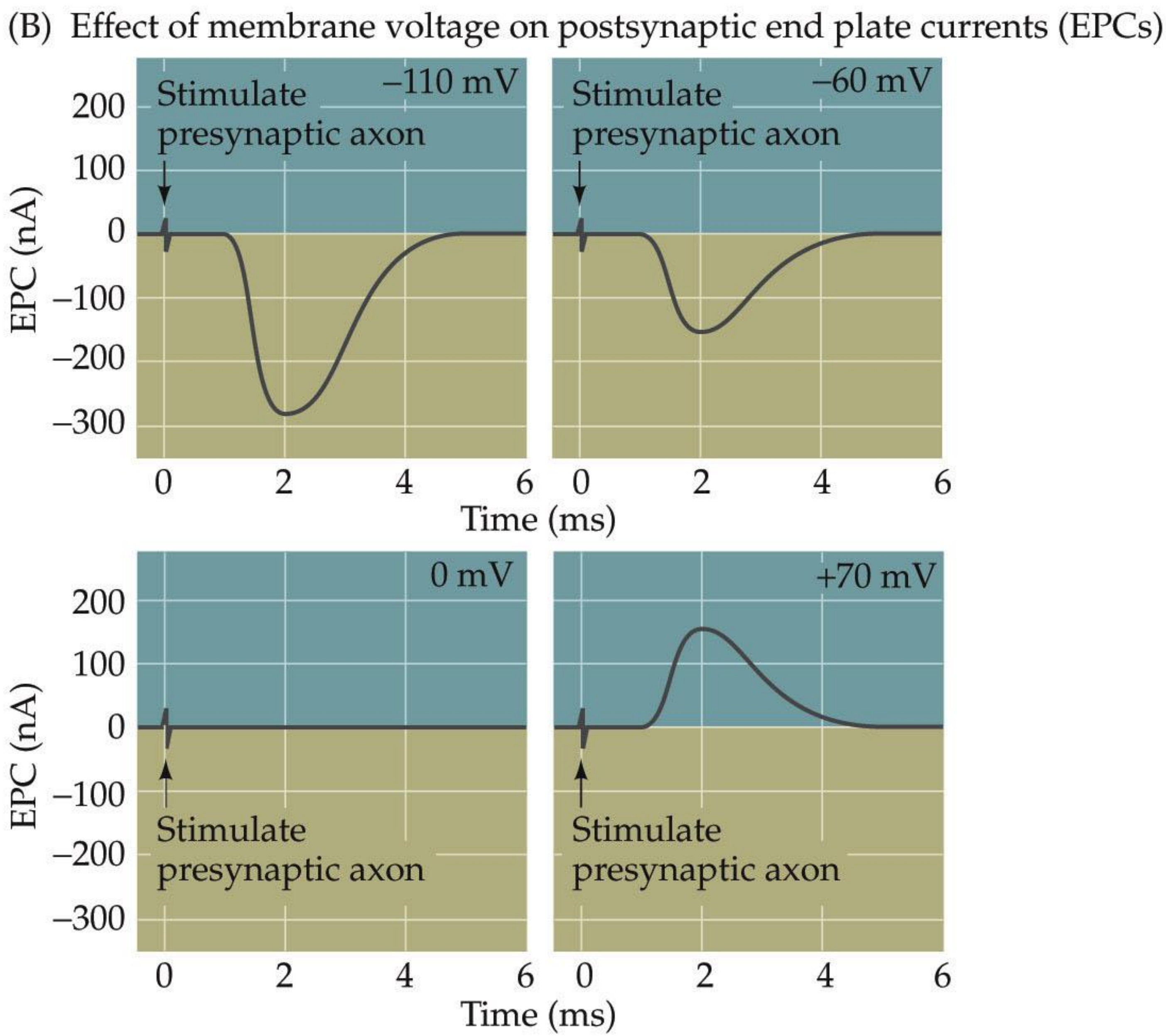
Figure 5.17 The influence of the postsynaptic membrane potential on end plate currents (Part 1)

(A) Scheme for voltage clamping postsynaptic muscle fiber



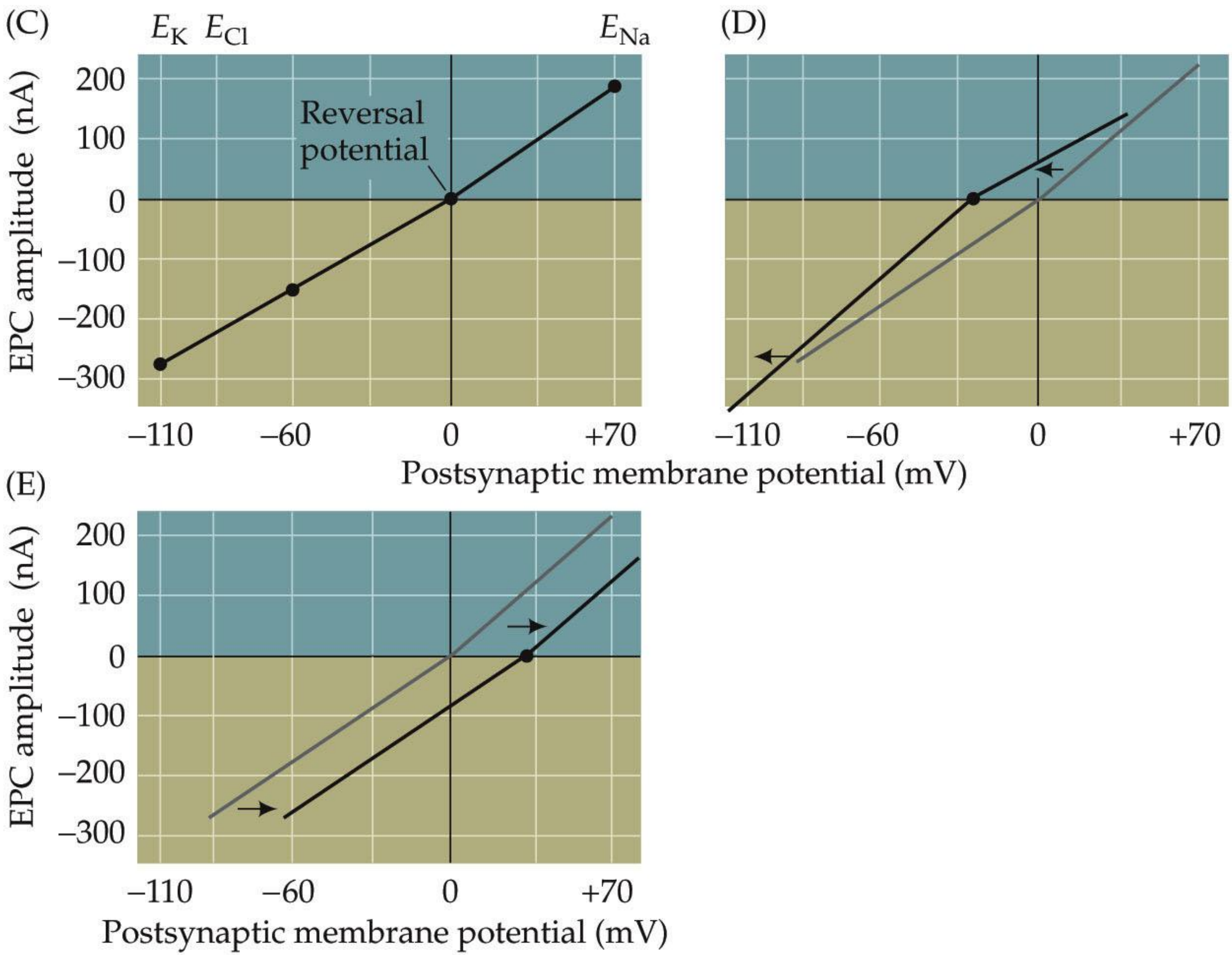
NEUROSCIENCE, Fourth Edition, Figure 5.17 (Part 1)

Figure 5.17 The influence of the postsynaptic membrane potential on end plate currents (Part 2)



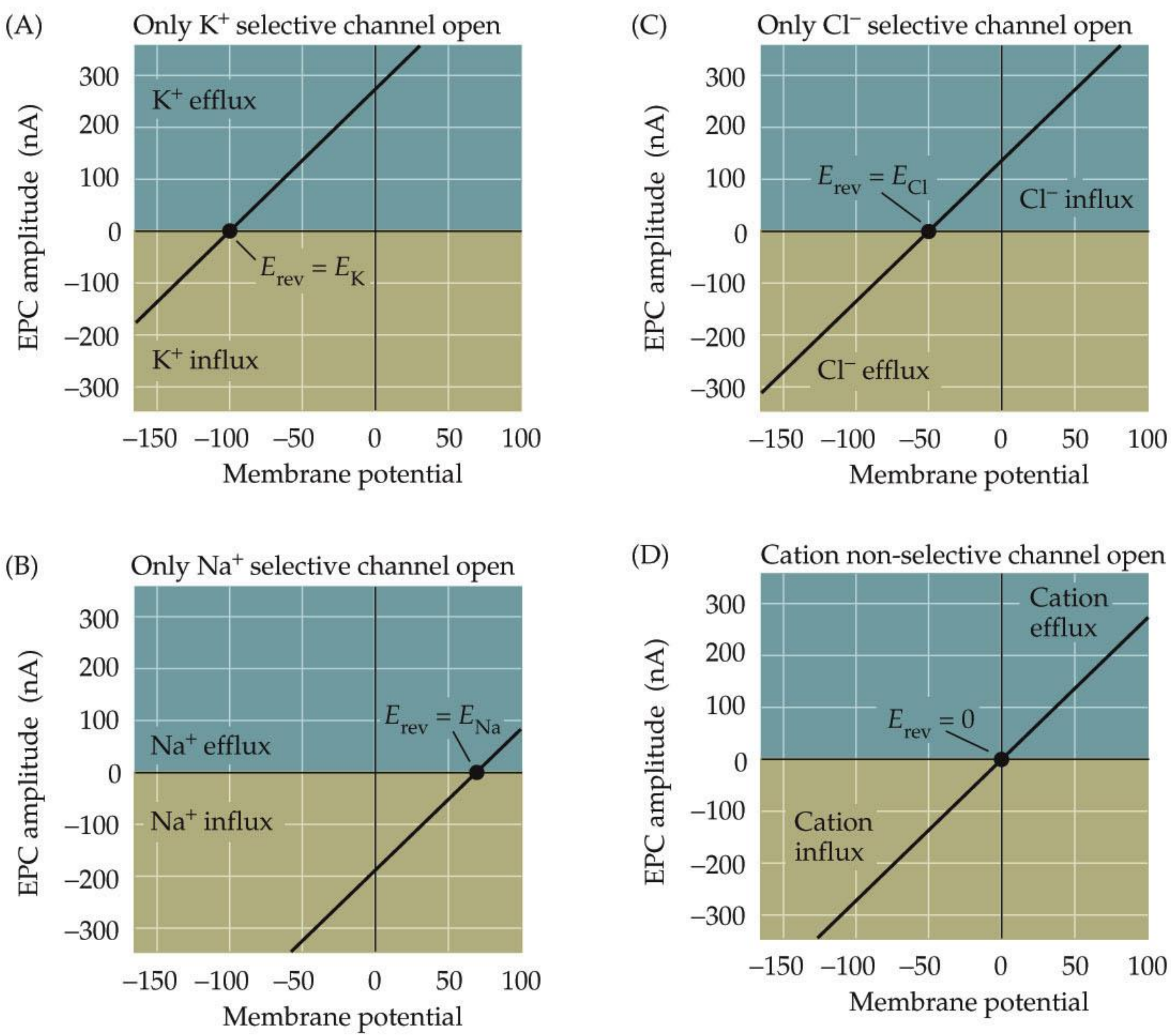
NEUROSCIENCE, _Fourth Edition_, Figure 5.17 (Part 2)

Figure 5.17 The influence of the postsynaptic membrane potential on end plate currents (Part 3)

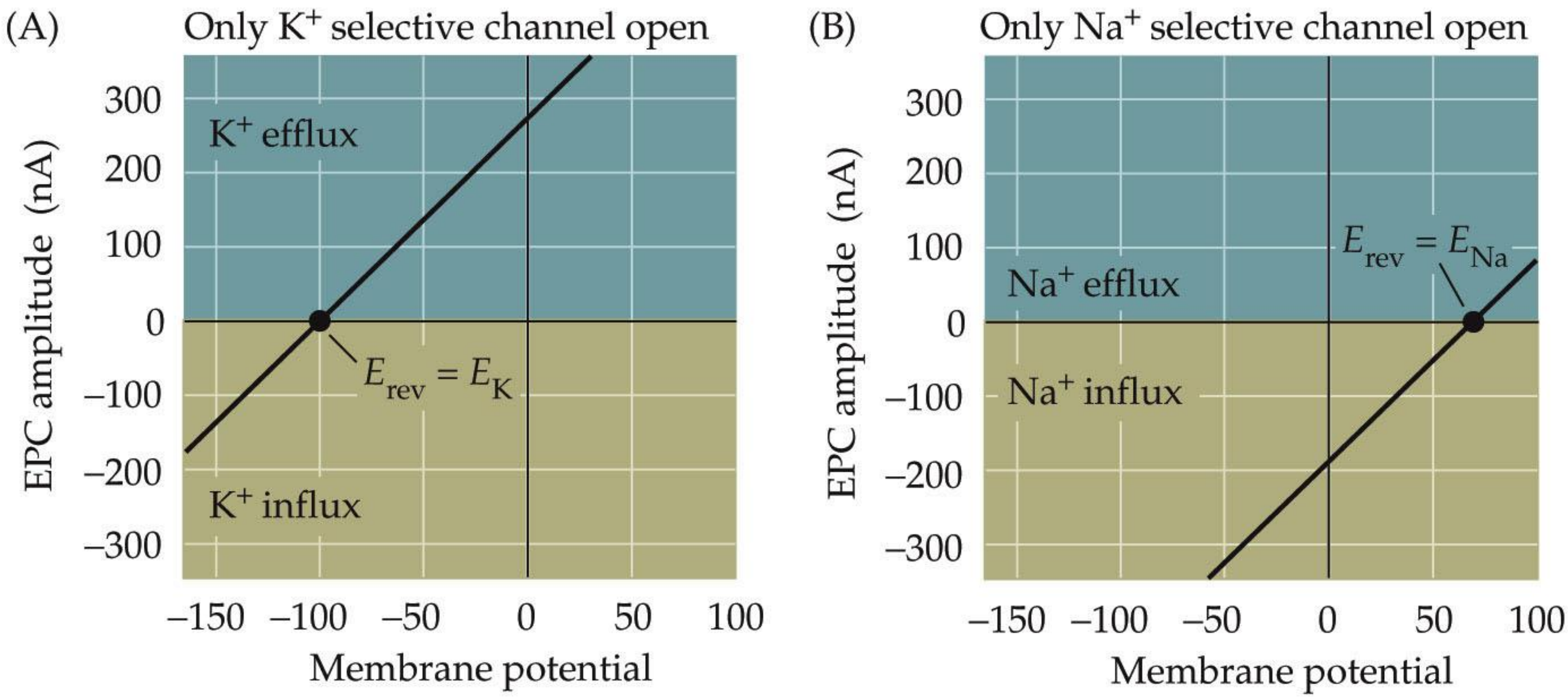


NEUROSCIENCE, Fourth Edition, Figure 5.17 (Part 3)

Figure 5.18 The effect of ion channel selectivity on the reversal potential



NEUROSCIENCE, Fourth Edition, Figure 5.18


(A)
Only K+ selective channel open
K+ efflux
K+ influx
$E_{rev} = E_K$
EPC amplitude (nA)
300
200
100
0
–100
–200
–300
–150
–100
–50
0
50
100
Membrane potential
(B)
Only Na+ selective channel open
Na+ efflux
Na+ influx
$E_{rev} = E_{Na}$
EPC amplitude (nA)
300
200
100
0
–100
–200
–300
–150
–100
–50
0
50
100
Membrane potential

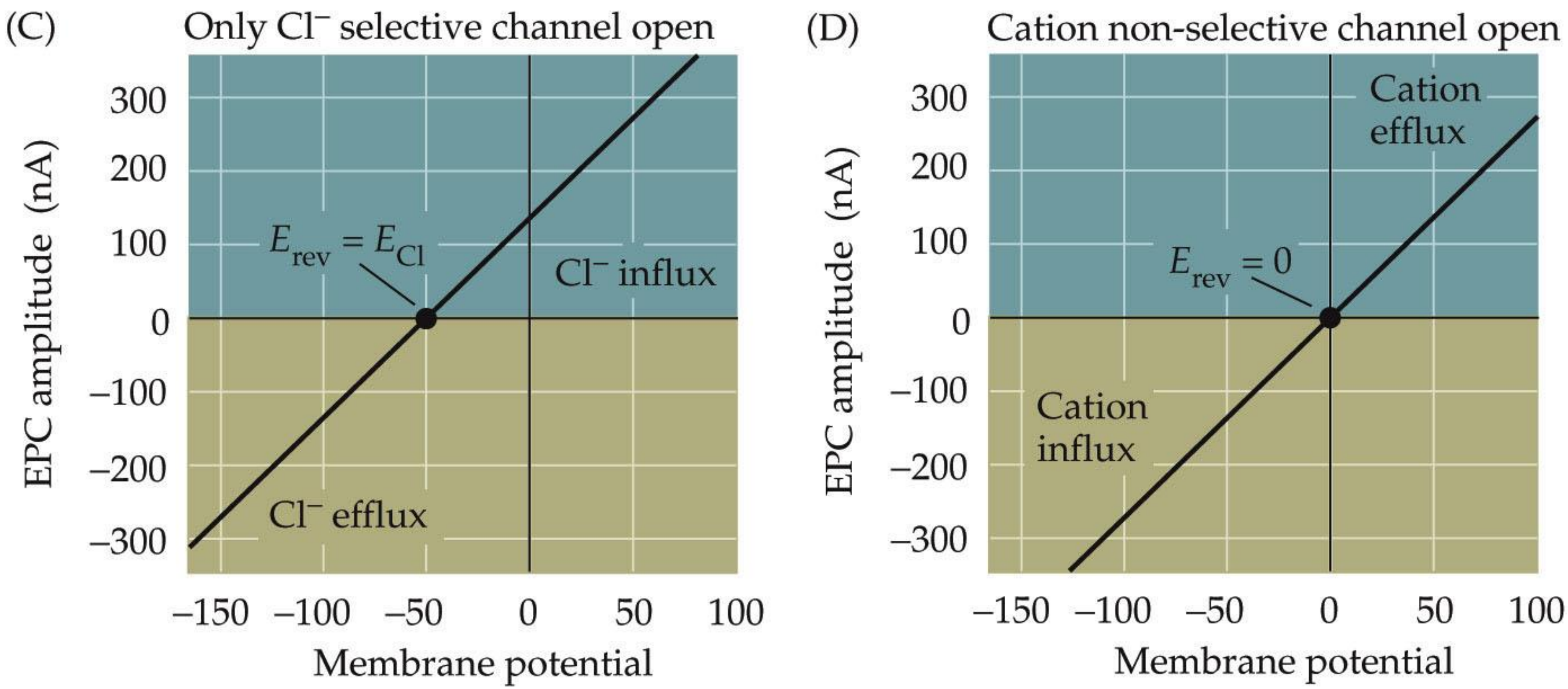
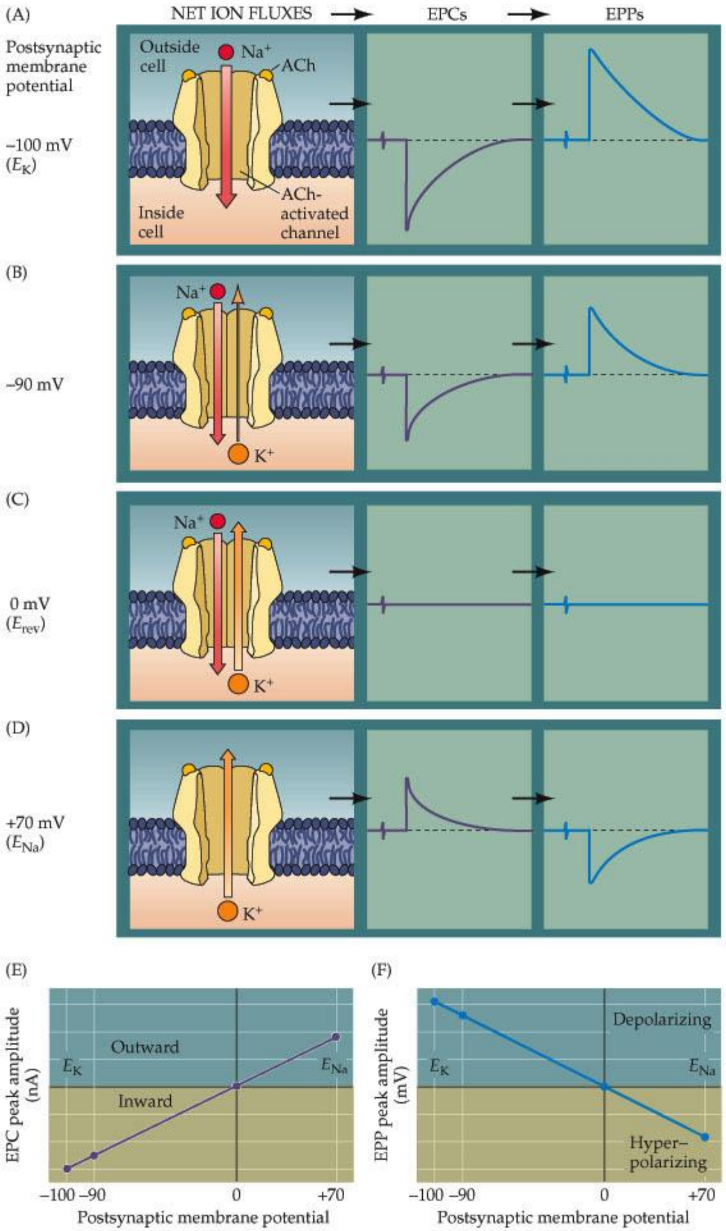
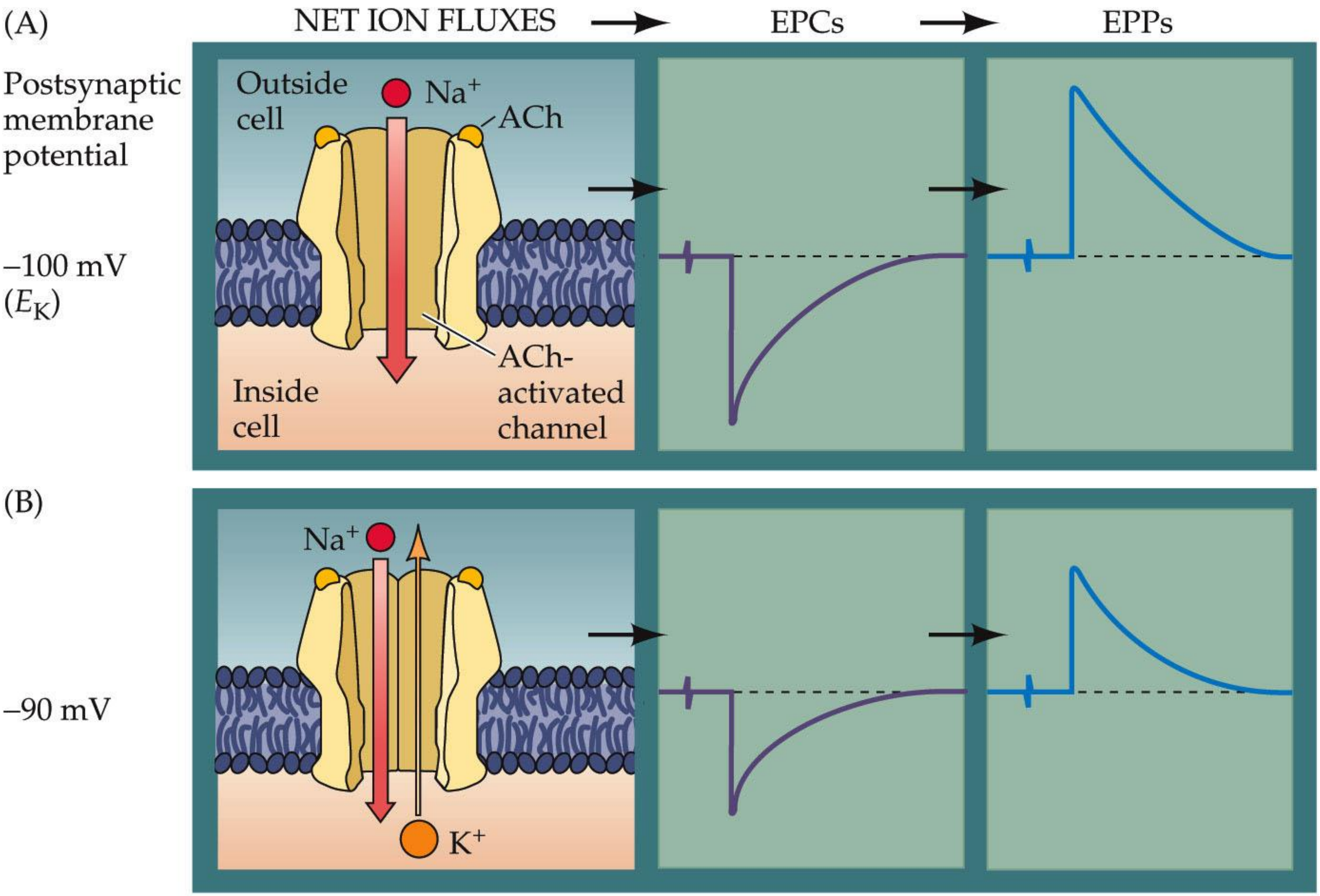

(C)
Only Cl⁻ selective channel open
EPC amplitude (nA)
300
200
100
0
–100
–200
–300
$E_{rev} = E_{Cl}$
Cl⁻ influx
Cl⁻ efflux
–150
–100
–50
0
50
100
Membrane potential
(D)
Cation non-selective channel open
EPC amplitude (nA)
300
200
100
0
–100
–200
–300
Cation efflux
$E_{rev} = 0$
Cation influx
–150
–100
–50
0
50
100
Membrane potential

Figure 5.19 Na+ and K+ movements during EPCs and EPPs



NEUROSCIENCE, Fourth Edition, Figure 5.19

Figure 5.19 Na+ and K+ movements during EPCs and EPPs (Part 1)



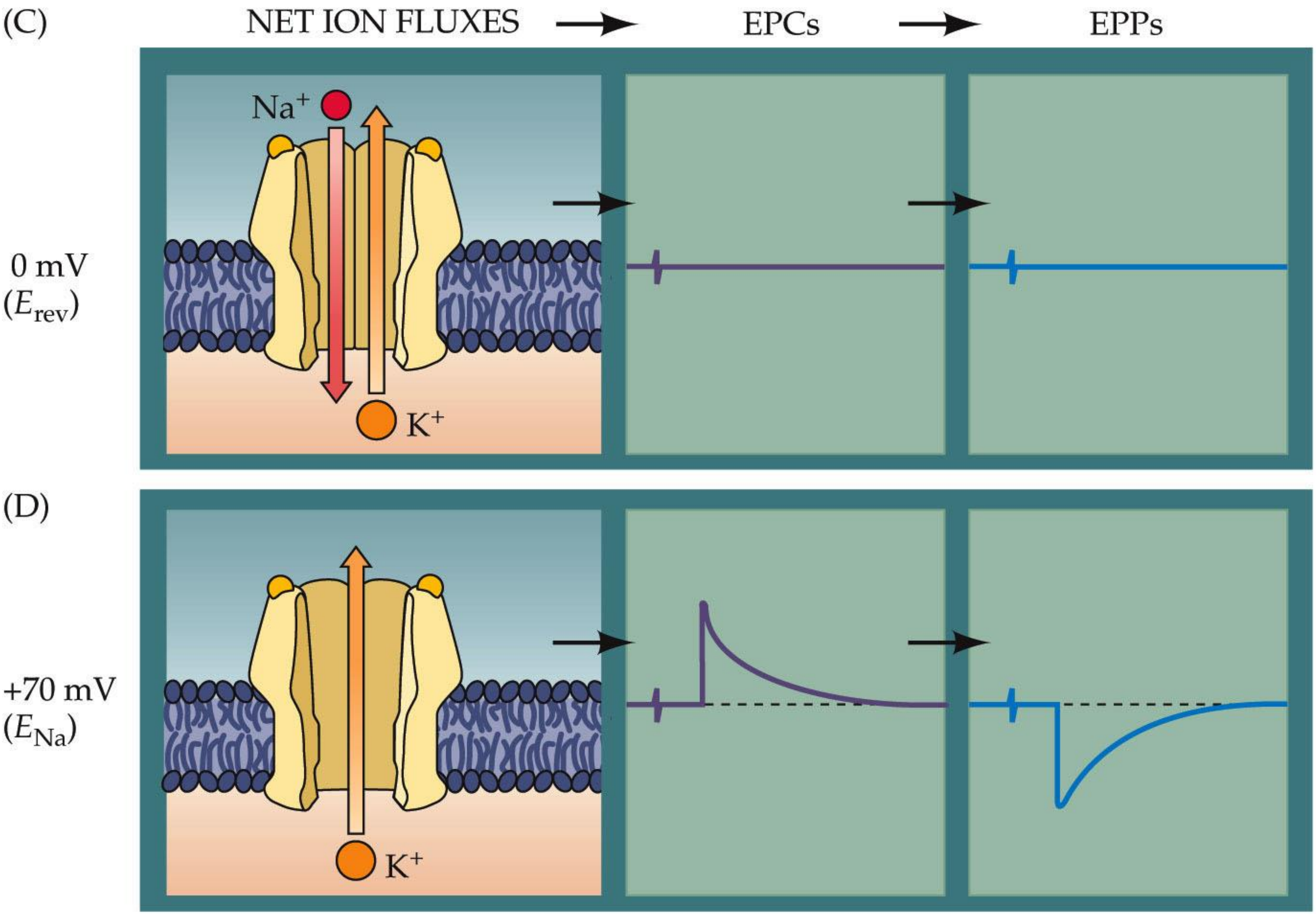

(C)
NET ION FLUXES
EPCs
EPPs
Na+
K+
0 mV
(E rev)
(D)
K+
+70 mV
(E Na)

Figure 5.19 Na⁺ and K⁺ movements during EPCs and EPPs (Part 3)

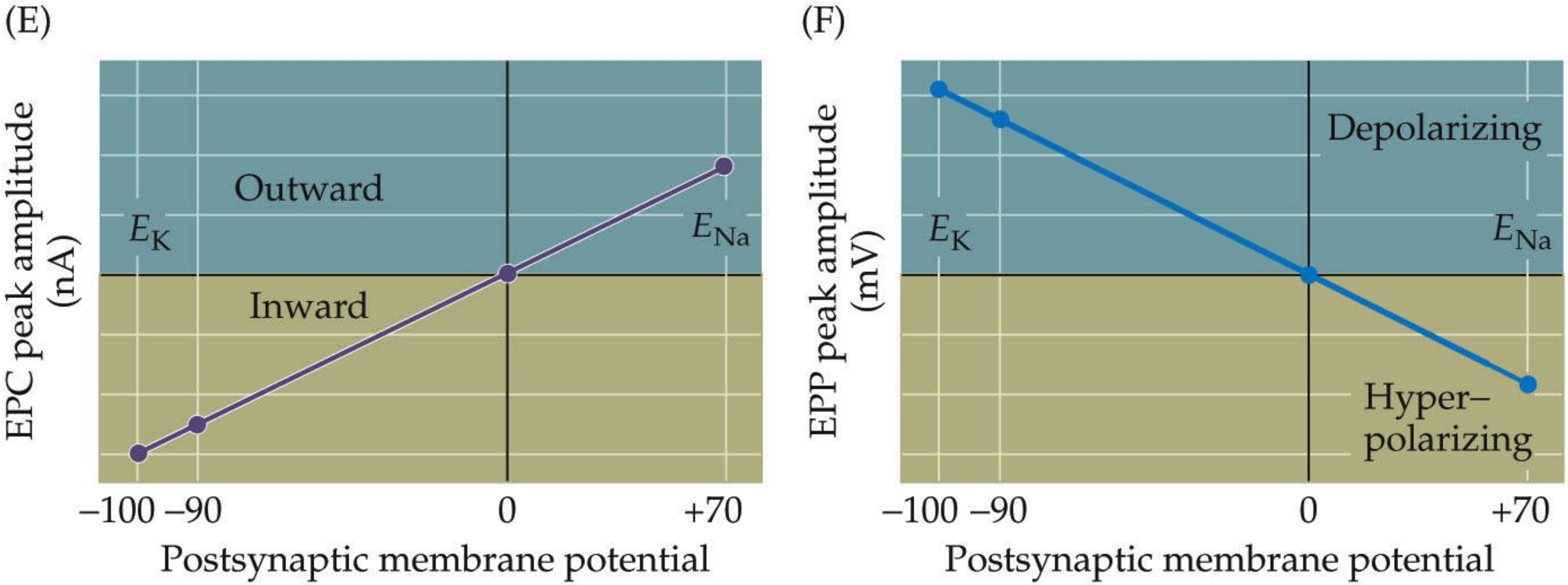


Figure 5.20 Reversal and threshold potentials determine postsynaptic excitation and inhibition

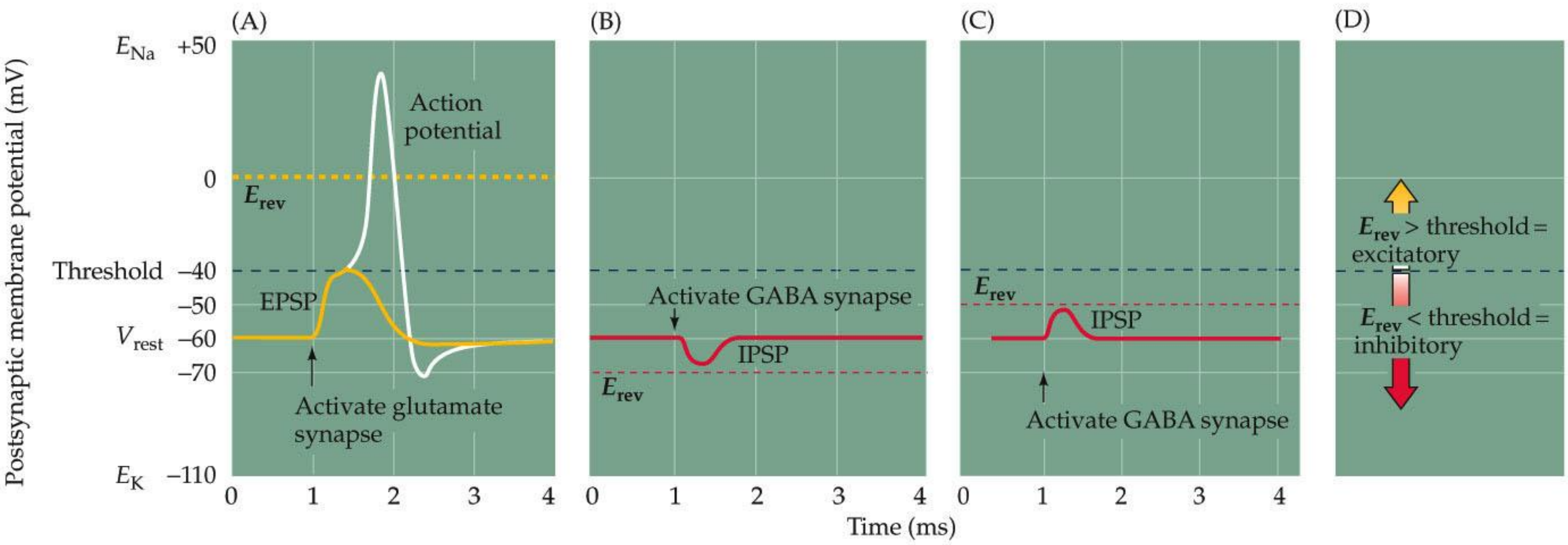


Figure 5.20 Reversal & threshold potentials determine postsynaptic excitation & inhibition (Part 1)

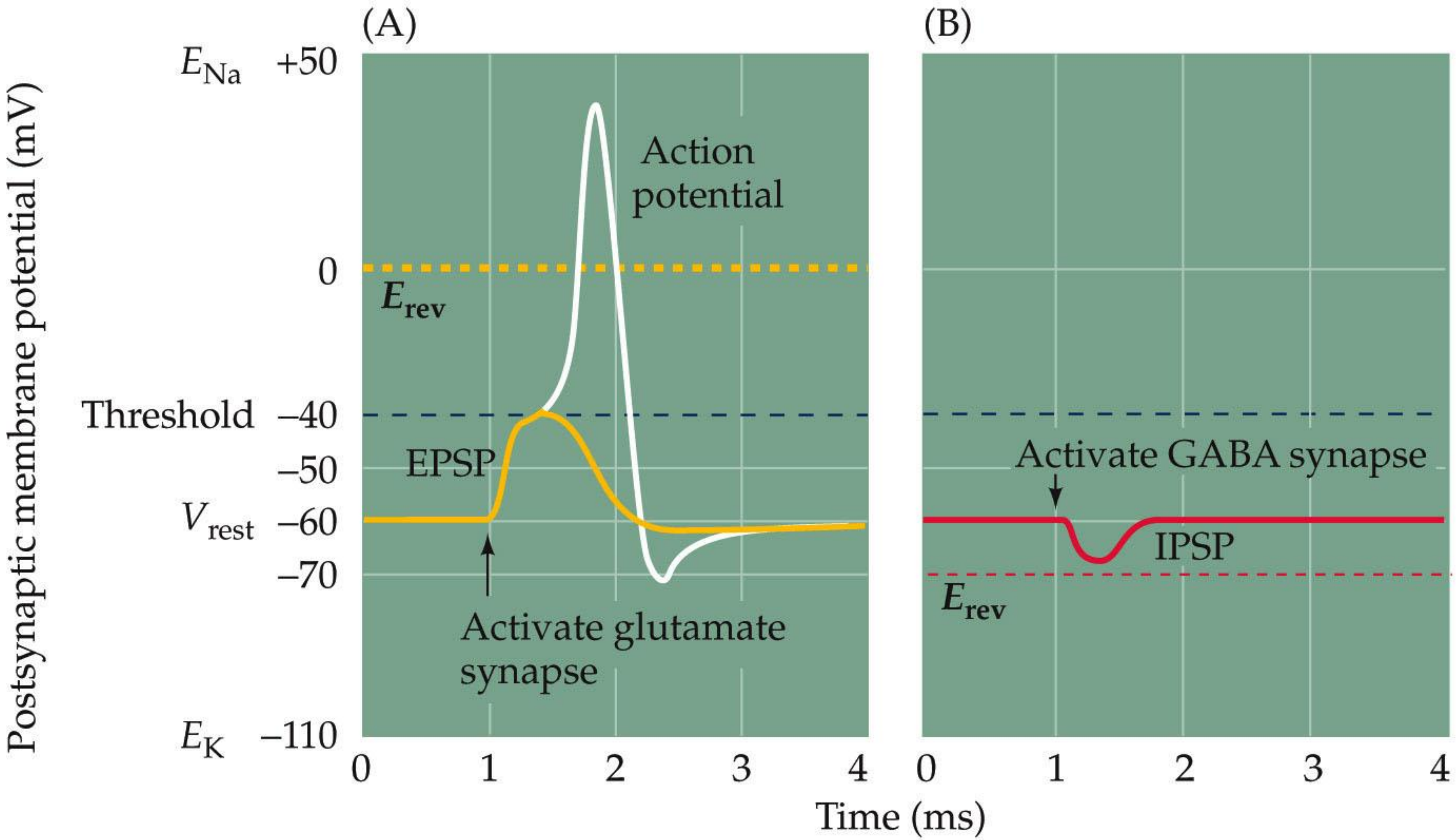


Figure 5.20 Reversal & threshold potentials determine postsynaptic excitation & inhibition (Part 2)

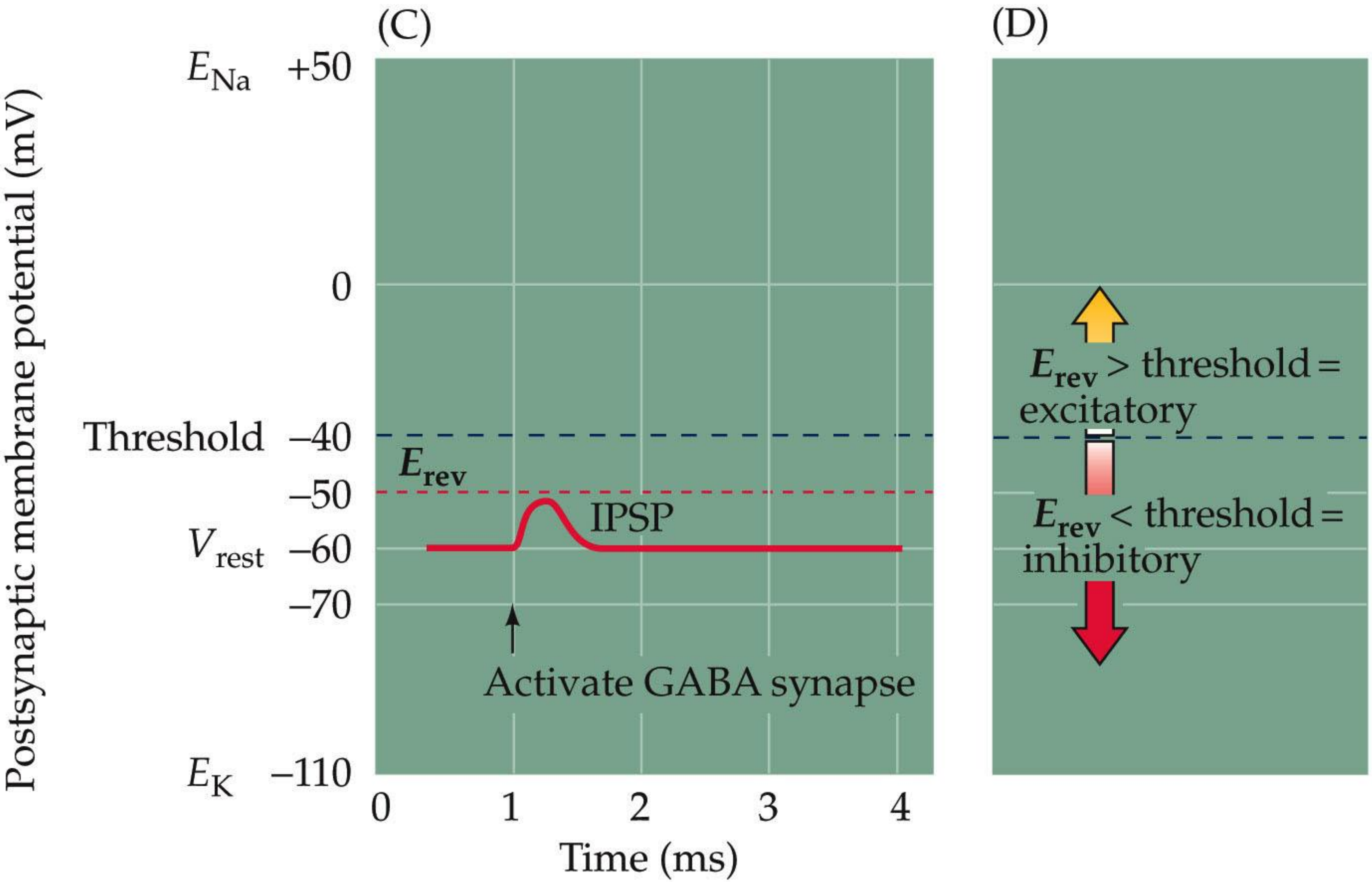
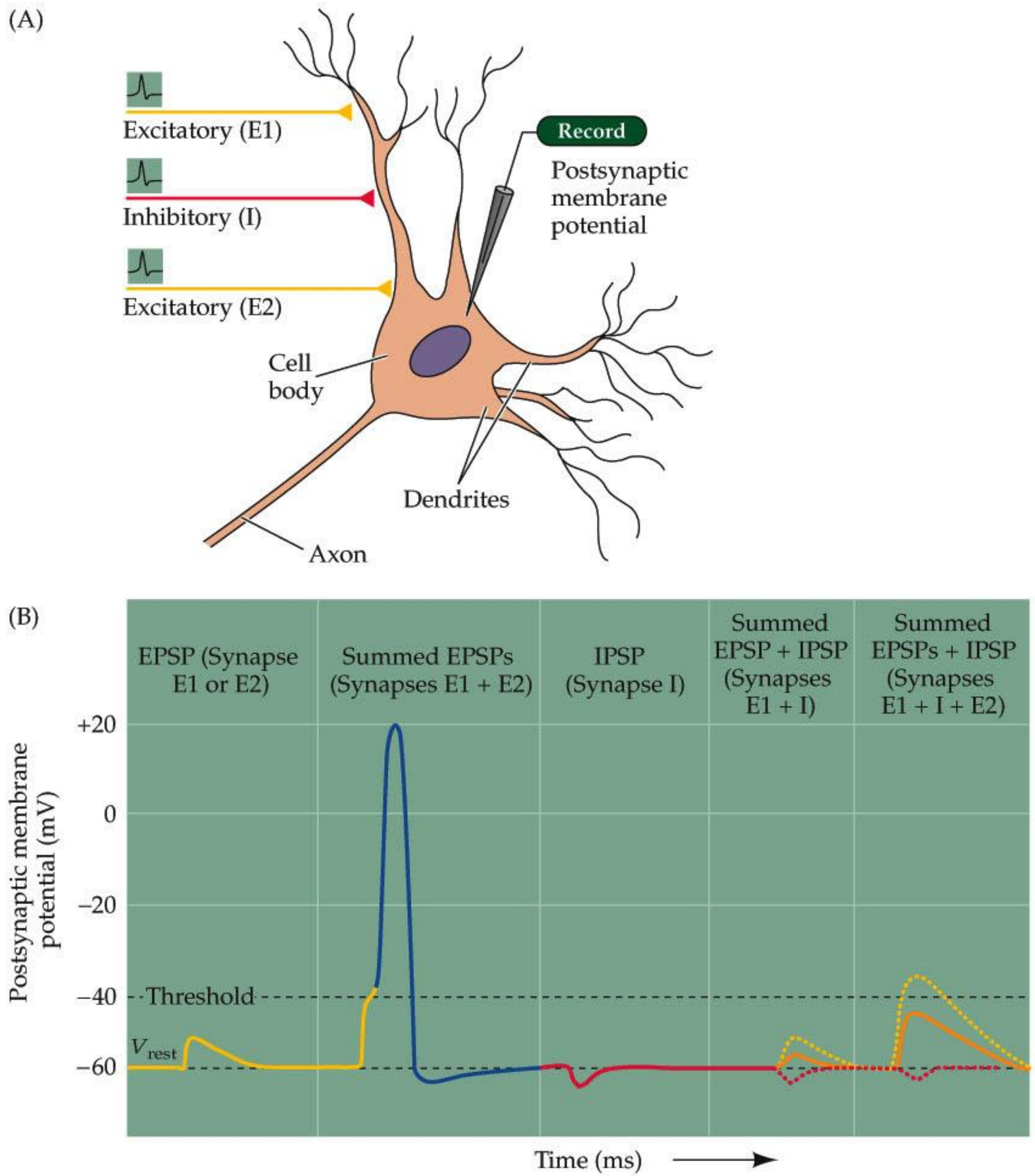
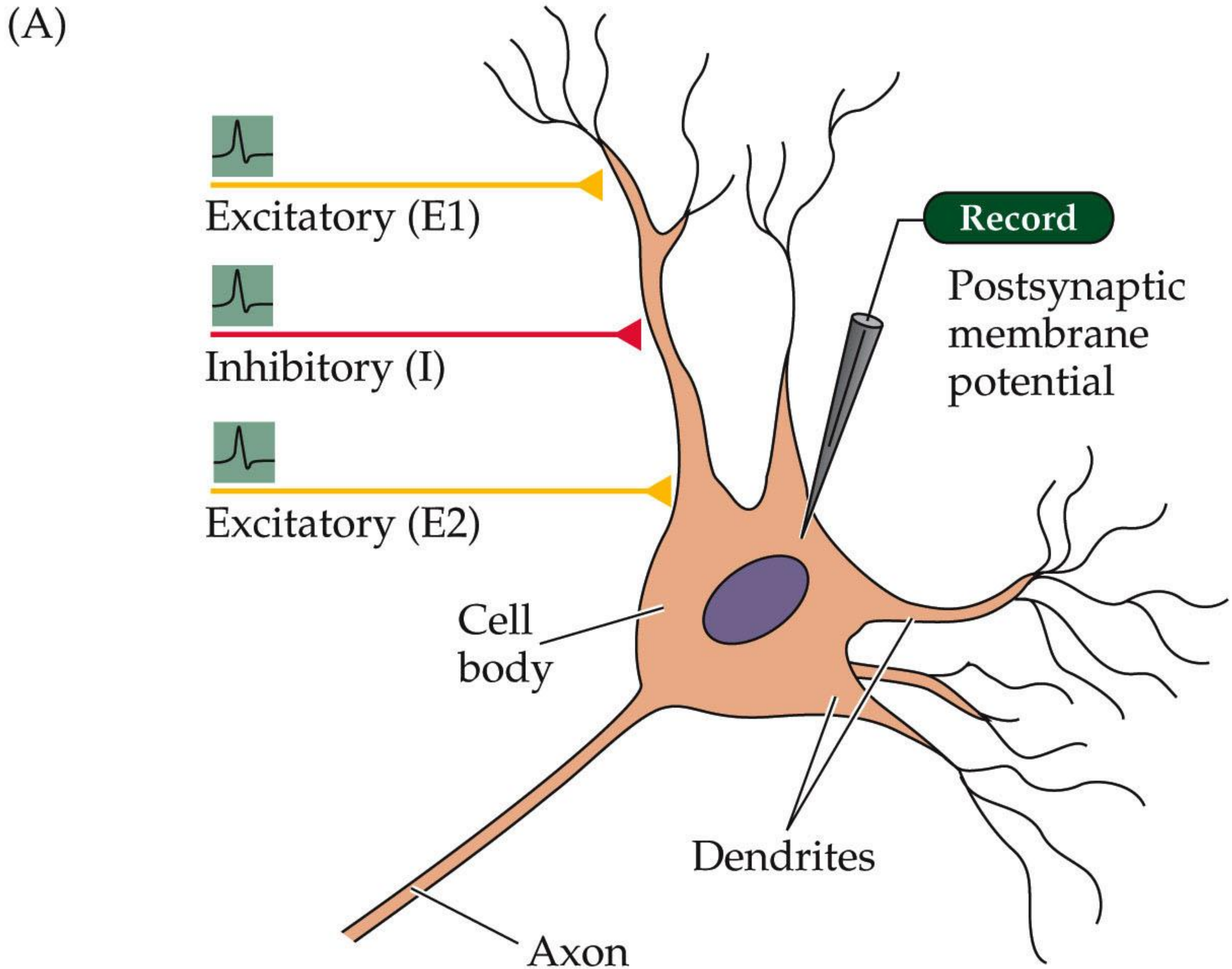


Figure 5.21 Summation of postsynaptic potentials



NEUROSCIENCE, Fourth Edition, Figure 5.21


(A)
Excitatory (E1)
Inhibitory (I)
Excitatory (E2)
Record
Postsynaptic membrane potential
Cell body
Dendrites
Axon

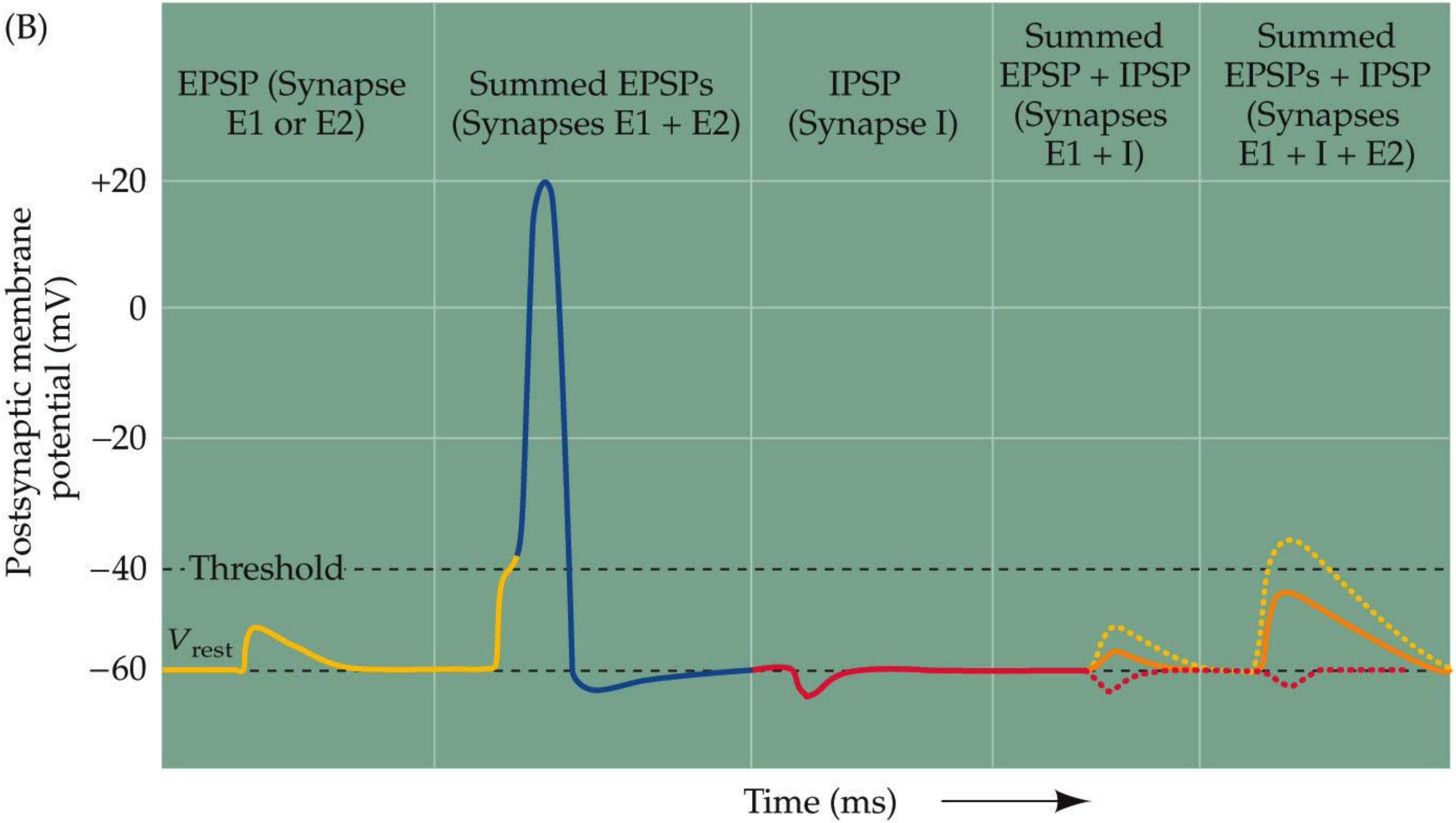
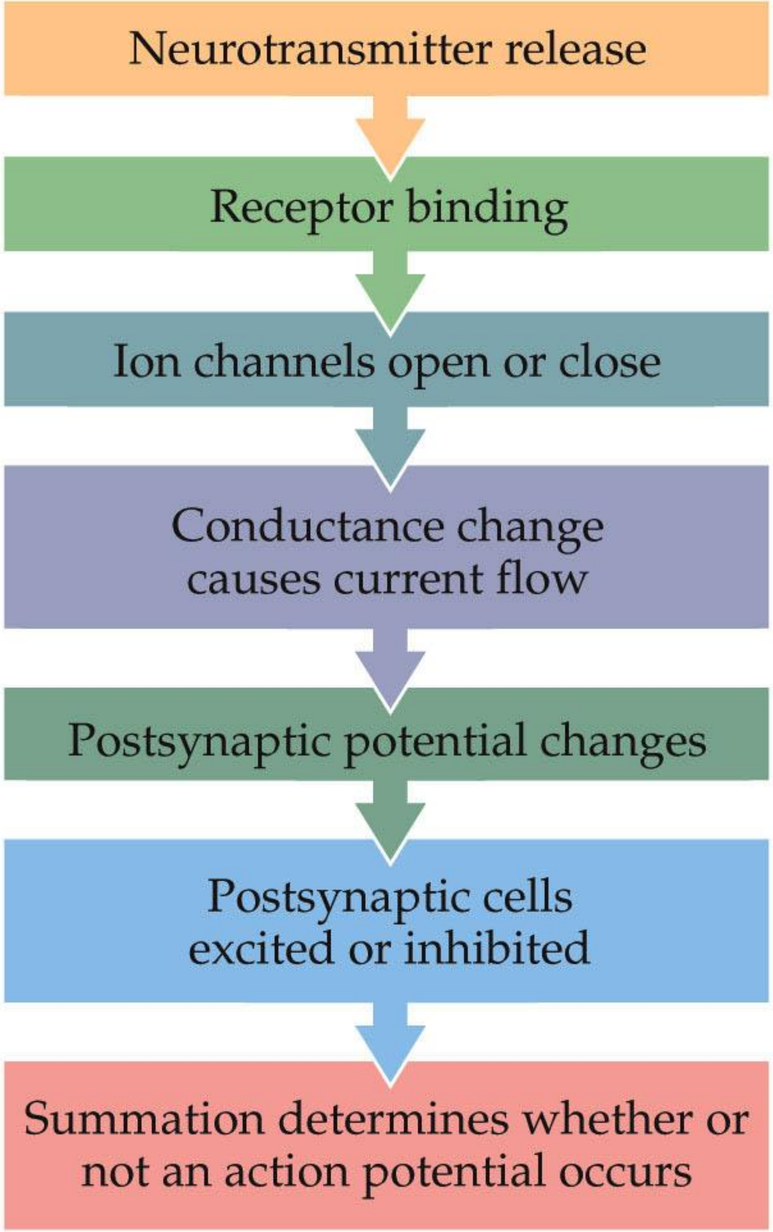

(B)
EPSP (Synapse E1 or E2)
Summed EPSPs (Synapses E1 + E2)
IPSP (Synapse I)
Summed EPSP + IPSP (Synapses E1 + I)
Summed EPSPs + IPSP (Synapses E1 + I + E2)
Postsynaptic membrane potential (mV)
+20
0
−20
−40
−60
Threshold
V rest
Time (ms)

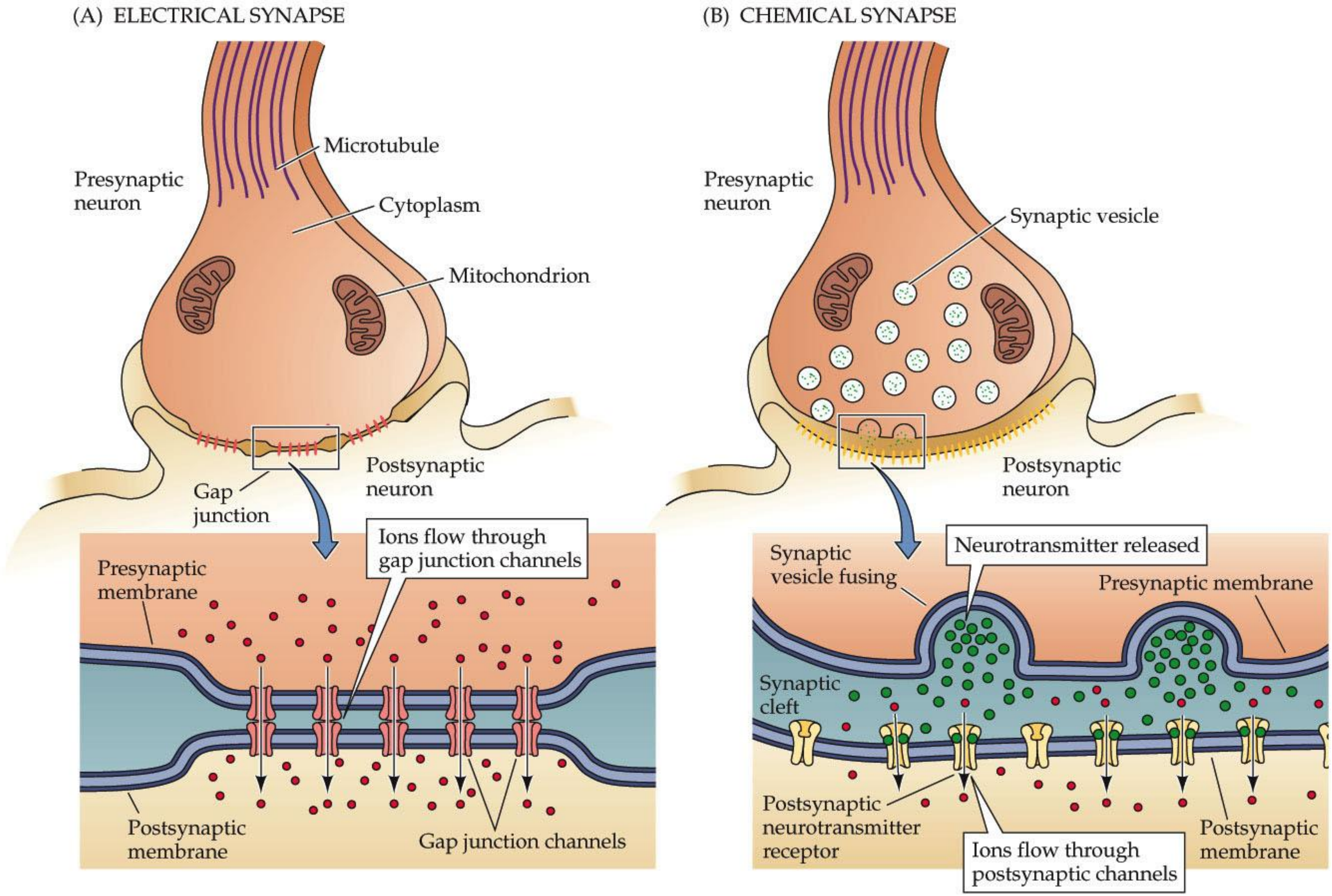
Figure 5.22 Events from neurotransmitter release to postsynaptic excitation or inhibition



***NEUROSCIENCE*, *Fourth Edition*, Figure 5.22**

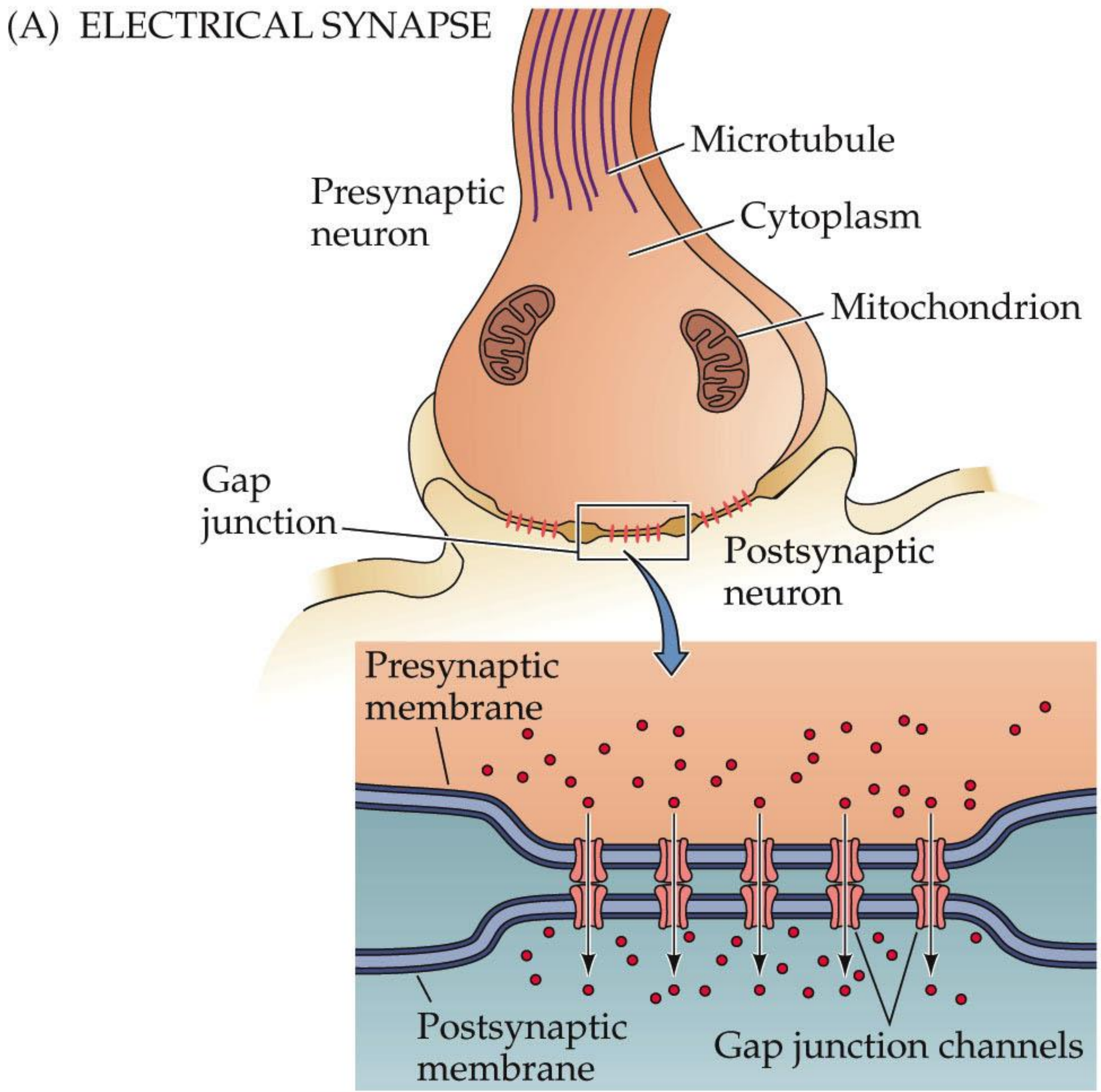
- Otto Loewi's experiments
- Bernard Katz's experiments
- Quantal analysis
- Synaptic transmission
- Synaptic reversal potentials
- Gap junctions

Figure 5.1 Electrical and chemical synapses differ in their transmission mechanisms



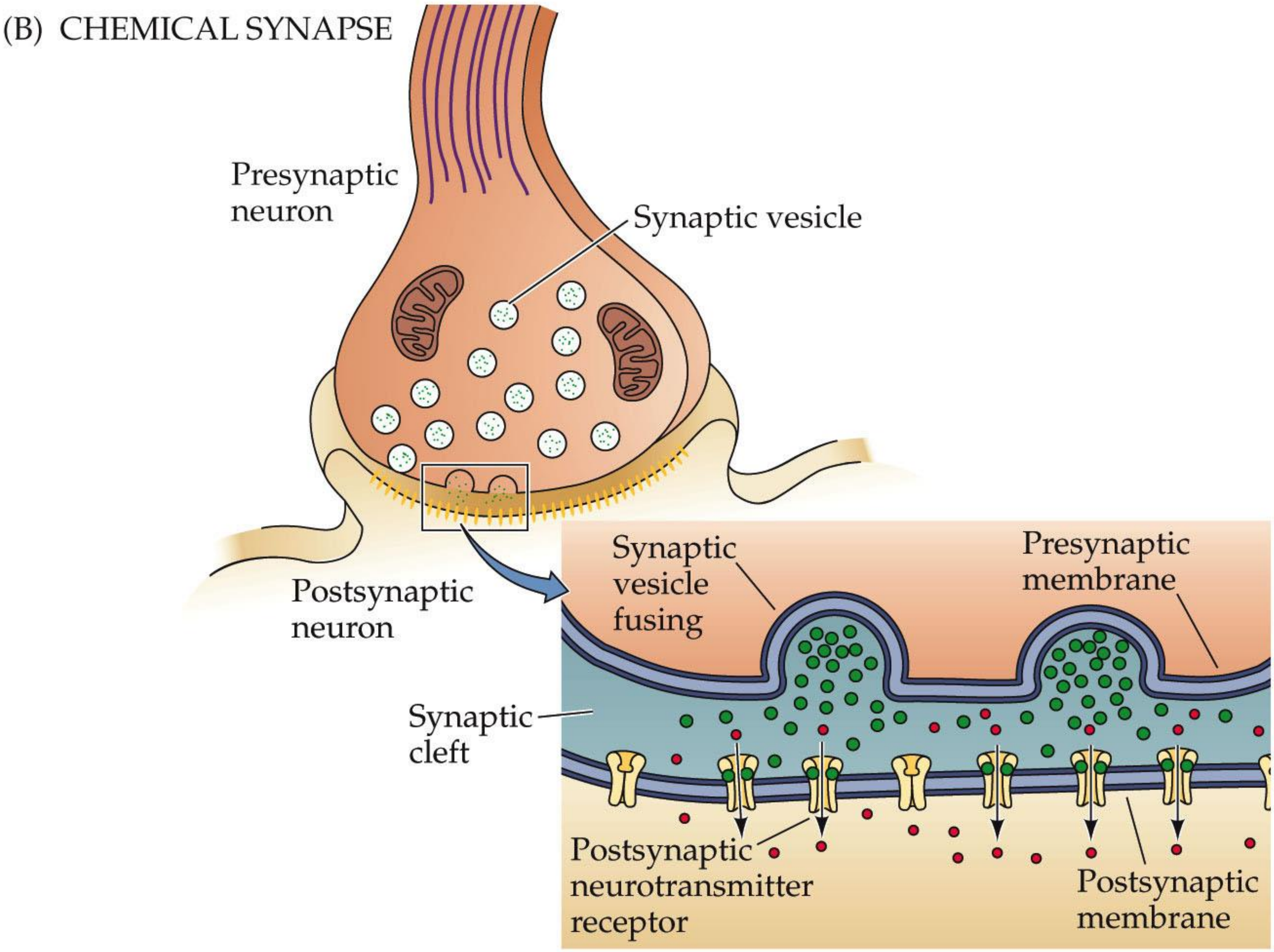
***NEUROSCIENCE*, *Fourth Edition*, Figure 5.1**

Figure 5.1 Electrical and chemical synapses differ in their transmission mechanisms (Part 1)



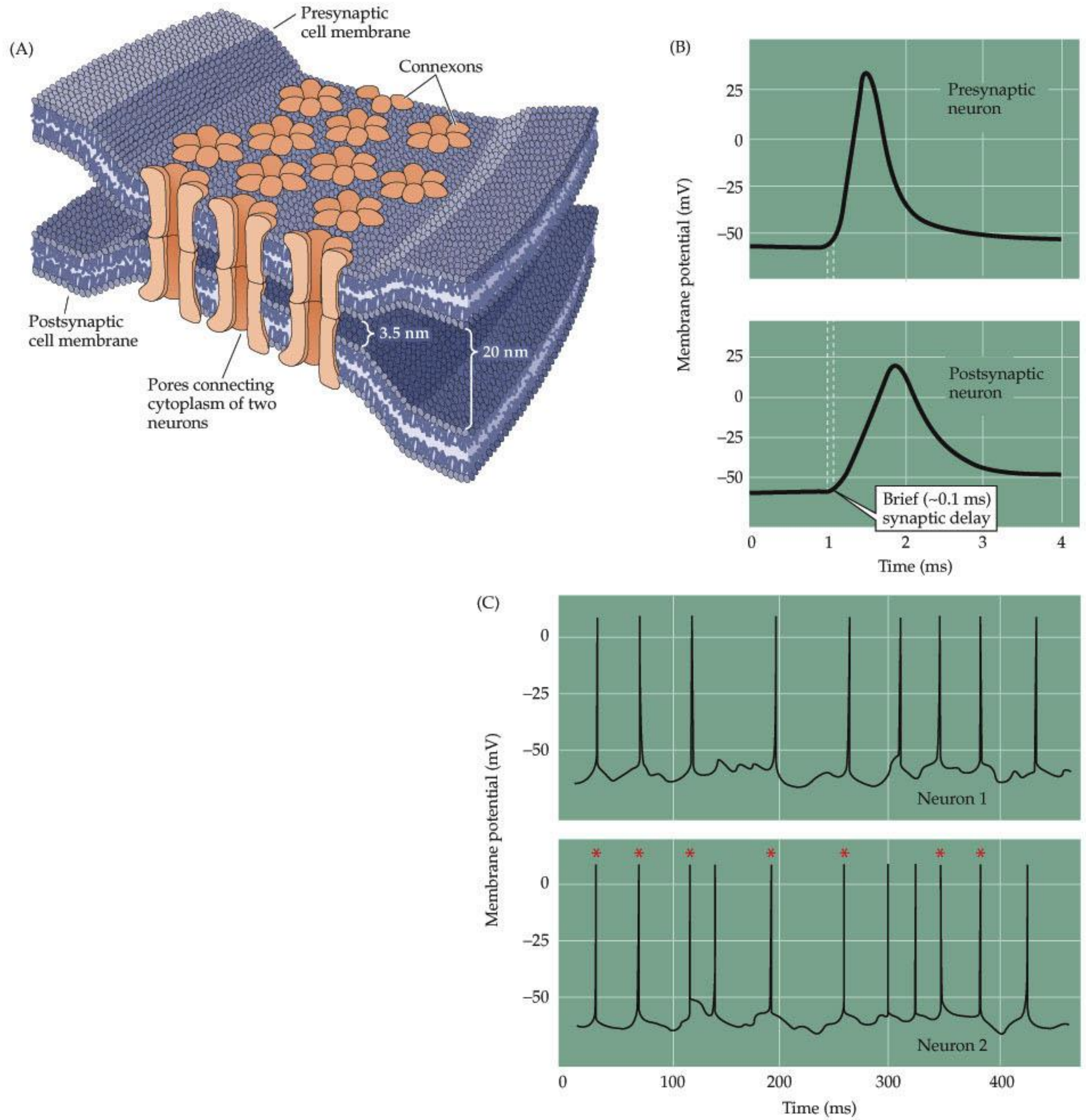
NEUROSCIENCE, Fourth Edition, Figure 5.1 (Part 1)

Figure 5.1 Electrical and chemical synapses differ in their transmission mechanisms (Part 2)



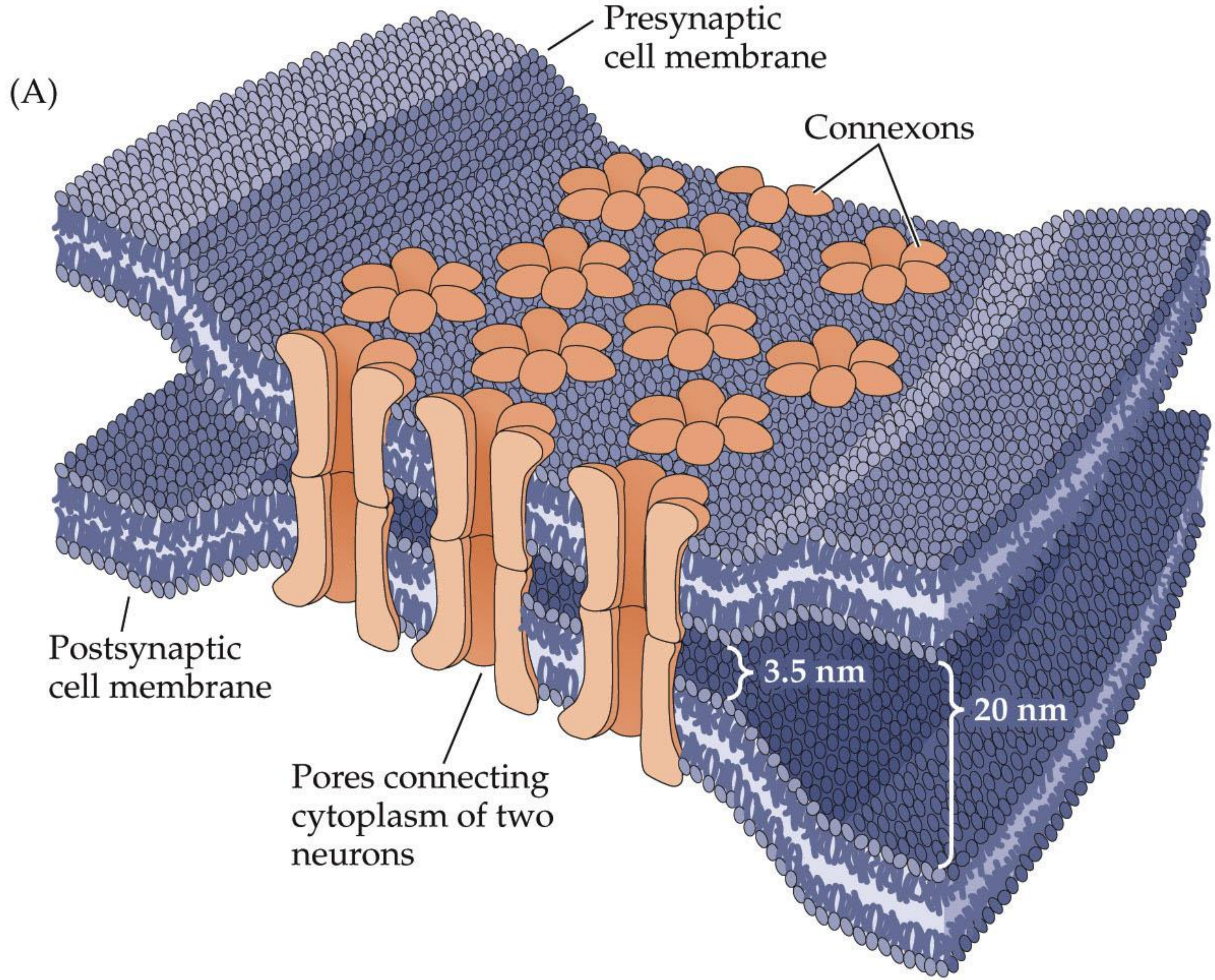
***NEUROSCIENCE*, *Fourth Edition*, Figure 5.1 (Part 2)**

Figure 5.2 Structure and function of gap junctions at electrical synapses



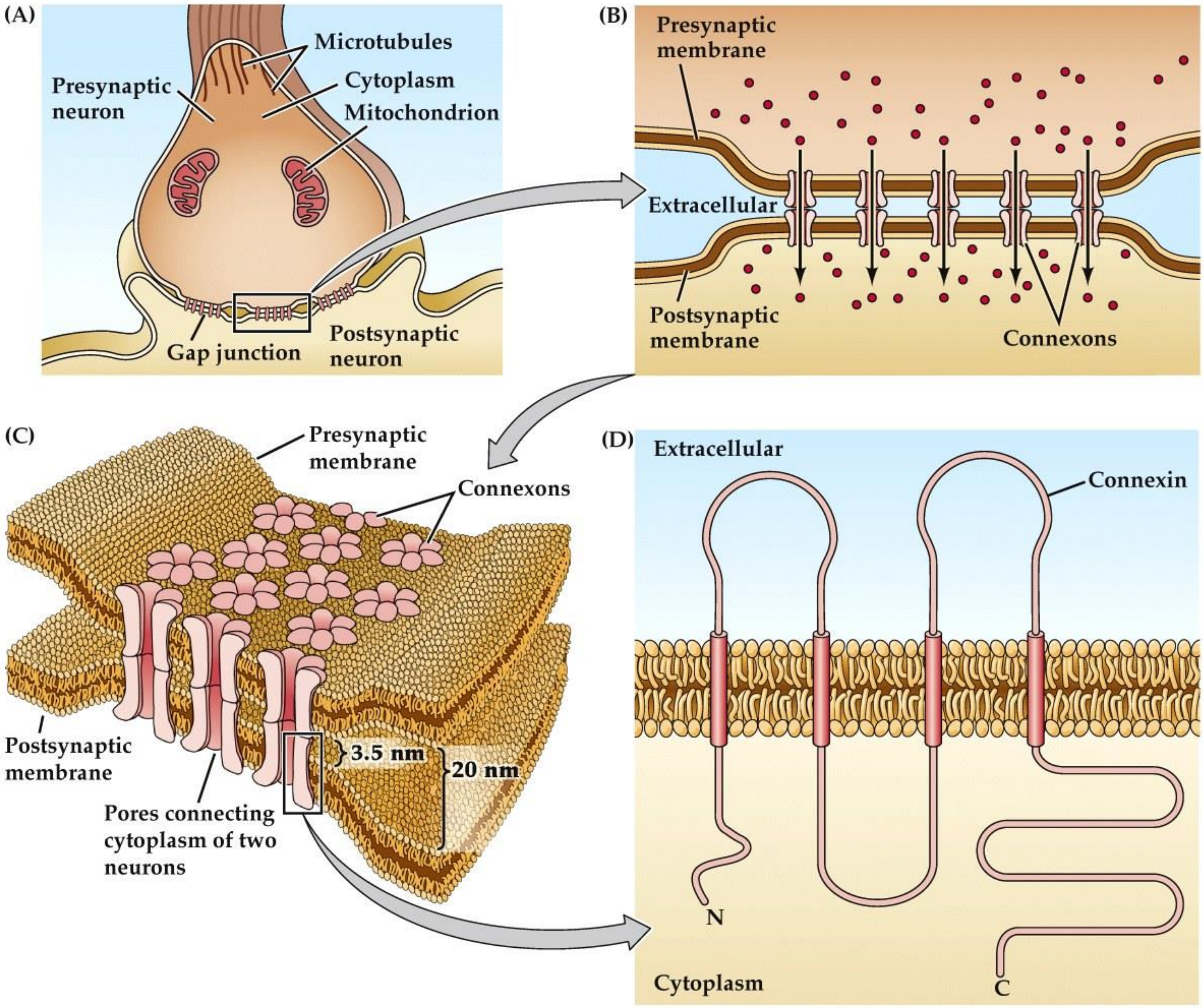
NEUROSCIENCE, Fourth Edition, Figure 5.2

Figure 5.2 Structure and function of gap junctions at electrical synapses (Part 1)

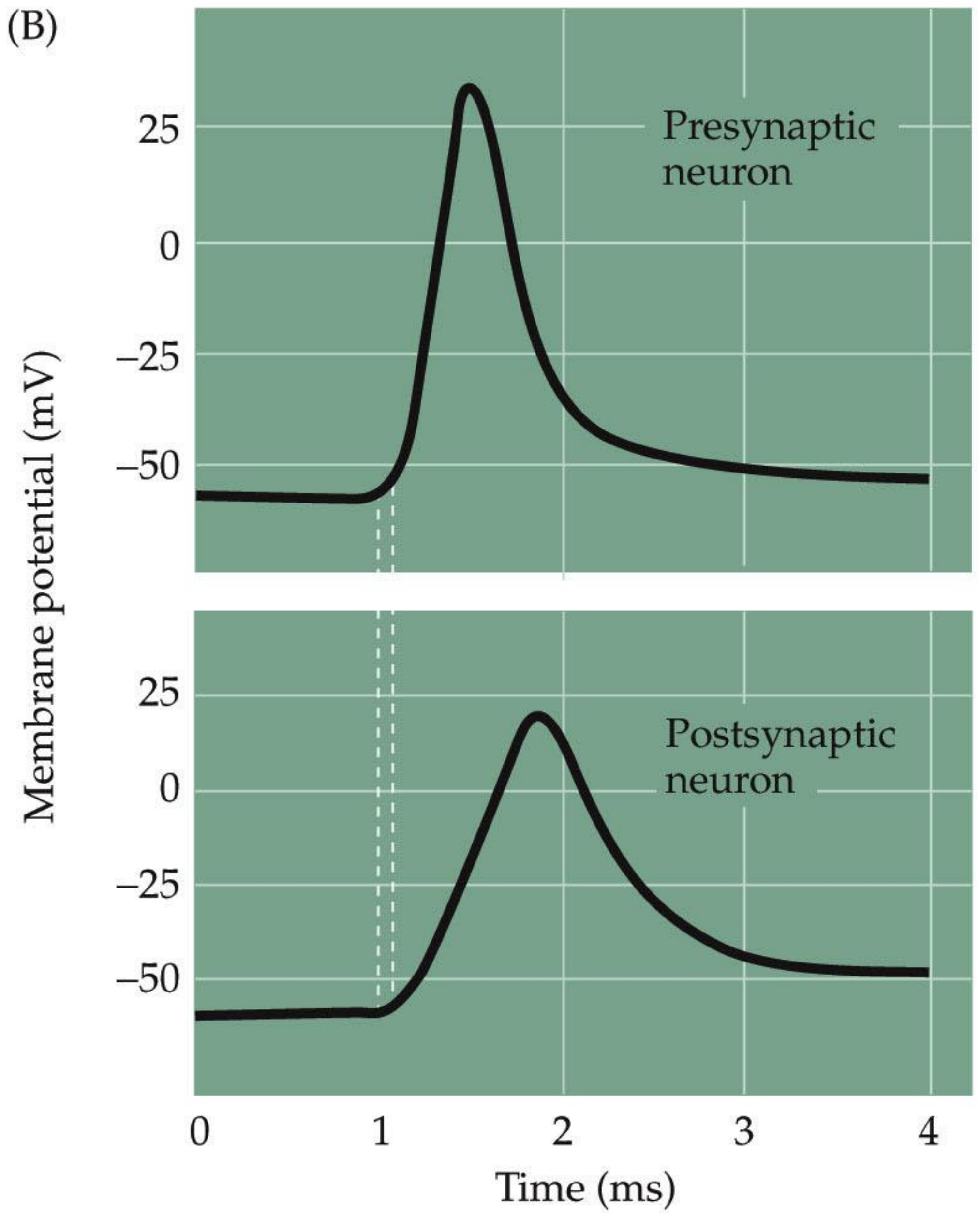


***NEUROSCIENCE*, *Fourth Edition*, Figure 5.2 (Part 1)**

Figure 5.1 Structure of electrical synapses

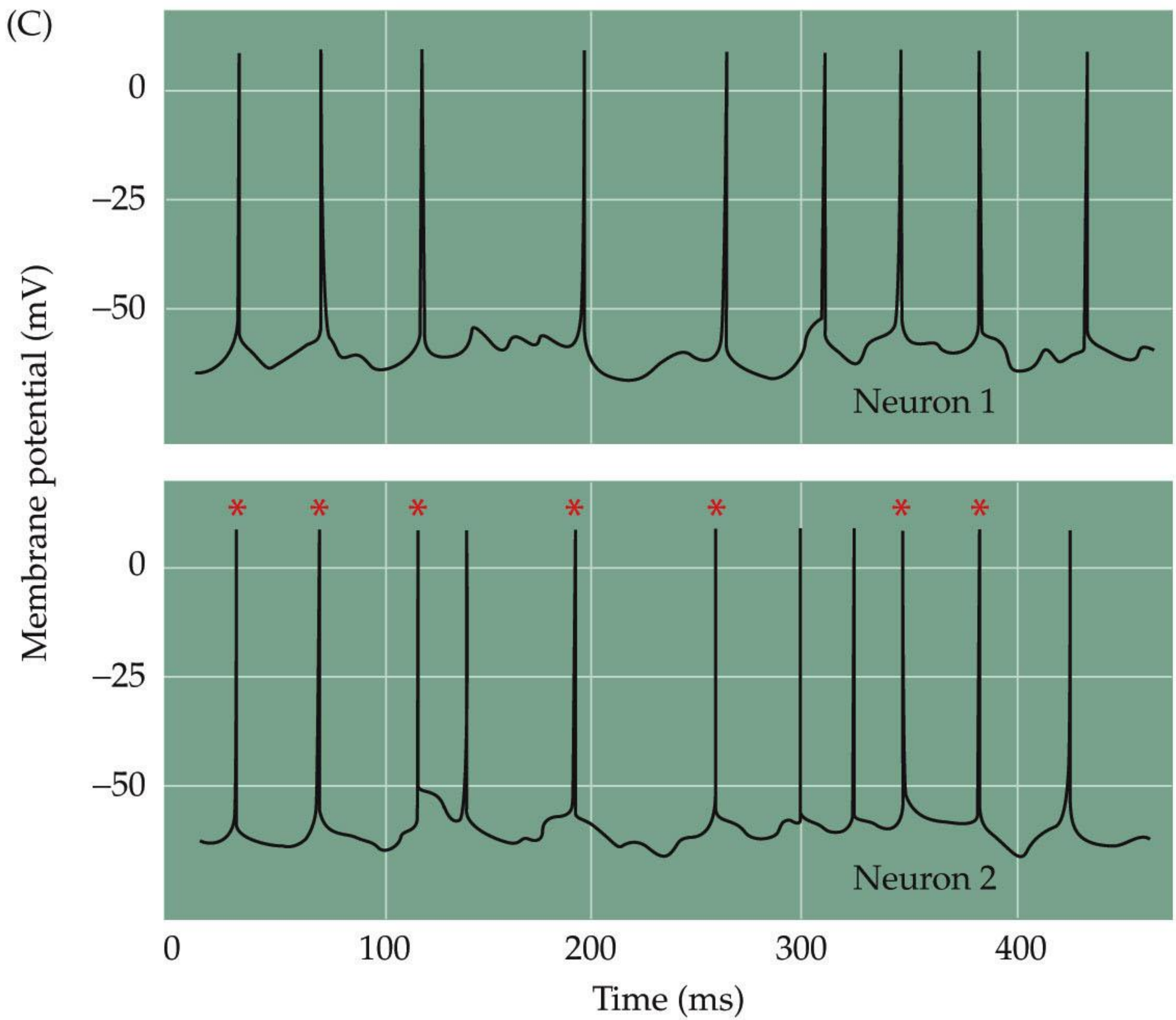


NEUROSCIENCE 5e, Figure 5.1



NEUROSCIENCE, Fourth Edition, Figure 5.2 (Part 2)

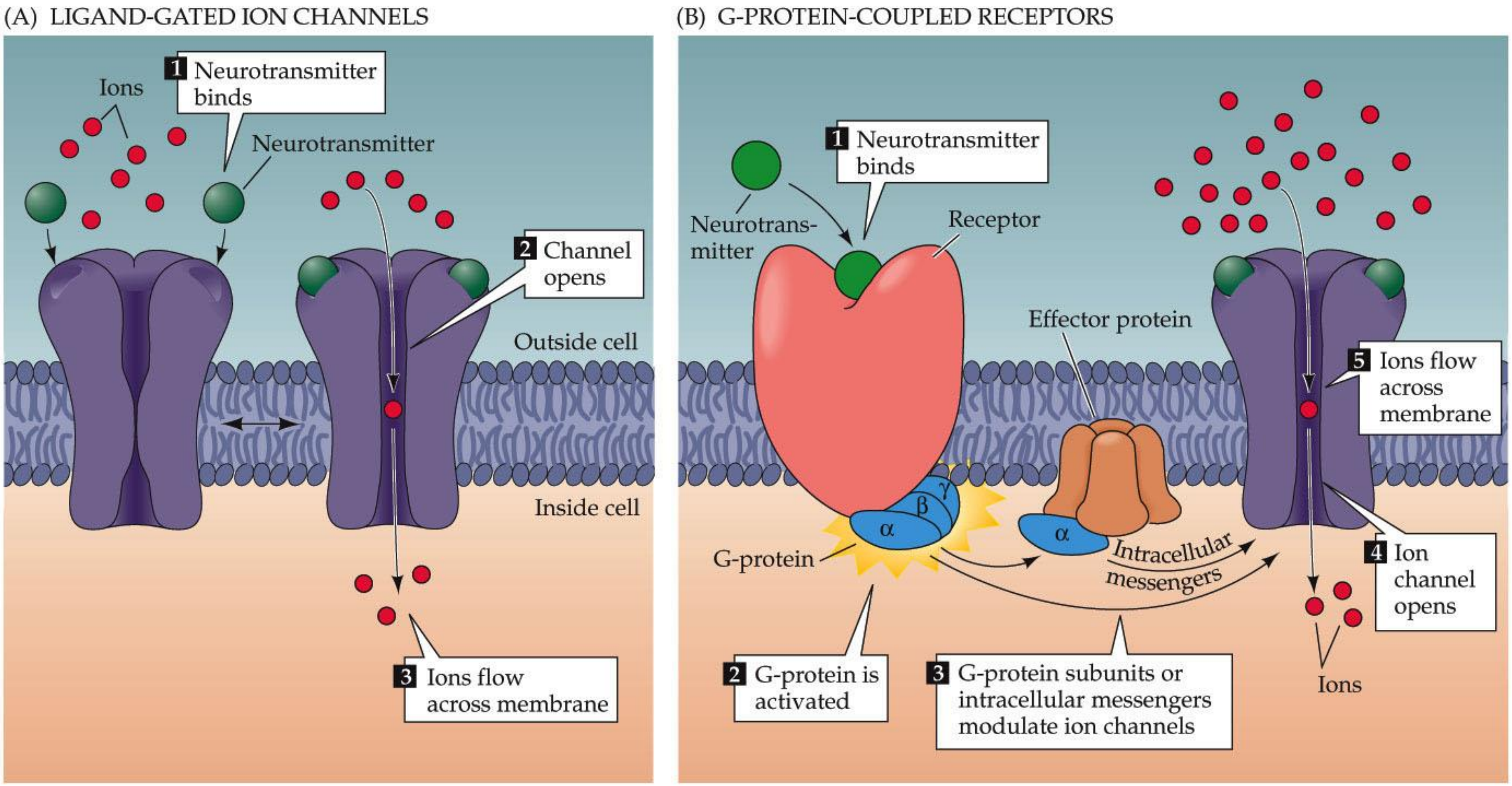
Figure 5.2 Structure and function of gap junctions at electrical synapses (Part 3)



NEUROSCIENCE, _Fourth Edition_, Figure 5.2 (Part 3)

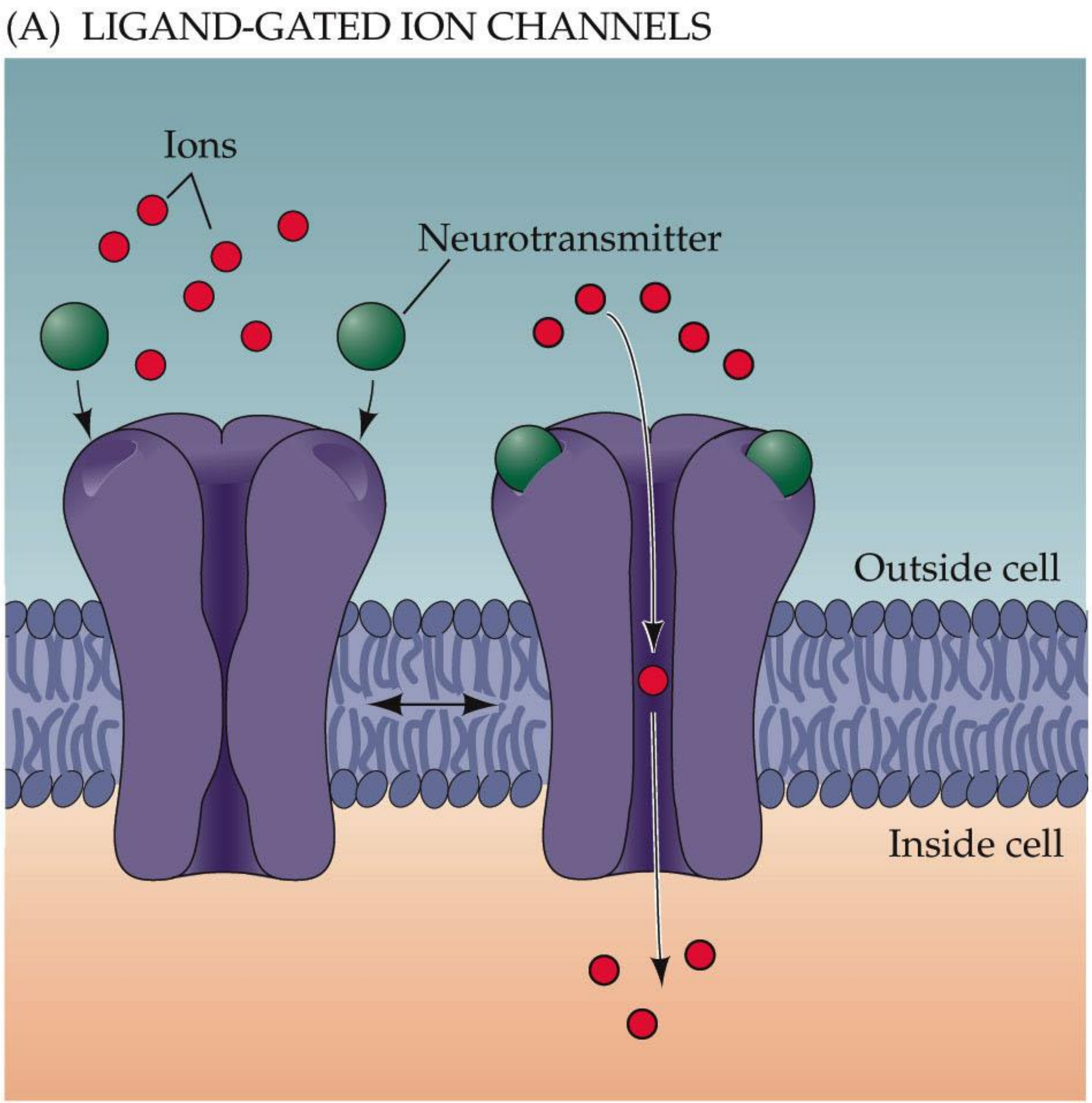
- Supplementary slides

metabotropic receptors



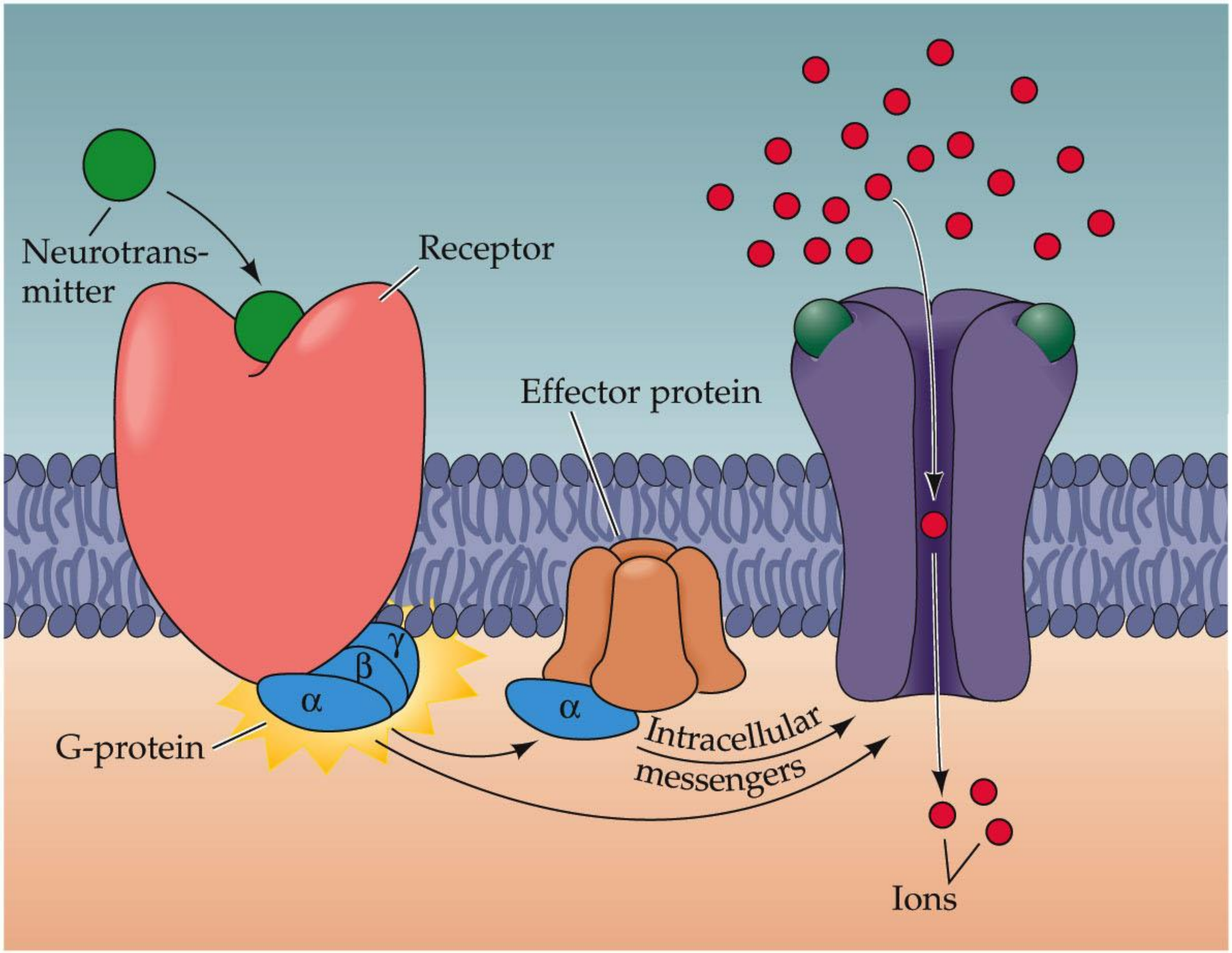
NEUROSCIENCE, Fourth Edition, Figure 5.23

metabotropic receptors (Part 1)



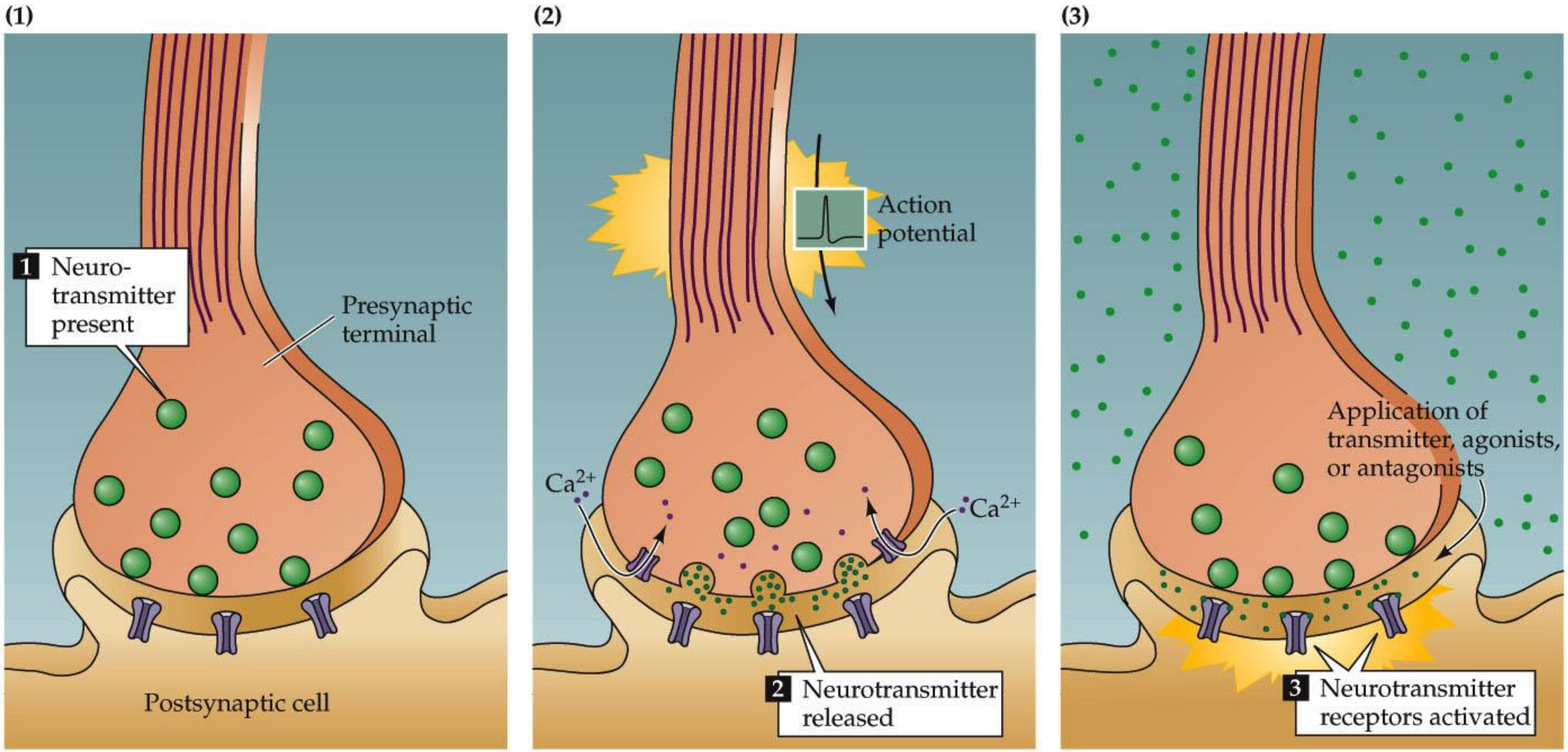
NEUROSCIENCE, Fourth Edition, Figure 5.23 (Part 1)

(B) G-PROTEIN–COUPLED RECEPTORS

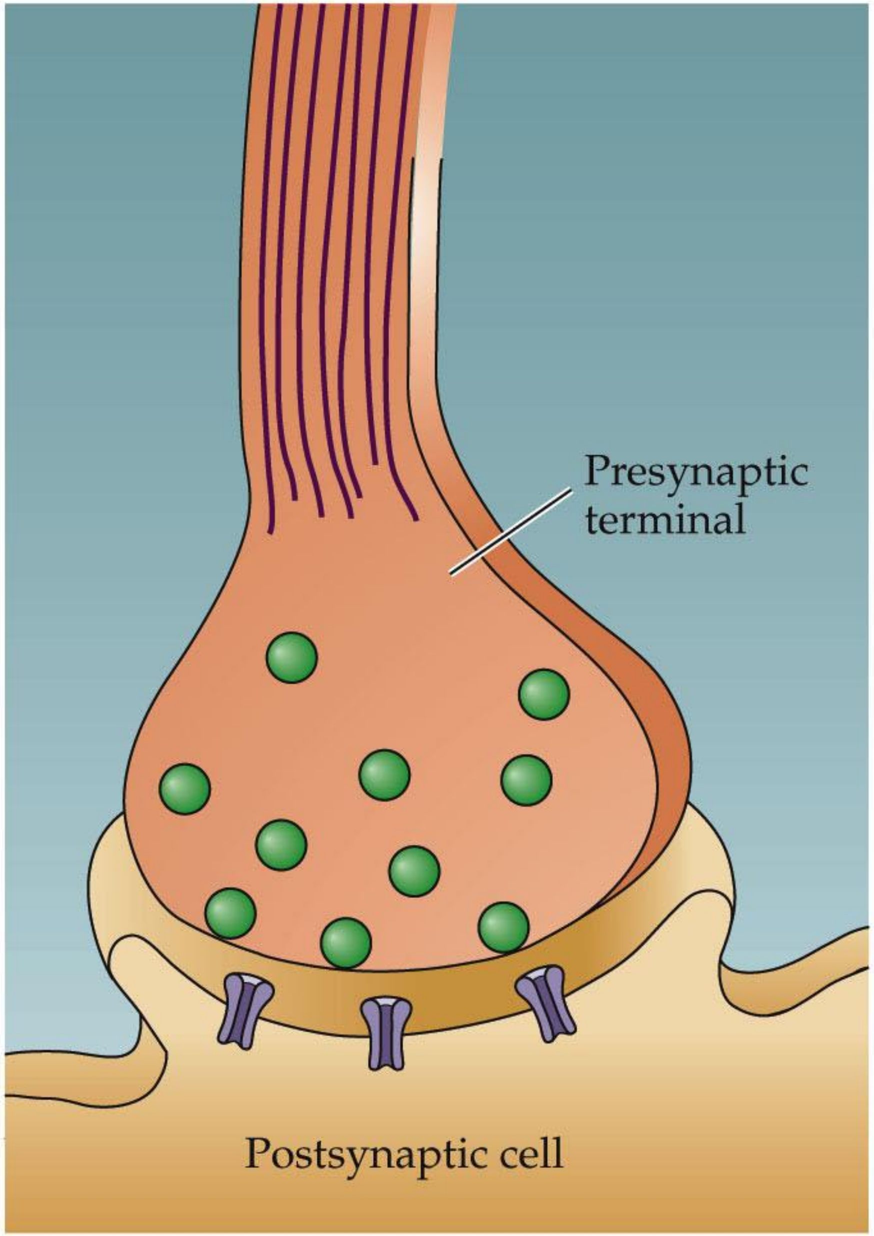


NEUROSCIENCE, *Fourth Edition,* Figure 5.23 (Part 2)

Box 5A Criteria That Define a Neurotransmitter

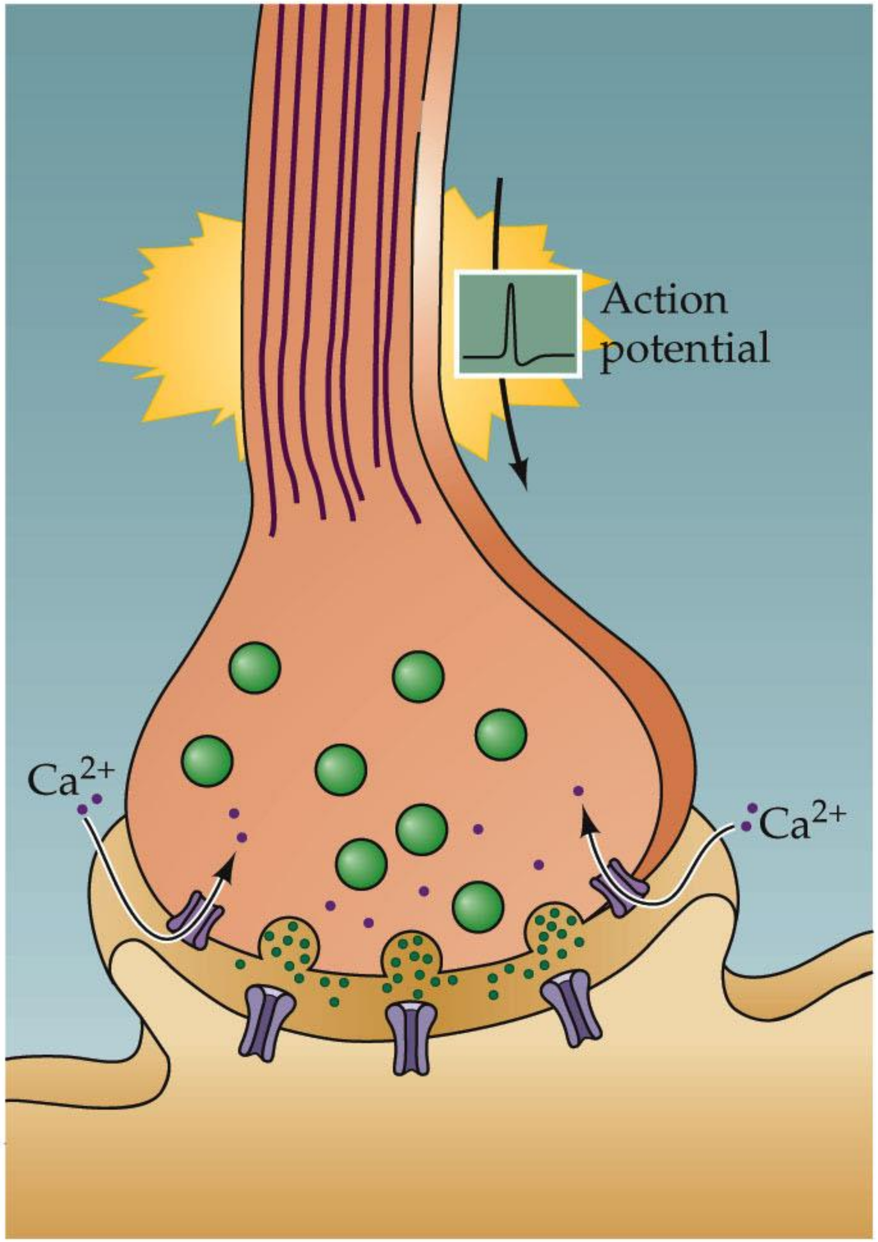


(1)



Box 5A Criteria That Define a Neurotransmitter (Part 2)

(2)



NEUROSCIENCE, Fourth Edition, Box 5A (Part 2)

Box 5A Criteria That Define a Neurotransmitter (Part 3)

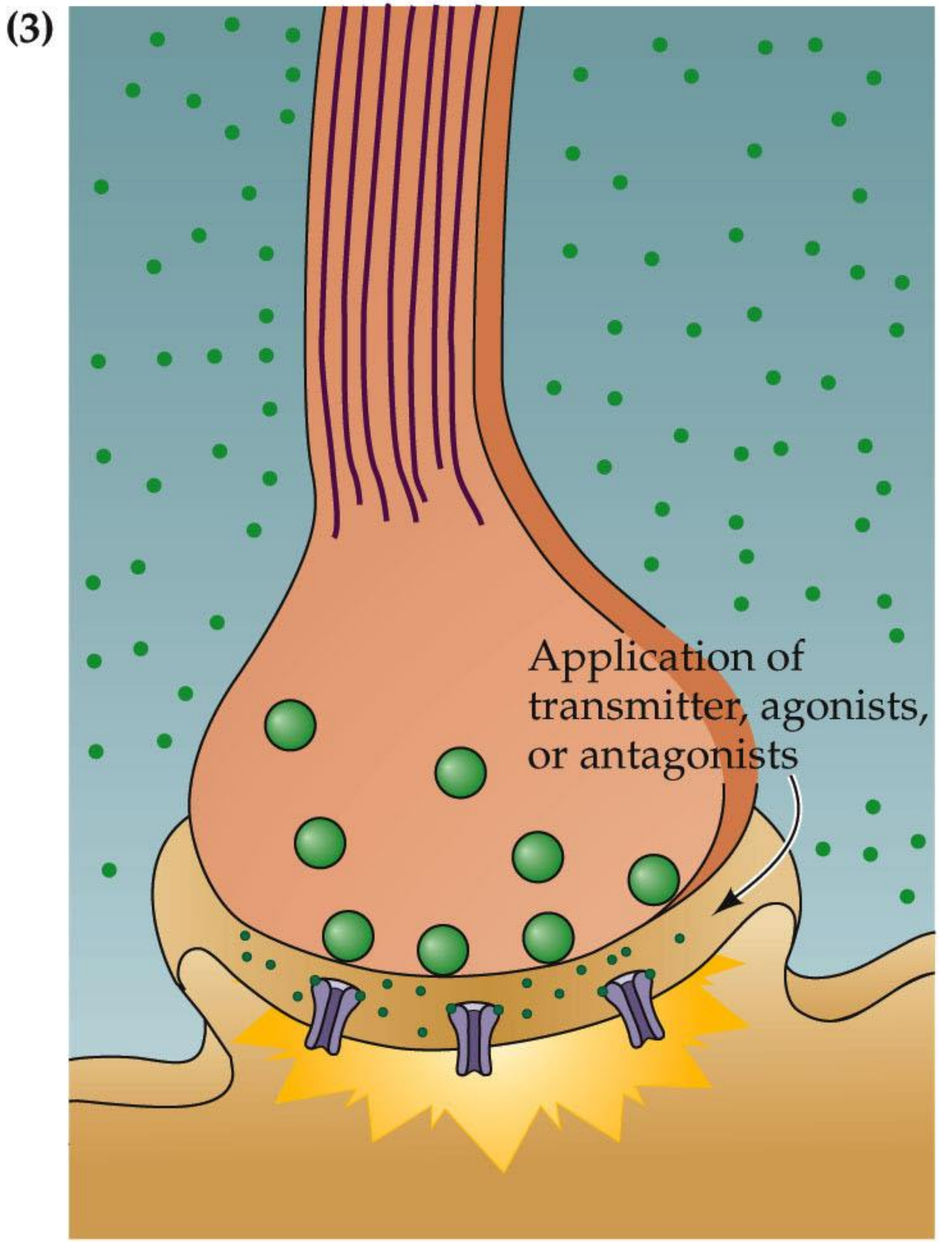
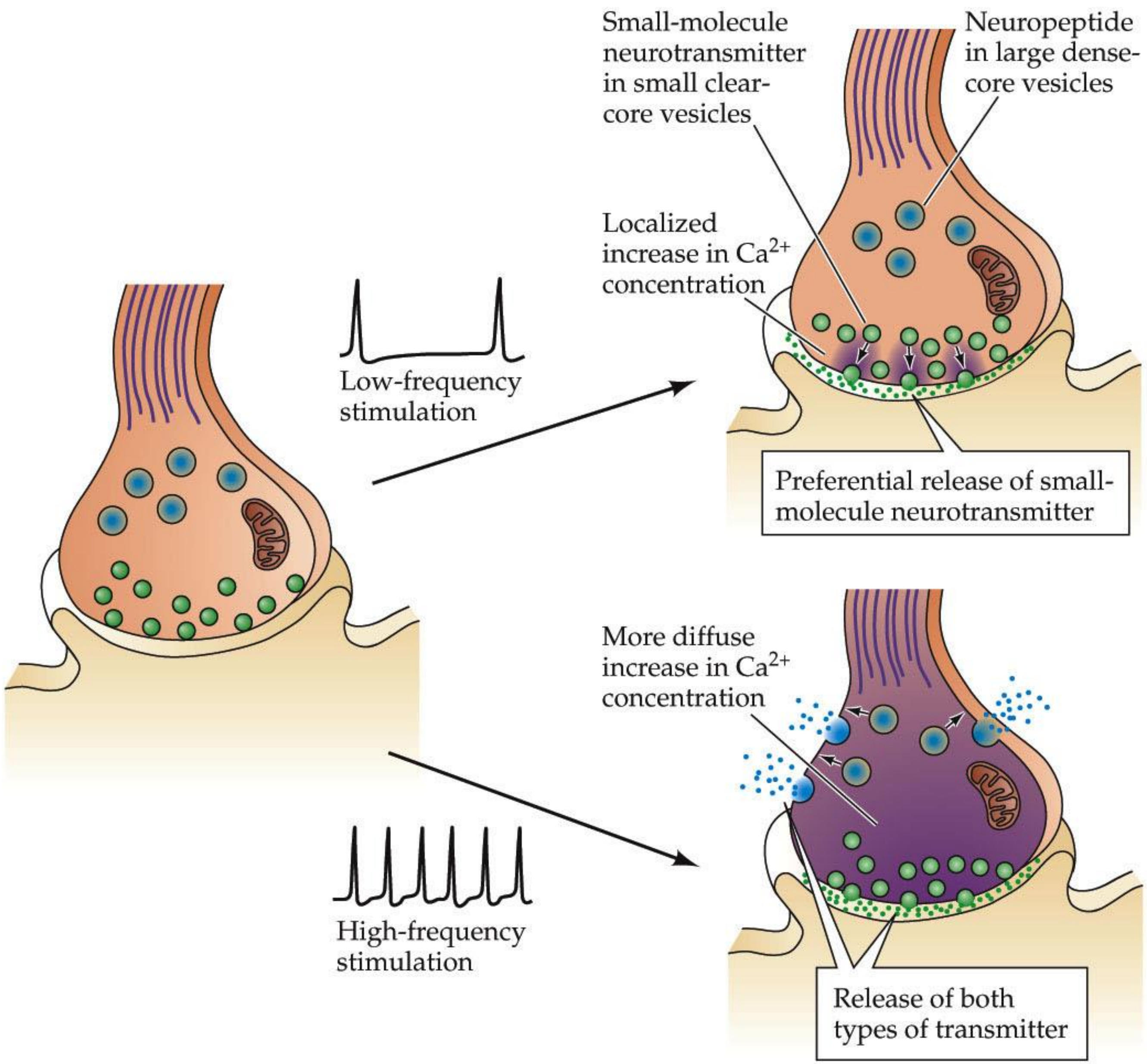
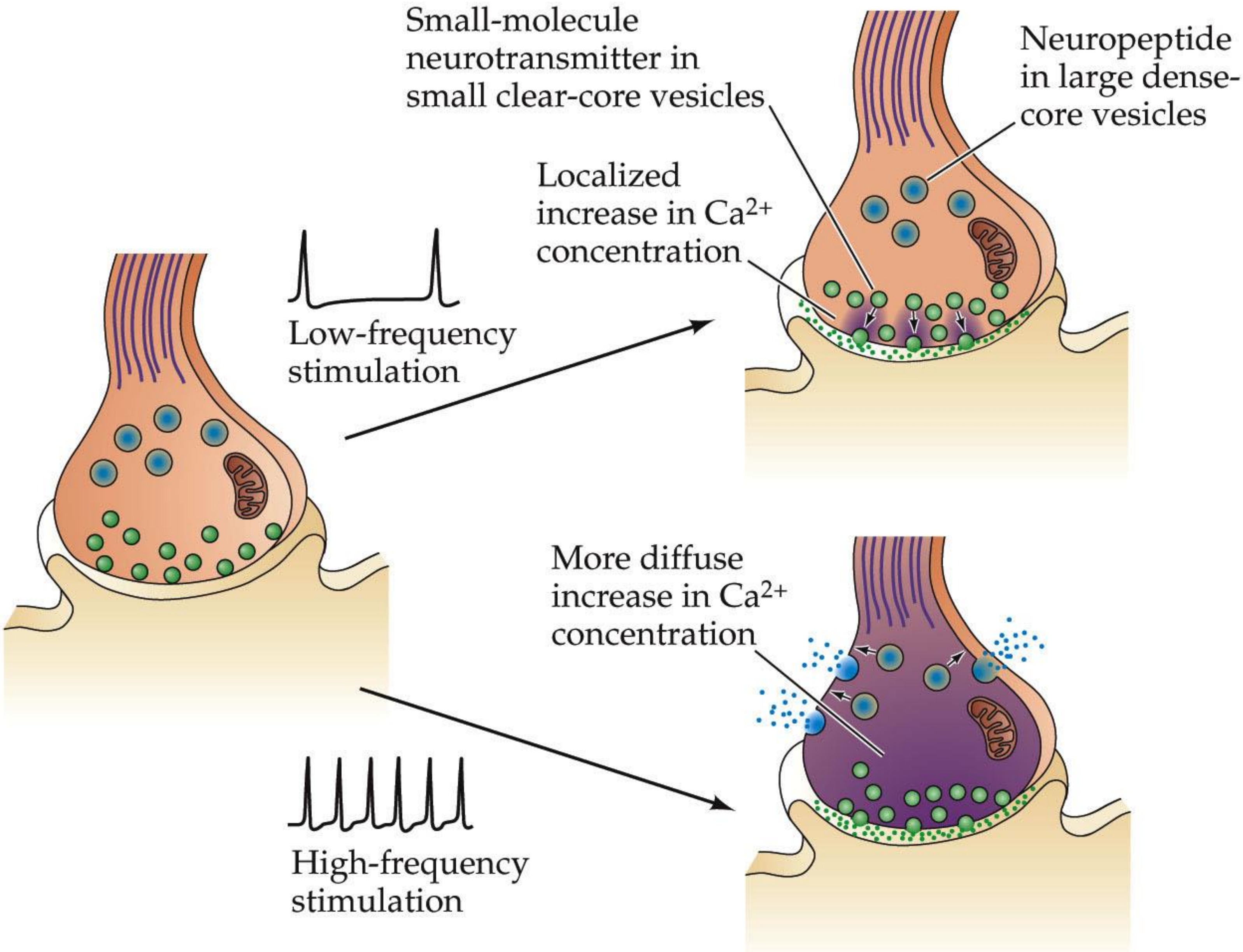


Figure 5.12 Differential release of neuropeptide and small-molecule co-transmitters



NEUROSCIENCE, *Fourth Edition*, Figure 5.12

Figure 5.12 Differential release of neuropeptide and small-molecule co-transmitters



NEUROSCIENCE, _Fourth Edition_, Figure 5.12

Figure 5.13 Presynaptic proteins and their roles in synaptic vesicle cycling

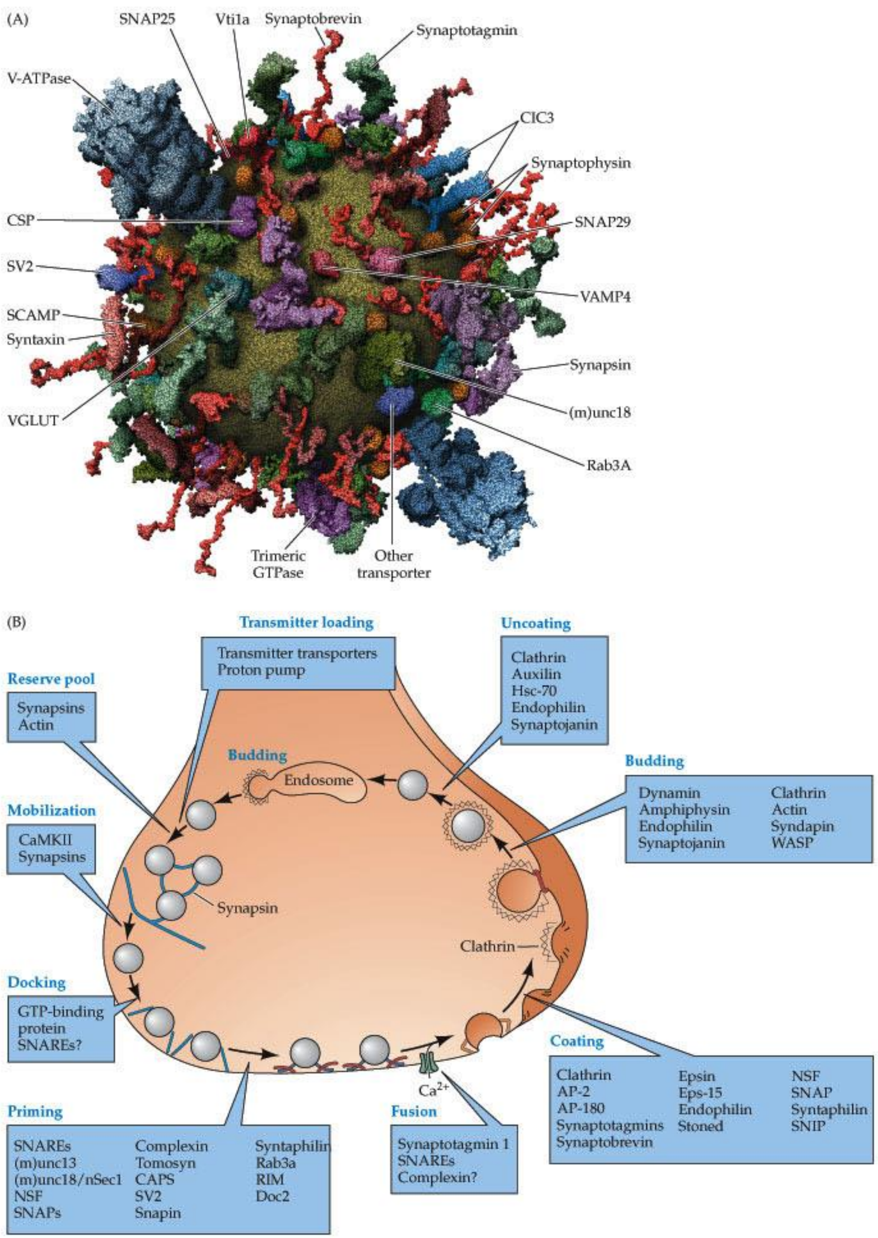
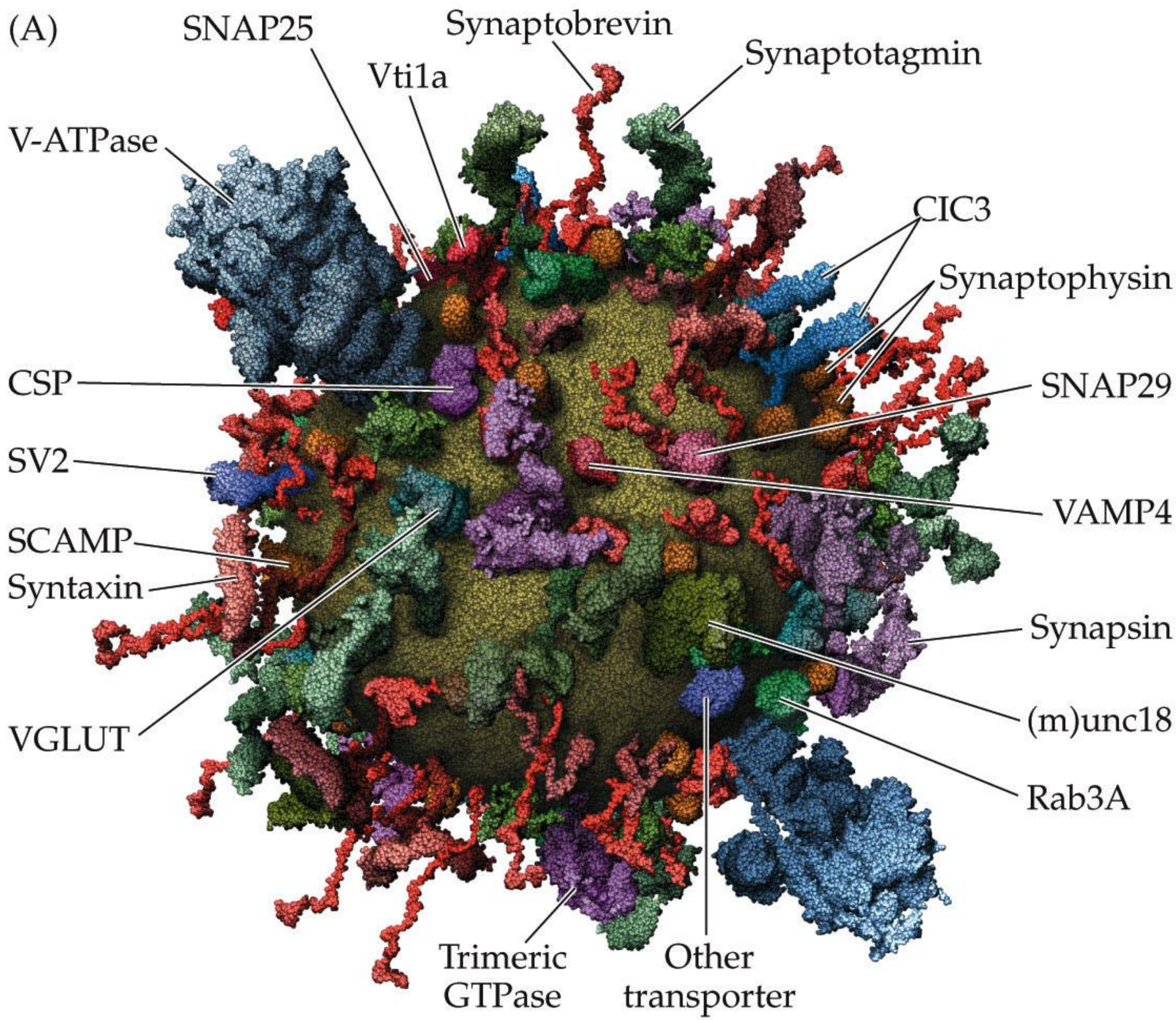
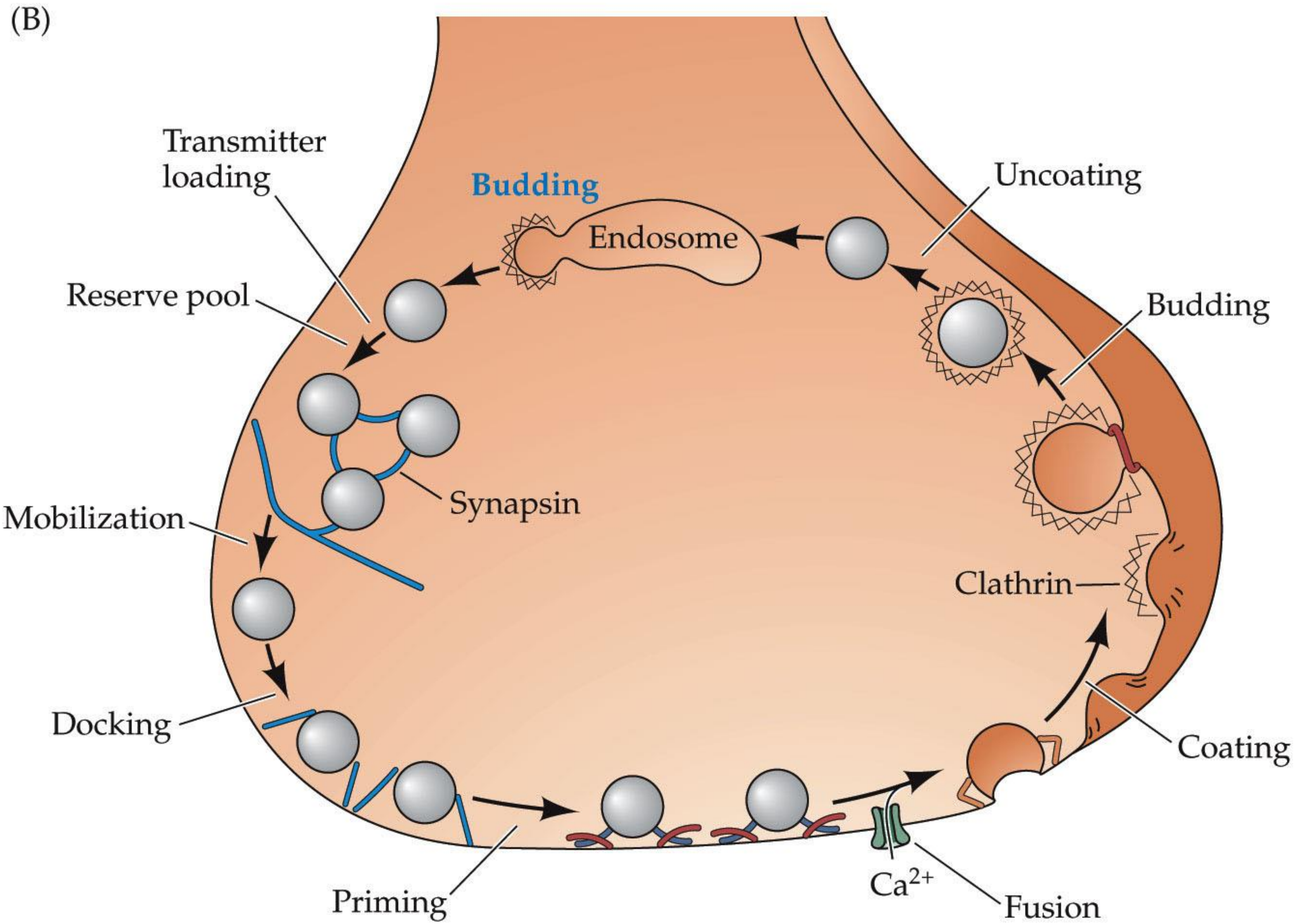


Figure 5.13 Presynaptic proteins and their roles in synaptic vesicle cycling (Part 1)



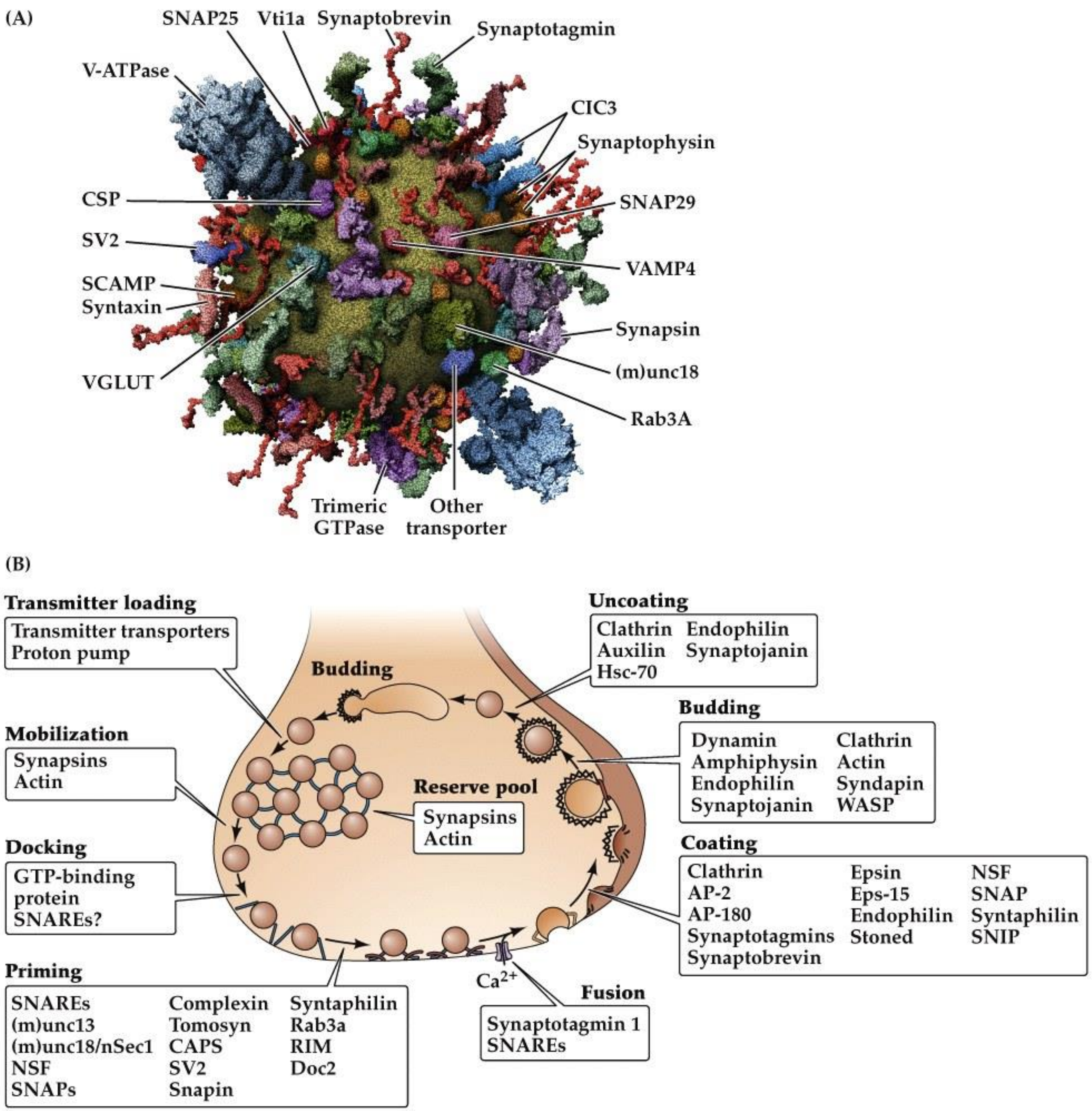
NEUROSCIENCE, Fourth Edition, Figure 5.13 (Part 1)

Figure 5.13 Presynaptic proteins and their roles in synaptic vesicle cycling (Part 2)



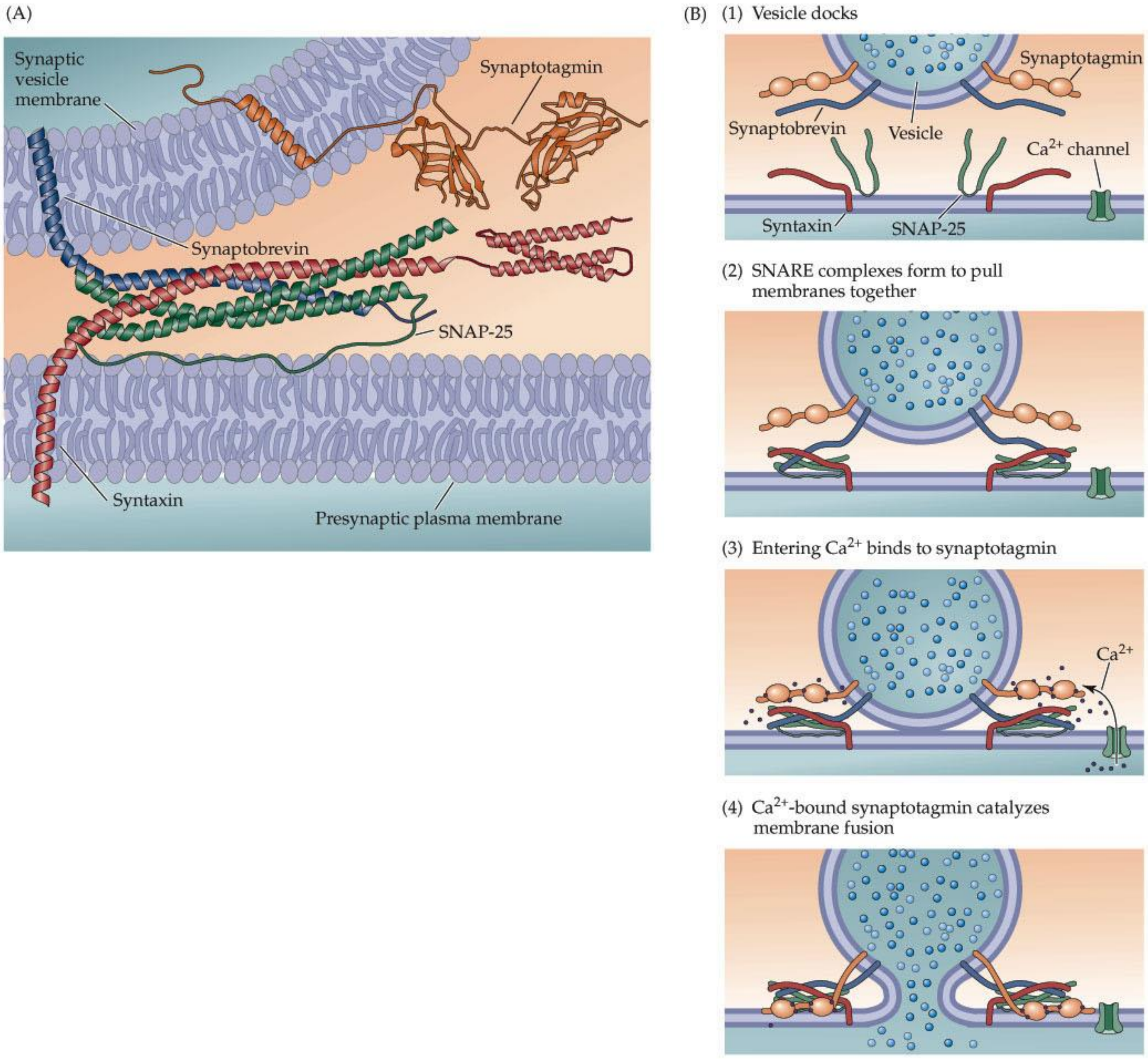
NEUROSCIENCE, Fourth Edition, Figure 5.13 (Part 2)

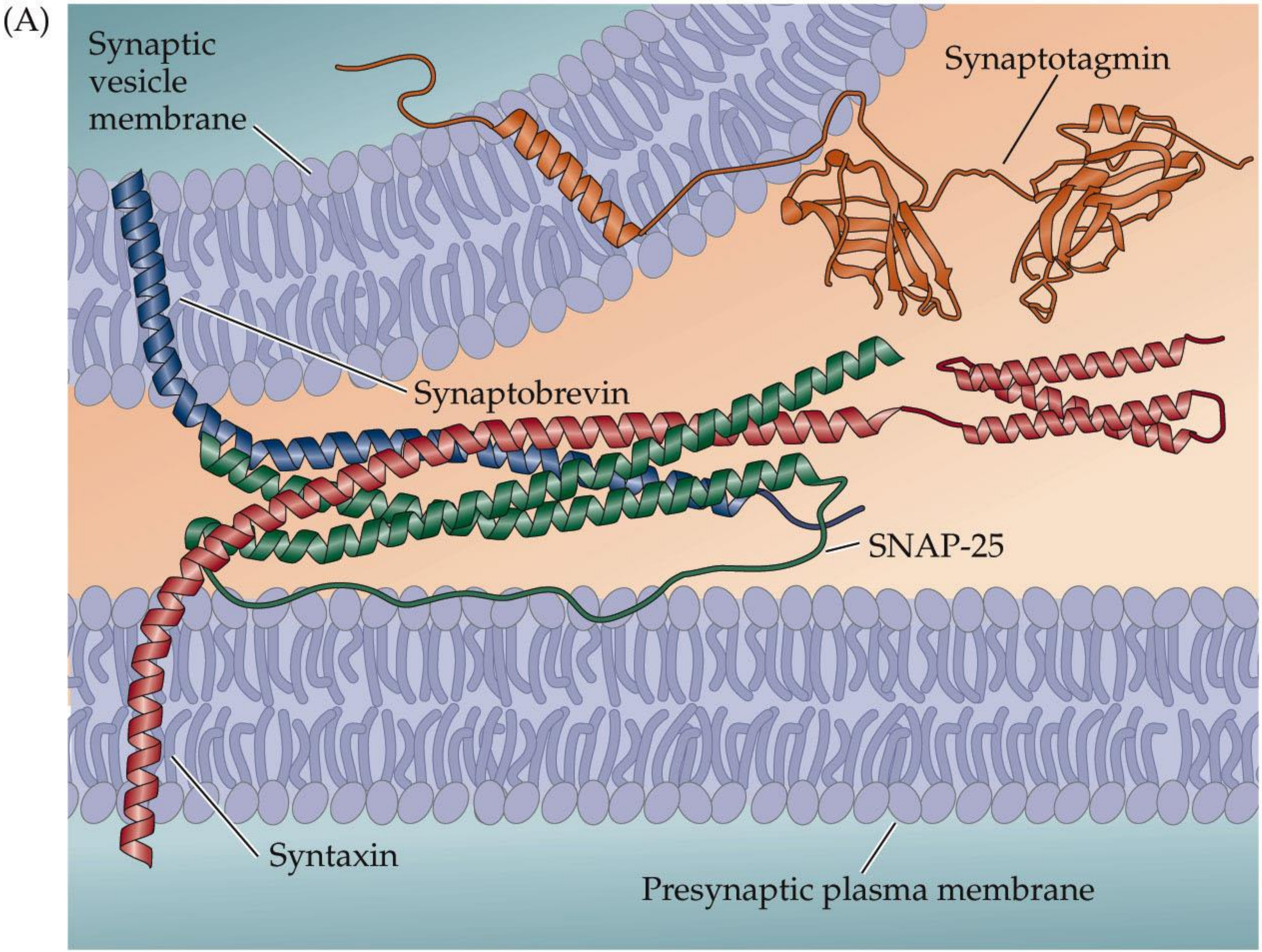
Figure 5.13 Presynaptic proteins and their roles in synaptic vesicle cycling

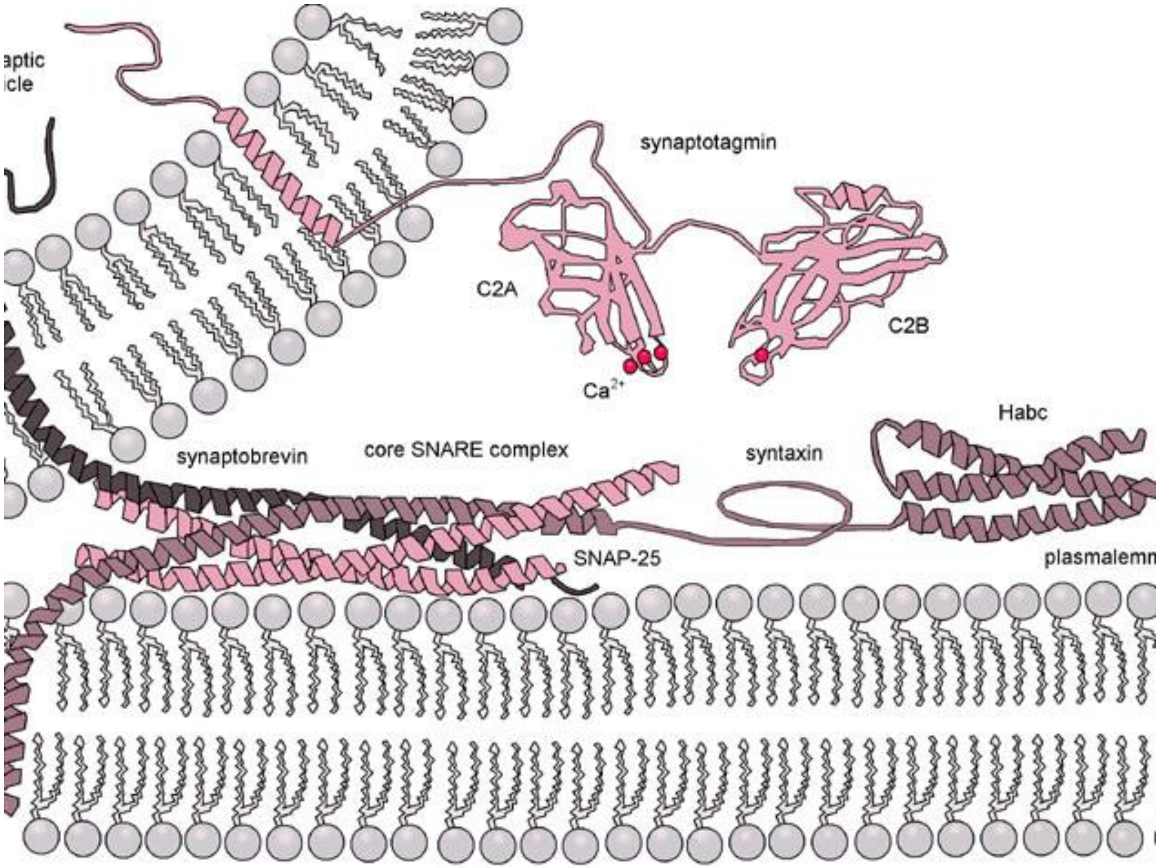


***NEUROSCIENCE 5e*, Figure 5.13**

Figure 5.14 Molecular mechanisms of exocytosis during neurotransmitter release




(A)
Synaptic vesicle membrane
Synaptotagmin
Synaptobrevin
SNAP-25
Syntaxin
Presynaptic plasma membrane



Molecular machinery driving vesicle fusion in neuromediator release. The core SNARE complex is formed by four α-helices contributed by synaptobrevin, syntaxin and SNAP-25, synaptotagmin serves as a calcium sensor and regulates intimately the SNARE zipping (**a, i**) Proteins capable of forming a fusion pore are present in the vesicle and plasma membranes. (**ii**) These proteins associate into a closed pore. (**iii**) A conformational change in this complex opens the pore. (**iv**) The lipid bilayers merge through a remodeling of the two lipid bilayers. (**b**) Lipid fusion according to the stalk model[23]. (**i**) Lipid bilayers are pulled together. In regulated exocytosis, proteins (not shown) exert the necessary force. (**ii**) An initial merger stage forms, in which the outer leaflets remodel to form a stalk. (**iii**) The outer leaflets draw apart and the inner leaflets form a bilayer in this hemifusion diaphragm. (**iv**) A pore forms in the new bilayer of inner leaflets.

From the following article

The fusion pores of Ca^{2+}-triggered exocytosis

Meyer B Jackson & Edwin R Chapman

Nature Structural & Molecular Biology **15**, 684 - 689 (2008)

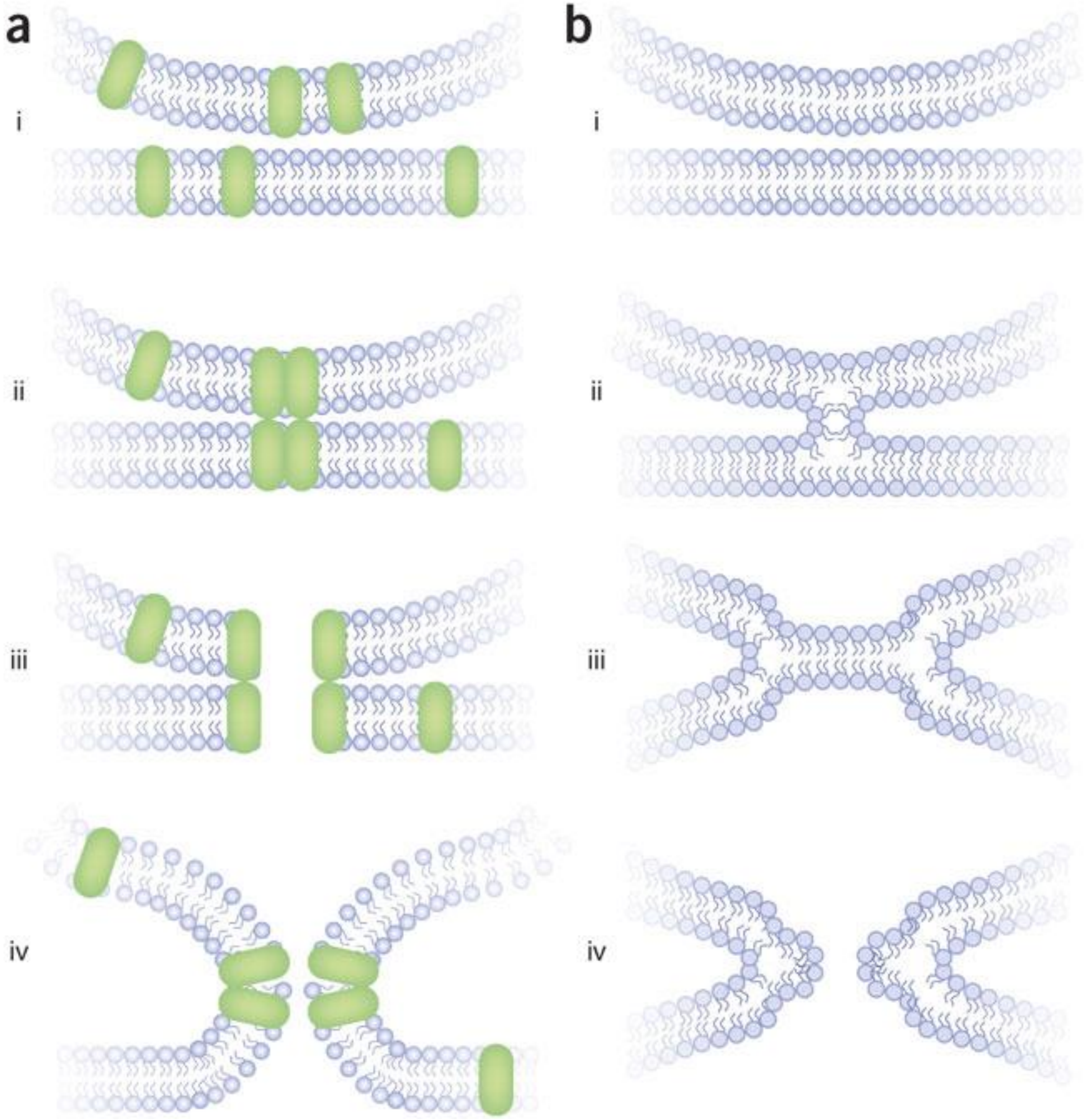
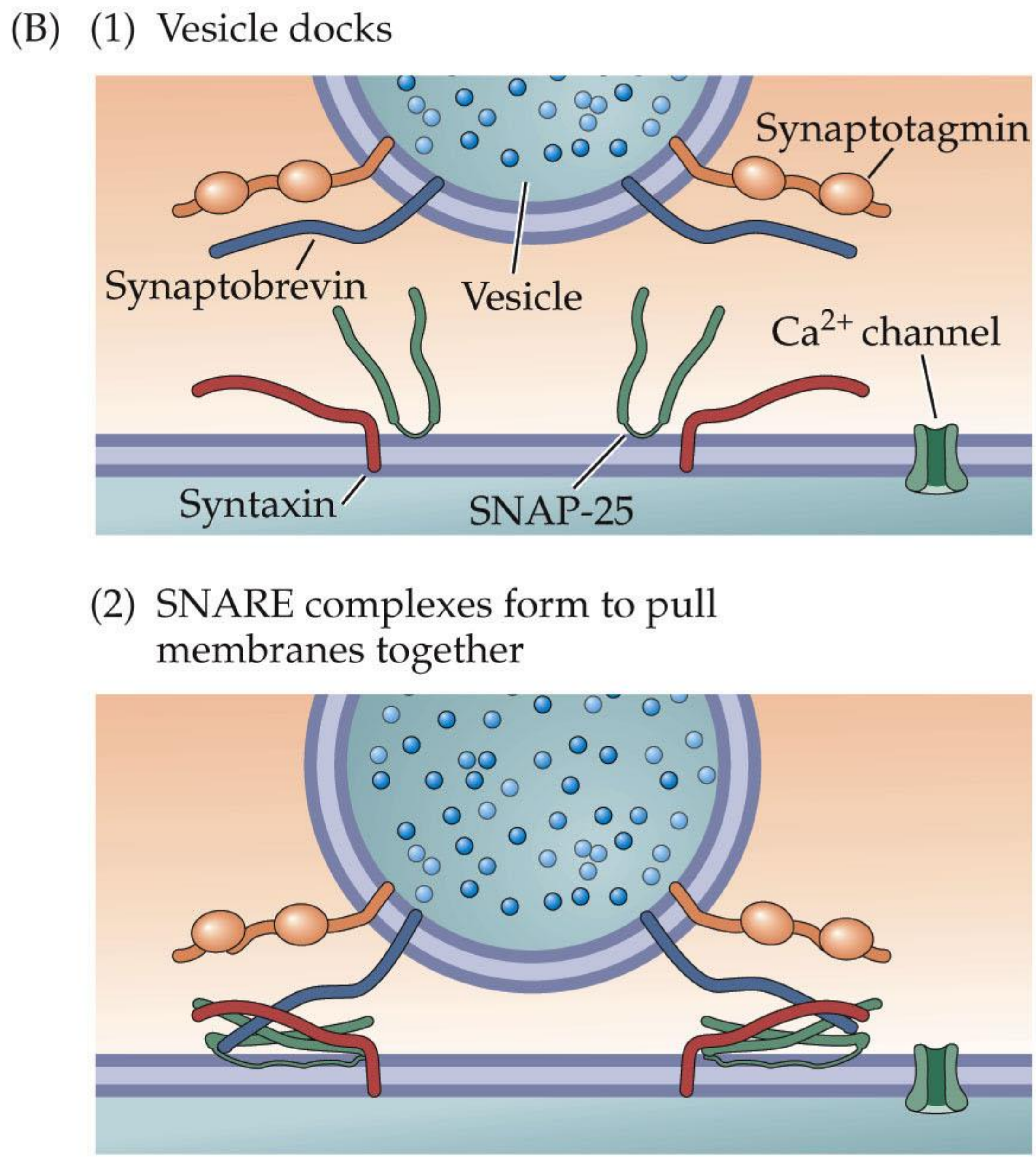


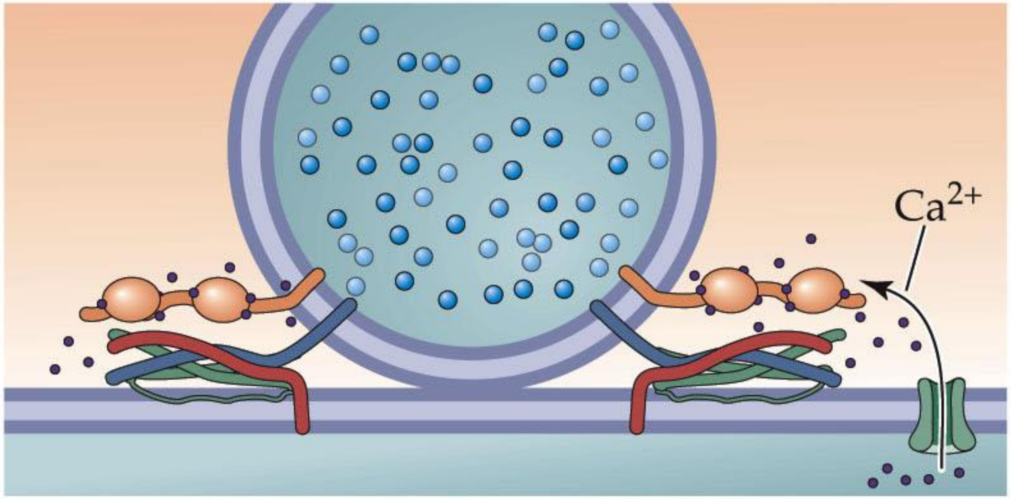
Figure 5.14 Molecular mechanisms of exocytosis during neurotransmitter release (Part 2)



NEUROSCIENCE, Fourth Edition, Figure 5.14 (Part 2)

Figure 5.14 Molecular mechanisms of exocytosis during neurotransmitter release (Part 3)

(3) Entering Ca^{2+} binds to synaptotagmin



(4) Ca^{2+}-bound synaptotagmin catalyzes membrane fusion

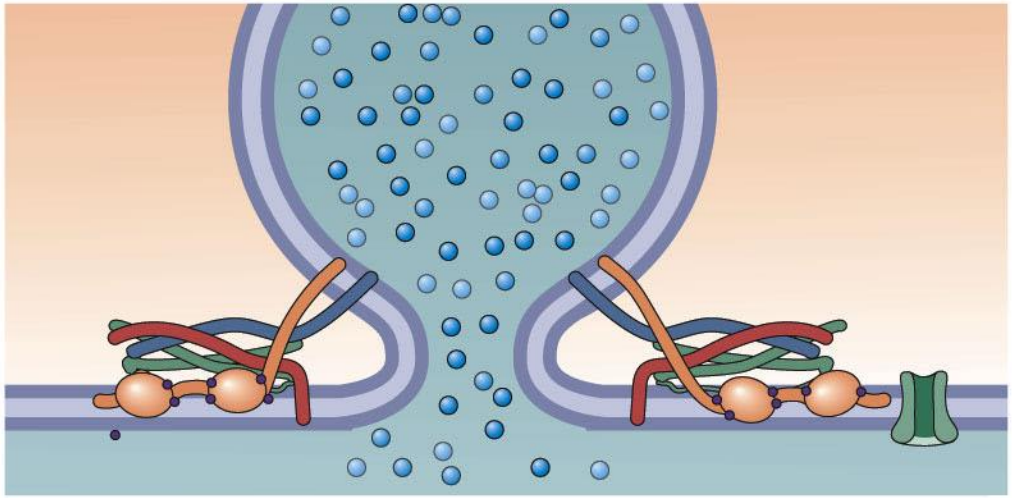
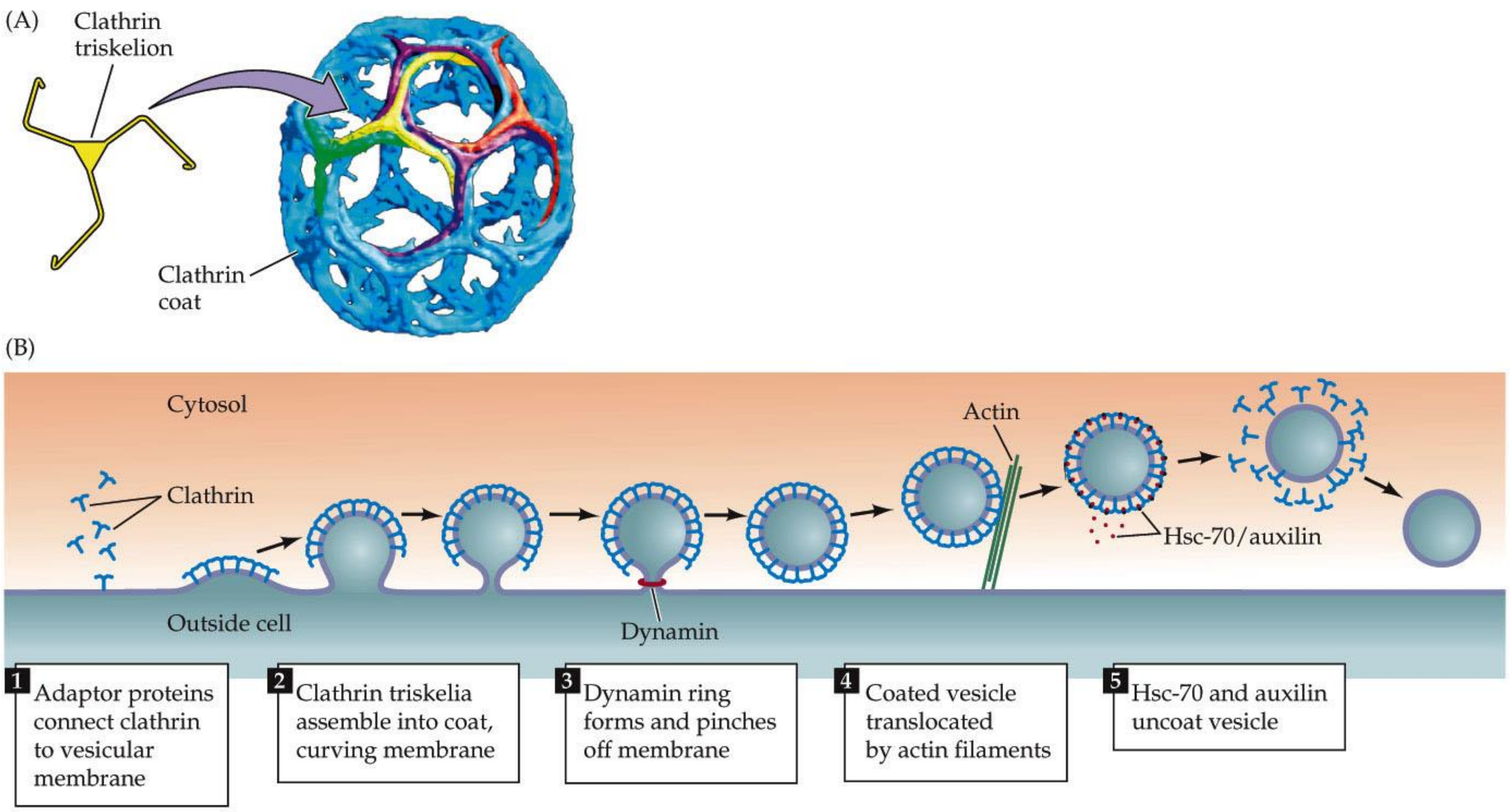
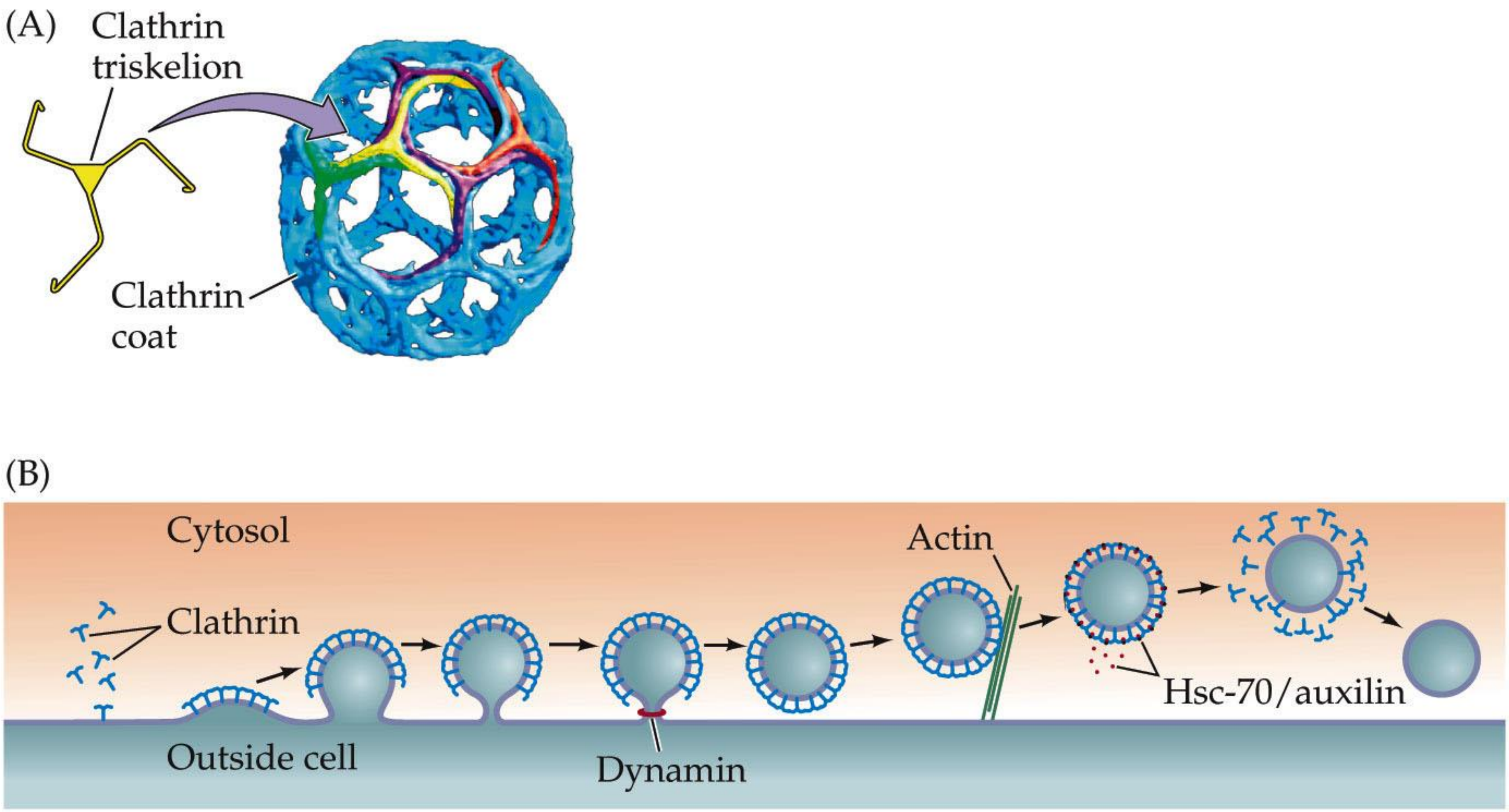


Figure 5.15 Molecular mechanisms of endocytosis following neurotransmitter release

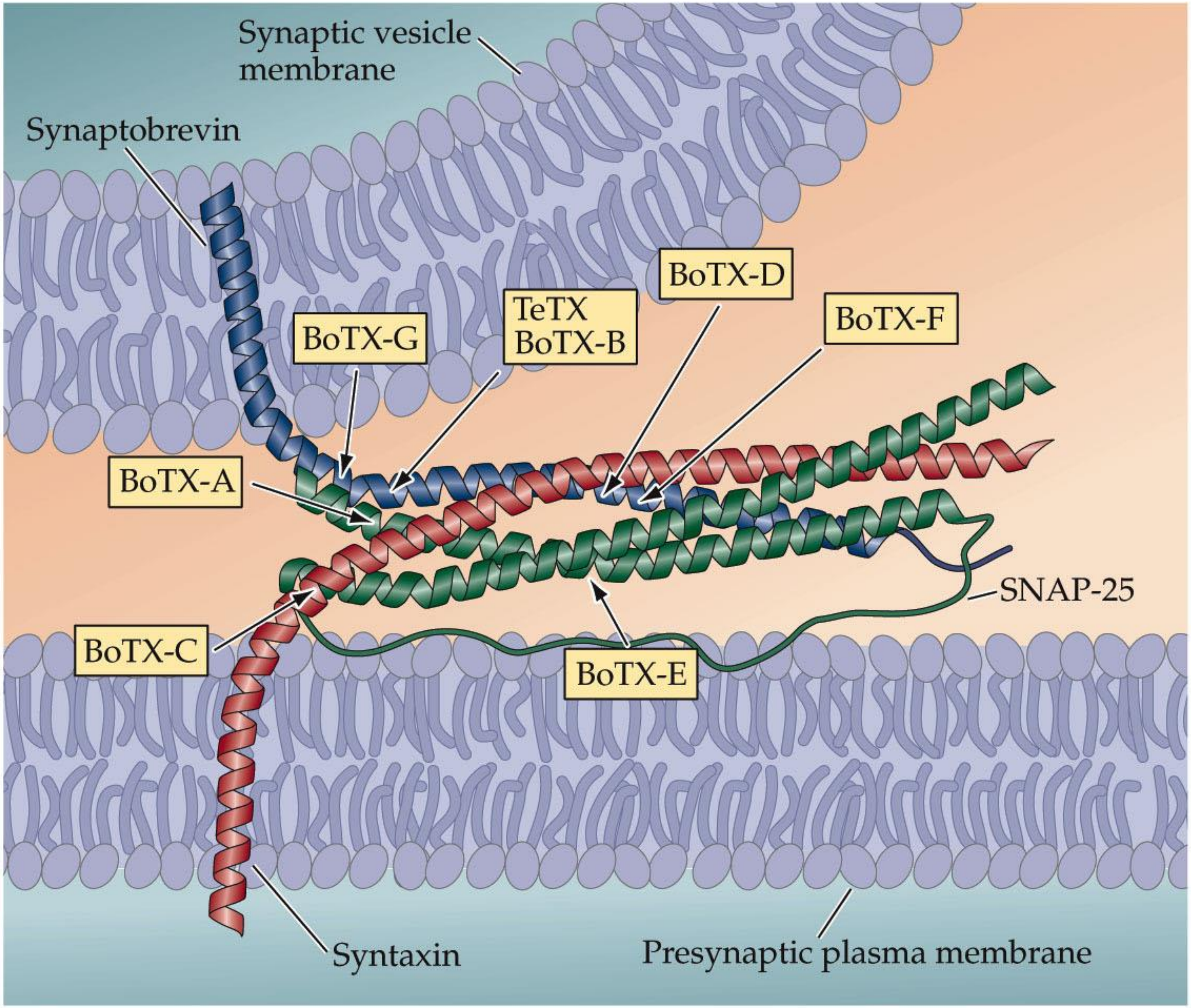


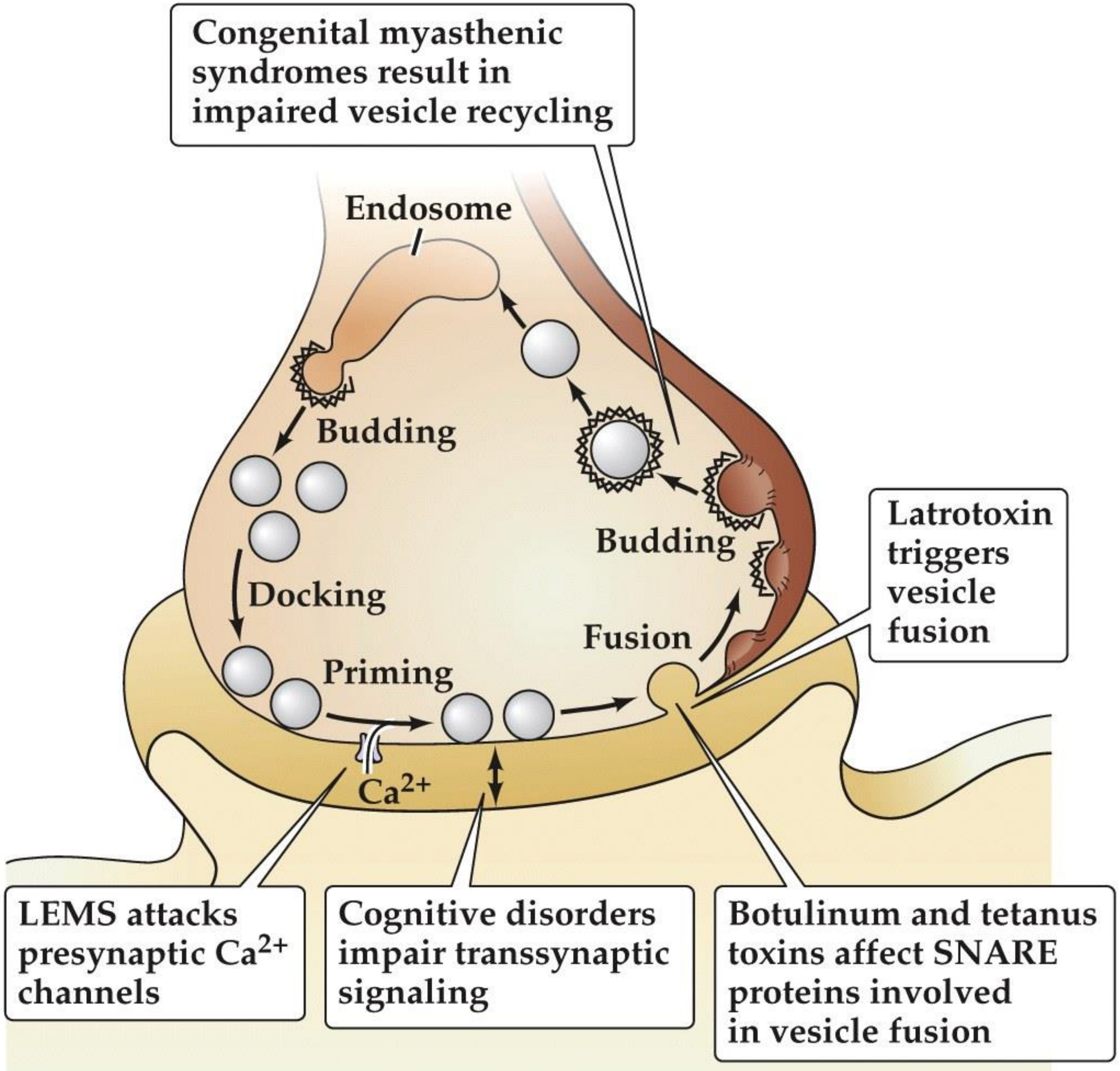
NEUROSCIENCE, *Fourth Edition*, Figure 5.15

Figure 5.15 Molecular mechanisms of endocytosis following neurotransmitter release



Box 5C Toxins That Affect Transmitter Release





***NEUROSCIENCE 5e*, Box 5B (Part 1)**