

HUMAN PHYSIOLOGY

FIFTEENTH EDITION

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Chapter 07

Lecture Outline



Because learning changes everything.[™]

I. Neurons and Supporting Cells

A. Introduction to the Nervous System

1. Divided into:
 - a. Central nervous system: brain and spinal cord
 - b. Peripheral nervous system: cranial and spinal nerves
2. Tissue is composed of two types of cells:
 - a. Neurons that conduct impulses but generally can not divide.
 - b. Glial cells (neuroglia) that support the neurons and can not conduct impulses, but can divide

Terminology Pertaining to the Nervous System

TABLE 7.1 Terminology Pertaining to the Nervous System

Term	Definition
Central nervous system (CNS)	Brain and spinal cord
Peripheral nervous system (PNS)	Nerves, ganglia, and nerve plexuses (outside of the CNS)
Interneuron	Multipolar neuron located entirely within the CNS
Sensory neuron (afferent neuron)	Neuron that transmits impulses from a sensory receptor into the CNS
Motor neuron (efferent neuron)	Neuron that transmits impulses from the CNS to an effector organ; for example, a muscle
Nerve	Cablelike collection of many axons in the PNS; may be “mixed” (contain both sensory and motor fibers)
Somatic motor nerve	Nerve that stimulates contraction of skeletal muscles
Autonomic motor nerve	Nerve that stimulates contraction (or inhibits contraction) of smooth muscle and cardiac muscle and that stimulates glandular secretion
Ganglion	Grouping of neuron cell bodies located outside the CNS
Nucleus	Grouping of neuron cell bodies within the CNS
Tract	Grouping of axons that interconnect regions of the CNS

B. Neurons

1. Structural and functional units of the nervous system
2. General functions
 - a. Respond to chemical and physical stimuli
 - b. Conduct electrochemical impulses
 - c. Release chemical regulators
 - d. Enable perception of sensory stimuli, learning, memory, and control of muscles and glands
3. Most can not divide, but can repair

Neurons (2)

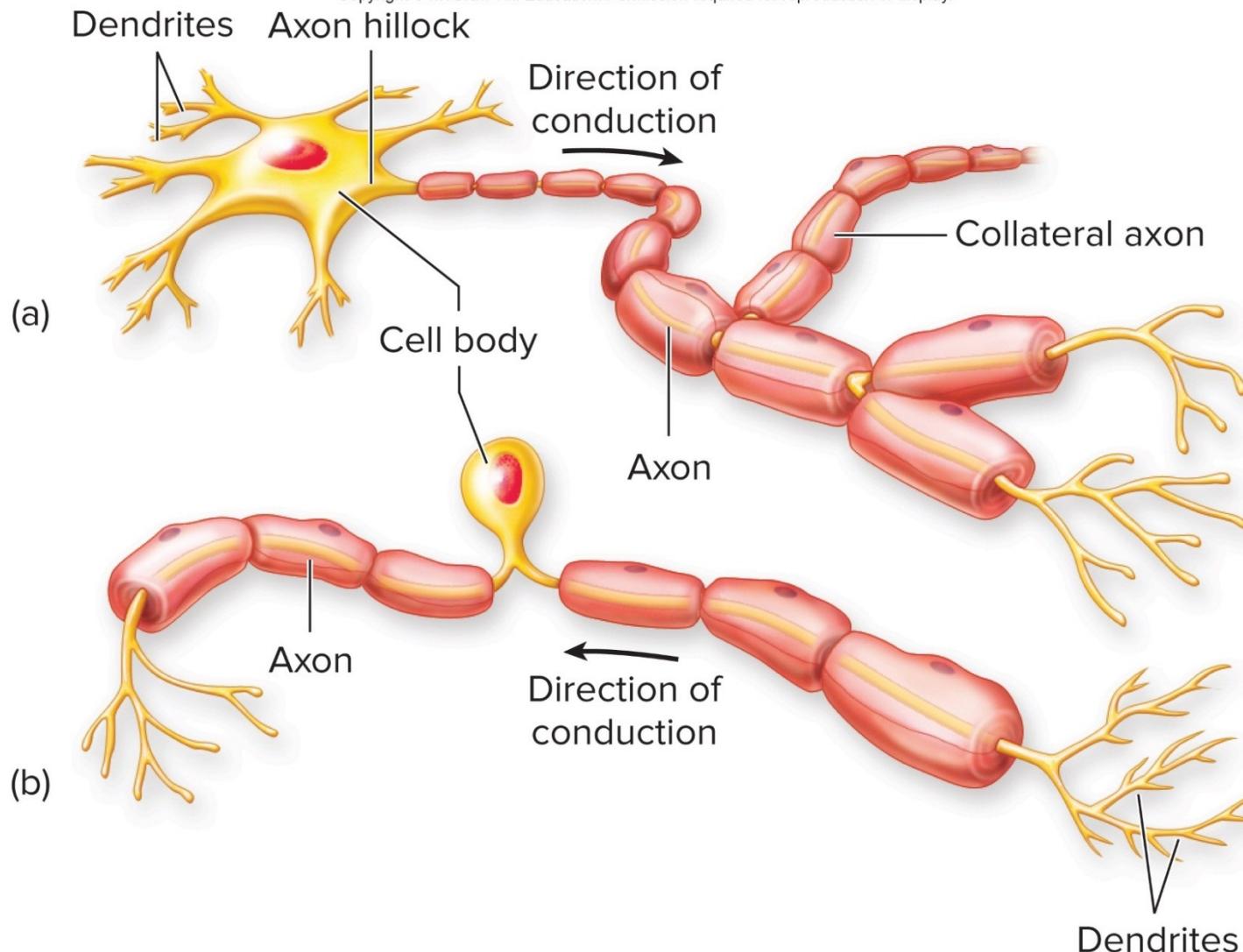
4. General Structure of Neurons

a. Neurons vary in size and shape, but they all have:

- 1) A cell body that contains the nucleus, Nissl bodies, and other organelles; cluster in groups called nuclei in the CNS and ganglia in the PNS
- 2) Dendrites: receive impulses and conducts a graded impulse toward the cell body
- 3) Axon: conducts action potentials away from the cell body

Structure of Two Kinds of Neurons

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Neurons (3)

b. Axons

- 1) Vary in length from a few millimeters to a meter
- 2) Connected to the cell body by the axon hillock where action potentials are generated at the initial segment of the axon.
- 3) Can form many branches called axon collaterals
- 4) Covered in myelin with open spots called nodes of Ranvier

Neurons (4)

5. Axonal Transport

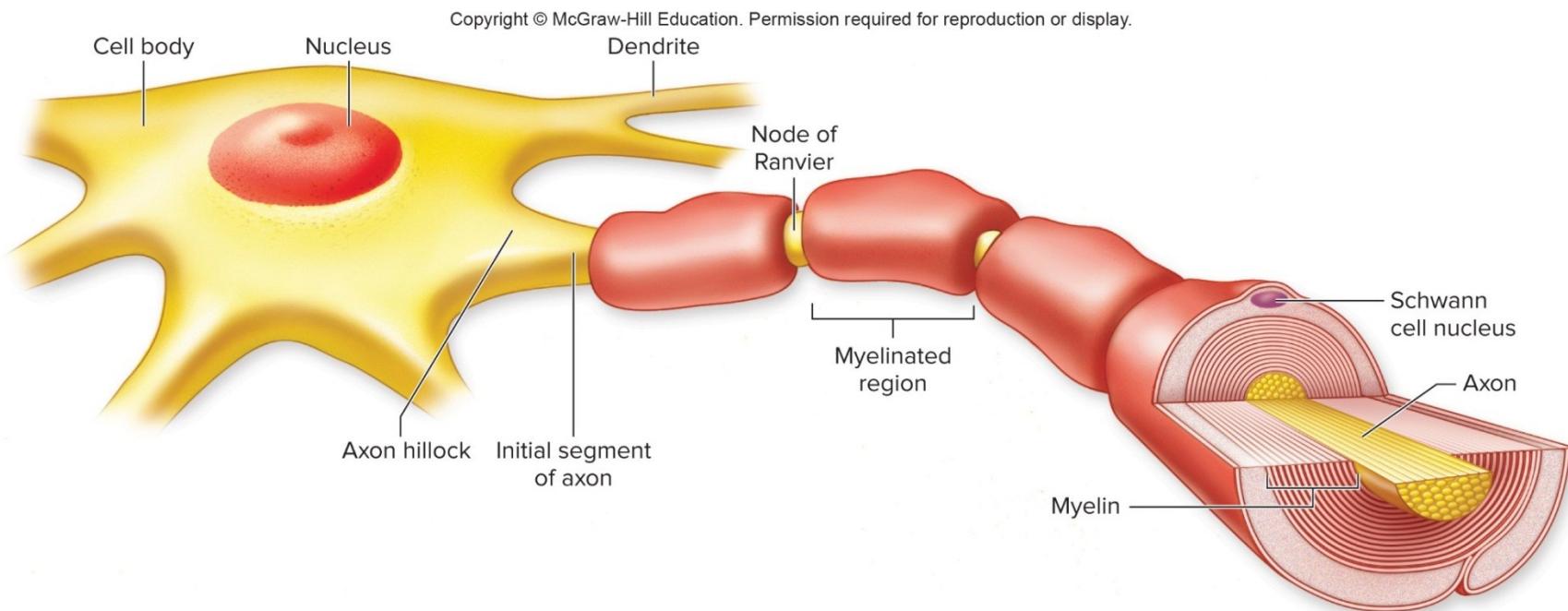
- a) An active process needed to move organelles and proteins from the cell body to axon terminals
- b) Fast component moves membranous vesicles
- c) Slow components move microfilaments, microtubules, and proteins

Neurons (5)

Axonal Transport, Continued

- d) Anterograde transport—from cell body to dendrites and axon; uses kinesin molecular motors
- e) Retrograde transport—from dendrites and axon to the cell body; uses dynein molecular motors

Parts of a Neuron



C. Classification of Neurons and Nerves

1. Functional classification of neurons—based on direction impulses are conducted
 - a. Sensory neurons: conduct impulses from sensory receptors to the CNS (afferent)
 - b. Motor neurons: conduct impulses from the CNS to target organs (muscles or glands; efferent)
 - c. Association/interneurons: located completely within the CNS and integrate functions of the nervous system

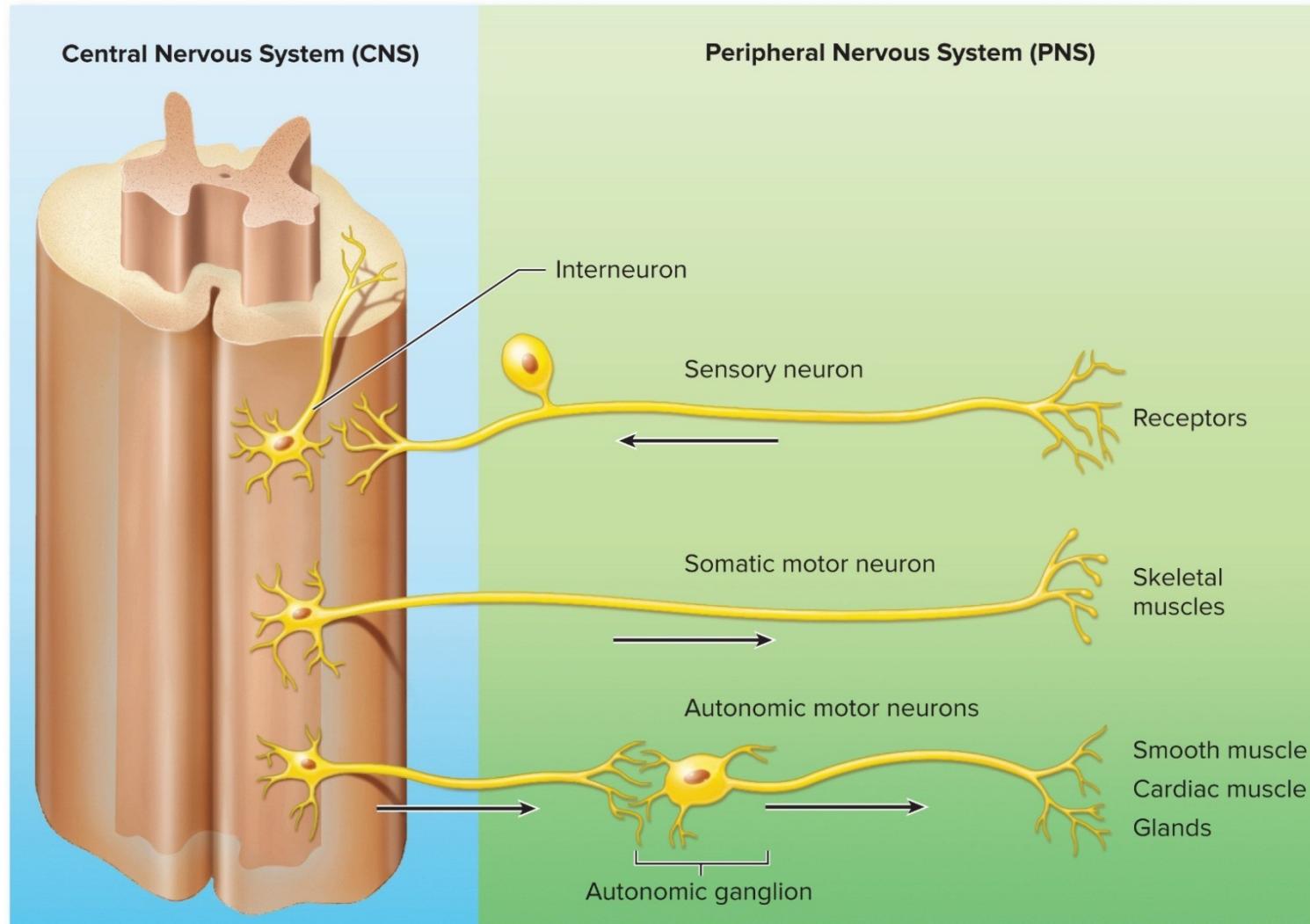
Classification of Neurons and Nerves (2)

2. Motor Neurons

- a. Somatic motor neurons: responsible for reflexes and voluntary control of skeletal muscles
- b. Autonomic motor neurons: innervate involuntary targets such as smooth muscle, cardiac muscle, and glands
 - 1) Sympathetic—emergency situations; “fight or flight”
 - 2) Parasympathetic—normal functions; “rest and digest”

Functional Categories of Neurons

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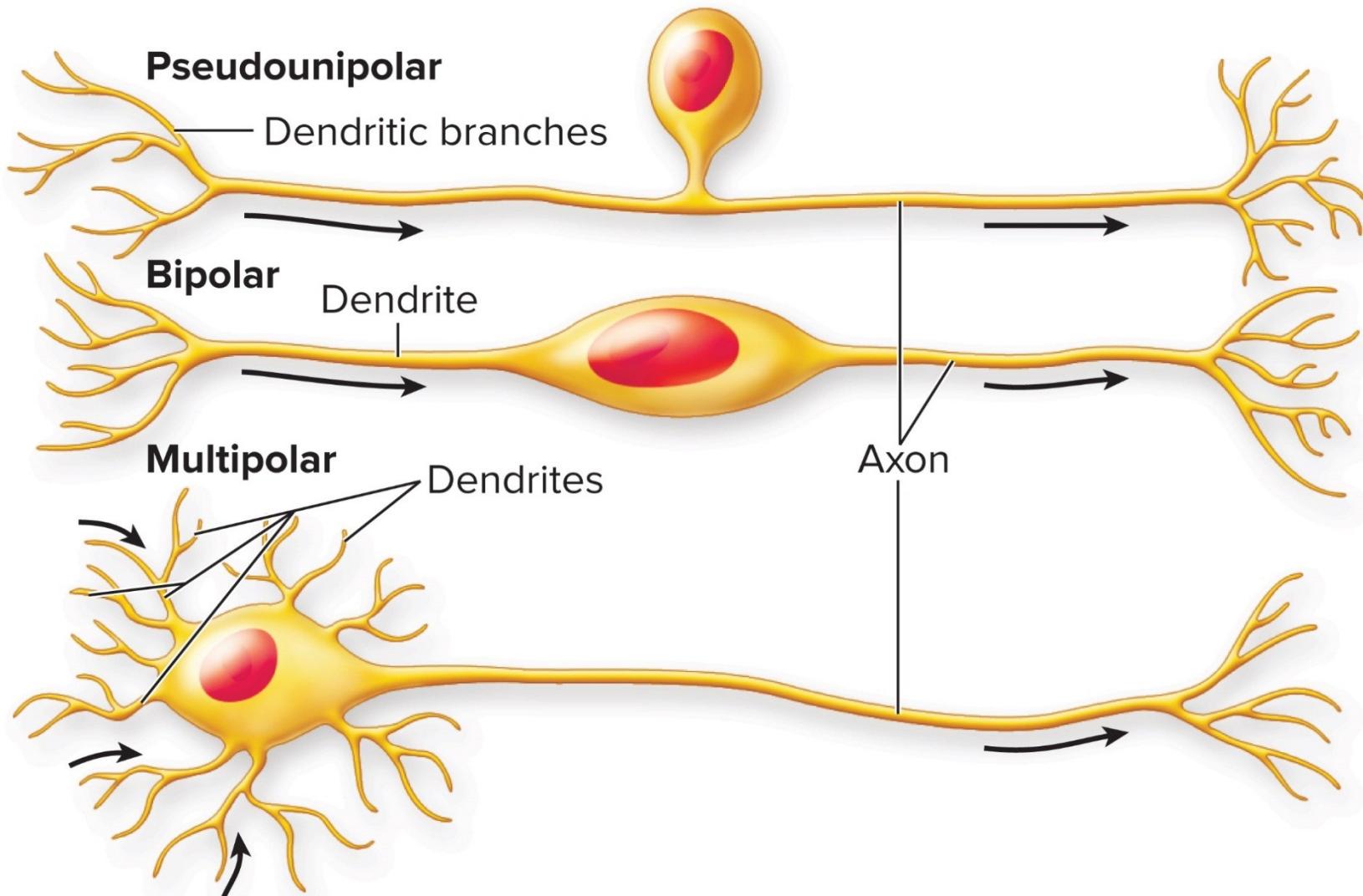
Classification of Neurons and Nerves (3)

3. Structural Classification of Neurons

- a. Based on the number of processes that extend from the cell body.
- b. Pseudounipolar: single short process that branches like a T to form 2 longer processes; sensory neurons
- c. Bipolar neurons: have two processes, one on either end; found in retina of eye
- d. Multipolar neurons: several dendrites and one axon; most common type

Structural Classification of Neurons

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Classification of Neurons and Nerves (4)

4. Classification of Nerves

- a. Nerves are bundles of axons located outside the CNS
- b. Most are composed of both sensory and motor neurons and are called mixed nerves.
- c. Some of the cranial nerves have sensory fibers only.
- d. A bundle of axons in the CNS is called a tract.

D. Neuroglia (Glial Cells)

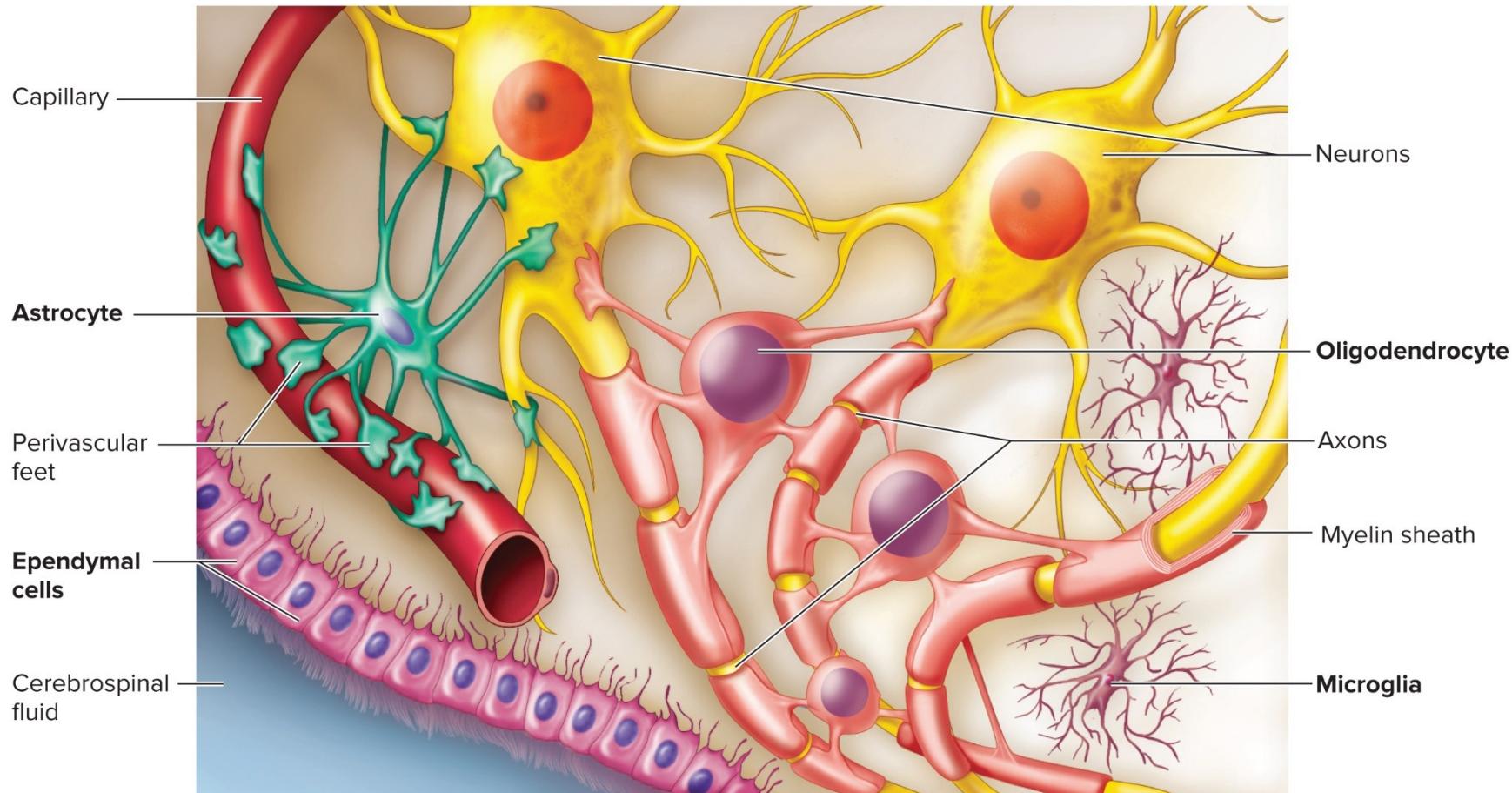
1. Cells that are non-conducting but support neurons
2. Two types are found in the PNS:
 - a. Schwann cells (neurolemmocytes): form myelin sheaths around peripheral axons
 - b. Satellite cells (ganglionic gliocytes): support cell bodies within the ganglia of the PNS

Neuroglia (Glial Cells) (2)

3. Four types are found in the CNS:
 - a. Oligodendrocytes: form myelin sheaths around the axons of CNS neurons
 - b. Microglia: migrate around CNS tissue and phagocytize foreign and degenerated material
 - c. Astrocytes: regulate the external environment of the neurons
 - d. Ependymal cells: line the ventricles and secrete cerebrospinal fluid

Types of CNS Neuroglial Cells

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Neuroglial Cells and Their Functions

TABLE 7.2 Neuroglia and Their Functions

Cell Type	Location	Functions
Schwann cells	PNS	Also called neurolemmocytes, produce the myelin sheaths around the myelinated axons of the peripheral nervous system; surround all PNS axons (myelinated and nonmyelinated) to form a neurilemmal sheath
Satellite cells	PNS	Support functions of neurons within sensory and autonomic ganglia
Oligodendrocytes	CNS	Form myelin sheaths around central axons, producing “white matter” of the CNS
Microglia	CNS	Phagocytose pathogens and cellular debris in the CNS
Astrocytes	CNS	Cover capillaries of the CNS and induce the blood-brain barrier; interact metabolically with neurons and modify the extracellular environment of neurons
Ependymal cells	CNS	Form the epithelial lining of brain cavities (ventricles) and the central canal of the spinal cord; cover tufts of capillaries to form choroid plexuses—structures that produce cerebrospinal fluid

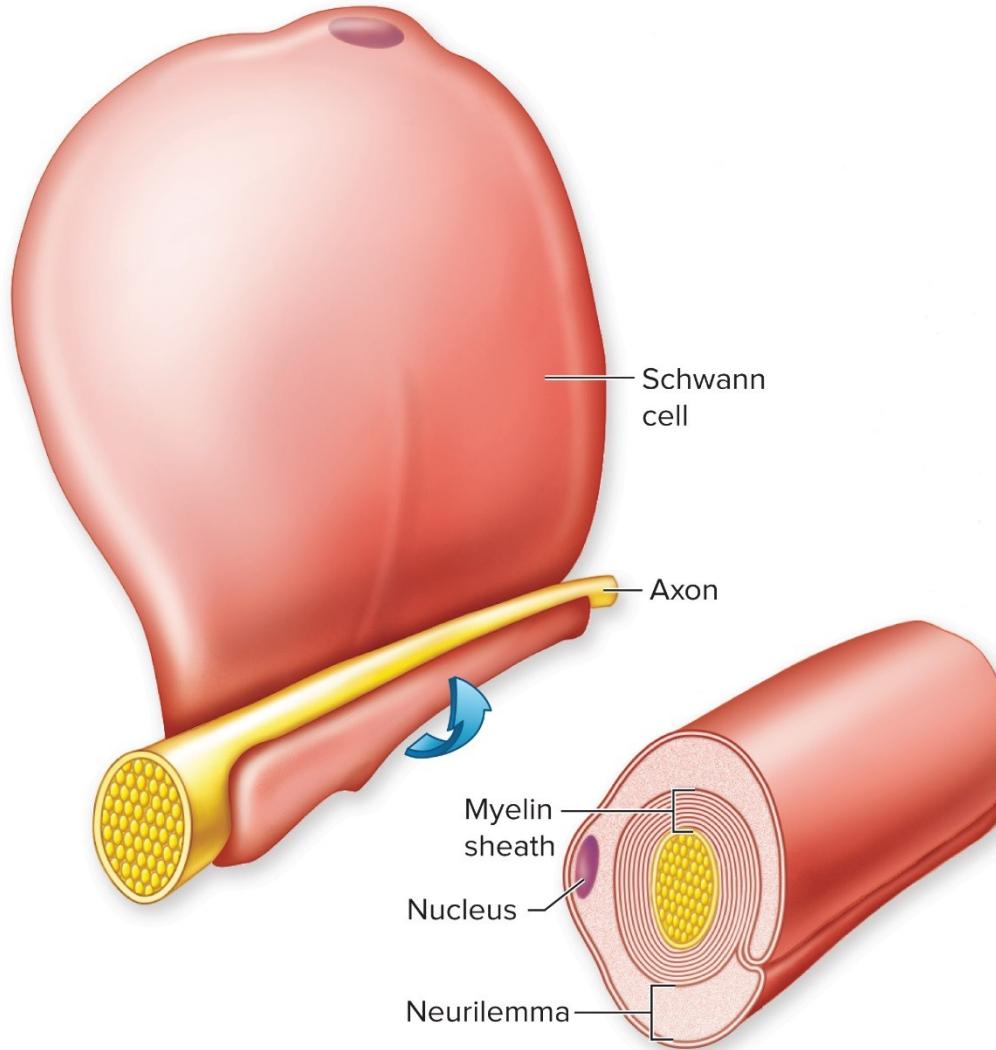
E. Neurilemma and Myelin

1. Myelin sheath in the PNS

- a. All axons in the PNS are surrounded by a sheath of Schwann cells called the neurilemma, or sheath of Schwann.
- b. These cells wrap around the axon to form the myelin sheath in the PNS.
- c. Gaps between Schwann cells, called nodes of Ranvier, are left open.

Neurilemma and Myelin (2)

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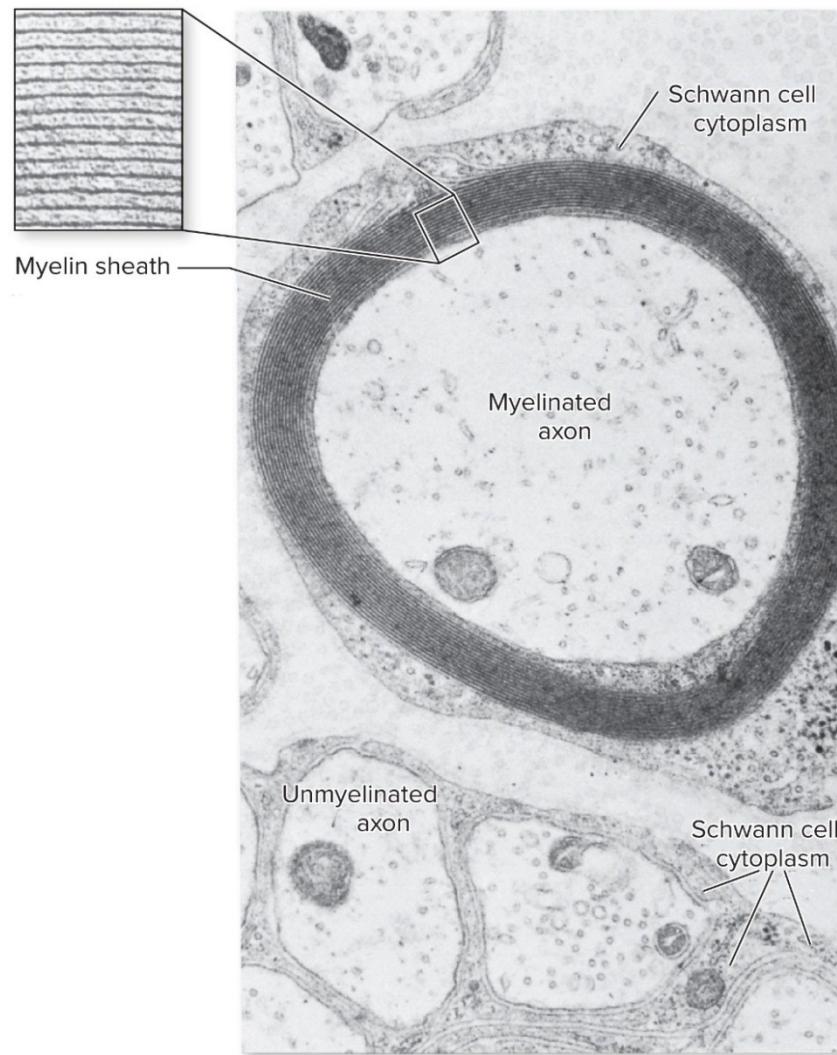
Neurilemma and Myelin (3)

Myelin sheath in the PNS, Continued

- d. Small axons (2 micrometers in diameter) are usually unmyelinated.
- e. Even unmyelinated axons in the PNS have a neurilemma but lack the multiple wrappings of the Schwann cell plasma membrane
- f. Myelinated axons conduct impulses more rapidly.

Unmyelinated & Myelinated Axons

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Neurilemma and Myelin (4)

2. Myelin Sheath in CNS

- a. In the CNS, the myelin sheath is produced by oligodendrocytes.
- b. One oligodendrocyte sends extensions to several axons and each wraps around a section of an axon
- c. Produces the myelin sheath but not a neurilemma

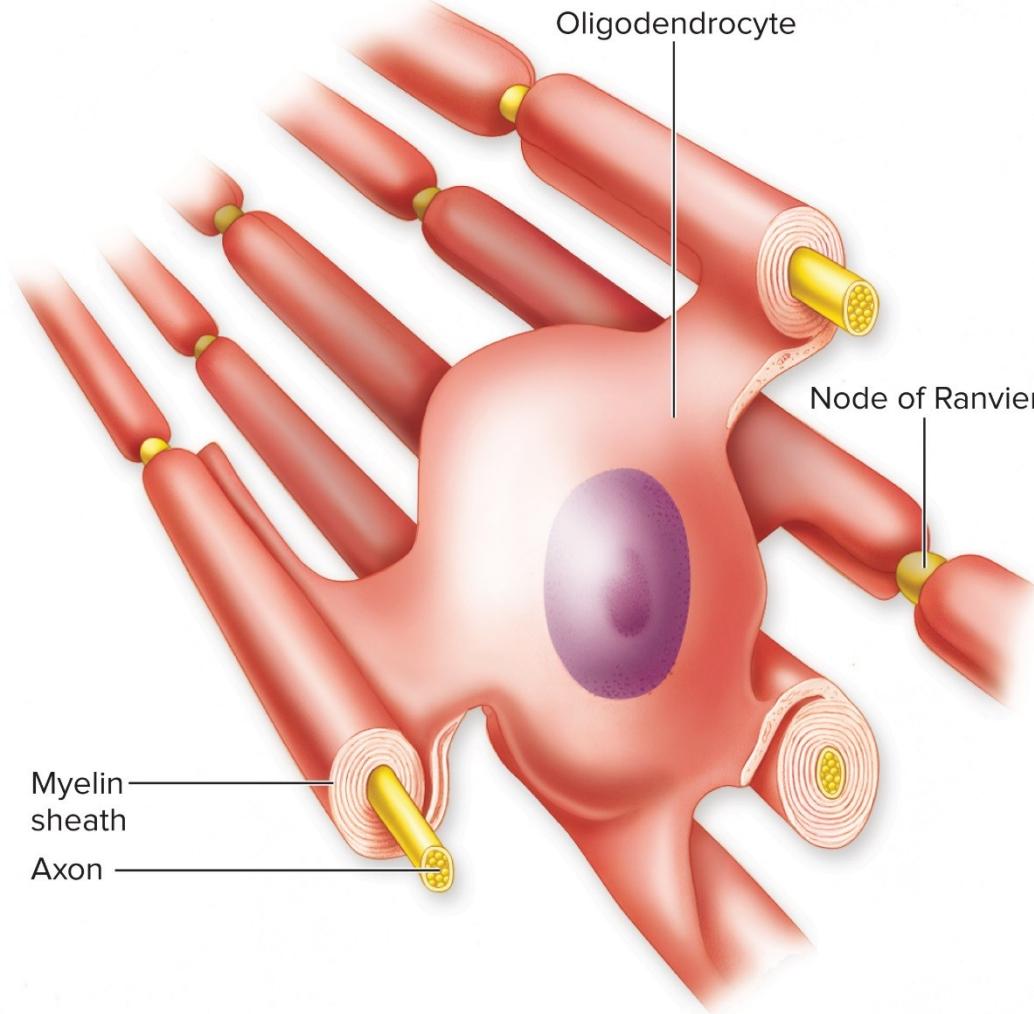
Neurilemma and Myelin (5)

Myelin Sheath in CNS, Continued

- d. Myelin gives these tissues (axons) a white color = white matter.
- e. Gray matter is cell bodies and dendrites which lack myelin sheaths

Myelin Sheath in CNS

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Demyelinating Diseases

Demyelinating diseases are those in which the myelin sheaths are specifically attacked.

- Guillain-Barre syndrome: the T cells of the immune system attack the myelin sheaths of the PNS. This produces rapid onset of symptoms that include muscle weakness.
- Multiple sclerosis (MS): produced by an autoimmune attack by T lymphocytes causing lymphocytes and monocyte-derived macrophages to enter the brain and target the myelin sheaths. causing demyelination.

Neurilemma and Myelin (6)

3. Regeneration of a Cut Neuron

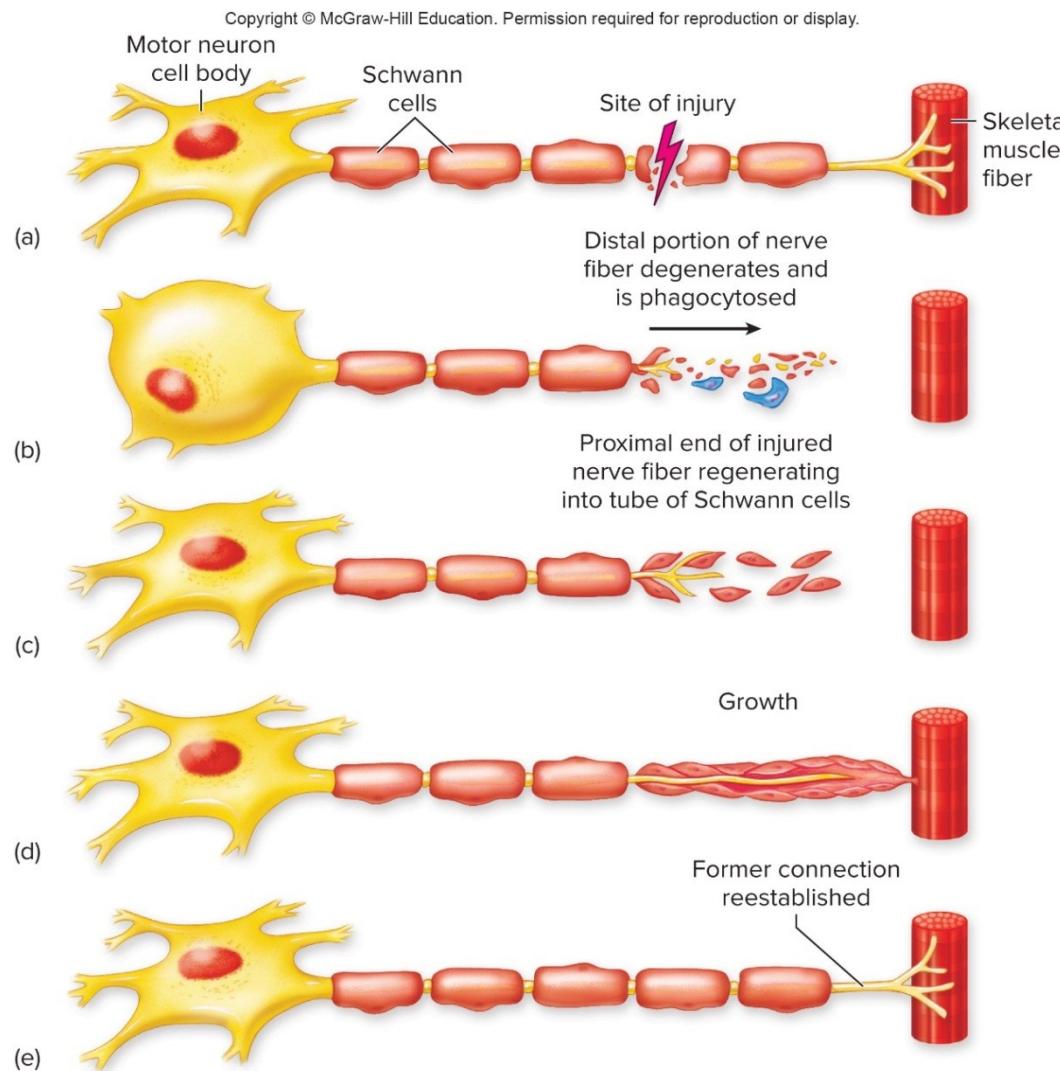
- a. When an axon in the PNS is cut, the severed part degenerates, and a regeneration tube is formed by Schwann cells.
 - 1) Growth factors are leased that stimulate growth of axon sprouts within the tube
 - 2) New axon eventually connects to the undamaged axon or the effector

Neurilemma and Myelin (7)

Regeneration of a Cut Neuron, Continued

- b. CNS axons are not as able to regenerate.
 - 1) Death receptors form that promote apoptosis of oligodendrocytes
 - 2) Inhibitory proteins in the myelin sheath prevents regeneration
 - 3) Glial scars from astrocytes form that also prevent regeneration

Process of PNS Regeneration



CNS Regeneration

4. CNS Regeneration

- a. Injury in the CNS stimulates growth of axon collaterals, but central axons have a much more limited ability to regenerate than peripheral axons.
- b. Proteins called *Nogo*, produced predominantly by oligodendrocytes, inhibit axon regeneration in the CNS.
- c. Studies of potential stem cell therapies for human spinal cord injuries offer hope but should be interpreted cautiously.

Neurilemma and Myelin (8)

5. Neurotrophins

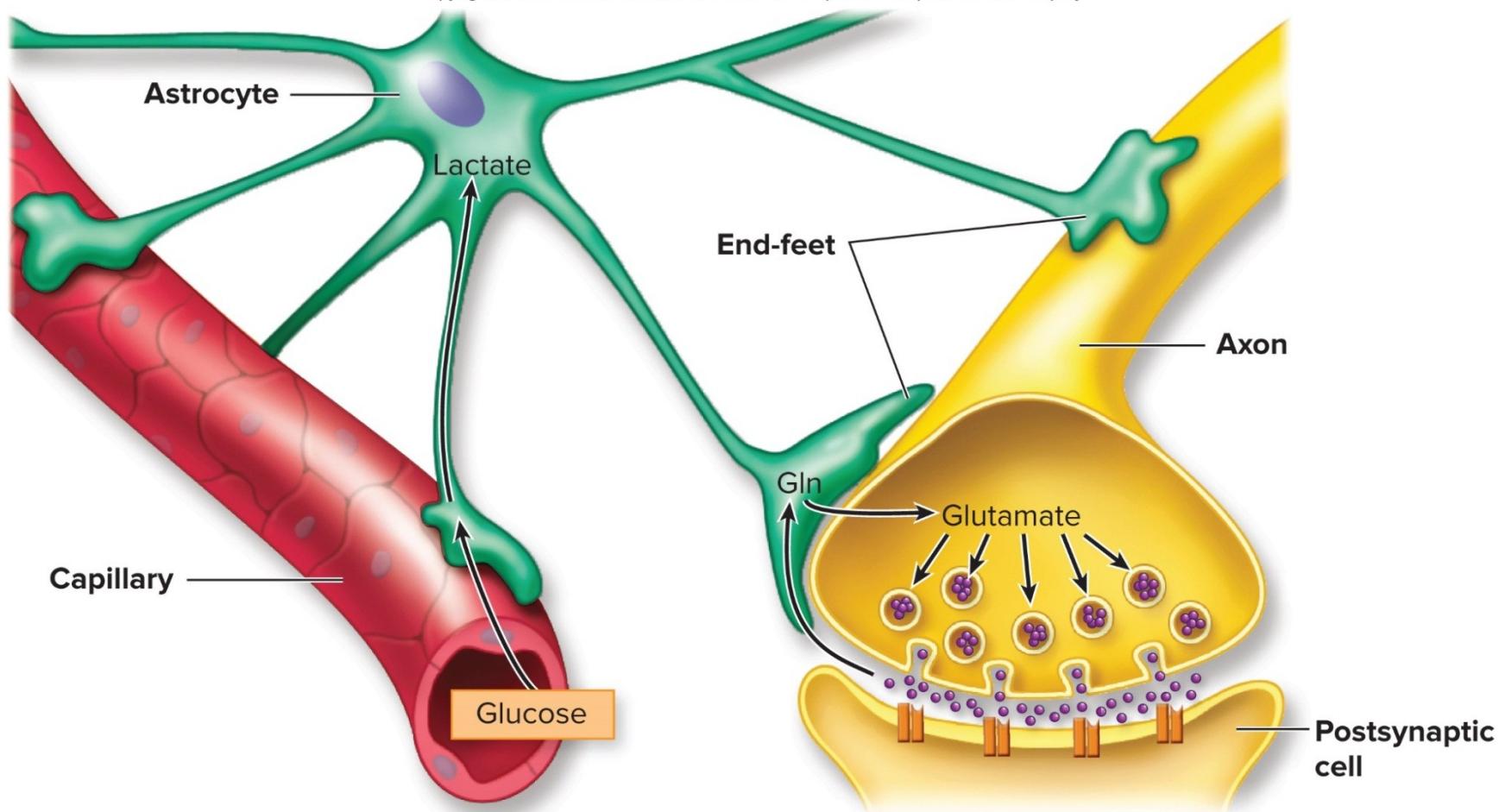
- a. Promote neuronal growth in the fetal brain
 - a. Nerve growth factor (NGF)
 - b. Brain-derived neurotrophic factor (BDNF)
 - c. Glial-derived neurotrophic factor (GDNF)
 - d. Neurotrophin-3, neurotrophin-4/5
- b. In adults, neurotrophins aid in the maintenance of sympathetic ganglia and the regeneration of sensory neurons.

F. Astrocytes

1. Most abundant glial cell
2. Processes with end-feet associate with blood capillaries and axon terminals
3. Influences interactions between neurons and between neurons and blood

Astrocyte Interactions

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Astrocytes (2)

4. Astrocyte Functions

- a. Take up K^+ from the extracellular environment to maintain ionic environment for neurons
- b. Take up extra neurotransmitter released from axon terminals, particularly glutamate. Chemicals are recycled.
- c. End-feet around capillaries take up glucose from blood for use by neurons to make ATP; converted first to lactic acid
- d. Can store glycogen and produce lactate for neurons to use

Astrocytes (3)

Astrocyte Functions, Continued

- e. Needed for the formation of synapses in the CNS
- f. Regulate neurogenesis in regions of the adult brain
- g. Form the blood-brain barrier
- h. Release transmitter molecules (gliotransmitters) that can stimulate or inhibit neurons; includes glutamate, ATP, adenosine, D-serine

Astrocytes (4)

5. Astrocytes and Neural Activity

- a. Although astrocytes do not produce action potentials, they are excited by changes in intracellular Ca^{2+} concentration.
- b. When some neurons are active, they release ATP, which increases the Ca^{2+} of adjacent astrocytes; creates a Ca^{2+} wave
- c. A rise in Ca^{2+} can also cause the astrocyte release prostaglandin E_2 from the end-feet on a blood capillary, increasing blood flow.

Astrocytes (5)

6. Blood-Brain Barrier

- a. Capillaries in the brain do not have pores between adjacent cells but are joined by tight junctions.
- b. Substances can only be moved by very selective processes of diffusion through endothelial cells, active transport, and bulk transport

Astrocytes (6)

Blood-Brain Barrier, Continued

- c. Movement is transcellular not paracellular
- d. Astrocytes influence the production of ion channels and enzymes that can destroy toxic substances by secreting glial-derived neurotrophic factor.
- e. Creates problems with chemotherapy of brain diseases because many drugs can not penetrate the blood-brain barrier.

II. Electrical Activity in Axons

A. Resting Membrane Potential

1. Neurons have a resting potential of -70mV .
 - a. Established by large negative molecules inside the cell
 - b. Na^+/K^+ pumps
 - c. Permeability of the membrane to positively charged, inorganic ions
2. At rest, there is a high concentration of K^+ inside the cell and Na^+ outside the cell.

Resting Membrane Potential (2)

3. Altering Membrane Potential
 - a. Neurons and muscle cells can change their membrane potentials.
 - b. Called excitability or irritability
 - c. Caused by changes in the permeability to certain ions
 - d. Ions will follow their electrochemical gradient = combination of concentration gradient and attraction to opposite charges.
 - e. Flow of ions are called ion currents which occur in limited areas where ion channels are located

Resting Membrane Potential (3)

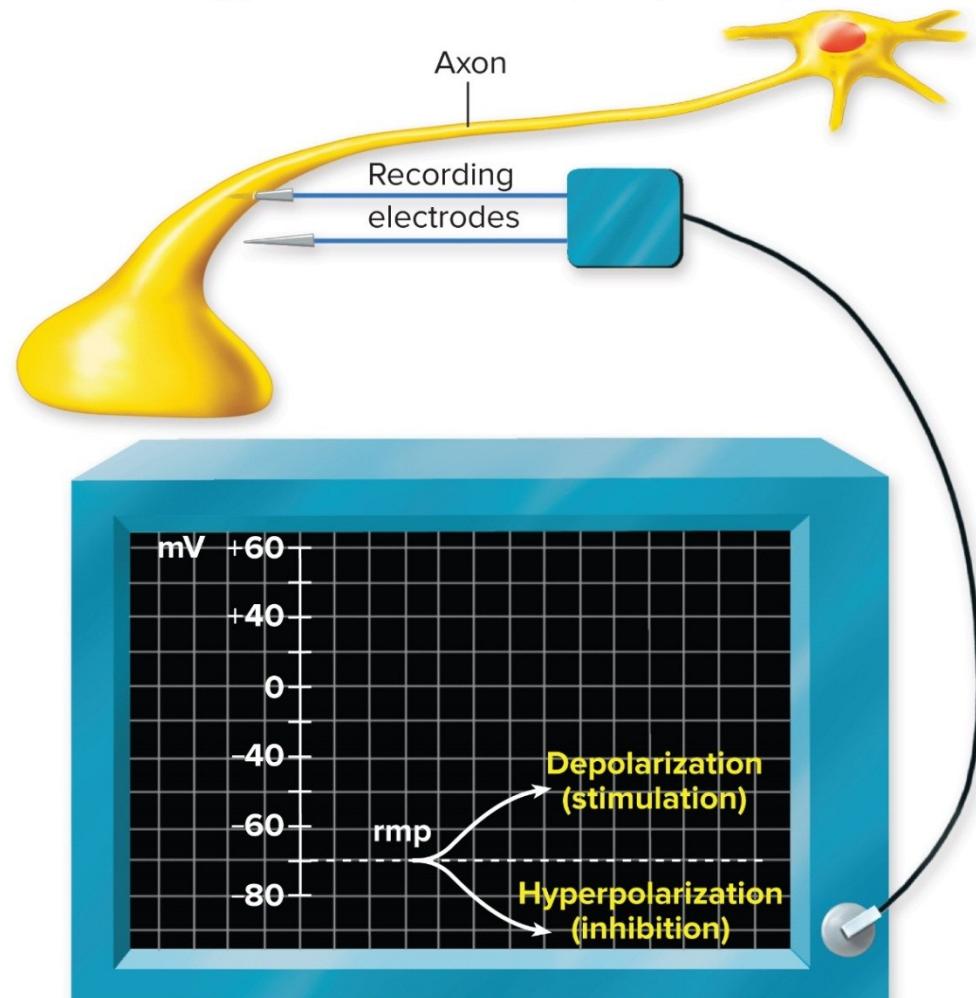
4. Changes in Membrane Potential

- a. At rest, a neuron is considered polarized when the inside is more negative than the outside.
- b. When the membrane potential inside the cell increases (becomes more positive), this is called depolarization.
- c. A return to resting potential is called repolarization.
- d. When the membrane potential inside the cell decreases (becomes more negative), this is called hyperpolarization.

Changes in Membrane Potential

Changes can be recorded on an oscilloscope by recording the voltage inside and outside the cell.

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Changes in Membrane Potential (2)

- e. Depolarization occurs when positive ions enter the cell (usually Na^+).
- f. Hyperpolarization occurs when positive ions leave the cell (usually K^+) or negative ions (Cl^-) enter the cell.
- g. Depolarization of the cell is excitatory.
- h. Hyperpolarization is inhibitory.

B. Ion Gating in Axons

1. Changes in membrane potential are controlled by changes in the flow of ions through channels.
 - a. K^+ has two types of channels:
 - 1) Not gated (always open); sometimes called K^+ leakage channels
 - 2) Voltage-gated K^+ channels; open when a particular membrane potential is reached; closed at resting potential
 - b. Na^+ has only voltage-gated channels that are closed at rest; the membrane is less permeable to Na^+ at rest.

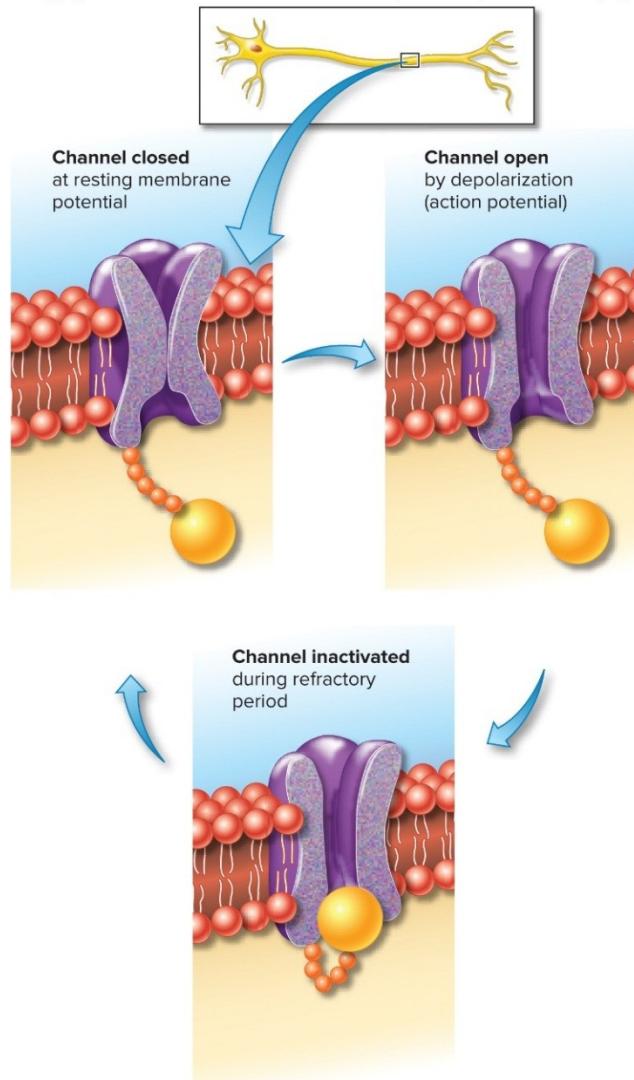
Ion Gating in Axons (2)

2. Voltage-Gated Na^+ Channels

- a. These channels open if the membrane potential depolarizes to -55mV .
- b. This is called the threshold.
- c. Sodium rushes in due to the electrochemical gradient.
- d. Membrane potential climbs toward sodium equilibrium potential.
- e. These channels are deactivated at $+30\text{mV}$.

A Voltage-Gated Ion Channel

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Ion Gating in Axons (3)

3. Voltage-Gated K⁺ Channels

- a. At around +30mV, voltage-gated K⁺ channels open, and K⁺ rushes out of the cell following the electrochemical gradient.
- b. This makes the cell repolarize back toward the potassium equilibrium potential.

C. Action Potentials

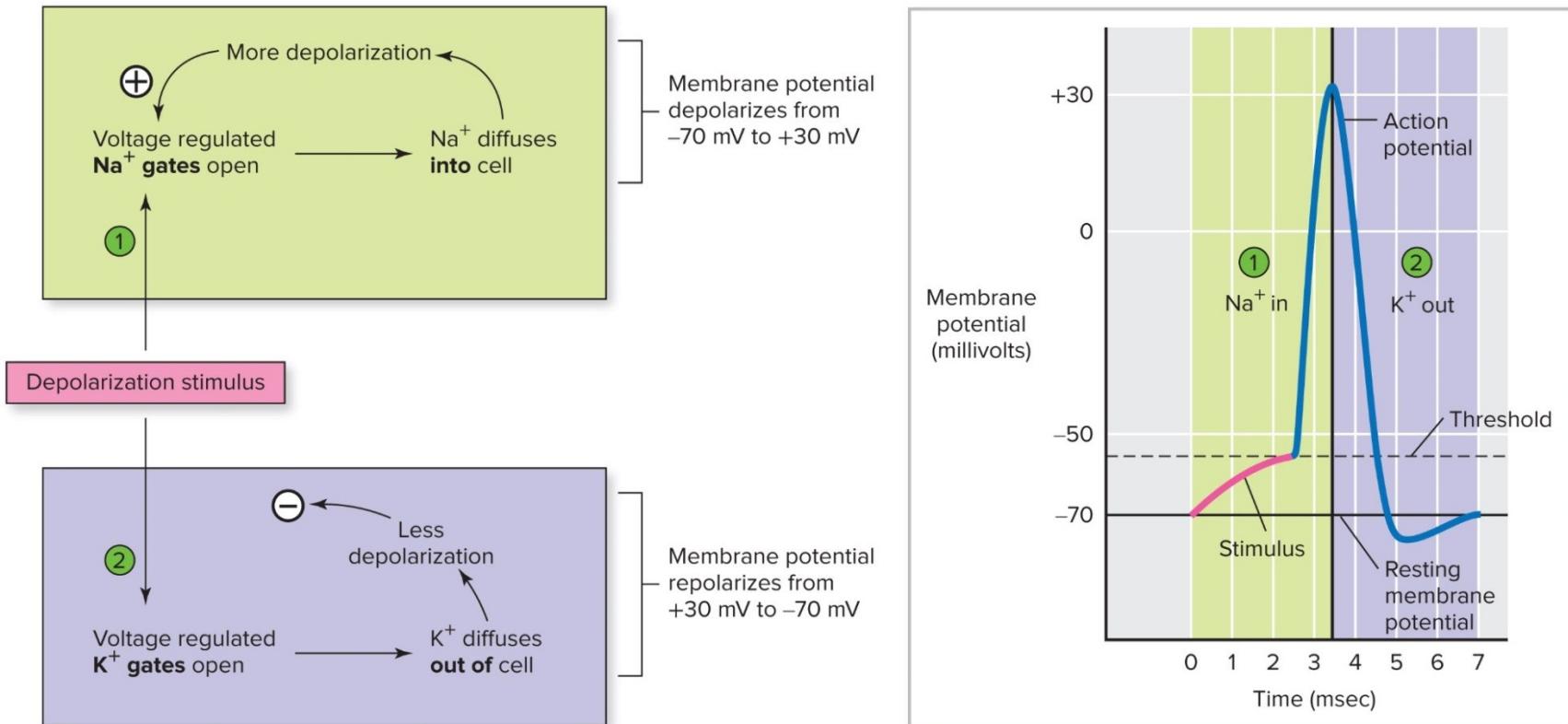
1. At threshold membrane potential (-55mV), voltage-gated Na^+ channels open, and Na^+ rushes in. As the cell depolarizes, more Na^+ channels are open, and the cell becomes more and more permeable to Na^+ .
 - a. This is a positive feedback loop.
 - b. Causes an overshoot of the membrane potential
 - c. Membrane potential reaches $+30\text{mV}$.
 - d. This is called depolarization

Action Potentials (2)

2. At +30mV, Na^+ channels close, and K^+ channels open.
 - a. Results in repolarization of membrane potential
 - b. This is a negative feedback loop

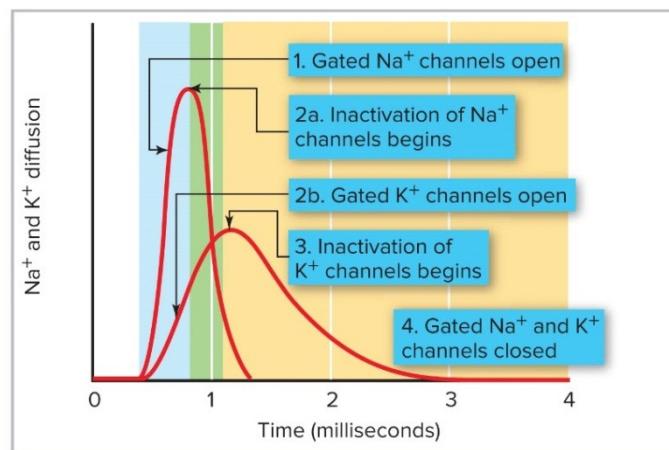
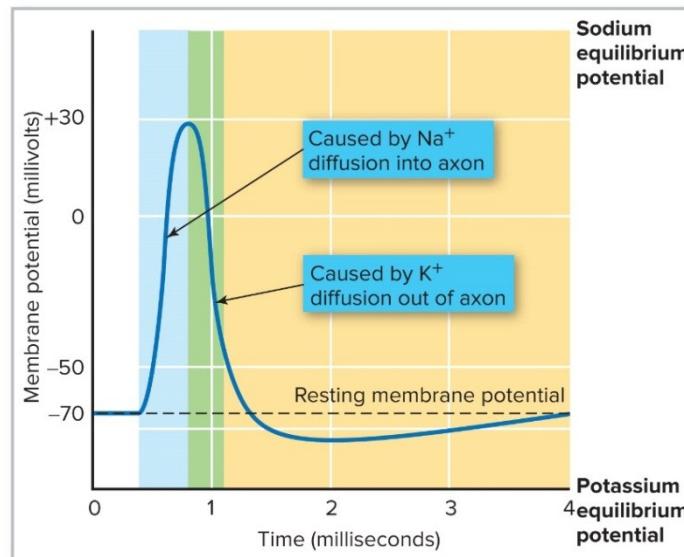
Depolarization of an Axon

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Action Potentials (3)

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Action Potentials (4)

3. After-Hyperpolarization

- a. Repolarization actually overshoots resting potential and gets down to -85mV .
- b. This does not reach potassium equilibrium potential because voltage-gated K^+ channels are inactivated as the membrane potential falls.
- c. Na^+/K^+ pumps quickly reestablish resting potential.

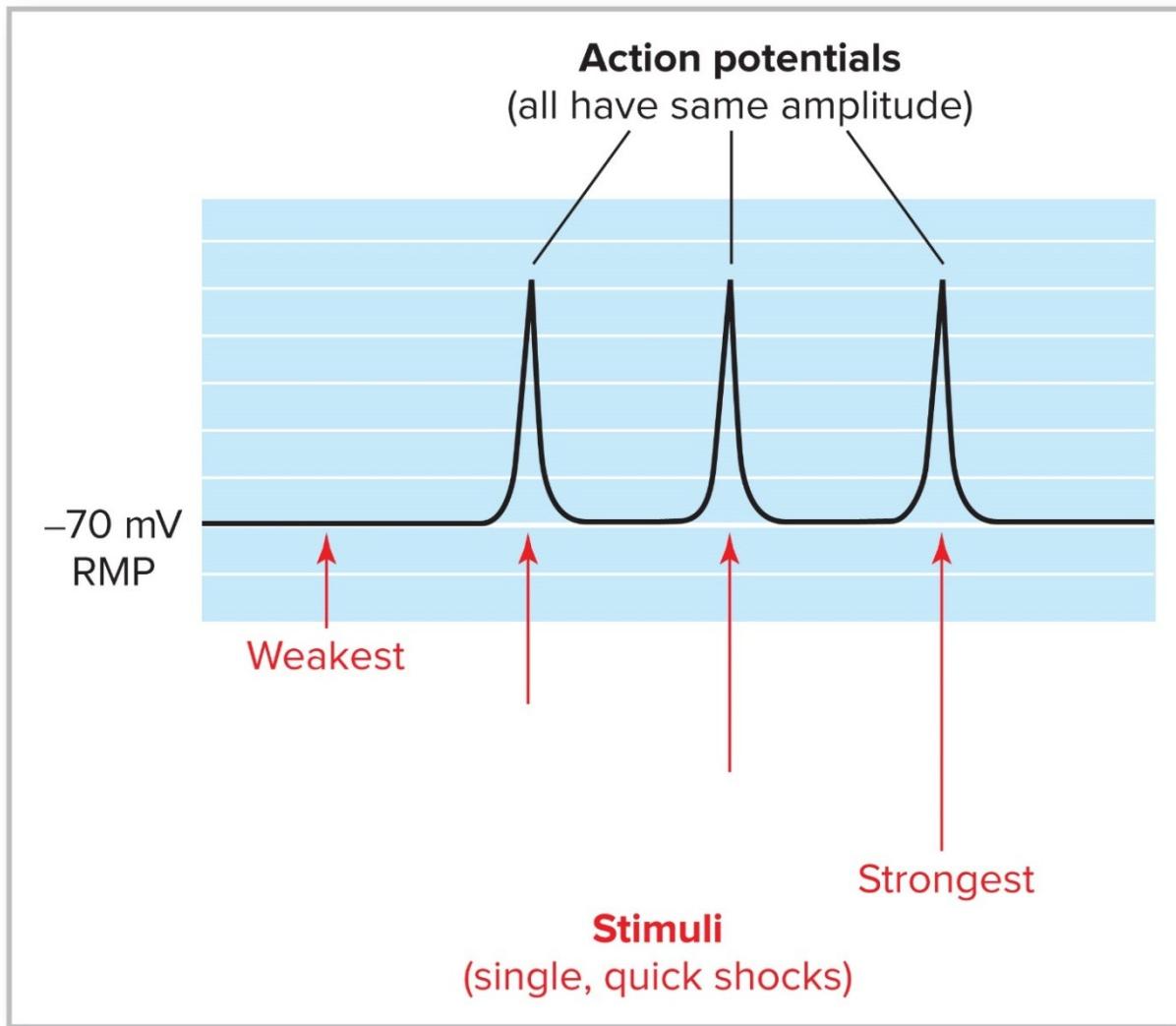
Action Potentials (5)

4. All-or-None Law

- a. Once threshold has been reached, an action potential will happen.
- b. The size of the stimulus will not affect the size of the action potential; it will always reach +30mV.
- c. The size of the stimulus will not affect action potential duration.

All-or-None Law

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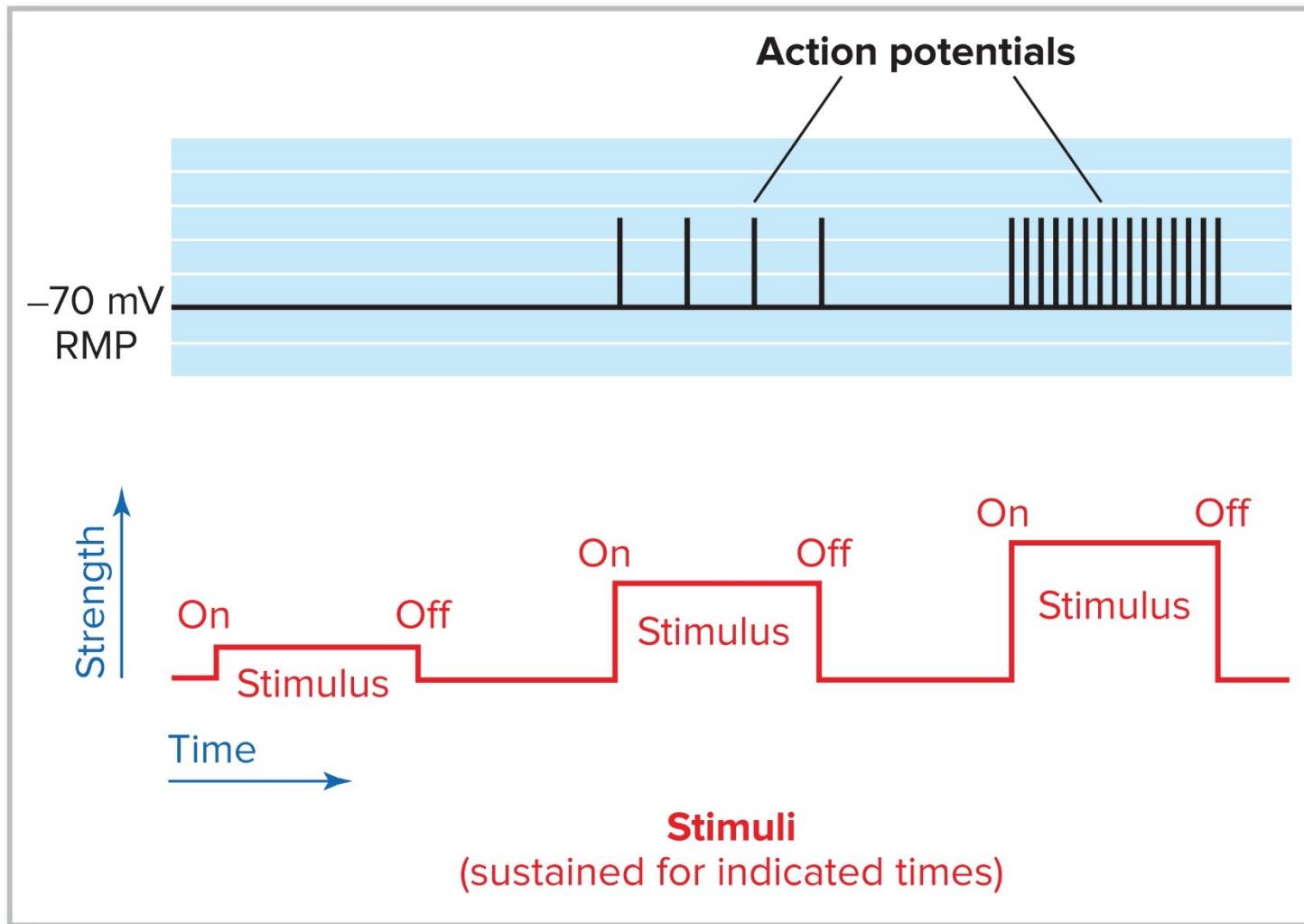
Action Potentials (6)

5. Coding for Stimulus Intensity

- a. A stronger stimulus will make action potentials occur more frequently. (frequency modulated)
- b. A stronger stimulus may also activate more neurons in a nerve. This is called recruitment.

Coding for Stimulus Intensity

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Action Potentials (7)

6. Refractory Periods

- a. Action potentials can only increase in frequency to a certain point. There is a refractory period after an action potential when the neuron cannot become excited again.
- b. The absolute refractory period occurs during the action potential. Na^+ channels are inactive (not just closed).

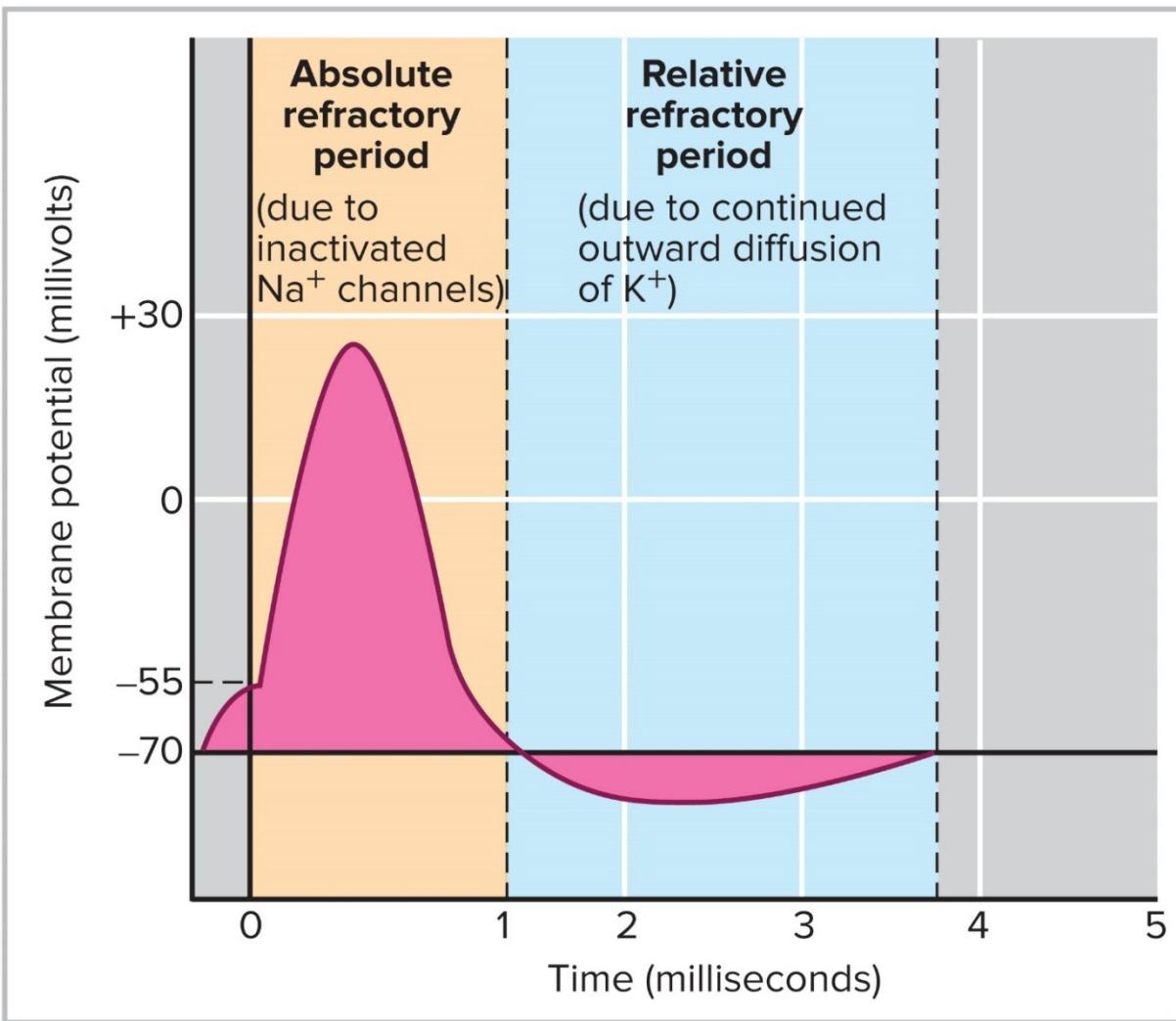
Action Potentials (8)

Refractory Periods, Continued

- c. The relative refractory period is when K⁺ channels are still open. Only a very strong stimulus can overcome this.
- d. Each action potential remains a separate, all-or-none event.

Refractory Periods

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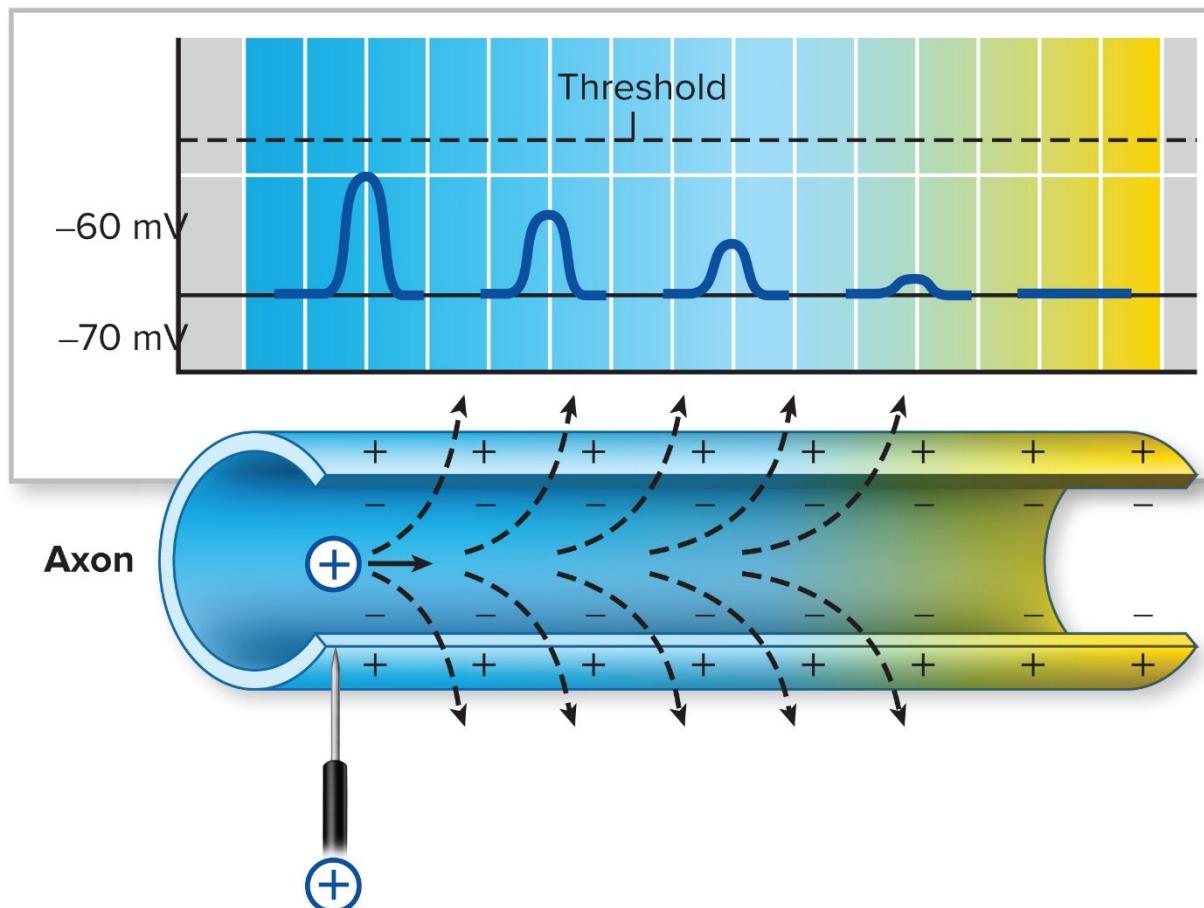
Action Potentials (9)

7. Cable Properties of Neurons

- a. The ability of neurons to conduct charges through their cytoplasm
- b. Poor due to high internal resistance to the spread of charges and leaking of charges through the membrane
- c. Neurons could not depend on cable properties to move an impulse down the length of an axon.

Cable Properties of Neurons

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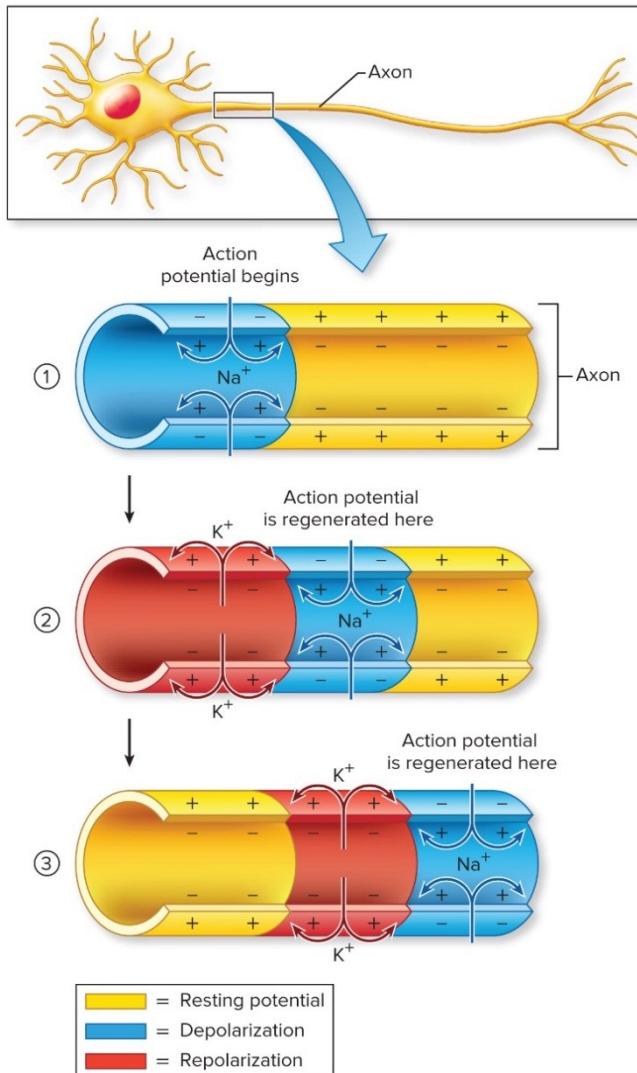
Injection of positive
charges (depolarization)
by stimulating electrode

D. Conduction of Nerve Impulses

1. When an action potential occurs at a given point on a neuron membrane, voltage-gated Na^+ channels open as a wave down the length of the axon.
2. The action potential at one location serves as the depolarization stimulus for the next region of the axon.

Conduction of Nerve Impulses (2)

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Conduction of Nerve Impulses (3)

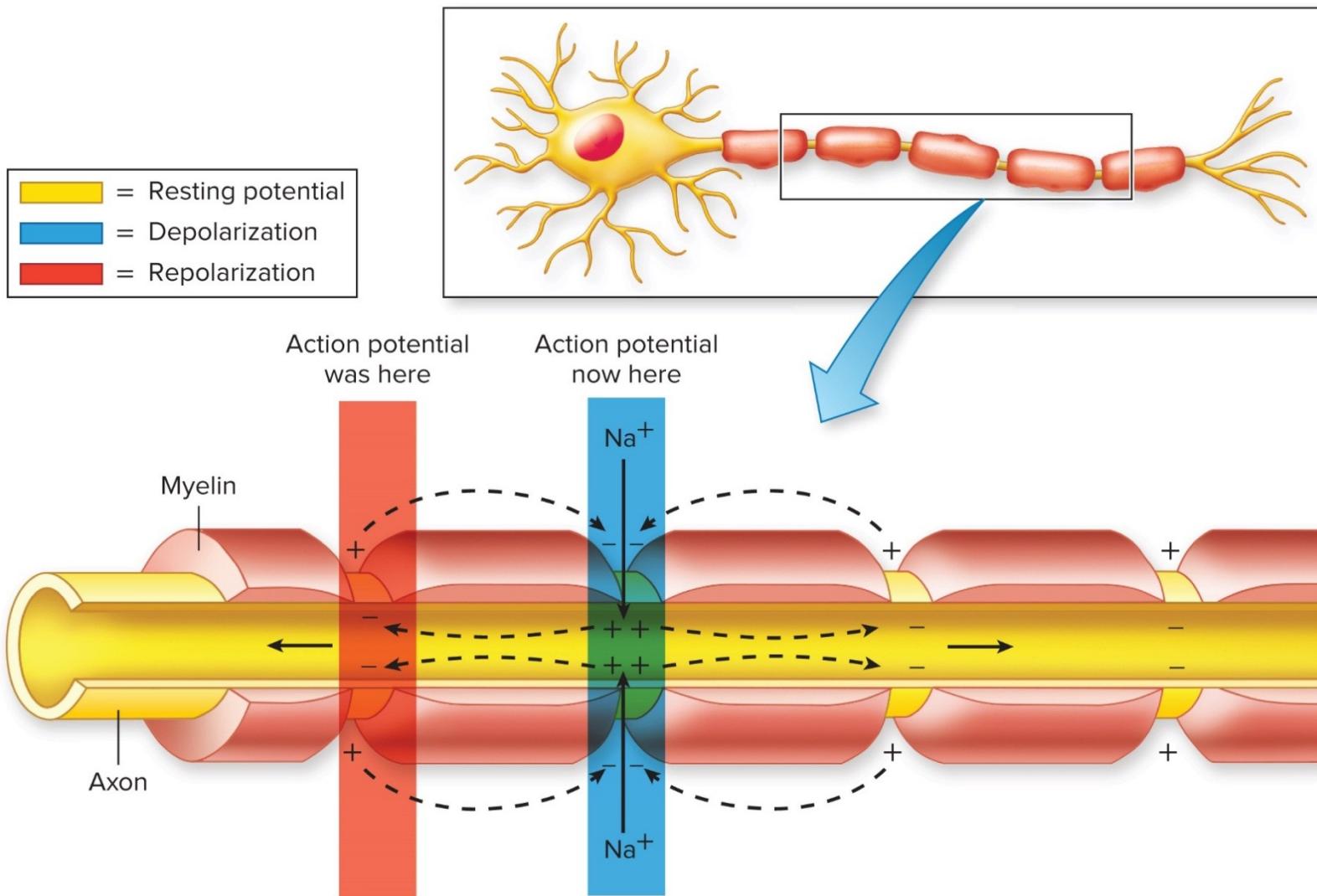
3. Conduction in an Unmyelinated Neuron
 - a. Axon potentials are produced down the entire length of the axon at every patch of membrane.
 - b. The conduction rate is slow because so many action potentials are generated, each one, an individual event.
 - c. The amplitude of each action potential is the same – conducted without decrement

Conduction of Nerve Impulses (4)

4. Conduction in a Myelinated Neuron
 - a. Myelin provides insulation, improving the speed of cable properties.
 - b. Nodes of Ranvier allow Na^+ and K^+ to cross the membrane every 1 to 2 mm.
 - c. Na^+ ion channels are concentrated at the nodes
 - d. Action potentials “leap” from node to node.
 - e. This is called saltatory conduction.

Conduction in a Myelinated Neuron

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Conduction of Nerve Impulses (5)

5. Action Potential Conduction Speed

a. Increased by:

- 1) Increased diameter of the neuron. This reduces resistance to the spread of charges via cable properties.
- 2) Myelination because of saltatory conduction

b. Examples

- 1) Thin, unmyelinated neuron speed 1.0m/sec
- 2) Thick, myelinated neuron speed 100m/sec

Conduction Velocities and Functions

TABLE 7.3 Conduction Velocities and Functions of Mammalian Nerves of Different Diameters*

Diameter (μm)	Conduction Velocity (m/sec)	Examples of Functions Served
12 to 22	70 to 120	Sensory: muscle position
5 to 13	30 to 90	Somatic motor fibers
3 to 8	15 to 40	Sensory: touch, pressure
1 to 5	12 to 30	Sensory: pain, temperature
1 to 3	3 to 15	Autonomic fibers to ganglia
0.3 to 1.3	0.7 to 2.2	Autonomic fibers to smooth and cardiac muscles

*See the *Test Your Quantitative Ability section of the Review Activities in chapters 8 and 9.*

III. The Synapse

A. Introduction to the Synapse

1. A synapse is the functional connection between a neuron and the cell it is signaling
 - a. In the CNS, this second cell will be another neuron.
 - b. In the PNS, the second cell will be in a muscle or gland; often called myoneural or neuromuscular junctions

Introduction to the Synapse (2)

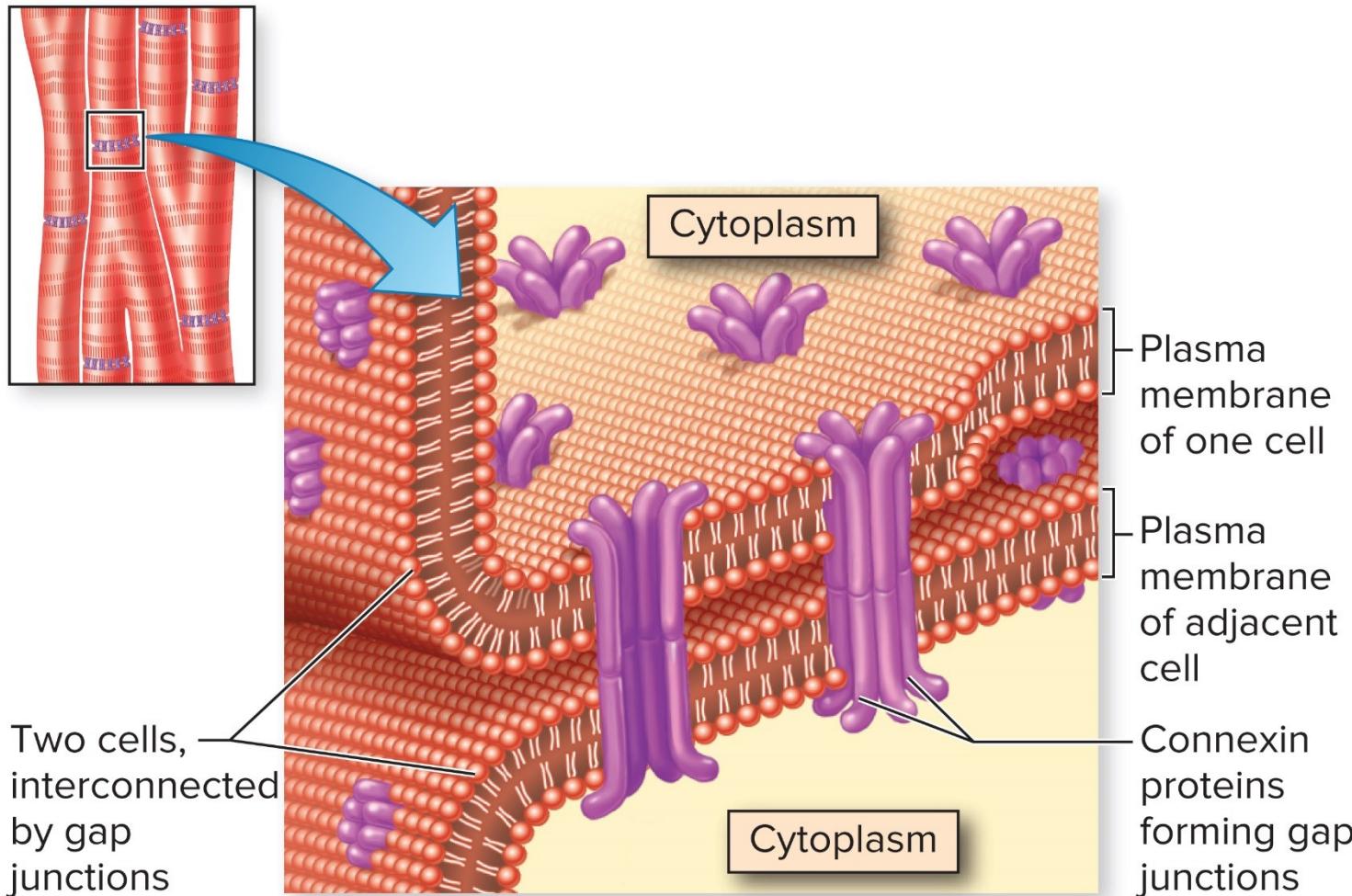
2. If one neuron is signaling another neuron, the first is called the presynaptic neuron, and the second is called the postsynaptic neuron.
 - a. A presynaptic neuron can signal the dendrite, cell body, or axon of a second neuron.
 - b. There are axodendritic, axosomatic, and axoaxonic synapses.
 - c. Most synapses are axodendritic and are 1 direction
3. Synapses can be electrical or chemical

B. Electrical Synapses

1. Electrical synapses occur in smooth muscle and cardiac muscle, between some neurons of the brain, and between glial cells.
2. Cells are joined by gap junctions.
3. Stimulation causes phosphorylation or dephosphorylation of connexin proteins to open or close the channels

Structure of Gap Junctions

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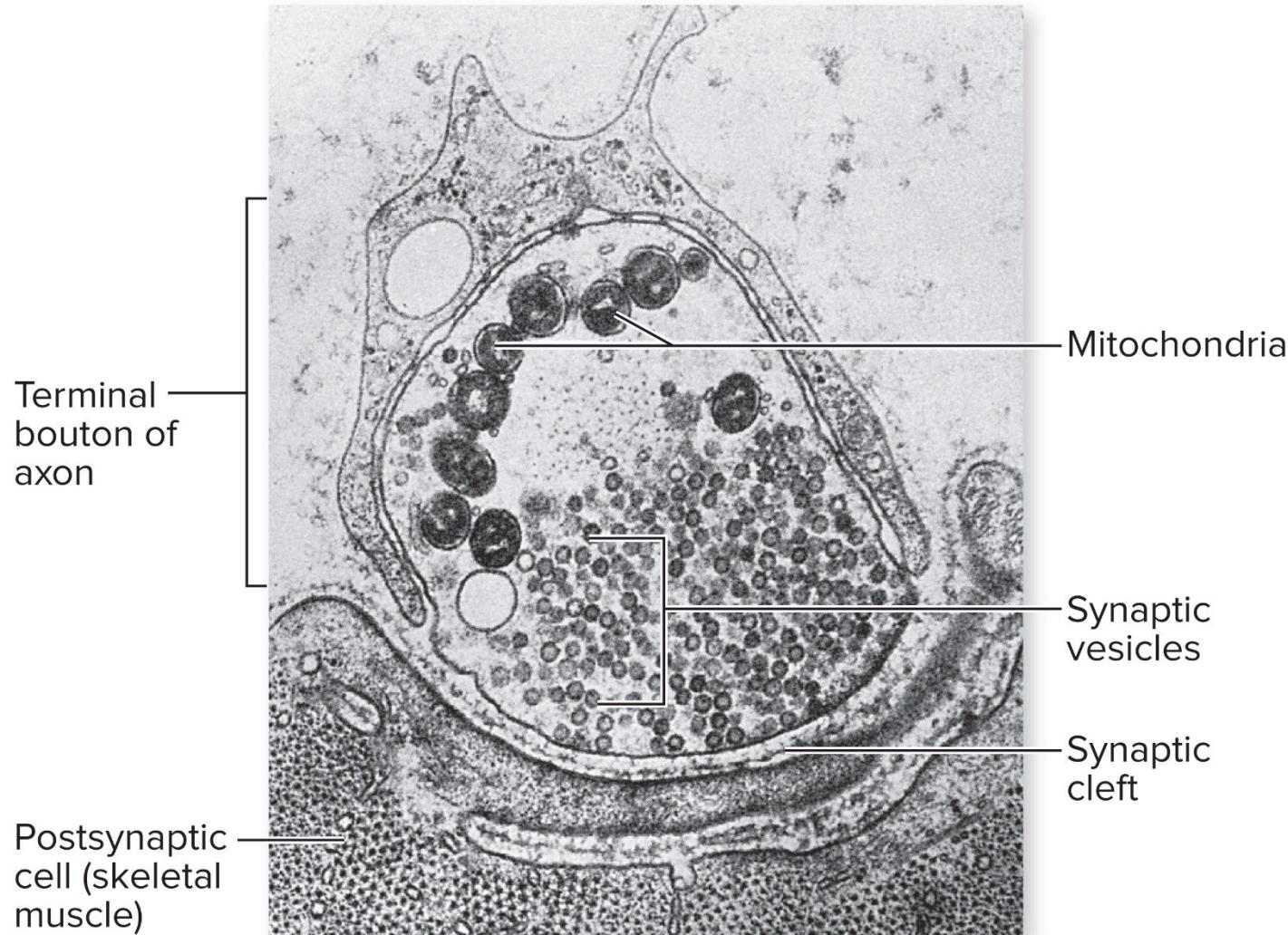


C. Chemical Synapses

1. Most synapses involve the release of a chemical called a neurotransmitter from the axon's terminal boutons.
2. The synaptic cleft is very small, and the presynaptic and postsynaptic cells are held close together by cell adhesion molecules (CAMs).

Chemical Synapses (2)

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Chemical Synapses (3)

3. Release of Neurotransmitter

- a. Neurotransmitter is enclosed in synaptic vesicles in the axon terminal.
 - 1) When the action potential reaches the end of the axon, voltage-gated Ca^{2+} channels open.
 - 2) Ca^{2+} stimulates the fusing of synaptic vesicles to the plasma membrane and exocytosis of neurotransmitter.
 - 3) A greater frequency of action potential results in more stimulation of the postsynaptic neuron.

Chemical Synapses (4)

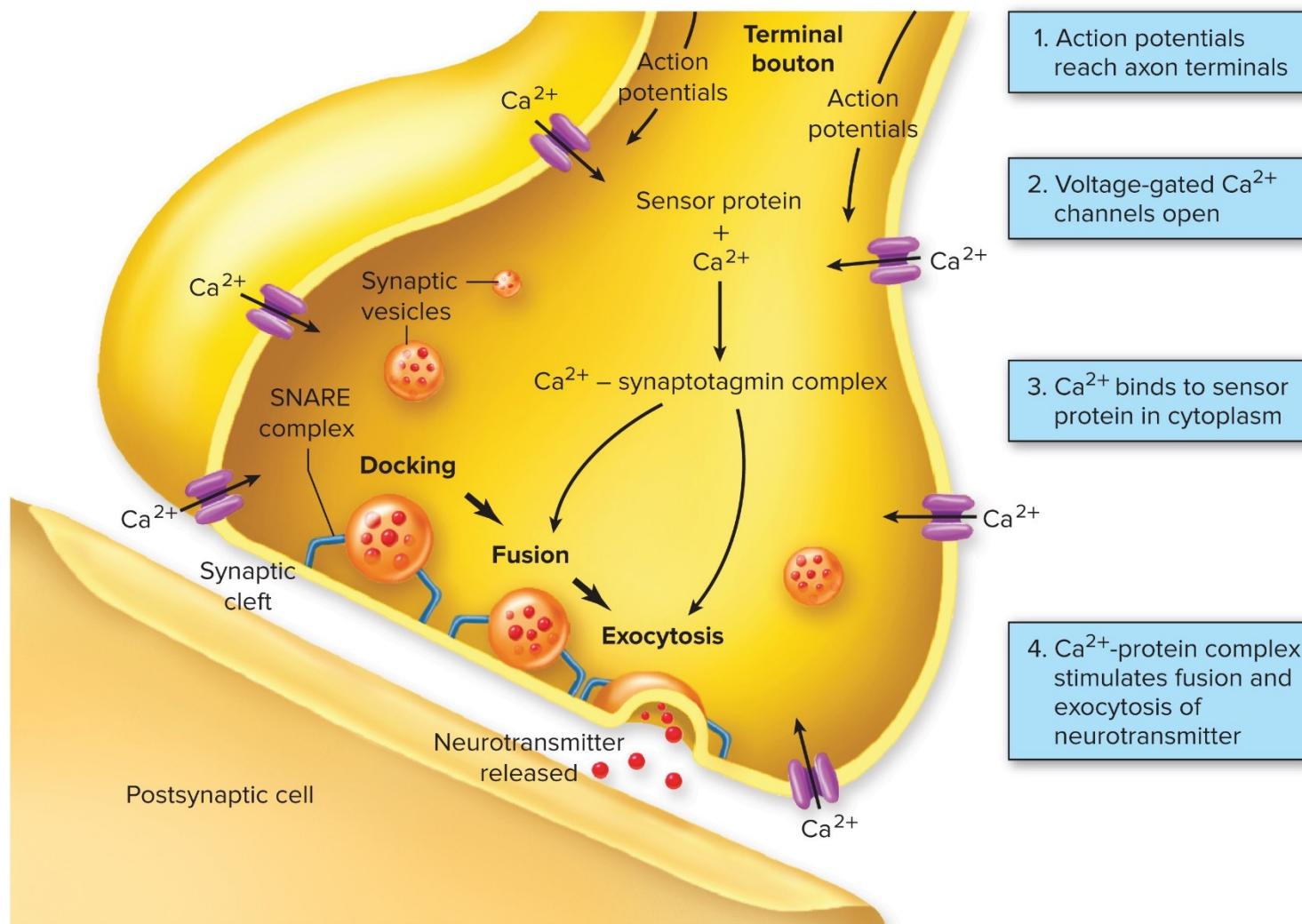
Release of Neurotransmitter, Continued

b. Ca^{2+} and Synaptic Vesicles

- 1) When Ca^{2+} enters the cell, it binds to a protein called synaptotagmin that serves as a Ca^{2+} sensor
- 2) Vesicles containing neurotransmitter are docked at the plasma membrane by three SNARE proteins.
- 3) The Ca^{2+} synaptotagmin complex displaces part of SNARE, and the vesicle fuses.
- 4) Forms a pore to release the NT

Release of Neurotransmitter

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Chemical Synapses (5)

4. Actions of Neurotransmitter

- a. Neurotransmitter diffuses across the synapse, where it binds to a specific receptor protein.
 - 1) The neurotransmitter is referred to as the ligand.
 - 2) This results in the opening of chemically regulated ion channels (also called ligand-gated ion channels).

Chemical Synapses (6)

Actions of Neurotransmitter, Continued

b. Graded Potential

- 1) When ligand-gated ion channels open, the membrane potential changes depending on which ion channel is open.
 - a) Opening Na^+ or Ca^{2+} channels results in a graded depolarization called an excitatory postsynaptic potential (EPSP).
 - b) Opening K^+ or Cl^- channels results in a graded hyperpolarization called inhibitory postsynaptic potential (IPSP).

Chemical Synapses (7)

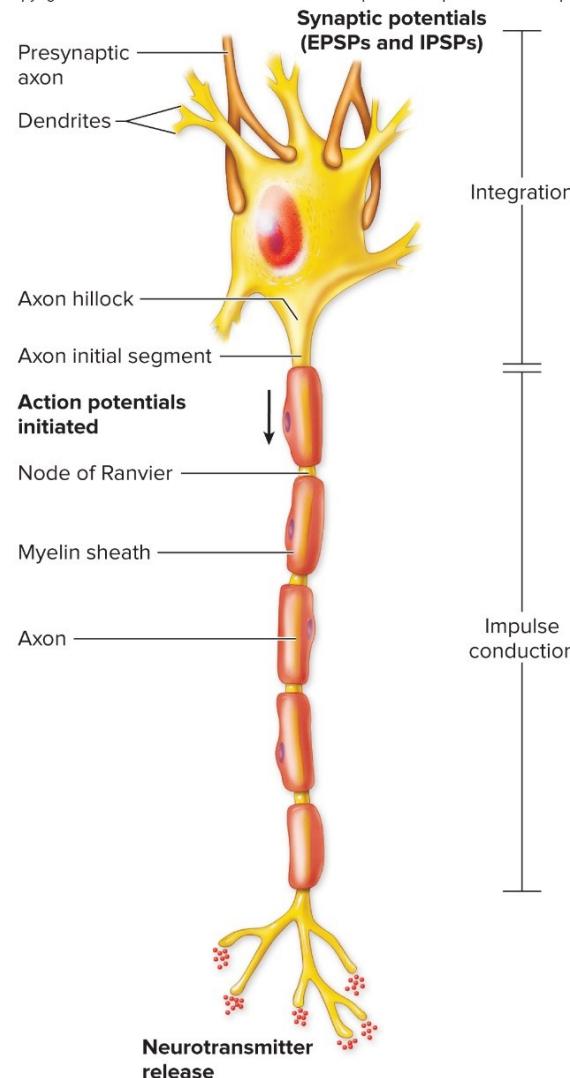
Actions of Neurotransmitter, Continued

2. EPSPs and IPSPs

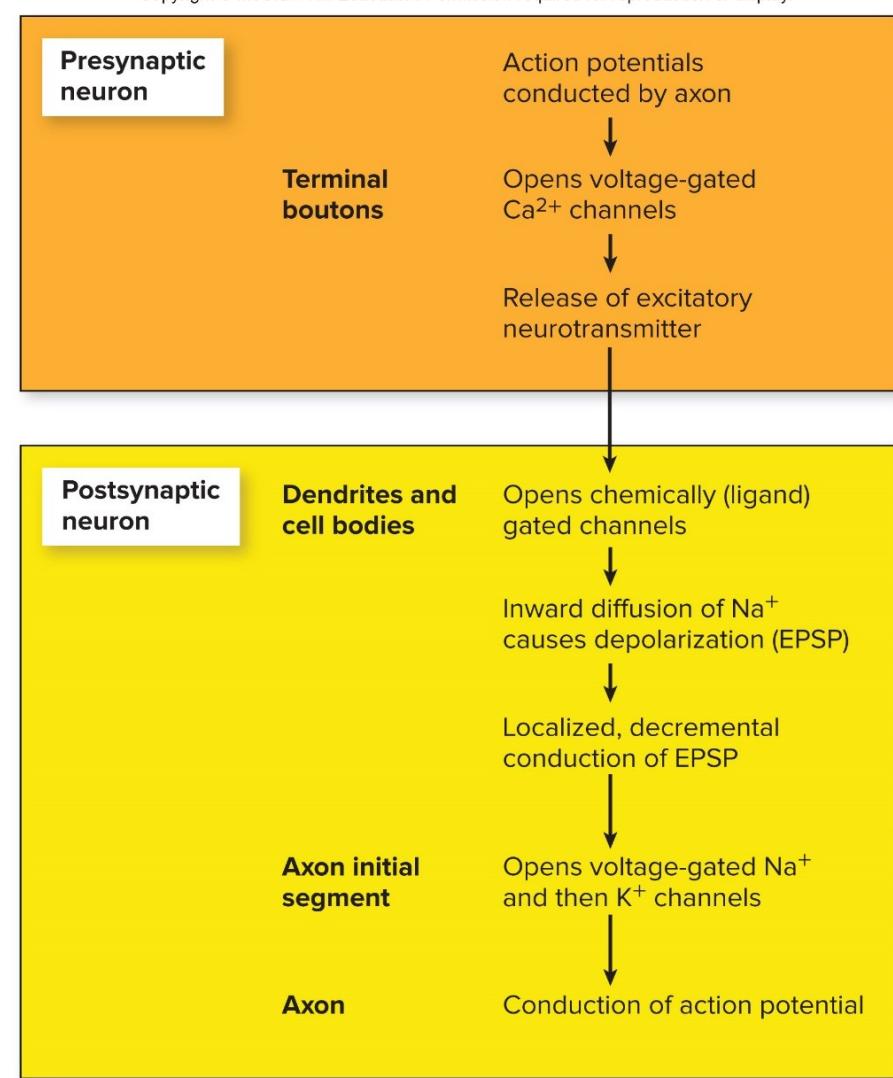
- a. EPSPs move the membrane potential closer to threshold; may require EPSPs from several neurons to actually produce an action potential
 - 1) IPSPs move the membrane potential farther from threshold.
 - 2) Can counter EPSPs from other neurons so summation of EPSPs and IPSPs at the initial segment of the axon (next to the axon hillock) determines whether an action potential occurs.

Summary of Neurotransmitter Action

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IV. Acetylcholine

A. Acetylcholine (ACh)

1. ACh is a neurotransmitter that directly opens ion channels when it binds to its receptor.
 - a. In some cases, ACh is excitatory, and in other cases it is inhibitory, depending on the organ involved
 - b. Excitatory in some areas of the CNS, in some autonomic motor neurons, and in all somatic motor neurons
 - c. Inhibitory in some autonomic motor neurons

Acetylcholine (ACh) (2)

2. Two Types of Acetylcholine Receptors

a. Nicotinic ACh receptors

- 1) Can be stimulated by nicotine
- 2) Found on the motor end plate of skeletal muscle cells, in autonomic ganglia, and in some parts of the CNS

Acetylcholine (ACh) (3)

Two Types of Acetylcholine Receptors, Continued

b. Muscarinic ACh receptors

- 1) Can be stimulated by muscarine (from poisonous mushrooms)
- 2) Found in CNS and plasma membrane of smooth and cardiac muscles and glands innervated by autonomic motor neurons

Acetylcholine (ACh) (4)

c. Agonists and Antagonists

- 1) Agonists: drugs that can stimulate a receptor
 - a) Nicotine for nicotinic ACh receptors
 - b) Muscarine for muscarinic ACh receptors
- 2) Antagonists: drugs that inhibit a receptor
 - a) Atropine is an antagonist for muscarinic receptors.
 - b) Curare is an antagonist for nicotinic receptors.

B. Chemically Regulated Channels

1. Binding of a neurotransmitter to a receptor can open an ion channel in one of two ways:
 - a. Ligand-gated channels
 - b. G-protein coupled channels

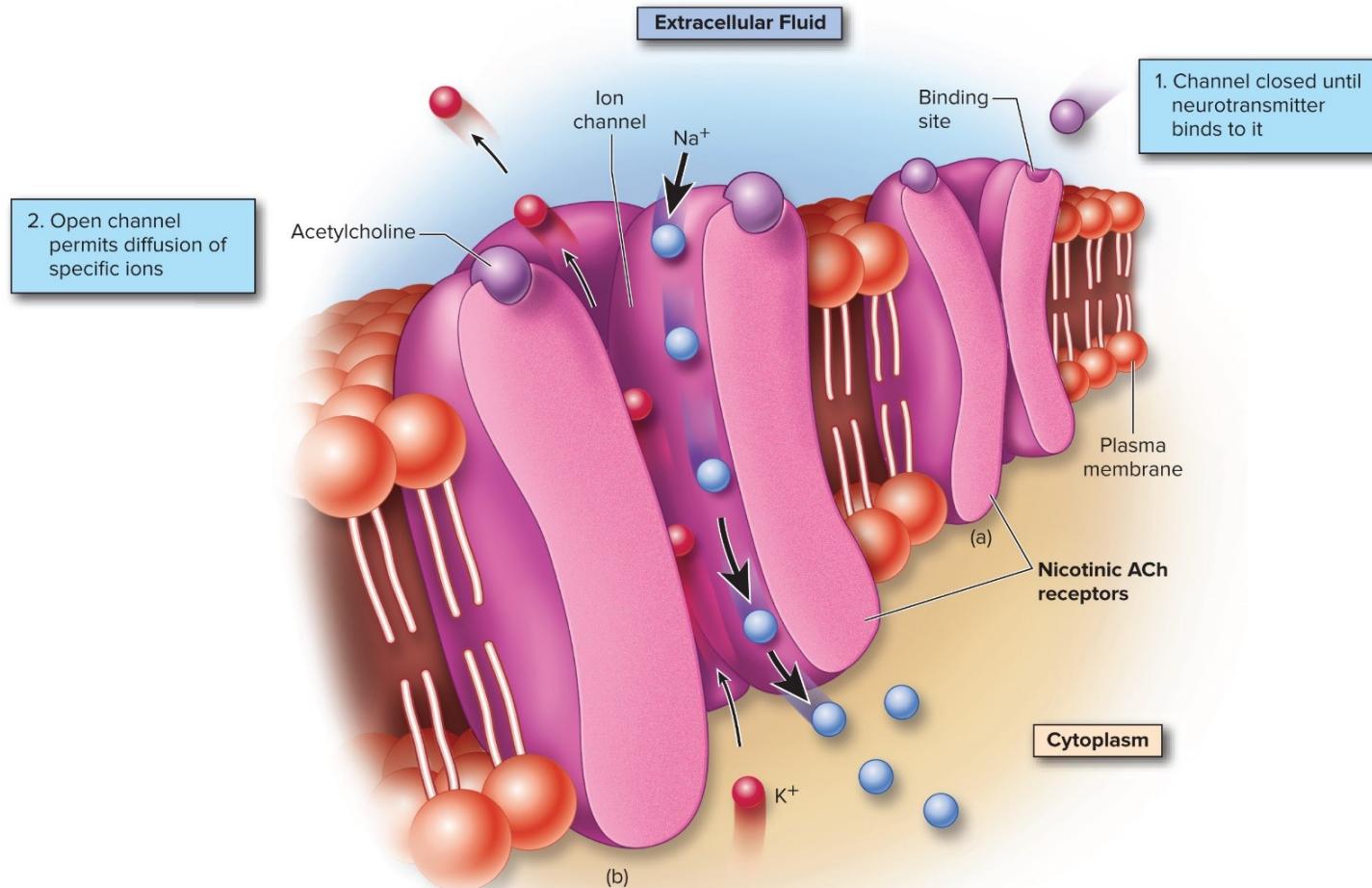
Chemically Regulated Channels (2)

2. Ligand-Gated Channels

- a. The receptor protein is also an ion channel; binding of the neurotransmitter directly opens the ion channel.
- b. Nicotinic ACh receptors are ligand-gated channels with two receptor sites for two AChs.
- c. Binding of 2 acetylcholine molecules opens a channel that allows both Na^+ and K^+ passage.
 - 1) Na^+ flows in, and K^+ flows out.
 - 2) Due to electrochemical gradient, more Na^+ flows in than K^+ out.

Nicotinic ACh Receptors

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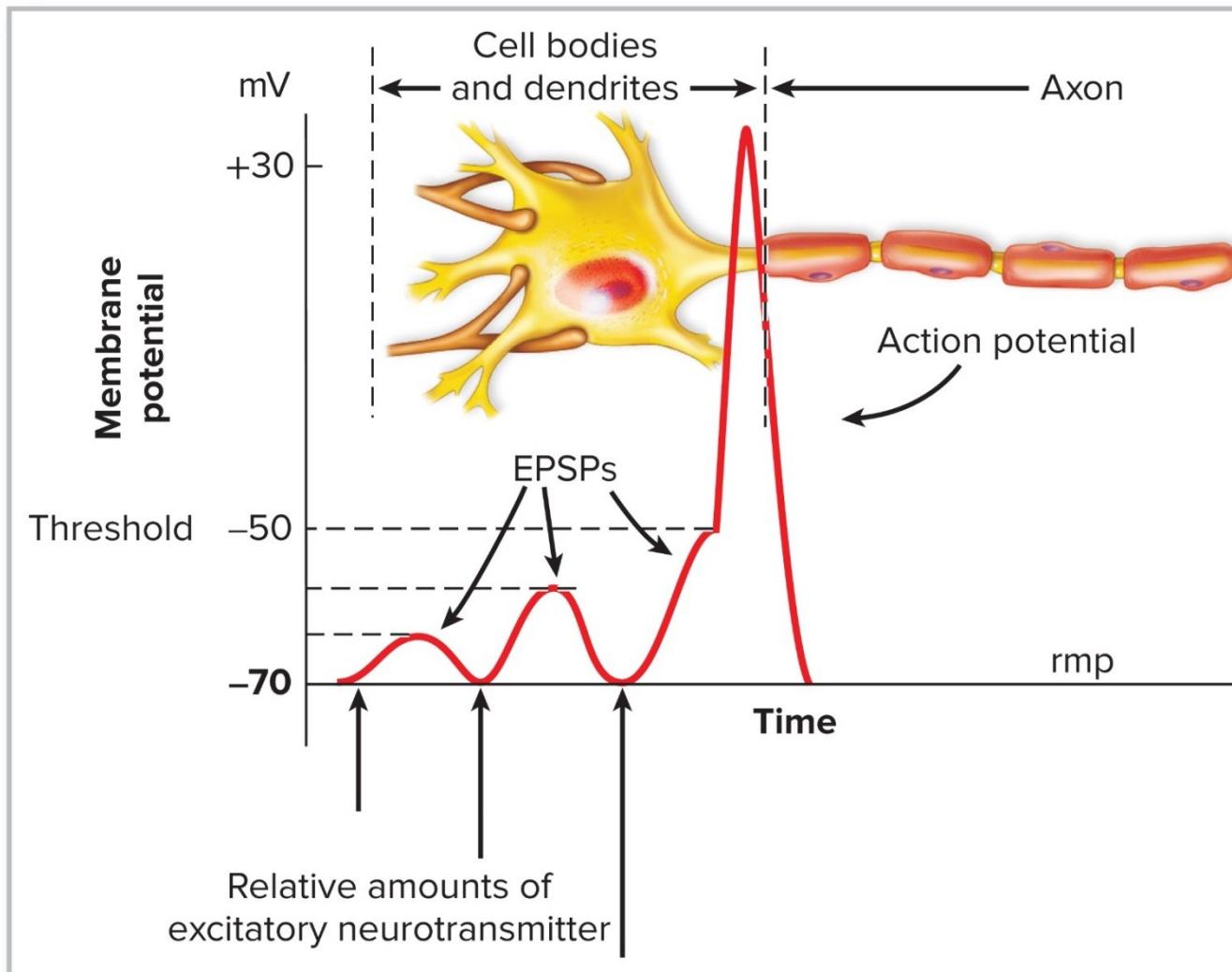
Chemically Regulated Channels (3)

Ligand-Gated Channels, Continued

- d. This inward flow of Na^+ depolarizes the cell, creating an EPSP.
 - 1) EPSPs occur in the dendrites and cell bodies.
 - 2) EPSPs from the binding of several ACh molecules can be added together to produce greater depolarization - graded
 - 3) This may reach the threshold for voltage-gated channels in the axon hillock, leading to action potential.

Graded Nature of EPSPs

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Comparison of EPSPs and Action Potentials

TABLE 7.4 Comparison of Action Potentials and Excitatory Postsynaptic Potentials (EPSPs)

Characteristic	Action Potential	Excitatory Postsynaptic Potential
Amplitude	All-or-none	Graded
Stimulus for opening of ionic gates	Depolarization	Acetylcholine (ACh) or other excitatory Neurotransmitter
Initial effect of stimulus	Na ⁺ channels open	Common channels for Na ⁺ and K ⁺ open
Cause of repolarization	Opening of K ⁺ gates	Loss of intracellular positive charges with time and distance
Conduction distance	Regenerated over length of the axon	1 to 2 mm; a localized potential
Positive feedback between depolarization and opening of Na ⁺ gates	Yes	No
Maximum depolarization	+40 mV	Close to zero
Summation	No summation—all-or-none event	Summation of EPSPs, producing graded depolarizations
Refractory period	Yes	No
Effect of drugs	ACh effects inhibited by tetrodotoxin, not by curare	ACh effects inhibited by curare, not by tetrodotoxin

Chemically Regulated Channels (4)

3. G-Protein Coupled Channels

- a. The neurotransmitter receptor is separate from the protein that serves as the ion channel.
 - 1) Binding at the receptor opens ion channels indirectly by using a G-protein.
 - 2) Muscarinic ACh receptors interact with ion channels in this way as well as dopamine and norepinephrine receptors

Chemically Regulated Channels (5)

G-Protein Coupled Channels, Continued

- b. Associated with a G-protein
 - 1) G-proteins have three subunits (alpha, beta, and gamma).
 - 2) Binding of one acetylcholine results in the dissociation of the alpha subunit.
 - 3) Either the alpha or the beta-gamma diffuses through the membrane to the ion channel.
 - 4) This opens the channel for short period of time.
 - 5) The G-protein subunits dissociate from the channel and it closes

Chemically Regulated Channels (6)

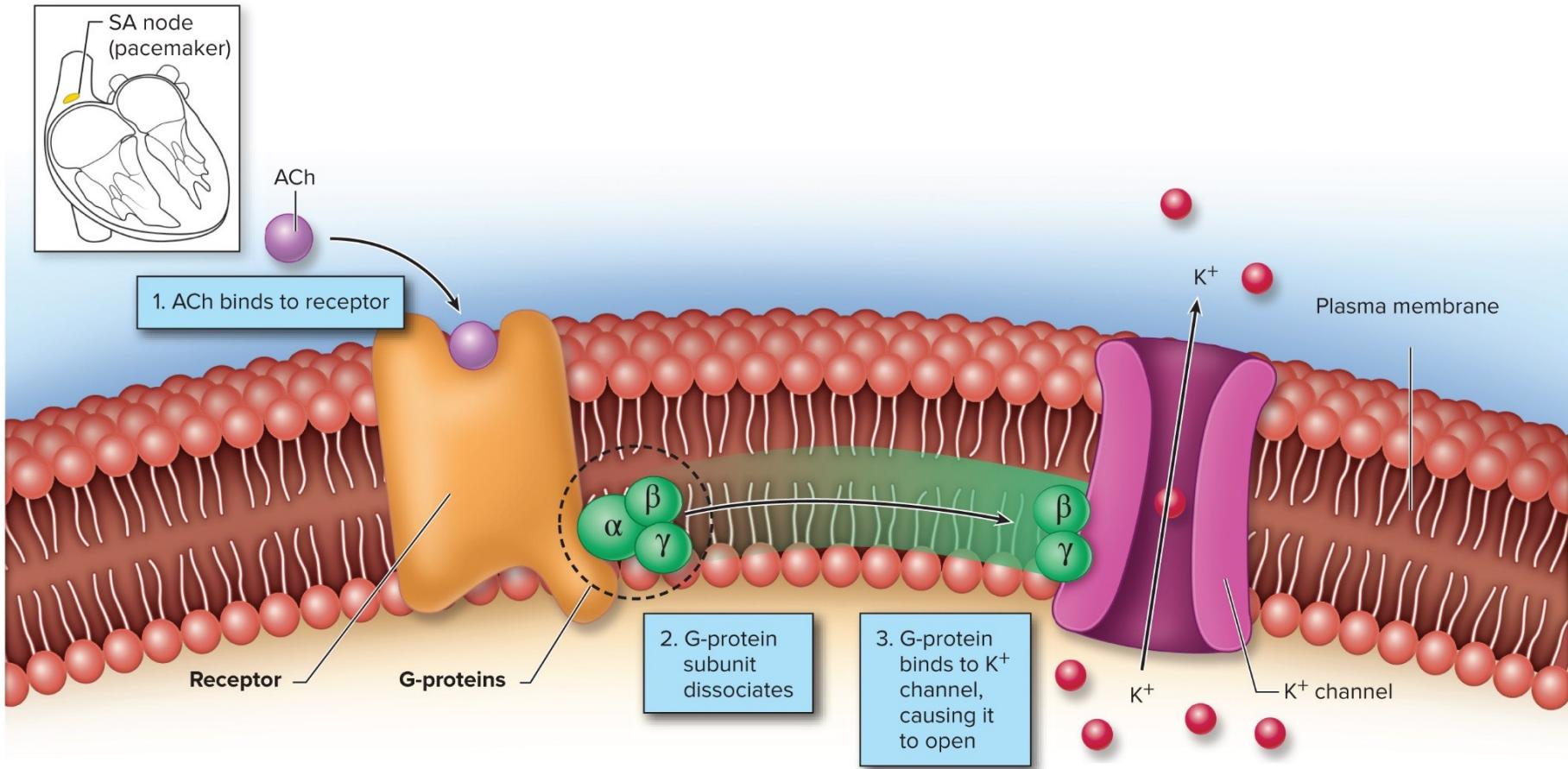
c. Steps in the Activation and Deactivation of G-Proteins

TABLE 7.6 Steps in the Activation and Inactivation of G-Proteins

Step 1	When the membrane receptor protein is not bound to its regulatory molecule ligand, the alpha, beta, and gamma G-protein subunits are aggregated together and attached to the receptor; the alpha subunit binds GDP.
Step 2	When the ligand (neurotransmitter or other regulatory molecule) binds to the receptor, the alpha subunit releases GDP and binds GTP; this allows the alpha subunit to dissociate from the beta-gamma subunits.
Step 3	Either the alpha subunit or the beta-gamma complex moves through the membrane and binds to a membrane effector protein (either an ion channel or an enzyme).
Step 4	Deactivation of the effector protein is caused by the alpha subunit hydrolyzing GTP to GDP.
Step 5	This allows the subunits to again reaggregate and bind to the unstimulated receptor protein (which is no longer bound to its regulatory molecule ligand).

G-Protein Coupled Channels

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Chemically Regulated Channels (7)

G-Protein Couple Channels, Continued

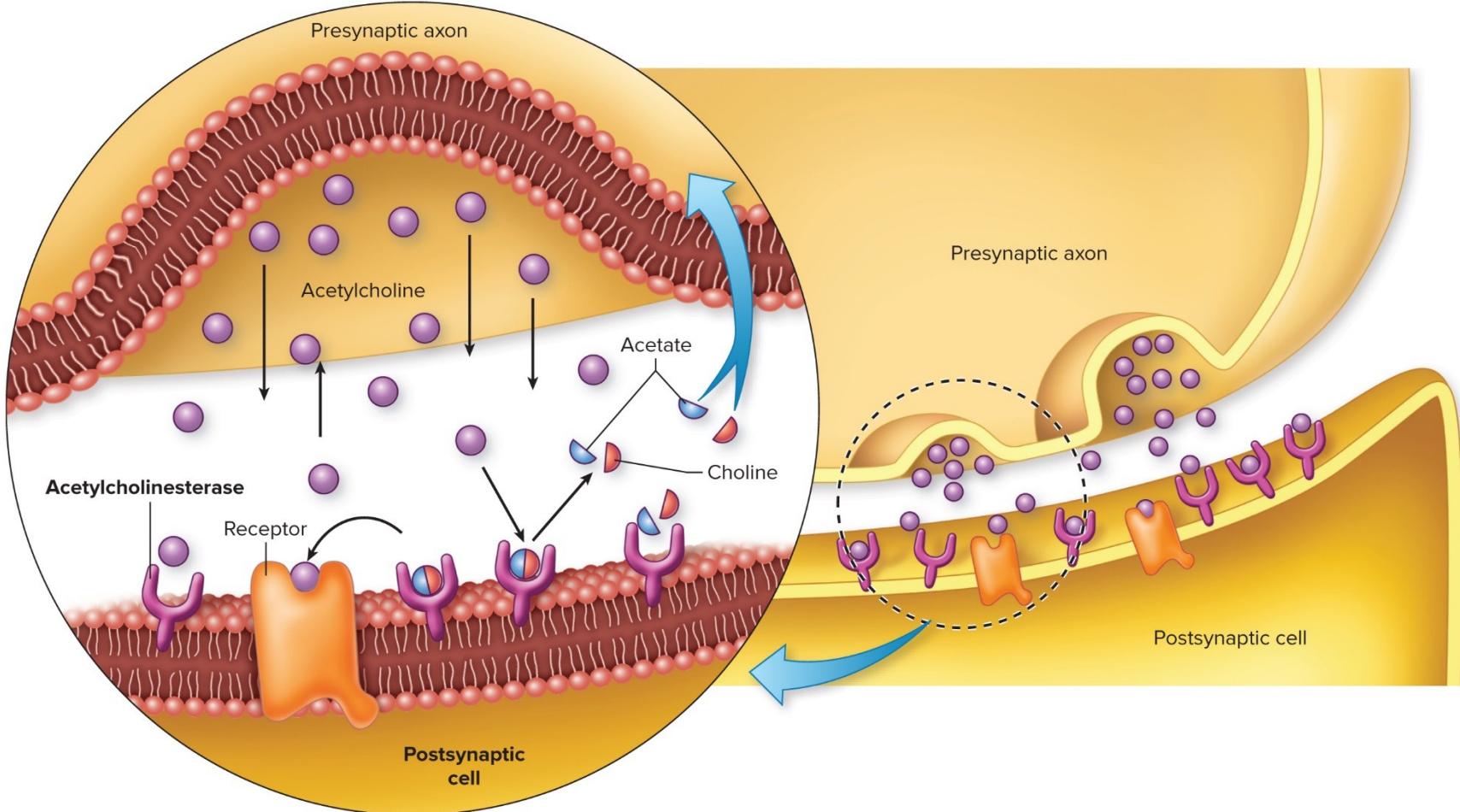
- d. Binding of acetylcholine opens K⁺ channels in some tissues (IPSP) or closes K⁺ channels in others (EPSP).
 - 1) In the heart, K⁺ channels are opened by the beta-gamma complex, creating IPSPs (hyperpolarization) that slow the heart rate.
 - 2) In the smooth muscles of the stomach, K⁺ channels are closed by the alpha subunit, producing EPSPs (depolarization) and the contraction of these muscles.

Acetylcholinesterase (AChE)

1. AChE is an enzyme that inactivates ACh activity shortly after it binds to the receptor.
2. Hydrolyzes ACh into acetate and choline, which are taken back into the presynaptic cell for reuse.

Action of Acetylcholinesterase (AChE)

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Cholinesterase Inhibitors

- a. Cholinesterase inhibitors are drugs that block the action of acetylcholinesterase (AChE), increasing the amount of ACh in the synaptic cleft and enhancing cholinergic synaptic transmission.
- b. Neostigmine, physostigmine, pyridostigmine, and others are used to treat myasthenia gravis and are important in the treatment of Alzheimer's disease.
- c. However, nerve gas and organophosphate pesticides can kill their intended victims by inhibiting AChE and overstimulating cholinergic synapses.

D. ACh in the PNS

1. Somatic motor neurons form interactions called neuromuscular junctions with muscle cells.
2. The area on the muscle cell with receptors for neurotransmitter is called the motor end plate.
 - a. EPSPs formed here are often called end plate potentials.
 - b. End plate potentials open voltage-gated Na^+ channels, which result in an action potential.
 - c. This produces muscle contraction

ACh in the PNS (2)

3. Interruption of Neuromuscular Transmission
 - a. Certain drugs can block neuromuscular transmission.
 - b. Curare is an antagonist of acetylcholine. It blocks ACh receptors so muscles do not contract.
 - 1) Leads to paralysis and death (due to paralyzed diaphragm)
 - 2) Used clinically as a muscle relaxant

Drugs that Affect the Neural Control of Skeletal Muscles

108

TABLE 7.5 Drugs That Affect the Neural Control of Skeletal Muscles

Drug	Origin	Effects
Botulinum toxin	Produced by Clostridium botulinum (bacteria)	Inhibits release of acetylcholine (ACh)
Curare	Resin from a South American tree	Prevents interaction of ACh with its nicotinic receptor proteins
α -Bungarotoxin	Venom of <i>Bungarus</i> snakes	Binds to ACh receptor proteins and prevents ACh from binding
Saxitoxin	Red tide (<i>Gonyaulax</i>) algae	Blocks voltage-gated Na ⁺ channels
Tetrodotoxin	Pufferfish	Blocks voltage-gated Na ⁺ channels
Nerve gas	Artificial	Inhibits acetylcholinesterase in postsynaptic membrane
Neostigmine	Nigerian bean	Inhibits acetylcholinesterase in postsynaptic membrane
Strychnine	Seeds of an Asian tree	Prevents IPSPs in spinal cord that inhibit contraction of antagonistic muscles

ACh in the PNS (3)

4. Alzheimer Disease

- a. Associated with loss of cholinergic neurons that synapse on the areas of the brain responsible for memory

Ach in the PNS (4)

5. Myasthenia Gravis

- a. Myasthenia gravis is an autoimmune disease caused by antibodies that block the nicotinic ACh receptors, particularly in the motor end plates (postsynaptic membranes) of skeletal muscle cells.
- b. This produces muscle weakness, especially in the eyes, eyelids, and face.
- c. Neostigmine and related drugs, which block the enzyme that degrades ACh (discussed shortly) in the synaptic cleft, can help treat symptoms.

V. Monoamines as Neurotransmitters

A. Monoamines

1. Monoamines are regulatory molecules derived from amino acids
 - a. Catecholamines: derived from tyrosine; include dopamine, norepinephrine, and epinephrine
 - b. Serotonin: derived from L-tryptophan
 - c. Histamine: derived from histidine

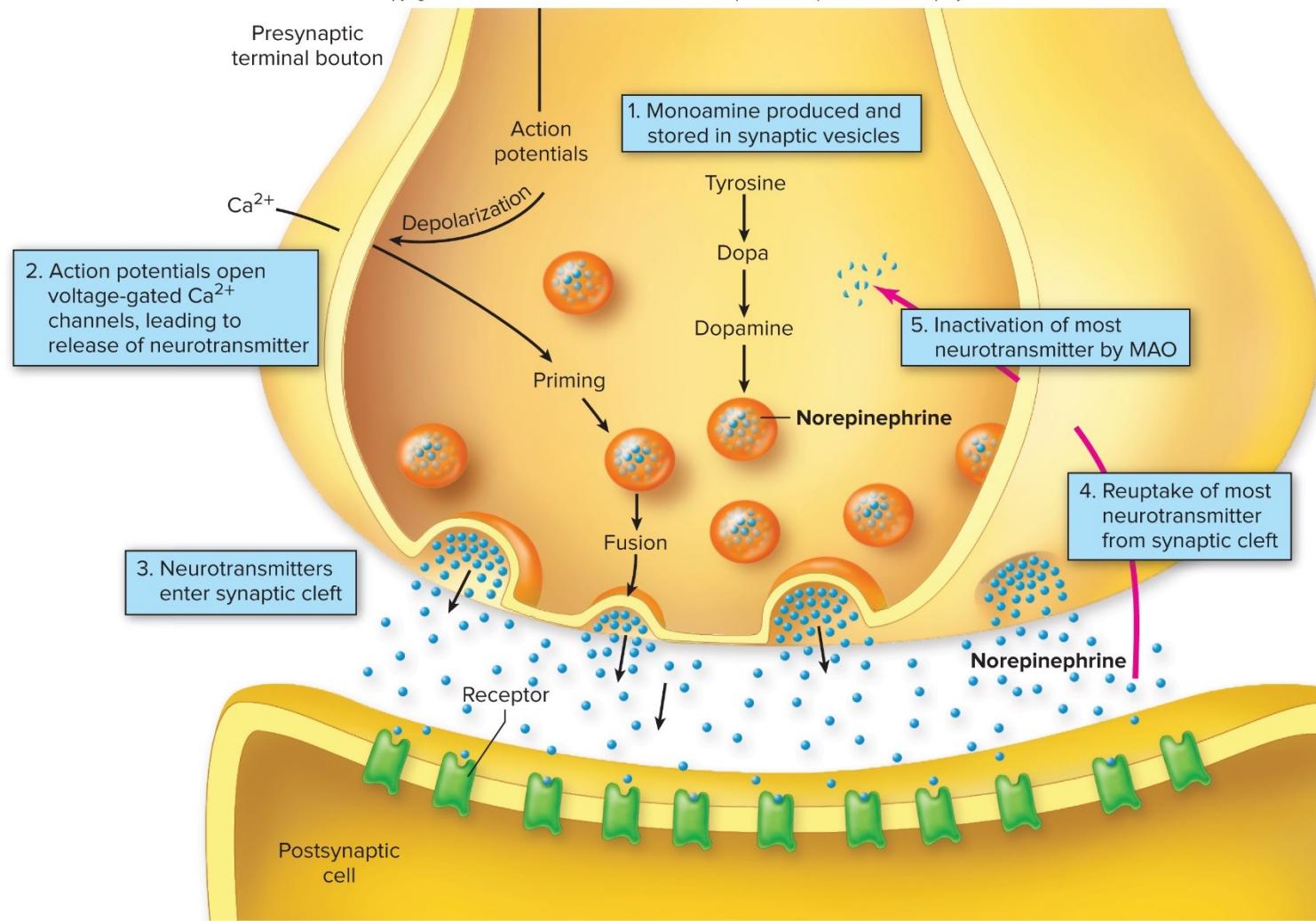
Monoamines (2)

2. Monoamine Action and Inactivation

- a. Like ACh, monoamines are made in the presynaptic axon, released via exocytosis, diffuse across the synapse, and bind to specific receptors.
- b. They are quickly taken back into the presynaptic cell (called reuptake) and degraded by monoamine oxidase (MAO).

Monoamine Action and Inactivation

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Monoamine Oxidase (MAO) Inhibitors

3. Monoamine Oxidase (MAO) Inhibitors

- a. Monoamine oxidase (MAO) inhibitors are drugs that block the degradation of monoamine neurotransmitters.
- b. MAO inhibitors have proven useful in the treatment of depression, as well as of panic disorder, anxiety, and Parkinson's disease.
- c. MAO inhibitors have potentially dangerous interactions with over-the-counter tryptophan, St. John's Wort, and foods such as that contain the tyramine.
- d. Such interactions could provoke a hypertensive crisis.

Monoamines (3)

4. Monoamine Action

- a. None of the receptors for these signals are direct ion channels.
- b. All use a second messenger system.
- c. Cyclic adenosine monophosphate (cAMP) is the most common second messenger for catecholamines.

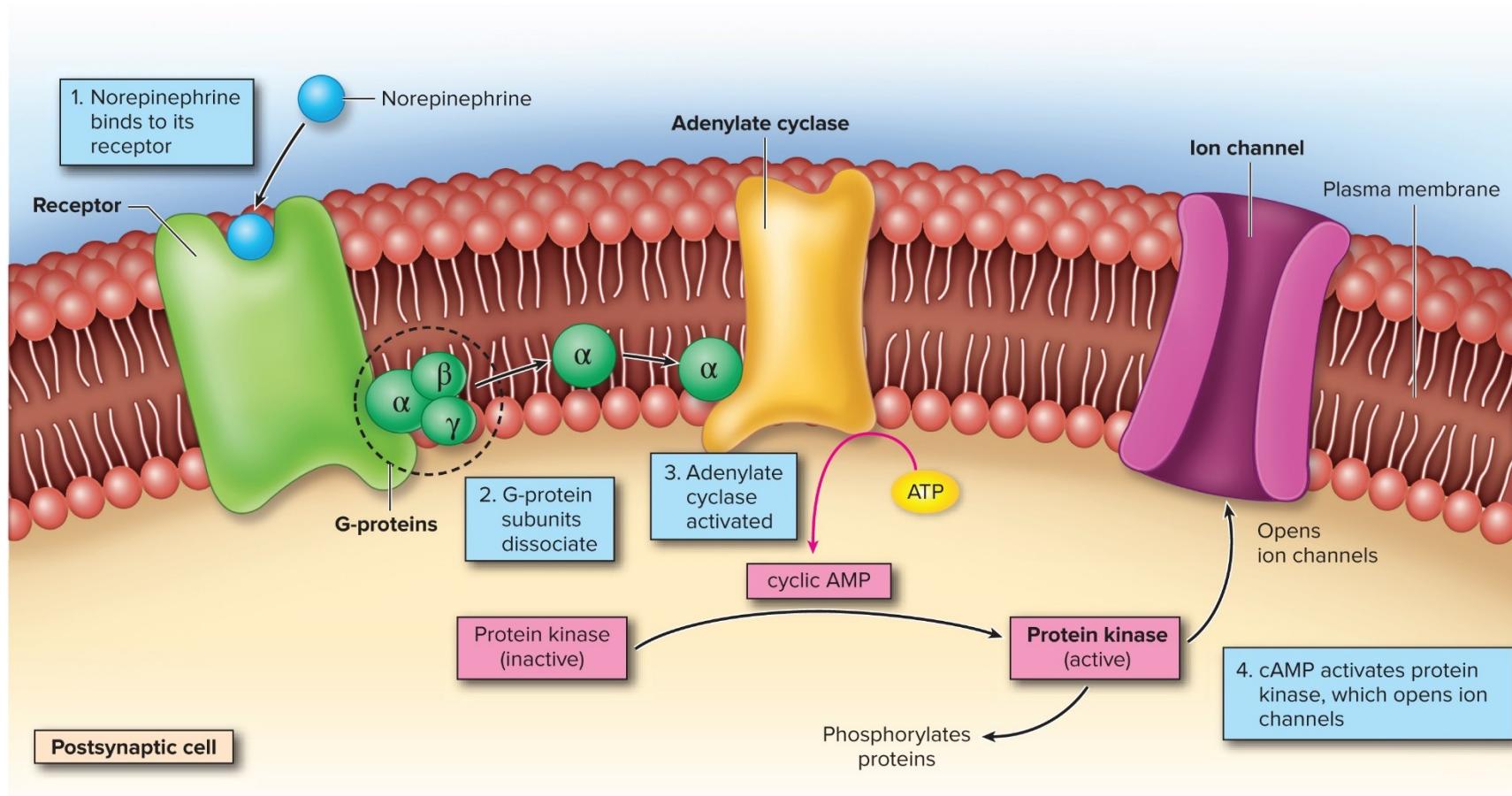
Monoamines (4)

Monoamine Action, Continued

- d. Binding of a catecholamine to its receptor activates a G-protein to dissociate and send the alpha subunit to an enzyme called adenylate cyclase which converts ATP to cAMP
- e. cAMP activates an enzyme called protein kinase, which phosphorylates other proteins.
- f. An ion channel opens.

Norepinephrine Action and G-Proteins

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B. Serotonin as a Neurotransmitter

1. Used by neurons in the raphe nuclei
(middle region of brain stem)
 - a. Implicated in mood, behavior, appetite, and cerebral circulation
 - b. The drug LSD and other hallucinogenic drugs may be agonists.
 - c. Serotonin specific reuptake inhibitors (SSRIs) are used to treat depression.
 - 1) Prozac, Paxil, Zoloft

Serotonin as a Neurotransmitter (2)

2. Over a dozen known receptors allow for diversity of serotonin function.
3. Different drugs that target specific serotonin receptors could be given for anxiety, appetite control, and migraine headaches.

C. Dopamine as a Neurotransmitter

1. Neurons that use dopamine (dopaminergic neurons) are highly concentrated in the midbrain in two main areas:
 - a. Nigrostriatal dopamine system: involved in motor control
 - b. Mesolimbic dopamine system: involved in emotional reward

Dopamine as a Neurotransmitter (2)

2. Nigrostriatal Dopamine System

- a. Neurons from the substantia nigra (part of the basal nuclei) of the brain send dopaminergic neurons to the corpus striatum.
- b. Important step in the control and initiation of movements
- c. Parkinson disease is caused by degeneration of these neurons.
 - 1) Patients are treated with L-dopa and MAOIs (monoamine oxidase inhibitors).

Dopamine as a Neurotransmitter (3)

3. Mesolimbis Dopamine System

- a. Regions of the midbrain send dopaminergic neurons to regions of the forebrain.
- b. Involved in emotional reward systems and associated with addictions such as nicotine, alcohol, and other drugs
- c. Schizophrenia is associated with too much dopamine in this system.
 - 1) Drugs that treat schizophrenia are dopamine antagonists.

D. Norepinephrine as a Neurotransmitter

1. Used in both the CNS and PNS
2. Sympathetic neurons of the PNS use norepinephrine on smooth muscles, cardiac muscles, and glands.
3. Used by neurons of the CNS in brain regions associated with arousal
4. Amphetamines work by stimulating norepinephrine pathways in the brain.

VI. Other Neurotransmitters

A. Amino Acids as NTs

1. Excitatory NT–glutamate
 - a. An amino acid used as the major excitatory neurotransmitter in the brain
 - b. Produces EPSPs in 80% of the synapses in the cerebral cortex
 - c. Energy required for all the EPSPs constitutes the major energy use in the brain
 - d. Astrocytes take glutamate from the synaptic cleft to increase glucose uptake and increase blood flow by vasodilation

Amino Acids as NTs (2)

e. Glutamate Receptors

- 1) All glutamate receptors also serve as ion channels
 - a) NMDA receptors
 - b) AMPA receptors
 - c) Kainate receptors
- 2) NMDA and AMPA receptors work together in memory storage.

Amino Acids as NTs (3)

2. Inhibitory NTs

a. Glycine

- 1) Amino acid used as a neurotransmitter to produce IPSPs
- 2) Binding of glycine opens Cl^- channels, causing an influx of Cl^- .
- 3) Makes it harder to reach threshold
- 4) Important in the spinal cord for regulating skeletal muscle movement. This allows antagonistic muscle groups to relax while others are contracting (for example, biceps relax while triceps contract).

Amino Acids as NTs (4)

Glycine, Continued

- 5) Also important in the relaxation of the diaphragm, which is necessary for breathing
 - a) The poison strychnine blocks glycine receptors, which produces death by asphyxiation.

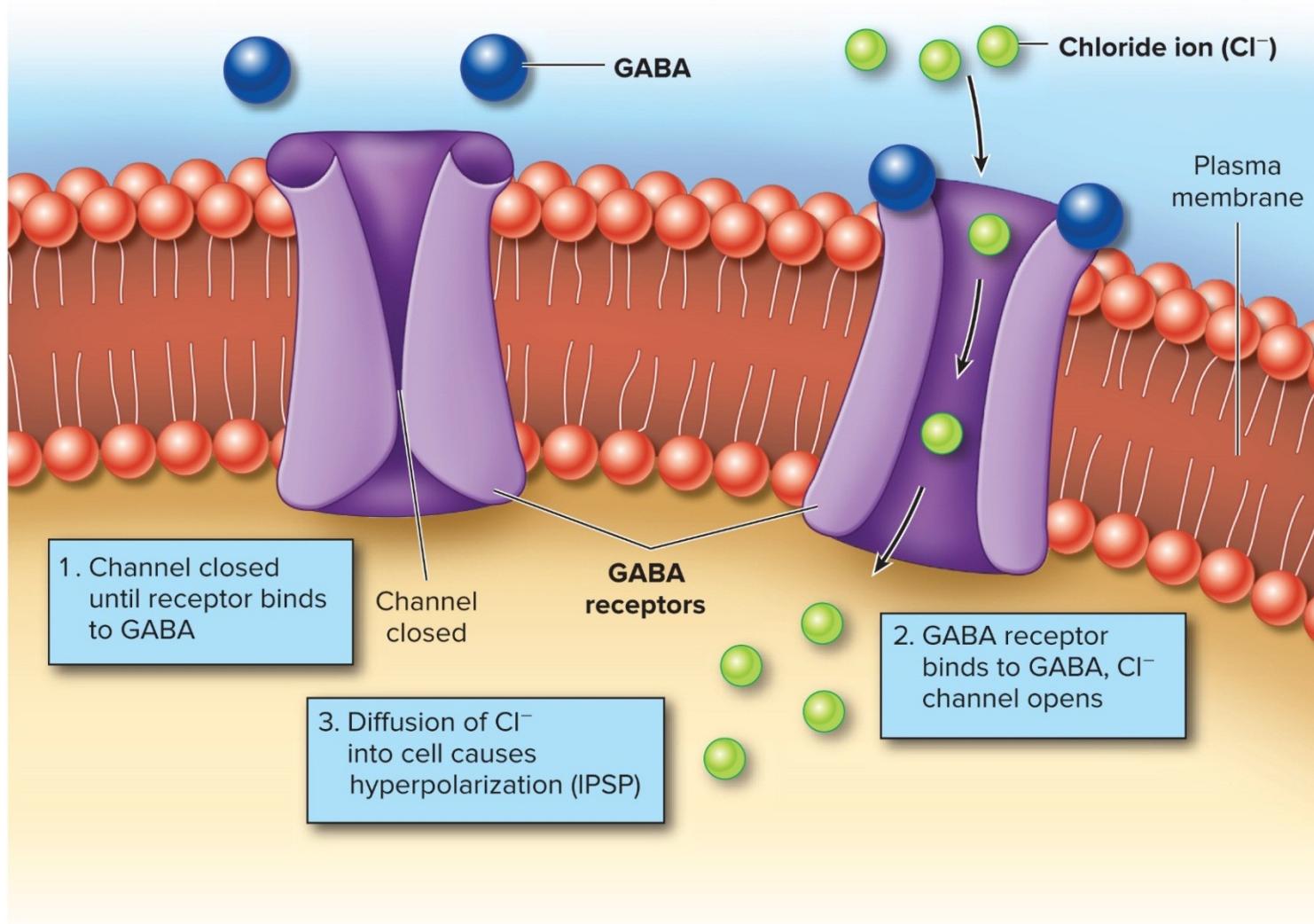
Amino Acids as NTs (5)

b. GABA

- 1) Gamma-aminobutyric acid is the most common neurotransmitter in the brain and is used by 1/3 of the brain's neurons.
- 2) It is inhibitory, opening Cl^- channels when it binds to its receptor.
- 3) It is involved in motor control. Degeneration of GABA-secreting neurons in the cerebellum results in Huntington disease.

GABA Receptors Contain a Chloride Channel

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B. Polypeptides as Neurotransmitters

1. Neuropeptides

- a. Many chemicals used as hormones or paracrine signals are also found in the brain acting as neurotransmitters.
 - 1) CCK: involved in a feeling of satiety after a meal
 - 2) Substance P: mediates sensations of pain

Polypeptides as Neurotransmitters (2)

b. Neuromodulators

- 1) Neurons that release a classical NT like Ach or norepinephrine along with a polypeptide
- 2) Can release either under different conditions
- 3) Called synaptic plasticity—capacity for alteration at the molecular level

Polypeptides as Neurotransmitters (3)

2. Endogenous Opioids

- a. Opioid receptors were discovered to bind with drugs such as opium and morphine, resulting in pain relief.
- b. Endogenous opioids are polypeptides produced by the brain and pituitary gland; includes enkephalin, β -endorphin, and dynorphin
- c. Opioids also produce euphoria so they may mediate reward pathways; may be related to feeling of well-being after exercise

Polypeptides as Neurotransmitters (4)

3. Neuropeptide Y

- a. Most abundant neuropeptide in the brain
- b. Plays a role in stress response, circadian rhythms, and cardiovascular control
- c. Powerful stimulator of hunger; leptin inhibits neuropeptide Y release to suppress appetite
- d. Works by inhibiting the release of glutamate in the hippocampus (excess glutamate release can cause convulsions)

C. Endocannabinoids

1. Neurotransmitters that bind to the same receptors that bind to the active ingredient in marijuana (THC)
2. Short fatty acids produced in the dendrites and cell bodies and released directly from the plasma membrane (no vesicle)
3. Retrograde neurotransmitters released from the postsynaptic neuron; inhibit further neurotransmitter release from the presynaptic axon

Endocannabinoids (2)

4. Endocannabinoids can inhibit IPSP-producing NTs from one neuron so EPSP-producing NTs from another neuron can have a greater effect.
5. Endocannabinoids may enhance learning and memory and have been shown to induce appetite; depolarization-induced suppression of inhibition
6. Marijuana use impairs learning and memory because the action of THC is widespread and not controlled.

D. Nitric Oxide and Carbon Monoxide

1. Nitric Oxide

- a. A gas produced by some neurons in the CNS and PNS from the amino acid L-arginine
- b. Diffuses across the presynaptic axon plasma membrane (no vesicle)
- c. Diffuses into the target cell and activates the production of cGMP as a second messenger
- d. Causes blood vessel dilation and helps kill bacteria
- e. May also act as a retrograde NT

Nitric Oxide and Carbon Monoxide (2)

- f. In the PNS, nitric oxide is secreted by autonomic neurons onto cells in the digestive tract, respiratory passages, and penis, causing muscle relaxation.
 - 1) Responsible for an erection
 - 2) The drug Viagra works by increasing NO release.

Nitric Oxide and Carbon Monoxide (3)

2. Carbon Monoxide (CO)
 - a. Another gas used as a neurotransmitter
 - b. Derived from the conversion of heme to biliverdin
 - 1) Also activates the production of cGMP in target cells
 - 2) Used in the olfactory epithelium and cerebellum

E. ATP and Adenosine as NTs

1. Used as cotransmitters released via vesicles with another neurotransmitter
2. Classified chemically as purines; bind to purinergic receptors
 - a. P1 receptor for ATP
 - b. P2 receptor for adenosine
3. Released with norepinephrine to stimulate blood vessel constriction and with ACh to stimulate intestinal contraction
4. Released by nonneural cells; act as paracrine regulators in blood clotting, taste, and pain

Chemicals that Are or May Be NTs

TABLE 7.7 Examples of Chemicals That Are Either Proven or Suspected Neurotransmitters

Category	Chemicals
<i>Amines</i>	Histamine
	Serotonin
<i>Catecholamines</i>	Dopamine
	(Epinephrine—a hormone)
	Norepinephrine
<i>Choline derivative</i>	Acetylcholine
<i>Amino acids</i>	Aspartic acid
	GABA (gamma-aminobutyric acid)
	Glutamic acid
	Glycine
<i>Polypeptides</i>	Glucagon
	Insulin
	Somatostatin
	Substance P
	ACTH (adrenocorticotrophic hormone)
	Angiotensin II
	Endogenous opioids (enkephalins and endorphins)
	LHRH (luteinizing hormone-releasing hormone)
	TRH (thyrotropin-releasing hormone)
	Vasopressin (antidiuretic hormone)
	CCK (cholecystokinin)
<i>Lipids</i>	Endocannabinoids
<i>Gases</i>	Nitric oxide
	Carbon monoxide
<i>Purines</i>	ATP

VII. Synaptic Integration

A. Introduction to Synaptic Integration

1. Neural pathways

- a. Divergence of neural pathways: Axons have collateral branches, so one presynaptic neuron can form synapses with several postsynaptic neurons.
- b. Convergence of neural pathways: Several different presynaptic neurons (up to a thousand) can synapse on one postsynaptic neuron.

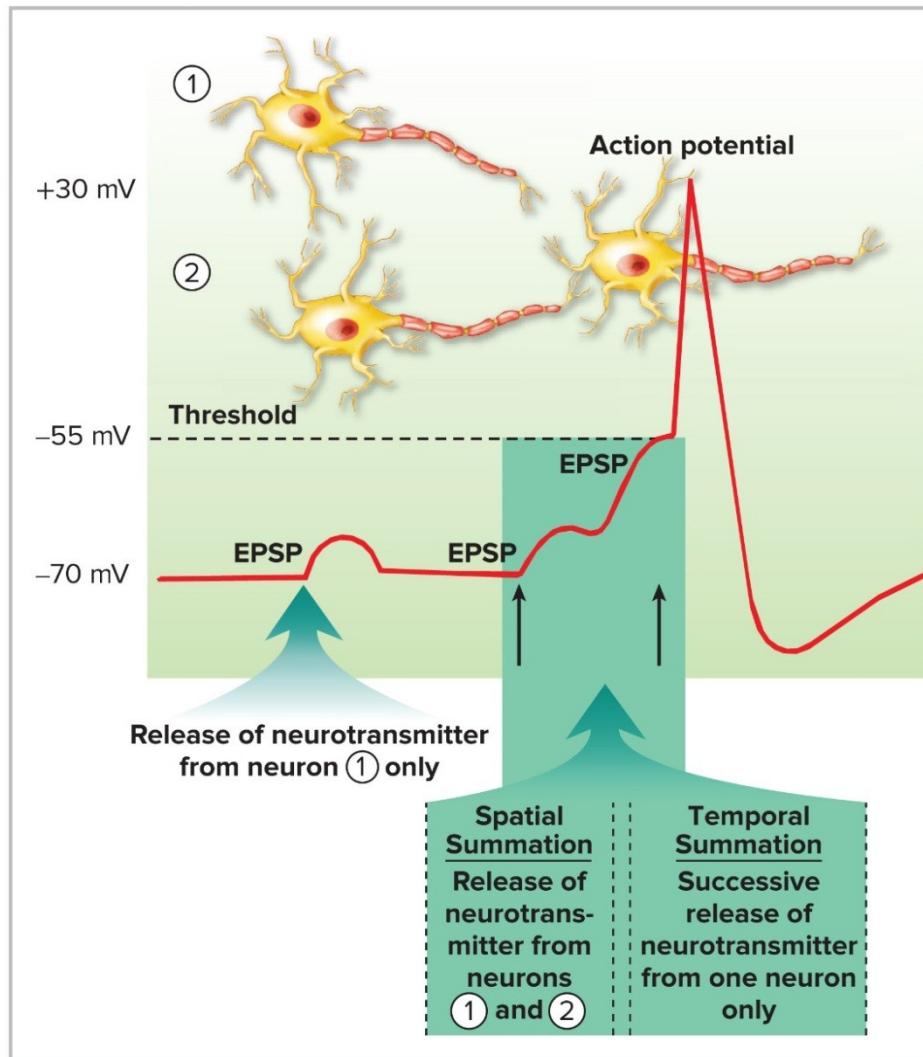
Introduction to Synaptic Integration (2)

2. Summation

- a. Spatial summation occurs due to convergence of signals onto a single postsynaptic neuron.
 - 1) All of the EPSPs and IPSPs are added together at the axon hillock.
- b. Temporal summation is due to successive waves of neurotransmitter release that add together at the initial segment of the axon

Spatial Summation

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B. Synaptic Plasticity

1. Repeated use of a neuronal pathway may strengthen or reduce synaptic transmission in that pathway.
2. When repeated stimulation enhances excitability, it is called long-term potentiation (LTP).
 - a. Found in the hippocampus of the brain where memories are stored
 - b. Associated with insertion of AMPA glutamate receptors

Synaptic Plasticity (2)

- c. Improves the efficacy of synaptic transmission that favors transmission along frequently used pathways
- d. Seen in learning and memory in the hippocampus

Synaptic Plasticity (3)

3. Long-term depression (LTD) occurs when glutamate-releasing presynaptic neurons stimulate the release of endocannabinoids.
 - a. This suppresses the further release of neurotransmitter.
 - b. Due to removal of AMPA receptors
 - c. Short-term (20 to 40 sec) is called DST, depolarization-induced suppression of inhibition

Synaptic Plasticity (4)

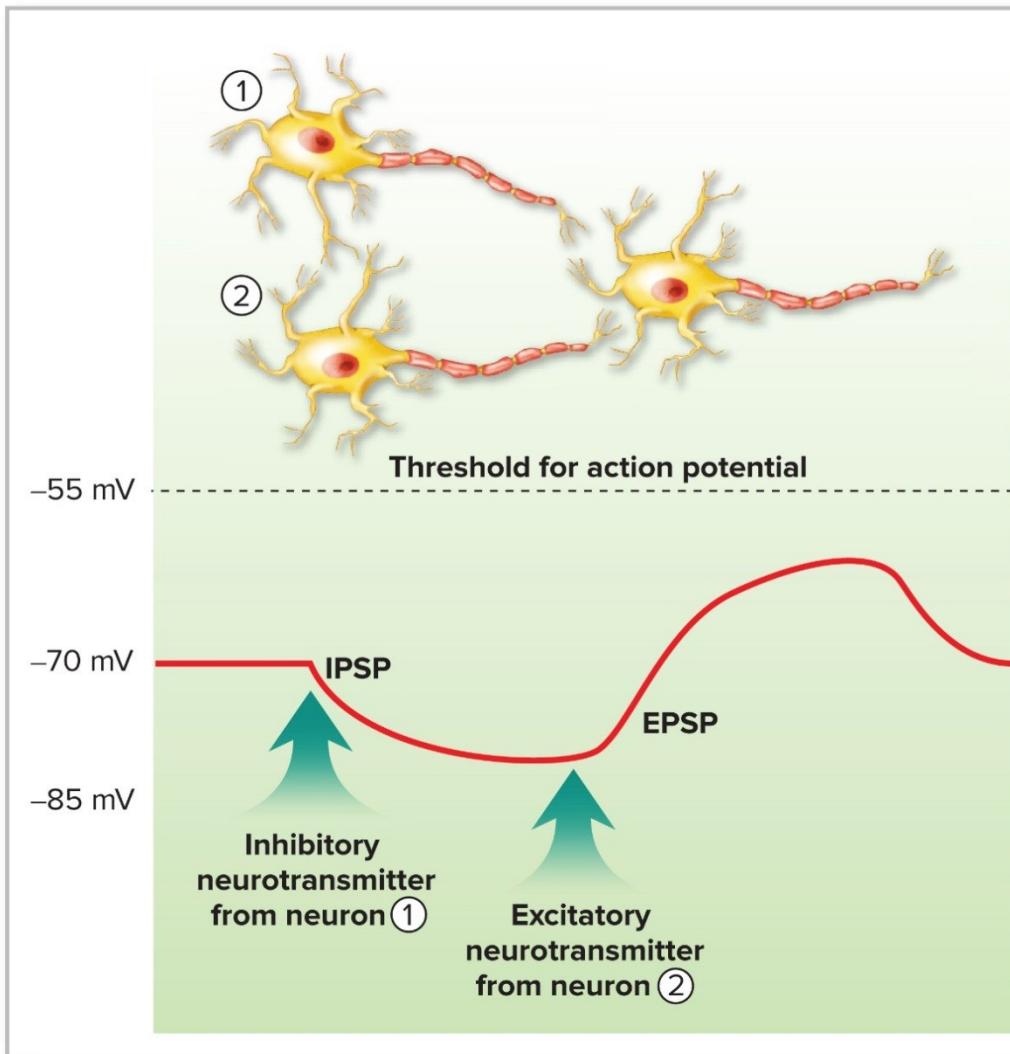
4. Both LTP and LTD depend on a rise in calcium ion concentration within the postsynaptic neuron
 - a. Rapid rise leads to LTP
 - b. Smaller but prolonged rise leads to LTD
5. Synaptic plasticity involves enlargement or shrinkage of dendritic spikes

B. Synaptic Inhibition

1. Postsynaptic inhibition is produced by inhibitory neurotransmitters such as glycine (spinal cord) and GABA (brain).
2. Hyperpolarizes the postsynaptic neuron and makes it less likely to reach threshold voltage at the axon hillock

Synaptic Inhibition (2)

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C. Presynaptic Inhibition

1. Sometimes a neuron synapses on the axon of a second neuron, inhibiting the release of excitatory neurotransmitter from the second neuron.
2. Calcium ion channels are inactivated
 - a. Seen in the action of endogenous opioids in pain reduction; inhibits the release of substance P that promotes pain transmission