Human Physiology I
Second Year Pharmacy Students
Chapter 4: Neuronal Physiology
Part 1 A

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First Semester 2020/2021

Neuronal physiology

■ **Nerve and muscle are excitable tissues:**

■ Nerve and muscle are considered excitable tissues because they produce electrical signals when excited.

■ Neurons use these electrical signals to receive, process, initiate, and transmit messages.

■ In muscle cells, these electrical signals initiate contraction.

■ Thus, electrical signals are critical to the function of the nervous system and all muscles.

■ **Membrane potential** becomes **less** negative during **depolarization** and **more** negative during **hyperpolarization**:

1. Polarization: Any time the value of the membrane potential is other than 0 mV, in either the positive (an excess positive charges are present on the inside of the membrane), or, negative (an excess negative charges are present on the inside of the membrane) direction, the membrane is in a state of polarization. At resting potential, the membrane is polarized at -70 mV in a typical neuron.

Neuronal physiology

2. Depolarization: The **membrane** becomes **less polarized**; **the inside** becomes **less negative** than at **resting potential**, with the **potential** moving **closer** to **0 mV** (for example, a change from -70 to -60 mV); **fewer charges** are separated than at resting potential. This term also refers to **the inside** even becoming **positive** as it does during **an action potential** when **the membrane potential reverses itself** (for example, becoming +30 mV).

3. Repolarization: The **membrane returns** to **resting potential** after having been **depolarized.**

4. Hyperpolarization: The **membrane** becomes **more polarized**; **the inside** becomes **more negative** than at **resting potential**, with **the potential moving** even **farther from** 0 mV (for instance, a change from -70 to -80 mV).

Neuronal physiology

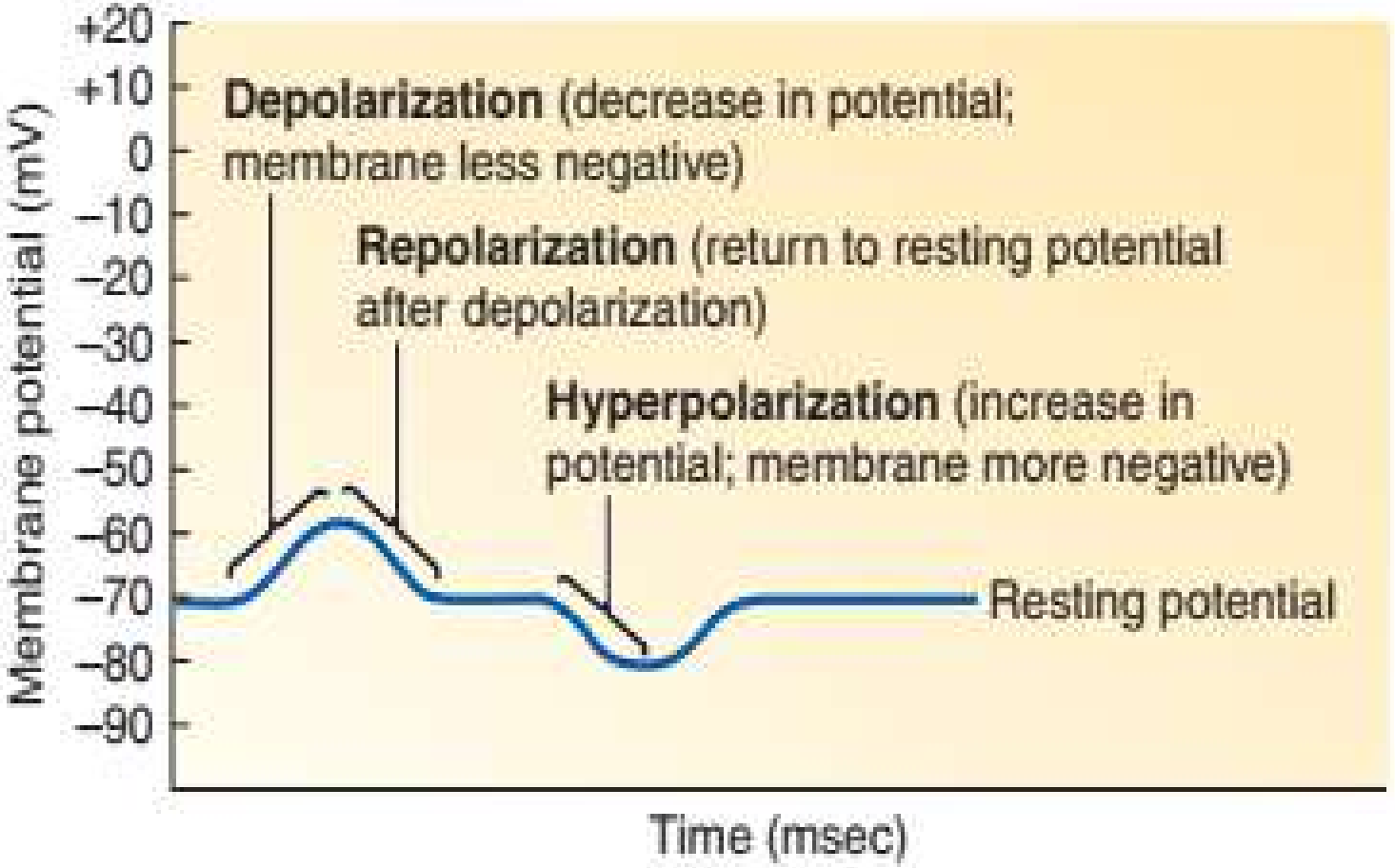


FIGURE 4-1 Types of changes in membrane potential.

Neuronal physiology

■ **Electrical signals** are **produced** by **changes** in **ion movement** across **the plasma membrane:**

■ Changes in ion movement are brought about by changes in membrane **permeability** in response to **triggering events**, which might be: **(1)** a change in the electrical field in the vicinity of an excitable membrane; **(2)** an interaction of a chemical messenger with a surface receptor on a nerve or muscle cell membrane; **(3)** a stimulus, such as sound waves stimulating specialized neurons in the ear; or **(4)** a change of potential caused by inherent cyclical changes in channel permeability.

Neuronal physiology

■ The **water-soluble ions** which carry **charge cannot penetrate** the plasma membrane's **lipid bilayer**; instead, these **charges** can **cross** the **membrane only** through **channels specific** for them or by **active transport mechanism.**

■ **Membrane channels** may be **either leak channels** or **gated channels:**

(1) leak channels: are **open all** the time, permit unregulated leakage of their specific ion across the membrane.

(2) Gated channels: which have **gates** that can be **open** or **closed**, **permitting** ion passage through the channels when **open** and **preventing** ion passage through the channels when **closed.**

■ **Gate opening** and **closing results** from **a change** in the **conformation** (shape) of **the protein** that **forms** the **gated channel.**

Neuronal physiology

■ There are **4 kinds** of **gated channels**, **depending** on the **factor** that **causes** the **change** in **channel conformation:**

(1) Voltage-gated channels: **open** or **close** in response to **changes** in **membrane potential.**

(2) Chemically (ligand) **gated channels:** change conformation in response to binding of a specific extracellular **chemical messenger** to **a surface membrane receptor.**

(3) Mechanically gated channels: respond to **mechanical deformation** (e.g., stretching).

(4) Thermally gated channels: respond to local changes in temperature (heat or cold).

■ **Triggering events** alter **membrane permeability** and consequently alter **ion flow** across the membrane by **opening** or **closing** the **gates** guarding **particular ion channels**. These **ion movements redistribute charge** across the **membrane**, causing **membrane potential** to **fluctuate.**

Neuronal physiology

■ There are **2 basic forms** of **electrical signals**:

1.Graded potentials: which **serve** as **short-distance signals.**

2.Action potentials: which **serve** as **long-distance signals.**

1. G**raded potentials**

■ **Graded potentials** are **local changes** in **membrane potential** that occur in **varying grades** (degrees) of **magnitude** (strength). For e.g., membrane potential could change from -70 to - 60 mV (a 10 mV graded potential).

■ The **stronger a triggering event** is, **the larger** the **resultant graded potential:**

■ **Graded potentials** are usually produced by **a specific triggering event** that causes **gated ion channels** to **open** in a specialized region of the excitable cell membrane. The resultant ion movement produces the graded potential, which **most commonly** is **a depolarization** resulting from **net Na^+ entry.**

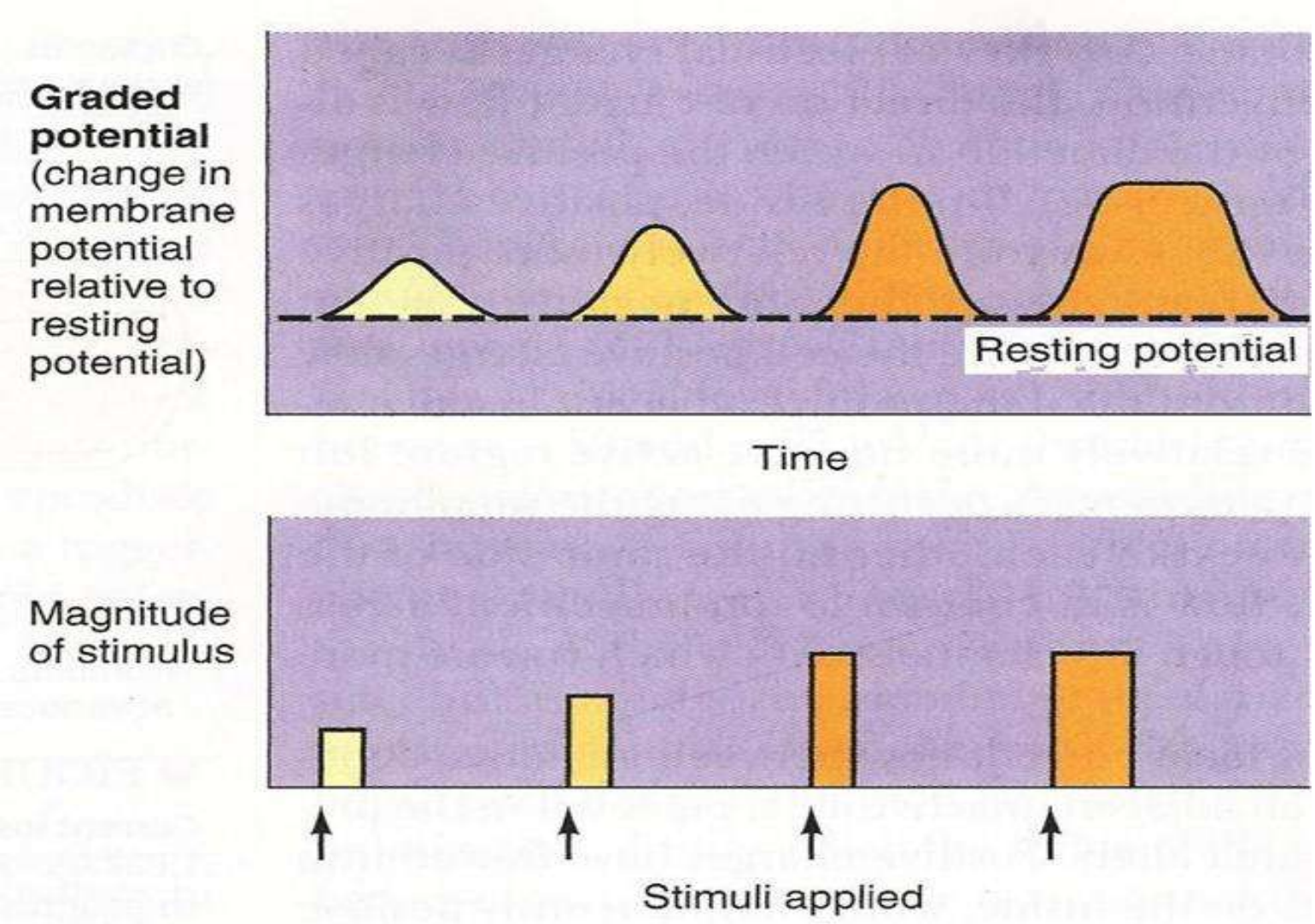
graded potential is **confined** to this **small,** ■ The **specialized region** of the **total plasma membrane.**

Neuronal physiology

■ The **magnitude** of the **initial graded potential** (that is, the difference between the new potential and resting potential) is related to **the magnitude** of the **triggering event**: The **stronger** the **triggering event**, the **more gated channels** (most commonly gated-Na^+ channels) that **open**, the **greater** is the **positive charge** entering the cell, and **the larger** is the **depolarizing graded potential** at **the point of origin**.

■ Also, the **longer** the **duration** of **the triggering event**, **the longer** is the **duration** of **the graded potential**.

Neuronal physiology



Human Physiology I

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Chapter 4: Neuronal Physiology

Part 1 B

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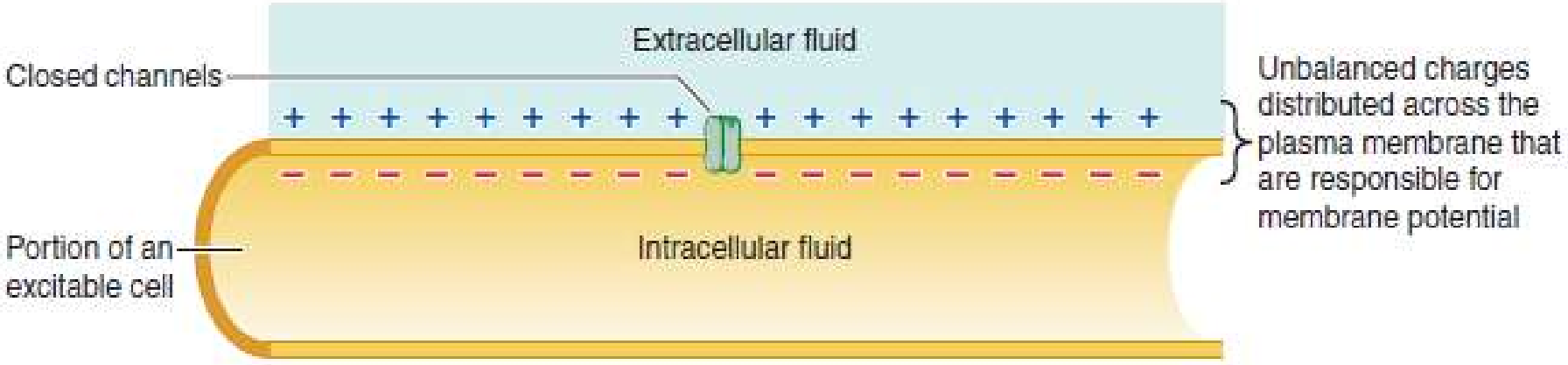
First Semester 2020/2021

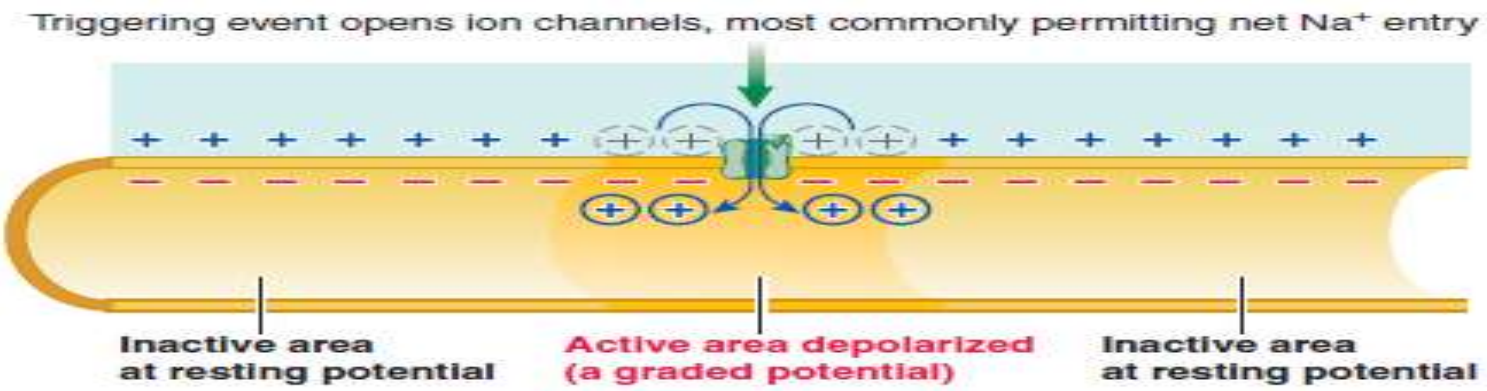
■ **Graded potentials spread by passive current flow:**

■ When a graded potential occurs locally in a nerve or muscle cell membrane, the rest of the membrane remains at resting potential. The temporarily depolarized region is called an **active area.**



(a) Entire membrane at resting potential

Neuronal physiology



(b) Inward movement of Na^+ depolarizes membrane, producing a graded potential

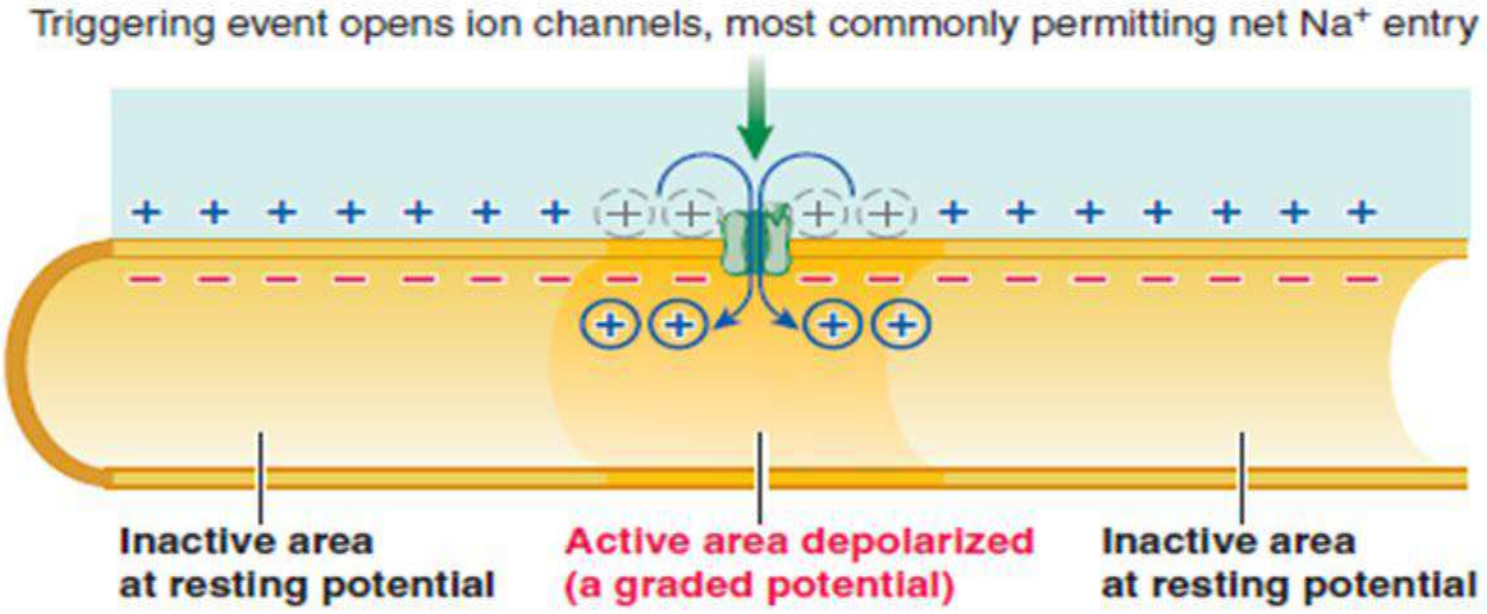
■ **Note** from the **Figure** above that:

(1) **inside** the **cell**, the **active area** is relatively **more positive** than the **neighboring** (adjacent) **inactive areas** that are still at **resting potential.**

(2) **Outside** the cell, the **active area** is relatively **less positive** than **adjacent inactive areas**.

Neuronal physiology

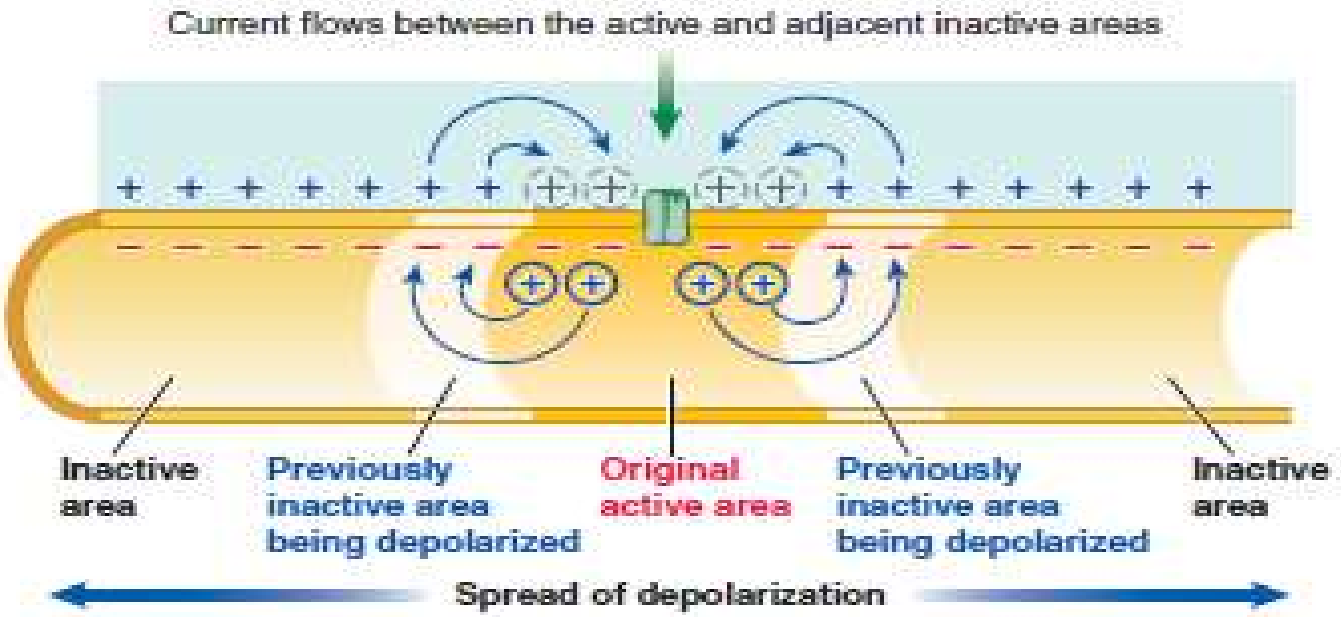
■ Because of **this difference** in **potential, electrical charges** (which are carried by ions) **passively flow** between the **active** and **adjacent resting regions** on **both** the **inside** and **outside** of the **membrane.**



(b) Inward movement of Na^+ depolarizes membrane, producing a graded potential

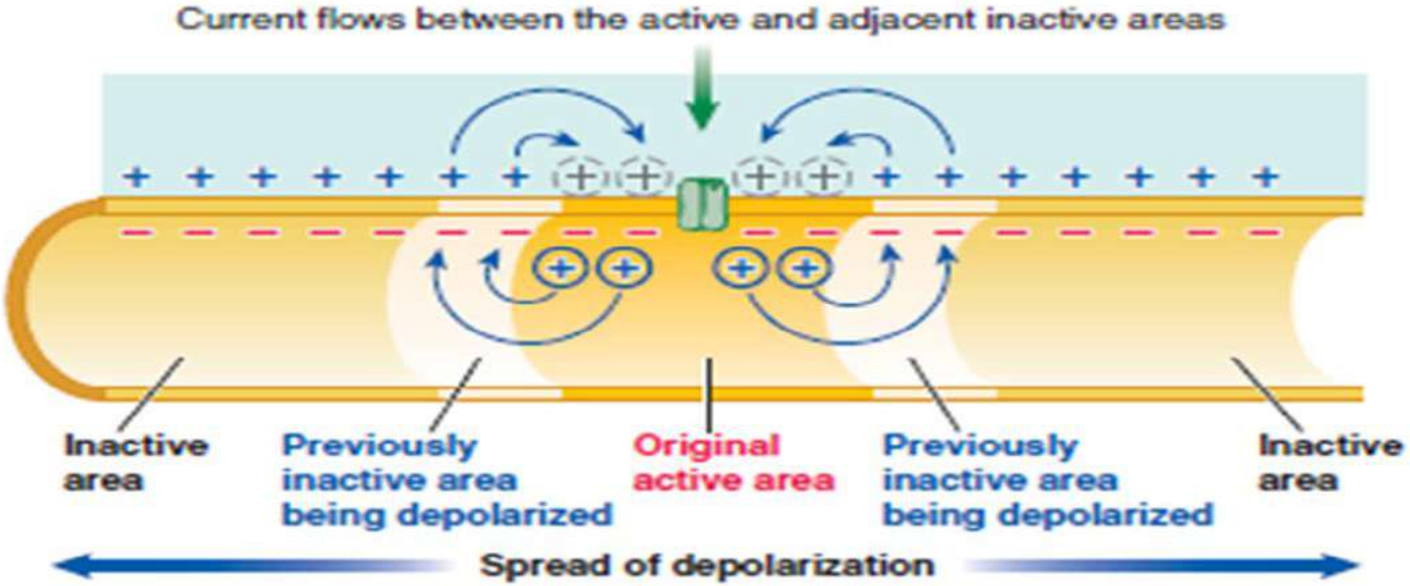
Neuronal physiology

■ Any **flow** of **electrical charges** is called **a current.** The **direction** of **current flow** is **always the same** as the **direction** in which the **positive charges** are moving (see Figure below):



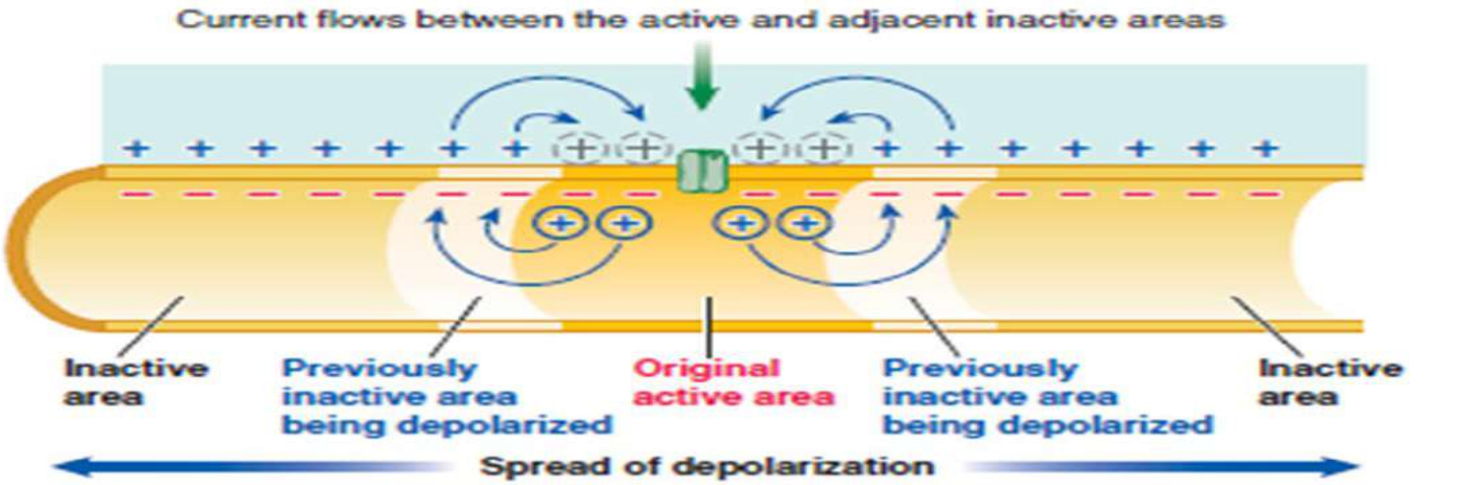
(c) Depolarization spreads by local current flow to adjacent inactive areas, away from point of origin

■ **Inside the cell**, **positive charges flow** through the ICF **away from** the **more positive depolarized active region toward** the **more negative adjacent resting regions.**



(c) Depolarization spreads by local current flow to adjacent inactive areas, away from point of origin

■ **Outside the cell, positive charges flow** through the ECF **from** the **more positive adjacent inactive regions toward** the **more negative active region.**



(c) Depolarization spreads by local current flow to adjacent inactive areas, away from point of origin

■ Note: current is occurring along the membrane between regions **next** to **each other** on the same side of the membrane.

■ As a result of **local current flow** between **an active depolarized area** and **an adjacent inactive area**, the **potential** changes in **the previously inactive area.**

■ Because **positive charges** have flowed **simultaneously** into **the adjacent inactive area** on the **inside** and **out** of **this area** on the **outside**, the **adjacent area** is now **more positive** on the **inside** than **before** and **less positive** on the **outside.** Stated differently, the **previously inactive adjacent area** has been **depolarized**, so **the graded potential** has **spread.**

■ This **area's potential** now **differs** from that of **the inactive region immediately next to it** on **the other side**, inducing **further current flow** at **this new site**, and **so on**. Thus, **current** spreads in **both directions away** from **the initial site** of **the change** in **potential.**

■ The **amount** of **current** that **flows** between **2 areas depends** on **the difference** in **potential** between **the 2 areas** and on **the resistance** (the hindrance to electrical charge movement) of **the material** through which the **charges** are moving. **The greater** the **difference** in **potential, the greater** is the **current flow**; and the **lower** the **resistance, the greater** is the **current flow**. The ICF and ECF (like electrical wires) are all **good conductors** (have low resistance to current flow), so current readily flows through them.

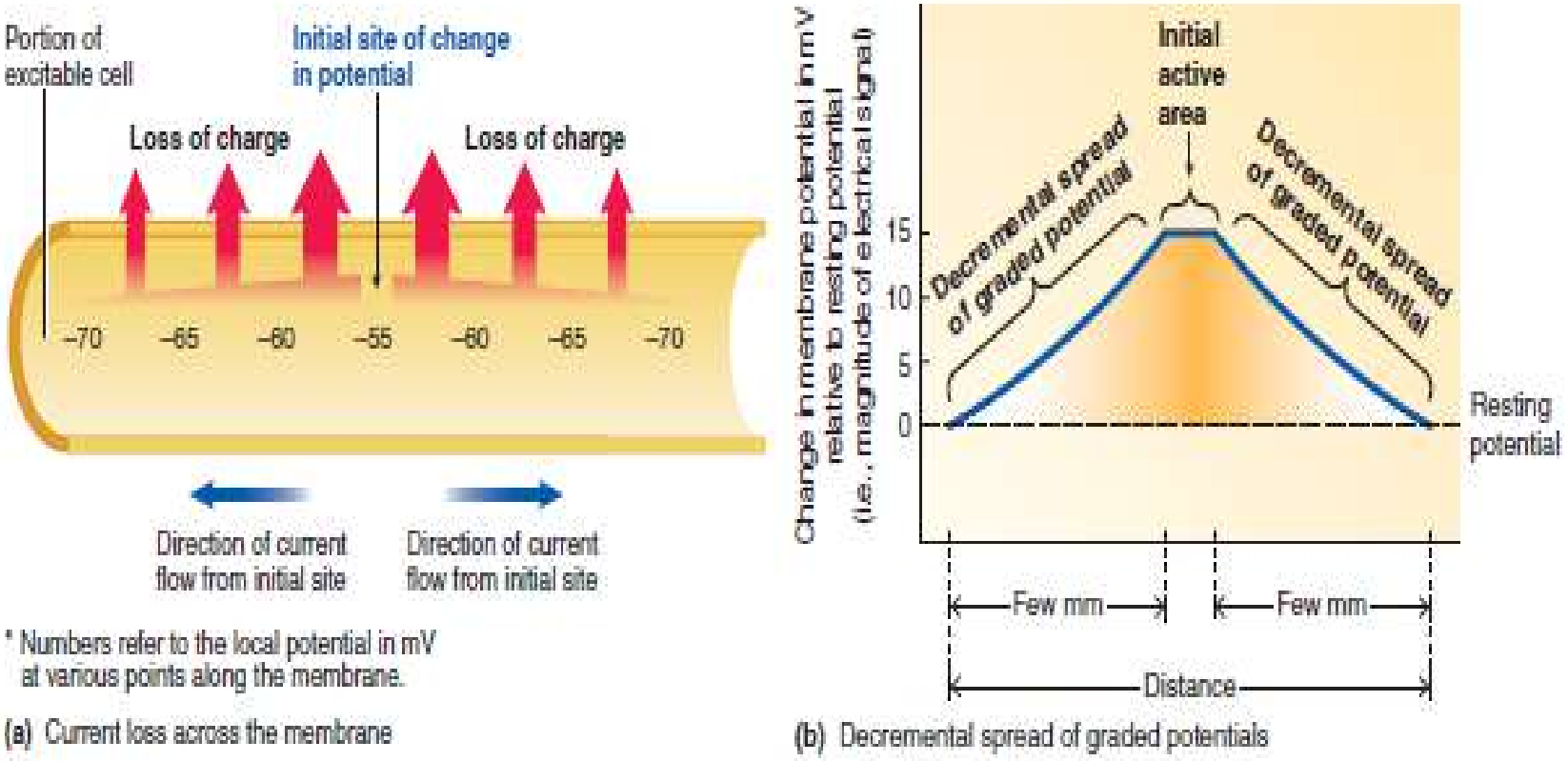
■ **Body lipids** (like the plastic surrounding electrical wires) are **insulators** (have high resistance and greatly hinder movement of charge). Thus, **current does not** flow across **the plasma membrane's lipid bilayer**. **Current**, **carried** by **ions**, can **move** across the **membrane only** through **ion channels.**

Neuronal physiology

Graded potentials die out over short distances

■ current is lost across the plasma membrane as charge-carrying ions in the form of K^+ **leak out** through the "uninsulated parts" of the membrane, that is, by diffusing outward **down** their electrochemical gradient through open channels. Because of this current loss, the magnitude of the local current, and thus the magnitude of **the graded potential,** progressively diminishes the farther it moves away from the initial active area, that is, the spread of a graded potential is decremental (gradually decreases).

Neuronal physiology



● **FIGURE 4-3 Current loss across the plasma membrane leading to decremental spread of a graded potential.** (a) Leakage of charge-carrying ions across the plasma membrane results in progressive loss of current with increasing distance from the initial site of the change in potential. (b) Because of leaks in current, the magnitude of a graded potential continues to decrease as it passively spreads from the initial active area. The potential dies out altogether within a few millimeters of its site of initiation.

■ Note that in the previous Figure, the magnitude of the initial change in potential is 15 mV (a change from -70 to -55 mV); the change in potential **decreases** as it moves along the membrane to a potential of 10 mV (a change from -70 to -60 mV) and continues to diminish the farther it moves away from the initial active area until there is no longer a change in potential. In this way, local currents **die out** within a few millimeters from the initial site of change in potential and consequently can function as signals for **only** very short distances.

Neuronal physiology

■ Although graded potentials have limited signaling distance, they are critically important to the body's function. The following are all graded potentials (that most excitable cells produce in response to a triggering event): postsynaptic potentials, receptor potentials, end-plate potentials, pacemaker potentials, and slow-wave potentials.

■ In turn, **graded potentials** can **initiate action potentials**, the long-distance signals, in an excitable cell.

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2. Action potentials

■ Action potentials are brief, rapid, large (100 mV) changes in membrane potential during which the potential actually reverses (the inside of the cell transiently becomes more positive than the outside).

■ **Like** a graded potential, **a single** action potential involves only a small portion of the total excitable cell membrane.

■ **Unlike** graded potentials, however, action potentials are conducted, or propagated, throughout the entire membrane in “non-decremental fashion”; that is, they **do not** diminish in strength as they travel from their site of initiation throughout the remainder of the cell membrane. Thus, they can serve as faithful long-distance signals. For example, big toe wiggle by nerve cells located in the spinal cord and extend throughout the leg to the big toe.

Neuronal physiology

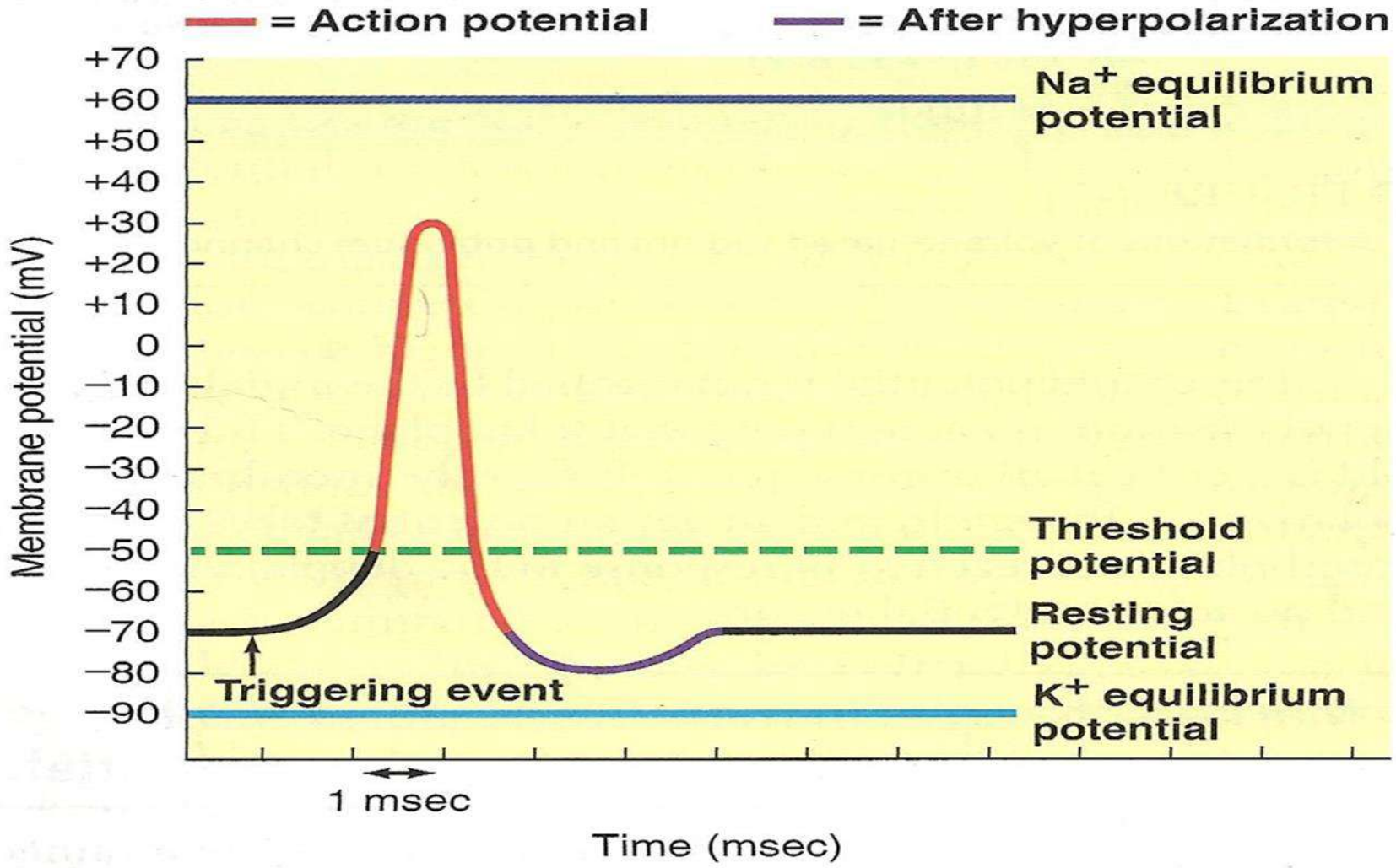
■ During an action potential, the membrane potential rapidly, transiently reverses:

■ If a graded potential is large enough, it can initiate an action potential before the graded change dies off. Typically, the region of the excitable membrane where graded potentials are produced in response to a triggering event **does not** undergo action potentials. Instead, passive current flow from the region where a graded potential is taking place **depolarizes** adjacent portions of the membrane where action potentials can occur.

Neuronal physiology

FIGURE 4-6

Changes in membrane potential during an action potential



Neuronal physiology

■ Depolarization from the resting potential of -70 mV proceeds slowly **at first**, until it **reaches** a critical level known as “threshold potential” (typically between -50 and -55 mV).

■ At threshold potential, an explosive depolarization takes place. A recording of the potential at this time shows a sharp upward deflection as the potential rapidly reverses itself so that the inside of the cell becomes positive compared to the outside. Peak potential is usually +30 to +40 mV, depending on the excitable cell.

■ Just as rapidly, the membrane **repolarizes**, dropping back to resting potential. Often the forces that repolarize the membrane push the potential **too far**, causing **a brief** after hyperpolarization, during which the inside of the membrane briefly becomes even more negative than normal (for example, -80 mV) before the resting potential is restored.

■ The action potential is the entire rapid change in potential from threshold to peak and then back to resting. **Unlike** the variable duration of a graded potential, the duration of an action potential is **always** the same in a given excitable cell. In a neuron, an action potential **lasts** for **only** 1 msec (0.001 sec). It **lasts** longer in muscle, with the duration depending on the muscle type. Often an action potential is **referred to** as a **spike**, because of its spike-like recorded appearance.

■ Alternatively, when an excitable membrane is triggered to undergo an action potential, it is said to **fire.** Thus, the terms action potential, spike, and firing all refer to the same phenomenon of rapid reversal of membrane potential. If the initial triggered depolarization **does not reach** threshold potential, no action potential takes place. Thus, threshold is **a critical all-or-none point**. Either the membrane is depolarized to threshold and an action potential takes place, or threshold is **not reached** in response to the depolarizing event and **no** action potential occurs.

■ **Marked changes in membrane permeability and ion movement lead to an action potential:**

■ How is the **membrane potential** (which is maintained at a constant resting level) altered to such an extent as to produce an action potential? During an action potential, marked changes in membrane permeability to Na^+ and K^+ take place, permitting their rapid fluxes down their electrochemical gradients. These ion movements carry the current responsible for the potential changes that occur during an action potential.

Neuronal physiology

■ Action potentials take place as a result of the triggered opening and subsequent closing of 2 specific types of channels: voltage-gated Na^+ channels and voltage-gated K^+ channels.

■ **Voltage-gated Na^+ and K^+ channels:**

■ Voltage-gated membrane channels consist of proteins that have a number of charged groups. The electrical field surrounding the channels can distort the channel structure as charged portions of the channel proteins are electrically attracted or repelled by charges in the fluids around the membrane.

■ Voltage-gated channel proteins are especially sensitive to voltage changes. Small distortions in shape induced by changes in potential can cause the channels to change their conformation.

■ The voltage-gated Na^+ channel has 2 gates: **an activation gate** and **an inactivation gate**. The **activation gate** guards the channel interior by opening and closing like a sliding door. The **inactivation gate** consists of a ball-and-chain–like sequence of amino acids at the channel opening facing the ICF.

■ This gate is open when the ball is dangling free on its chain and closed when the ball binds to the channel opening, thus blocking the opening. Both gates must be open to **permit** passage of Na^+ through the channel, and closure of either gate **prevents** passage. This voltage-gated Na^+ channel can exist in 3 different conformations: (1) closed but capable of opening (activation gate closed, inactivation gate open); (2) open, or "activated" (both gates open); and (3) closed and not capable of opening, or "inactivated" (activation gate open, inactivation gate closed).

Neuronal physiology

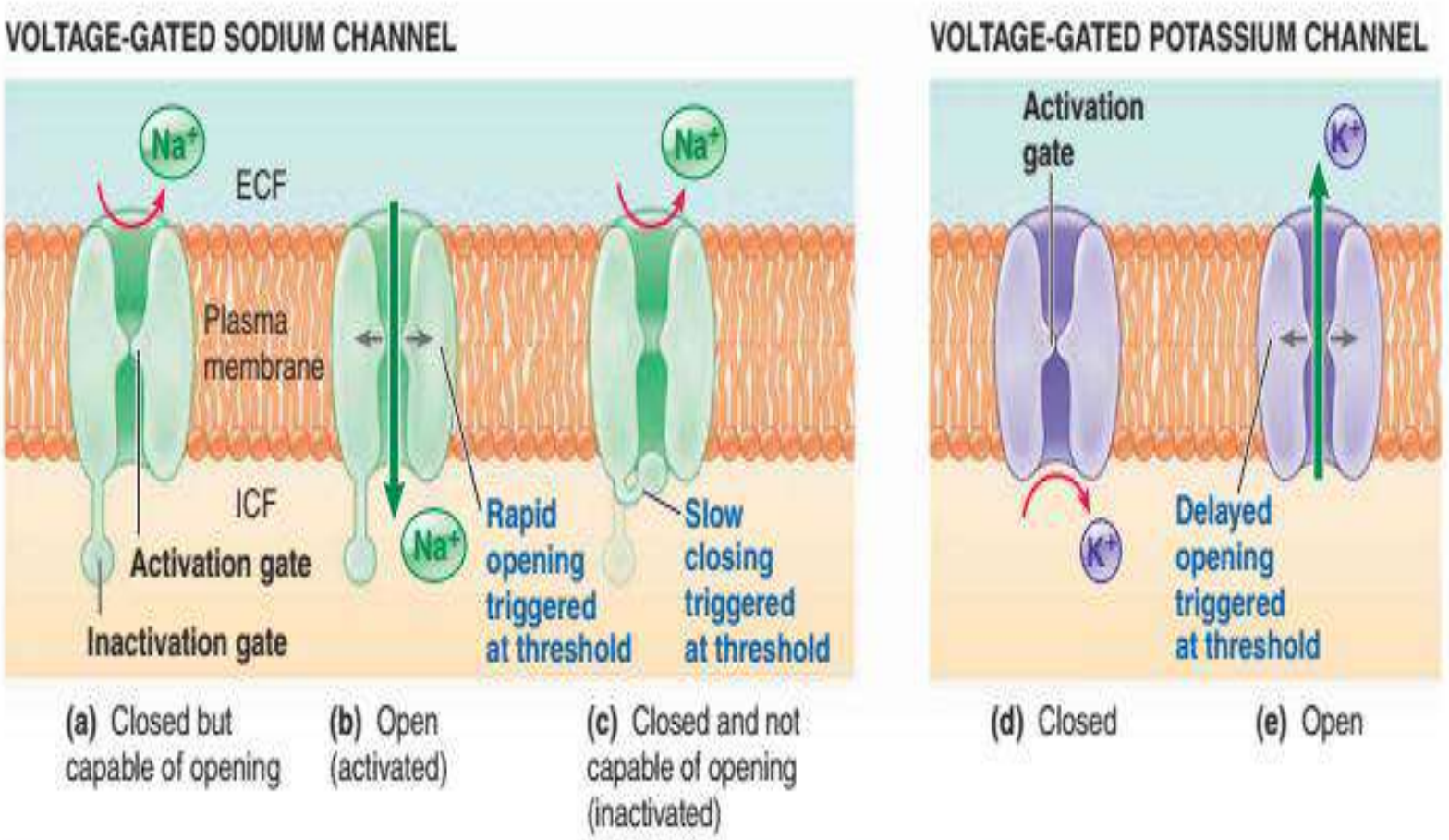
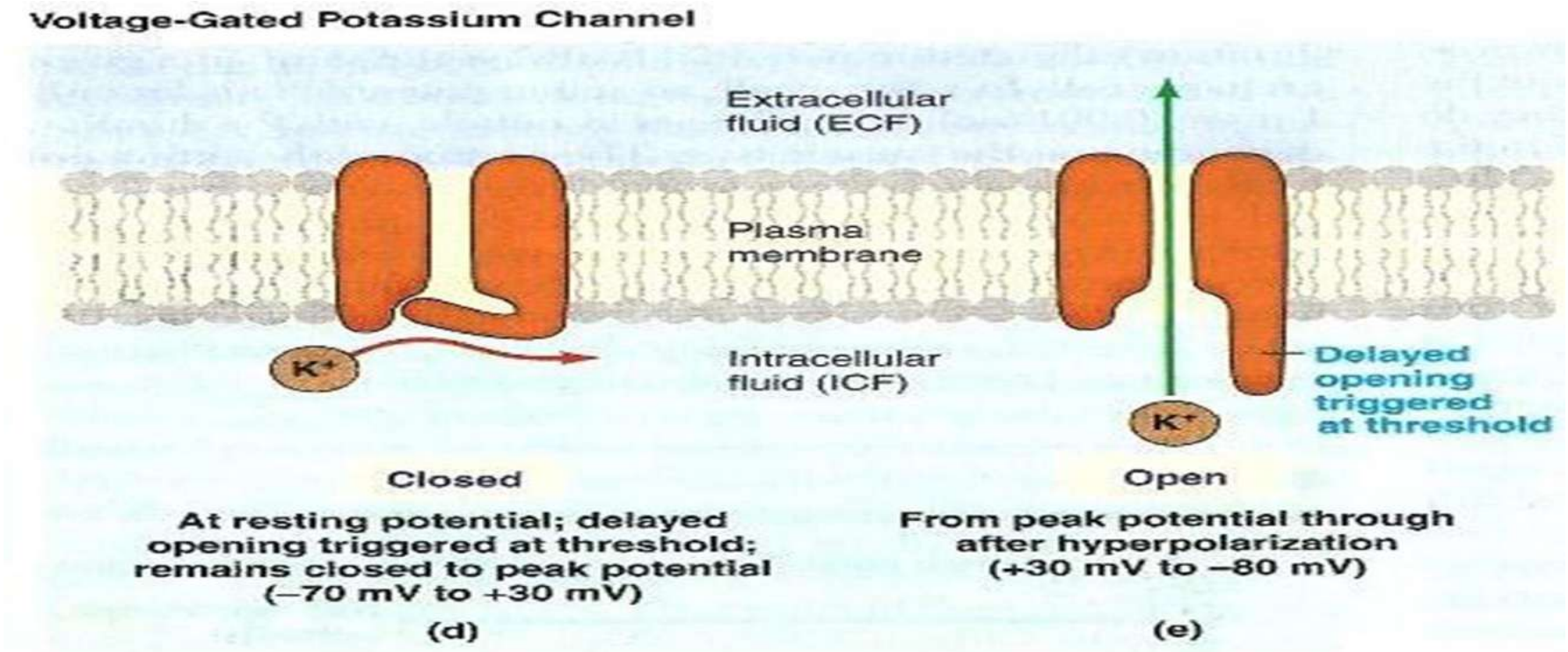


FIGURE 4-5 Conformations of voltage-gated sodium and potassium channels.

■ The voltage-gated K^+ channel is simpler. It has **only an activation gate**, which can be **either** closed or open. These voltage-gated Na^+ and K^+ channels exist in addition to the Na^+–K^+ pump and the leak channels for these ions.



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Part 2 B

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■ **Changes in permeability and ion movement during an action potential:**

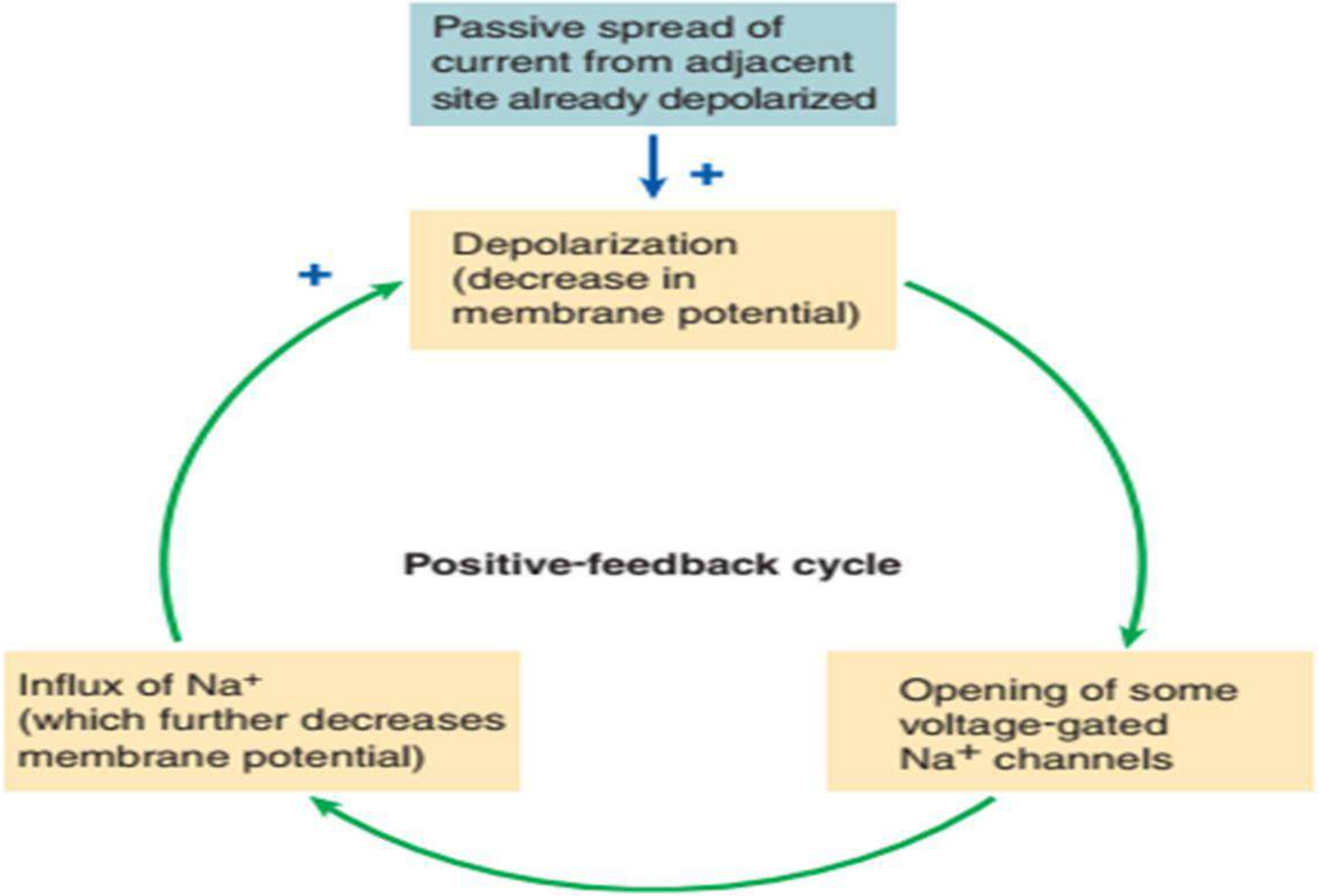
■ At resting potential (-70 mV), **all** the voltage-gated Na^+ and K^+ channels are **closed**, with the **activation** gates of the Na^+ channels being **closed** and their **inactivation** gates being **open**; that is, “closed but capable of opening” conformation. Therefore, Na^+ and K^+ **cannot pass** through these voltage-gated channels at resting potential. However, the **resting membrane** is 25-30 times **more permeable** to K^+ than to Na^+.

■ When **current** spreads **passively** from an adjacent site **already depolarized** into **a new** region at **resting potential**, the **new** region of membrane starts to **depolarize** toward **threshold**, causing **the activation gates** of **some** of **its voltage-gated Na^+ channels** to **open**, so that **both** gates of **these activated channels** are now **open**. Because **both** the **concentration** and **electrical** gradients for **Na^+ favor** its **movement into** the cell, **Na^+ starts** to **move in**.

Neuronal physiology

■ The **inward** movement of **positively charged Na^+ depolarizes** the membrane **further**, **opening** even **more voltage-gated Na^+ channels** and allowing **more** Na^+ to **enter**, and **so on**, in **a positive-feedback cycle.**

Neuronal physiology



● **FIGURE 4-6 Positive-feedback cycle responsible for opening Na^+ channels at threshold.**

■ At **threshold potential**, there is **an explosive increase** in **Na^+ permeability** (P_{Na+}), as **the membrane** swiftly becomes about **600 times more permeable** to Na^+ than to K^+. Each **individual channel** is **either** closed or open and **cannot** be **partially open.**

■ However, the **delicately poised gating mechanisms** of the various voltage-gated Na^+ channels are **jolted open** by **slightly different voltage changes**.

■ During the **early depolarizing phase**, **more** and **more** Na^+ channels **open** as **the potential progressively decreases**.

■ At **threshold**, **enough** Na^+ gates have **opened** to **set off** the positive-feedback cycle that rapidly causes the remaining Na^+ gates to **open**. Now **Na^+ permeability dominates** the membrane**,** in contrast to the **K^+ domination** at **resting potential**.

■ Thus, **at threshold,** Na^+ **rushes into** the cell, **rapidly** eliminating the **internal negativity** and even making the **inside** of the cell **more positive** than the **outside** in an attempt to drive the **membrane potential** to the **Na^+ equilibrium potential** (+61 mv). **The potential reaches approximately** +30 mV, close to the Na^+ equilibrium potential. The potential **does not** become any more positive, because, **at the peak** of the **action potential**, the Na^+ channels **start** to **close** to the **inactivated state**, and P_{Na+} **starts** to **fall** to **its low resting value.**

■ **What causes** the **Na^+ channels** to **close**? When the membrane potential **reaches threshold**, **2 closely related events** take place in **the gates** of **each** Na^+ channel**:** the **activation gates** are triggered to **open rapidly** in response to the depolarization, converting the channel to **its open conformation.** Surprisingly, the conformational change that **opens** the channel also **allows** the **inactivation gate's ball** to **bind** to the **channel opening** , thereby **blocking** the **mouth** of the **channel.**

■ However, this **closure process takes time**, so the **inactivation gate closes slowly** compared to the **rapidity** of **channel opening**. Meanwhile, during the **0.5 msec delay** after the **activation gate opens** and before the **inactivation gate closes**, **both gates** are **open** and Na^+ **rushes** into the cell through these open channels, bringing the **action potential** to **its peak.** Then, the **inactivation gate closes**, **membrane permeability** to Na^+ **plummets** to **its low resting value**, and **further** Na^+ **entry** is **prevented.**

■ The **channel** remains in this **inactivated conformation** until the **membrane potential** has been **restored** to **its resting value.**

■ **Simultaneous** with **inactivation** of **Na^+ channels**, the **voltage-gated K^+ channels start** to **slowly open** at **the peak** of the action potential. **Opening** of the **K^+ channel gate** is a **delayed voltage-gated response** triggered by **the initial depolarization** to **threshold.**

■ Thus, **3 action potential-related events** occur at **threshold**: **(1)** The **rapid opening** of the **Na^+ activation gates**, which **permits** Na^+ to **enter**, moving the potential from threshold to its positive peak. **(2)** The **slow closing** of the **Na^+ inactivation gates**, which **halts further Na^+ entry** after **a brief time delay**, thus keeping the **potential** from **rising any further.**

(3) The **slow opening** of the **K^+ gates**, which is responsible for the potential **plummeting** from **its peak** back to **resting.**

■ The **membrane potential** would **gradually return** to **resting** after **closure** of the **Na^+ channels** as **K^+ continued** to **leak out** but **no further Na^+** entered. However, the return to **resting** is **hastened** by the **opening of K^+ gates** at **the peak** of the action potential. **Opening** of **the voltage-gated K^+ channels greatly increases K^+ permeability** (P_{K^+}) to about **300 times** the **resting P_{Na+}** . This **marked increase** in **P_{K}+** causes **K^+** to **rush out** of the cell **down** its **electrochemical gradient**, carrying **positive charges back** to **the outside.**

■ **Note that** at **the peak** of the **action potential**, the **positive potential inside** the cell tends to **repel** the **positive K^+ ions**, so **the electrical gradient** for K^+ is **outward**, **unlike** at **resting potential.** (Of course, **the concentration gradient** for **K^+** is **always outward**.) The **outward movement** of **K^+ rapidly restores** the **negative resting potential.**

■ To **review:**

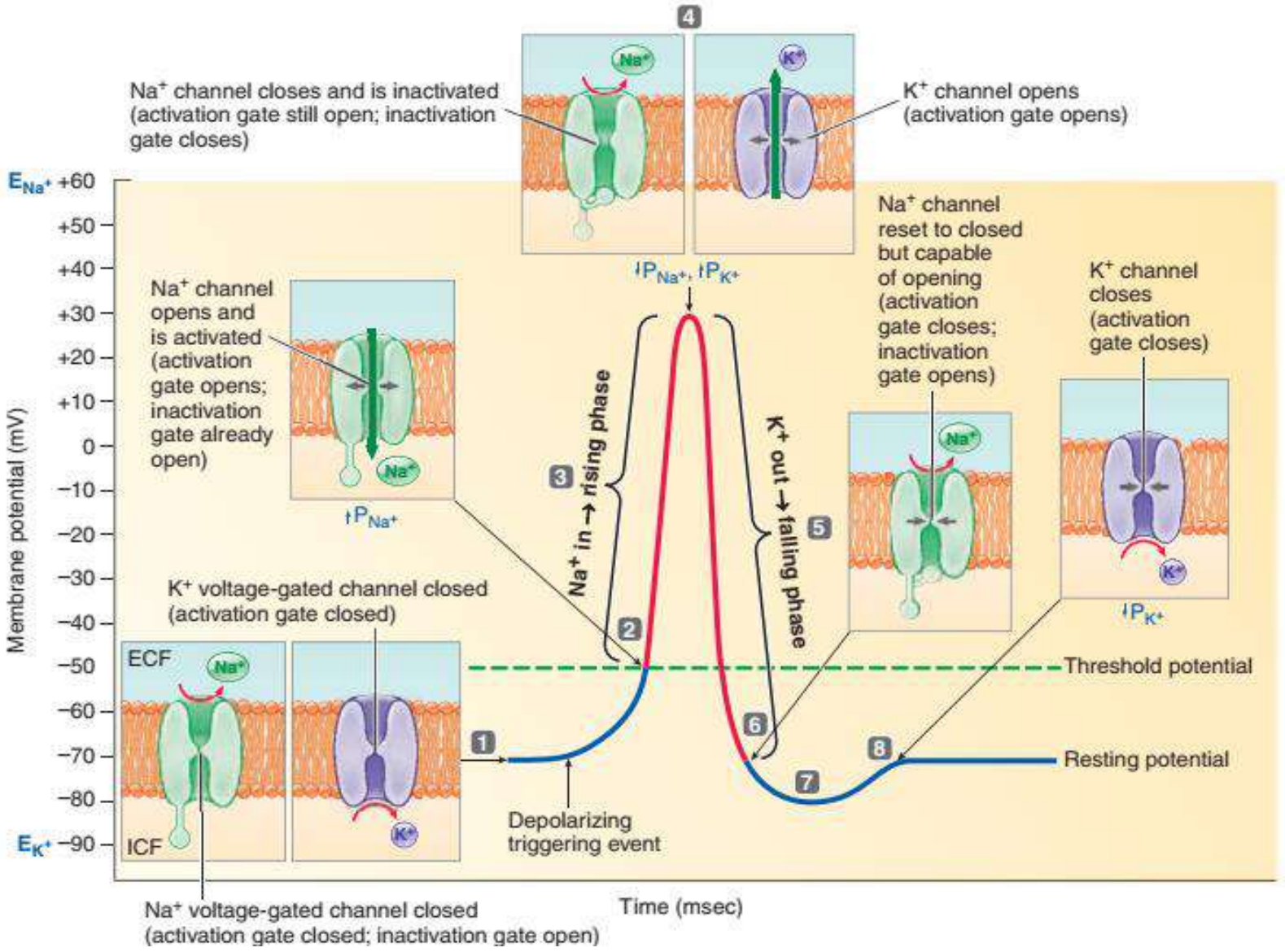
■ The **rising phase** of the **action potential** (from threshold to +30 mV) is due to **Na^+ influx** induced by an **explosive increase** in **P_{Na+}** at **threshold.**

■ The **falling phase** (from +30 mV to resting potential) is brought about **largely** by **K^+ efflux** caused by **the marked increase** in **P_{K+}** occurring **simultaneously** with **the inactivation** of the **Na^+ channels** at **the peak** of **the action potential.**

■ As the **potential returns** to **resting**, **the changing voltage shifts** the **Na^+ channels** to their **"closed but capable of opening"** conformation, with **the activation gate closed** and the **inactivation gate open**. Now **the channel** is **reset**, **ready** to **respond** to **another** triggering event. **The newly opened voltage-gated K^+ channels** also **close**, so **the membrane returns** to **the resting number** of **open K^+ leak channels.** Typically, **the voltage-gated K^+ channels** are **slow** to **close.**

■ As **a result** of this **persistent increased permeability** to **K^+, more K^+** may **leave** than is **necessary** to bring the **potential** to **resting**. **This slight excessive K^+ efflux** makes **the interior** of the cell **transiently even more negative** than **resting potential**, causing **the afterhyperpolarization.** Then, **K^+ activation gate closes,** and **membrane returns** to **resting potential.**

Neuronal physiology



Neuronal physiology

1. Resting potential: all voltage-gated channels closed.

2. At threshold, Na^+ activation gate opens and P_{Na^+} rises.

3. Na^+ enters cell, causing explosive depolarization to +30 mV, which generates rising phase of action potential.

4. At peak of action potential, Na^+ inactivation gate closes and P_{Na^+} falls, ending net movement of Na^+ into cell. At the same time, K^+ activation gate opens and P_{K^+} rises.

5. K^+ leaves cell, causing its repolarization to resting potential, which generates falling phase of action potential.

6. On return to resting potential, Na^+ activation gate closes and inactivation gate opens, resetting channel to respond to another depolarizing triggering event.

7. Further outward movement of K^+ through still-open K^+ channel briefly hyperpolarizes membrane, which generates after hyperpolarization.

8. K^+ activation gate closes, and membrane returns to resting potential.

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■ **The Na^+-K^+ pump gradually restores the concentration gradients disrupted by action potential:**

■ At **the completion** of an **action potential**, the **membrane potential** has been **restored** to **its resting condition**, but **the ion distribution** has been **altered** slightly. **Na^+ entered** the cell during **the rising phase**, and **a comparable amount** of **K^+ left** during **the falling phase. The Na^+–K^+ pump restores** these ions to **their original locations** in **the long run**, but **not after each action potential**.

■ The **active pumping process** takes **much longer** to **restore** Na^+ and K^+ to **their original locations** than it takes for **the passive fluxes** of these ions during **an action potential**. However, the **membrane does not need** to **wait** until the **concentration gradients** are **slowly restored** before it can **undergo** another action potential.

■ Actually, the **movement** of relatively **few** Na^+ and K^+ ions causes the **large swings** in **membrane potential** that occur during **an action potential.**

■ **Only** about 1 **out of** 100,000 K^+ ions present in the cell **leaves** during **a single** action potential, while a comparable number of Na^+ ions enter from the ECF. The movement of this extremely small proportion of the total Na^+ and K^+ during a **single action potential** produces dramatic 100 mV changes in potential (between -70 and +30 mV) but **only** infinitesimal changes in the ICF and ECF concentrations of these ions. Much more K^+ is **still inside** the cell than outside, and Na^+ is **still predominantly** an extracellular cation.

■ Consequently, the Na^+ and K^+ concentration gradients **still exist**, so **repeated action potentials** can **occur without the pump** having to keep pace to **restore the gradients.**

■ Were it **not** for **the pump**, even **tiny fluxes** accompanying **repeated action potentials** would **eventually** "**run down**" the **concentration gradients** so that **further action potentials** would be **impossible.**

■ Thus, the **Na^+–K^+ pump** is **critical** to **maintaining** the **concentration gradients** in **the long run**. However, it **does not** have to **perform its role between action potentials**, **nor** is it **directly involved** in the **ion fluxes** or **potential changes** that occur **during an action potential.**

■ **Action potentials are propagated from the axon hillock to the axon terminals:**

■ **A single action potential** involves **only** a small patch of the total surface membrane of an excitable cell. But if **action potentials** are to serve as **long-distance signals**, they **cannot** be merely isolated events occurring in a limited area of a nerve or muscle cell membrane. So,

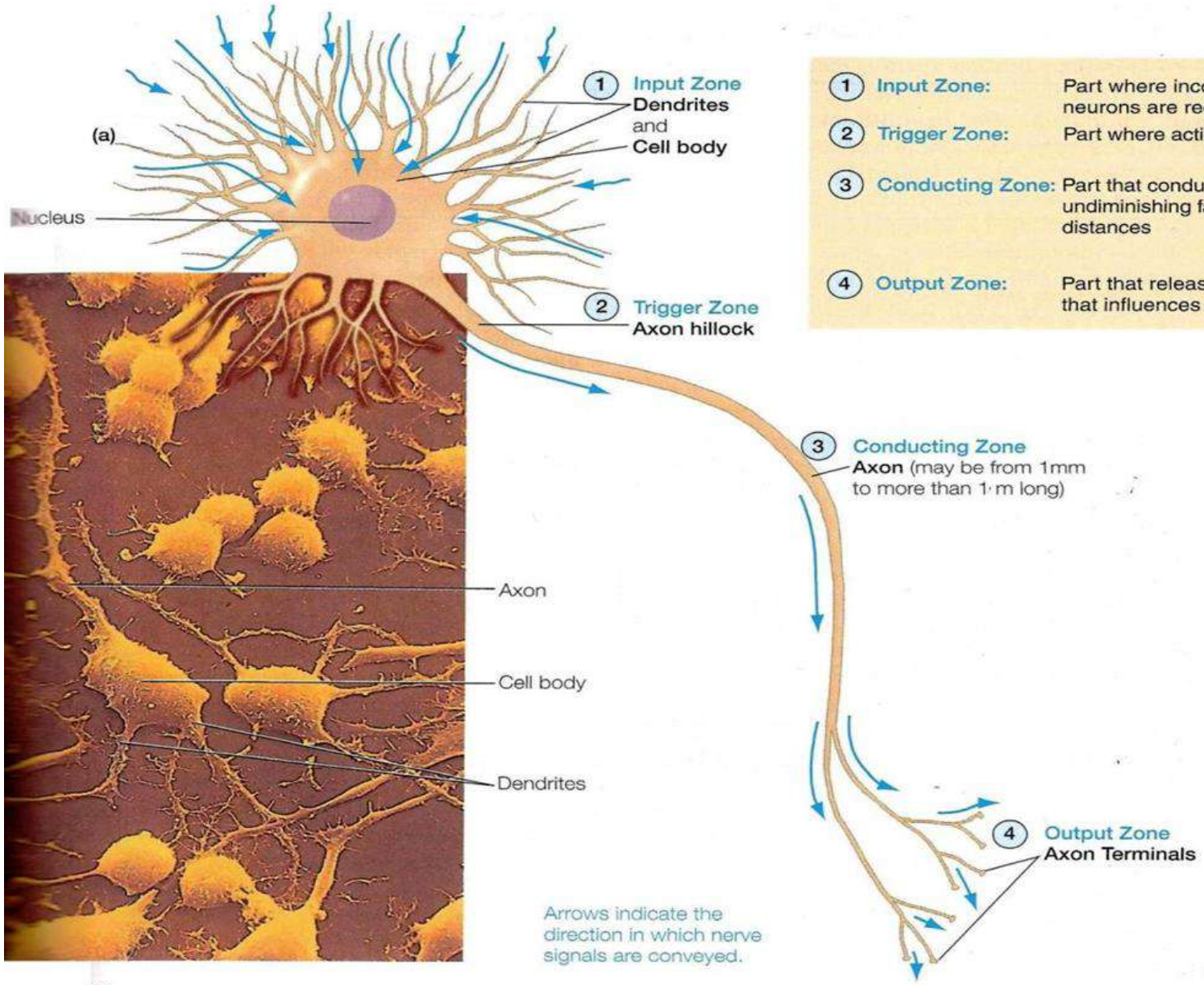
(1) Mechanisms must exist to conduct or spread or propagate the action potential throughout the entire cell membrane.

(2) Furthermore, **the signal** must be **transmitted** from **one cell** to **the next** (for example, along specific nerve pathways).

■ **Neuronal structure**

■ **A single neuron** typically **consists** of **3 basic parts** (although there are variations in structure, depending on the location and function of the neuron).

Neuronal physiology



1 **Input Zone:** Part where incoming signals from other neurons are received

2 **Trigger Zone:** Part where action potentials are initiated

3 **Conducting Zone:** Part that conducts action potentials in undiminishing fashion, often over long distances

4 **Output Zone:** Part that releases a neurotransmitter that influences other cells

Neuronal physiology

(1) The cell body: The nucleus and organelles are housed in the cell body.

(2) the dendrites: numerous extensions **project** from the cell body (like antennae) to increase the surface area available for receiving signals from other neurons. Some neurons have up to 400,000 dendrites. In most neurons, the **plasma membrane** of the dendrites and cell body contains **protein receptors** that **bind** chemical messengers from other neurons. Therefore, the **dendrites** and **cell body** are **the neuron's input zone** because they **receive** and **integrate** incoming signals.

■ This is **the region** where **graded potentials** are **produced** in **response** to triggering events (in this case, **incoming chemical messengers).**

(3) The axon (or nerve fiber), is a single, elongated, tubular extension that **conducts action potentials away from** the **cell body** and eventually **terminates** at **other cells. The first portion** of **the axon plus the region** of **the cell body** from which the axon **leaves** is known as the **axon hillock.**

Neuronal physiology

■ The **axon hillock** is **the neuron's trigger zone**, because it is **the site** where **action potentials** are **triggered** (or initiated) by the **graded potential** if it is of **sufficient magnitude.**

■ The **action potentials** are then **conducted along** the axon from the **axon hillock** to **the highly branched ending** at **the axon terminals**. These **terminals release chemical messengers** that **simultaneously influence** numerous **other cells** with which they **come into** close association. therefore, **the axon** is **the conducting zone** of the neuron, and the **axon terminals** constitute its **output zone**.

■ **Axons vary** in **length** (from **less than** a millimeter in neurons that communicate **only** with neighboring cells to **longer than** a meter in neurons that **communicate with** distant parts of the nervous system or with peripheral organs).

■ **Action potentials** can be **initiated only** in **portions** of the **membrane** with **abundant voltage-gated Na^+ channels** that can be triggered to **open** by **a depolarizing event.** Typically, **regions** of **excitable cells** where **graded potentials** take place **do not** undergo **action potentials** because voltage-gated Na^+ channels are **sparse** there.

■ Therefore, **sites specialized** for **graded potentials do not** undergo **action potentials**. However, **before** dying out, **graded potentials** can **trigger action potentials** in **adjacent portions** of the membrane by bringing these more sensitive regions to **threshold** through **local current flow** spreading from **the site** of **the graded potential.**

■ In **a typical neuron**, for example, **graded potentials** are **generated** in **the dendrites** and **cell body** in **response** to **incoming chemical signals**. If these **graded potentials** have **sufficient magnitude** by **the time** they have **spread** to **the axon hillock**, they **initiate an action potential** at **this triggering zone**.

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■ **Once initiated, action potentials are conducted throughout a nerve fiber:**

■ Once an action potential is initiated at the axon hillock, **no further** triggering event is necessary to activate the remainder of the nerve fiber. **The impulse** is **automatically conducted** throughout the neuron **without** further stimulation by one of 2 methods of propagation: **contiguous conduction** or **saltatory conduction.**

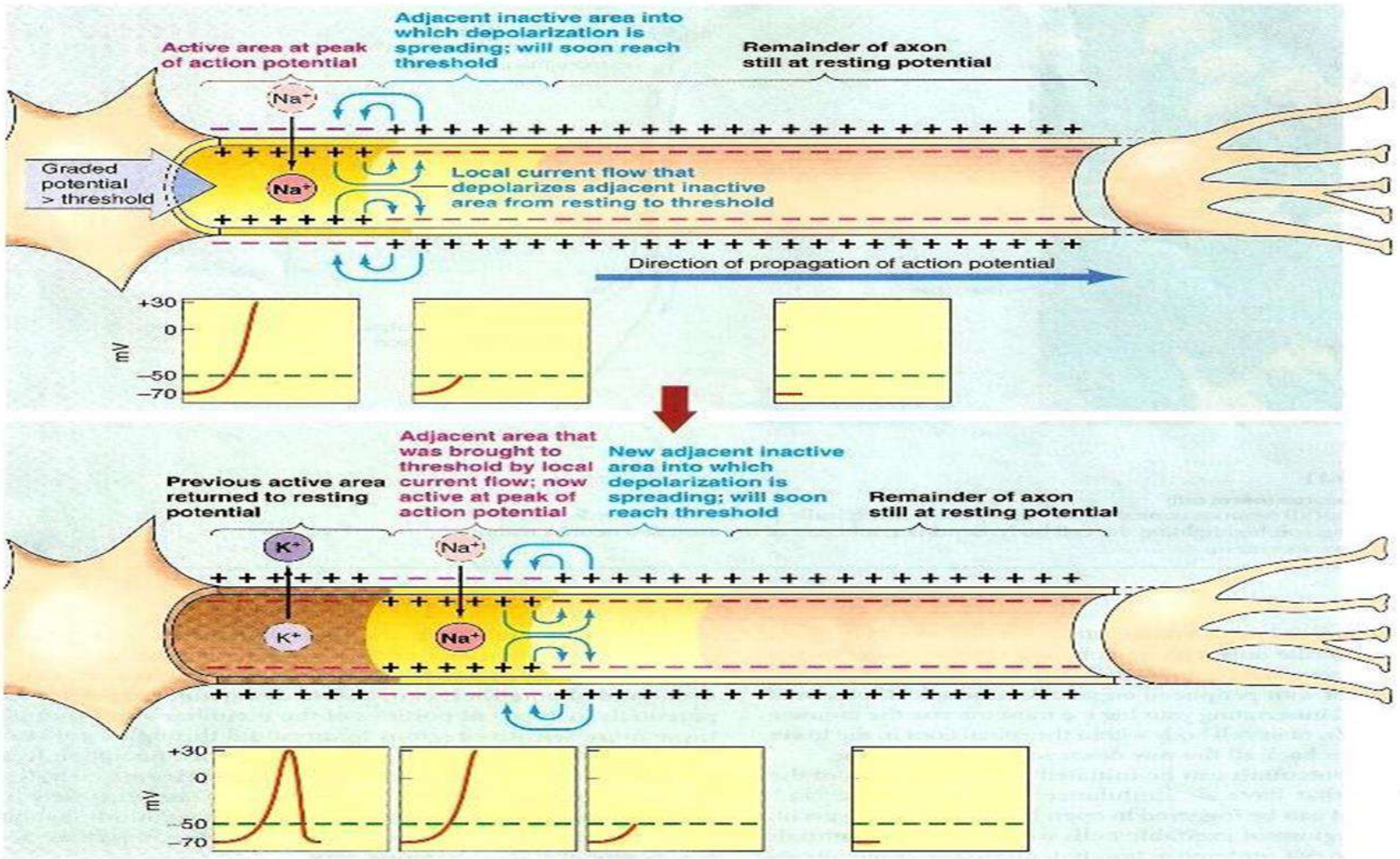
1. Contiguous conduction involves the spread of the action potential **along every patch** of the membrane **down the length** of **the axon**. (Fig 4-12) represents a longitudinal section of the axon hillock and the portion of the axon immediately beyond it. The membrane at the axon hillock is at the peak of an action potential. The inside of the cell is positive in this active area, because Na^+ has already rushed in here. **The remainder** of the axon, still at resting potential and negative inside, is considered **inactive**

Neuronal physiology

FIGURE 4-12

Contiguous conduction

Local current flow between the active area at the peak of an action potential and the adjacent inactive area still at resting potential reduces the potential in this contiguous inactive area to threshold, which triggers an action potential in the previously inactive area. The original active area returns to resting potential, and the new active area induces an action potential in the next adjacent inactive area by local current flow as the cycle repeats itself down the length of the axon.



■ For the action potential to spread from the **active** to the **inactive** areas, the **inactive areas** must somehow be depolarized to **threshold**. This depolarization is accomplished by **local current flow** between the area already undergoing an action potential and the adjacent inactive area on both sides of the membrane. This local current flow in effect neutralizes or eliminates some of the unbalanced charges in the inactive area; that is, it reduces the potential in this area. Meanwhile, the **original active area** returns to **resting potential**.

■ This **depolarizing effect** quickly brings the **involved inactive area** to **threshold**, at which time the **voltage-gated Na^+ channels** in **this region** of **the membrane** are all **thrown open**, leading to **an action potential** in this **previously inactive area**. Beyond the new active area is another inactive area, so the same thing happens again. This cycle repeats itself in **a chain reaction** until the action potential has spread to the end of the axon.

Neuronal physiology

■ Once an action potential is initiated in one part of a neuron's cell membrane, **a self-perpetuating cycle** is initiated so that the action potential is propagated along the rest of the fiber automatically. In this way, the axon is like **a firecracker fuse** that needs to be lit at only one end. Once ignited, the fire spreads down the fuse; it is not necessary to hold a match to every separate section of the fuse. During propagation of the action potential down the axon, each new action potential is initiated by depolarizing local current flow spreading from the preceding site undergoing an action potential.

■ **Note that** the **original action potential does not travel** along the membrane. Instead, it triggers **an identical new action potential** in the bordering (neighboring) area of the membrane, with this process being **repeated** along the axon's length. Each **new** action potential is **a fresh local event** that depends on induced permeability changes and electrochemical gradients that are **identical** down the length of the axon. Therefore, the **last** action potential at **the end** of the axon is identical to the original one, no matter how long the axon is.

■ In this way, action potentials can serve as long-distance signals without attenuation or distortion. This **non-decremental** propagation of an **action potential contrasts with** the **decremental** spread of **a graded potential**, which dies out over a very short distance because it **cannot regenerate itself**.

■ **The refractory period** ensures **one-way propagation** of **action potentials** and **limits their frequency:**

■ once the action potential has been regenerated at a new neighboring site (now positive inside) and the original active area has returned to resting (once again negative inside), the **close proximity** of **opposite charges** between **these 2 areas** is **conducive** to **local current flow** in the **backward direction**, as well as in the **forward direction** into as yet **unexcited portions** of **the membrane.**

■ If such **backward current flow** were able to bring the just **inactivated area** to **threshold**, **another action potential** would be **initiated** here, which would **spread both forward** and **backward**, initiating **other action potentials**, and so on.

■ But if **action potentials** were to **move** in **both directions**, the situation would be **chaotic**, with **numerous action potentials bouncing back** and **forth** along **the axon** until the **neuron** eventually **fatigued.**

■ Fortunately, **neurons** are **saved** from **this fate** of **oscillating action potentials** by **the refractory period**, during which **a new action potential cannot** be **initiated** by **normal events** in **a region** that **has just undergone an action potential**. Because of **the changing status** of the voltage-gated Na^+ and K^+ channels **during** and **after an action potential**, the **refractory period** has **2 components**: the **absolute refractory period** and the **relative refractory period.**

■ During **the time** that **a particular patch** of axonal membrane is **undergoing an action potential**, it **cannot initiate another action potential**, **no matter how strong** the **depolarizing triggering event** is. This **time period** when **a recently activated patch** of **membrane** is **“completely” refractory** to **further stimulation** is known as **the “absolute” refractory period.**

■ Once the voltage-gated Na^+ channels have **opened**, they **cannot** open **again** in response to another depolarizing triggering event, no matter how strong, until resting potential is restored and the channels are **reset** to their original conformations. Accordingly, the **absolute** refractory period **lasts** the **entire time** from **opening** of the **Na^+ channels' activation gates** at **threshold**, through **closure** of their **inactivation gates** at **the peak** of **the action potential**, until **the return** to **resting potential** when **the activation gates close** and **inactivation gates open** once again.

■ that is, until **the channels** are **reset** to their **"closed but capable of opening"** conformation. **Only** then can they **respond** to **another depolarization** with an **explosive increase** in P_{Na+} to **initiate** another action potential. Because of the **absolute** refractory period, **one action potential** must be **over before another** can be initiated at **the same site**. **Action potentials cannot overlap** or be **added** one on top of another "piggyback fashion."

Neuronal physiology

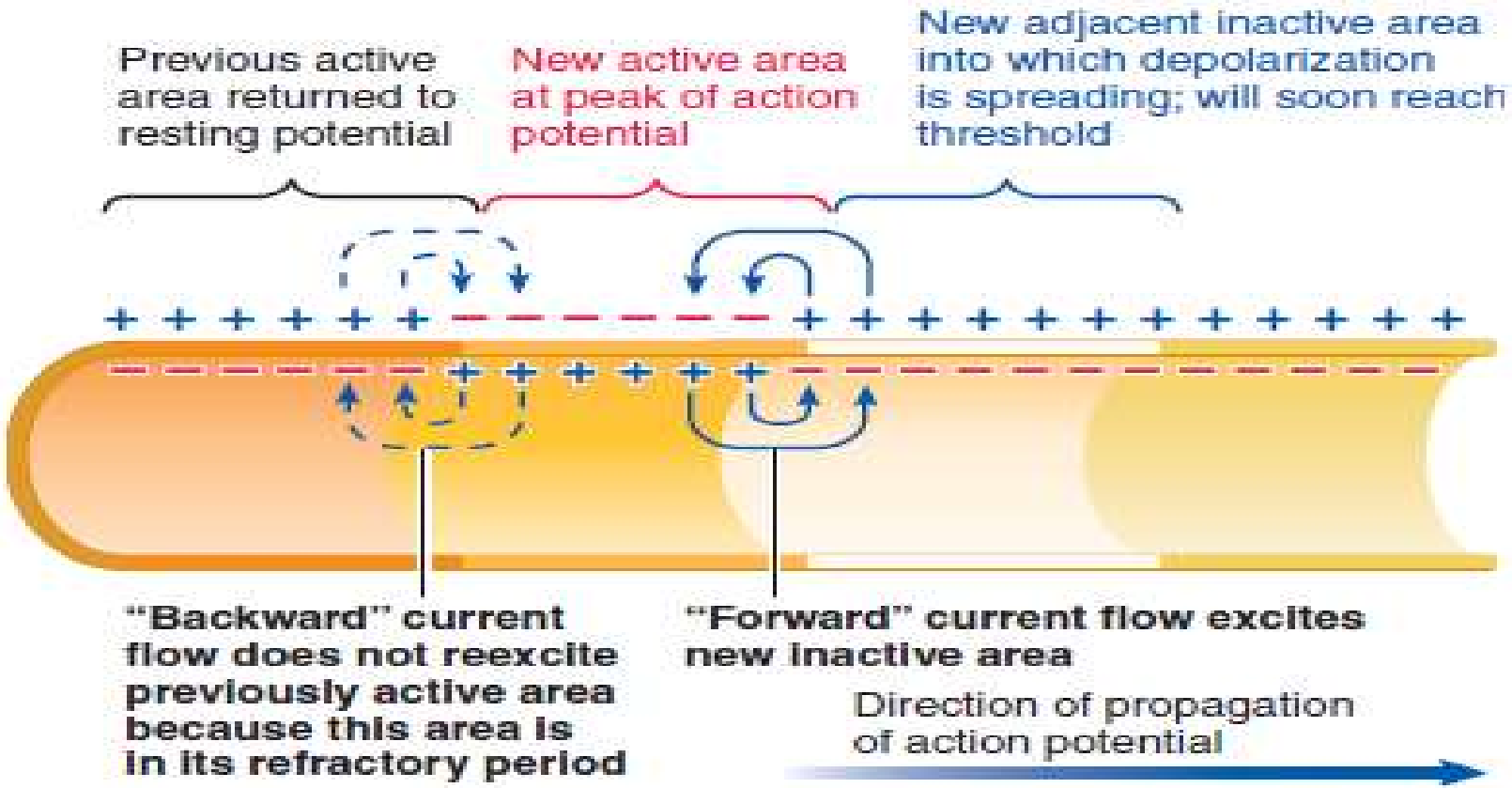


FIGURE 4-10 Value of the refractory period. The refractory period prevents "backward" current flow. During an action potential and slightly afterward, an area cannot be restimulated by normal events to undergo another action potential. Thus, the refractory period ensures that an action potential can be propagated only in the forward direction along the axon.

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■ Following the **absolute refractory period** is **a relative refractory period**, during which **a second action potential** can be **produced only** by **a triggering event considerably stronger** than **usual.** The **relative refractory period** occurs after the **action potential** is **completed** because of **a 2-fold effect:**

(1) lingering inactivation of the voltage-gated Na^+ channels.

(2) slowness to close of the voltage-gated K^+ channels that **opened** at **the peak** of **the action potential.**

■ During this time, **fewer** voltage-gated Na^+ channels than **normal** are in a position to be open by a depolarizing triggering event. Simultaneously, K^+ is **still** leaving through its slow-to-close channels during the after hyperpolarization. The less-than-normal Na^+ **entry** in response to another triggering event is **opposed** by a persistent hyperpolarizing outward leak of K^+ through its not-yet-closed channels, and thus **a greater depolarizing triggering event** than **normal** is needed to bring the membrane to threshold during the **relative refractory period.**

■ By the time the **original site** has **recovered** from its **refractory period** and is capable of being **re-stimulated** by **normal** current flow, **the action potential** has been **propagated** in the **forward direction only** and is so far **away** that it can **no longer influence** the **original site**. Thus, **the refractory period ensures** the **one-way propagation** of the **action potential down the axon** away from **the initial site** of **activation.**

■ **The Refractory period** also **limits the frequency** of **action potential:**

■ The **refractory period** is also responsible for setting an **upper limit** on **the frequency** of **action potentials**; that is, it **determines** the **maximum number** of **new action potentials** that can be **initiated** and **propagated** along a fiber in **a given period of time**. **The original site** must **recover** from **its refractory period before a new action potential** can be **triggered** to follow the **preceding action potential.**

■ **The length** of the **refractory period varies** for **different types** of **neurons. The longer** the **refractory period**, **the greater** the **delay before a new action potential** can be **initiated** and **the lower** the **frequency** with which **a neuron** can **respond** to **repeated** or **ongoing stimulation.**

■ **Action potentials occur in all-or-none fashion:**

■ A triggering event **stronger** than is **necessary** to bring the membrane to **threshold does not** produce **a larger action potential.** However, a triggering event that **fails** to **depolarize** the membrane to **threshold does not** trigger an action potential **at al**l. Thus, an excitable membrane **either** responds to a triggering event with a maximal action potential that spreads **nondecrementally** throughout the membrane, **or** it **does not** respond with an action potential **at all**. This **property** is called the **all-or-none law** (like a firing gun).

■ The **threshold** phenomenon **allows** some **discrimination** between important and unimportant stimuli or other triggering events. Stimuli **too weak** to bring the membrane to threshold **do not initiate** action potentials and therefore **do not** clutter up the nervous system by **transmitting** insignificant signals.

■ **The strength** of **a stimulus** is **coded** by **the frequency** of **action potentials: How** is it possible to **differentiate** between **2 stimuli** of **varying strengths** when **both stimuli** bring the membrane to **threshold** and generate **action potentials** of the same magnitude?

■ The **answer** lies, in part, on **the frequency** with which the **action potentials** are **generated**. **A stronger** stimulus **does not** produce **a larger action potential**, but it does **trigger a greater number** of **action potentials** per **second.**

■ In addition, **a stronger stimulus** in **a region** causes **more neurons** to reach **threshold**, **increasing** the **total information sent** to **the CNS.**

■ Once i**nitiated**, the **velocity** (speed) with which **an action potential travels** down the axon **depends on 2 factors:**

(1) Whether **the fiber** is **myelinated**, and

(2) The diameter of **the fiber.**

■ **Contiguous conduction** occurs in **unmyelinated fibers**.

■ **A faster** method of propagation, **saltatory conduction**, takes place in **myelinated** fibers.

■ **Myelination** increases **the speed** of **conduction** of **action potentials:** Myelinated fibers are axons covered with **myelin**, (a thick layer composed primarily of lipids, at regular intervals along their length). Because the water-soluble ions responsible for carrying current across the membrane **cannot** permeate this myelin coating, it acts as **an insulator**, to **prevent** leakage of current across the myelinated portion of the membrane. **Myelin** is not actually a part of the neuron but consists of separate myelin-forming cells that wrap themselves around the axon in jelly-roll fashion.

■ These **myelin-forming cells** are **Schwann cells** in the **peripheral nervous system** (PNS) [the nerves running between the CNS and the various regions of the body], and **oligodendrocytes** in the CNS (the brain and spinal cord).

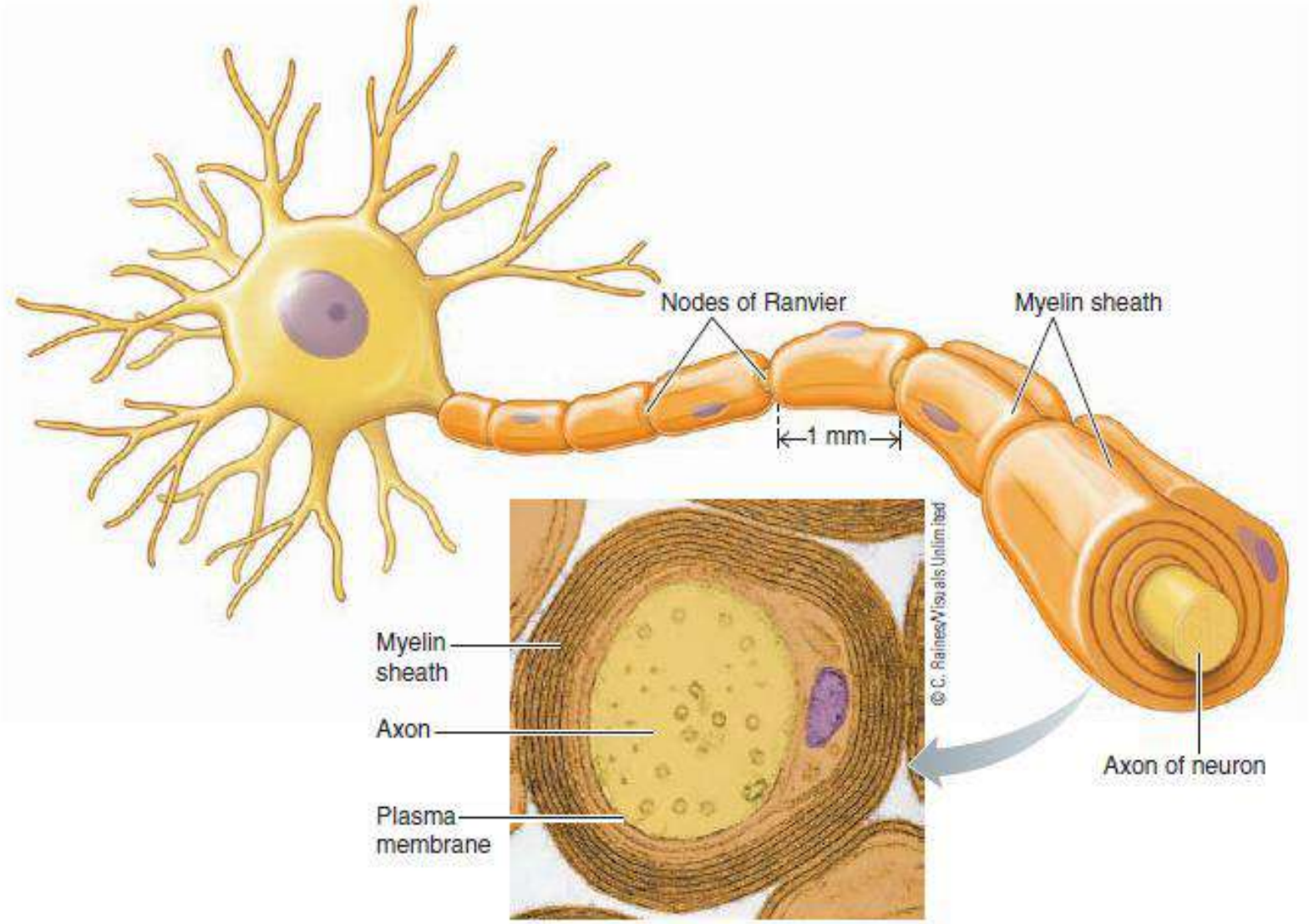
■ Each patch of lipid-rich myelin consists of multiple layers of the myelin-forming cell's plasma membrane (the lipid bilayer) as the cell **wraps itself** around and around the axon. A patch of myelin might be made up of as many as 300 layers of **wrapped** lipid bilayers.

■ Between the **myelinated regions**, at **the nodes of Ranvier**, **the axonal membrane** is **bare** and **exposed** to **the ECF. Current** can **flow** across **the membrane only** at **these bare spaces** to produce **action potentials.**

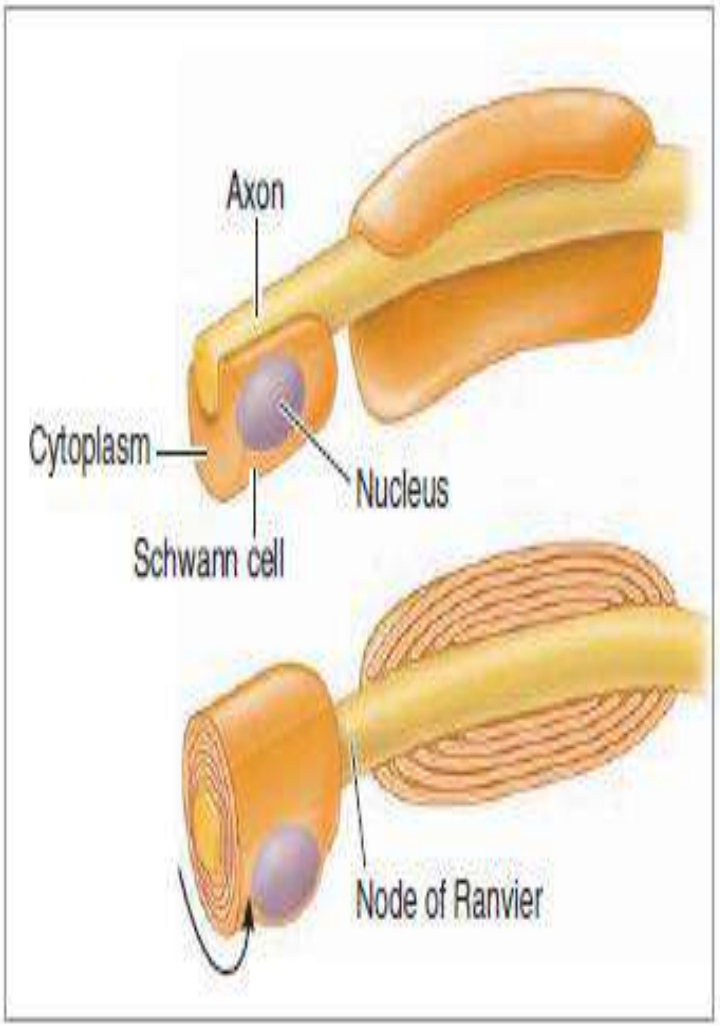
■ **Voltage-gated Na^+ channels** are **concentrated** at the **nodes**, whereas the **myelin-covered regions** are almost **devoid** of these **special passageways**. By contrast, **an unmyelinated fiber** has **a high density** of **voltage-gated Na^+ channels** along **its entire length.**

■ The **distance** between **the nodes** is **short enough** that **local current** can **flow** between **an active node** and **an adjacent inactive node** before **dying off.**

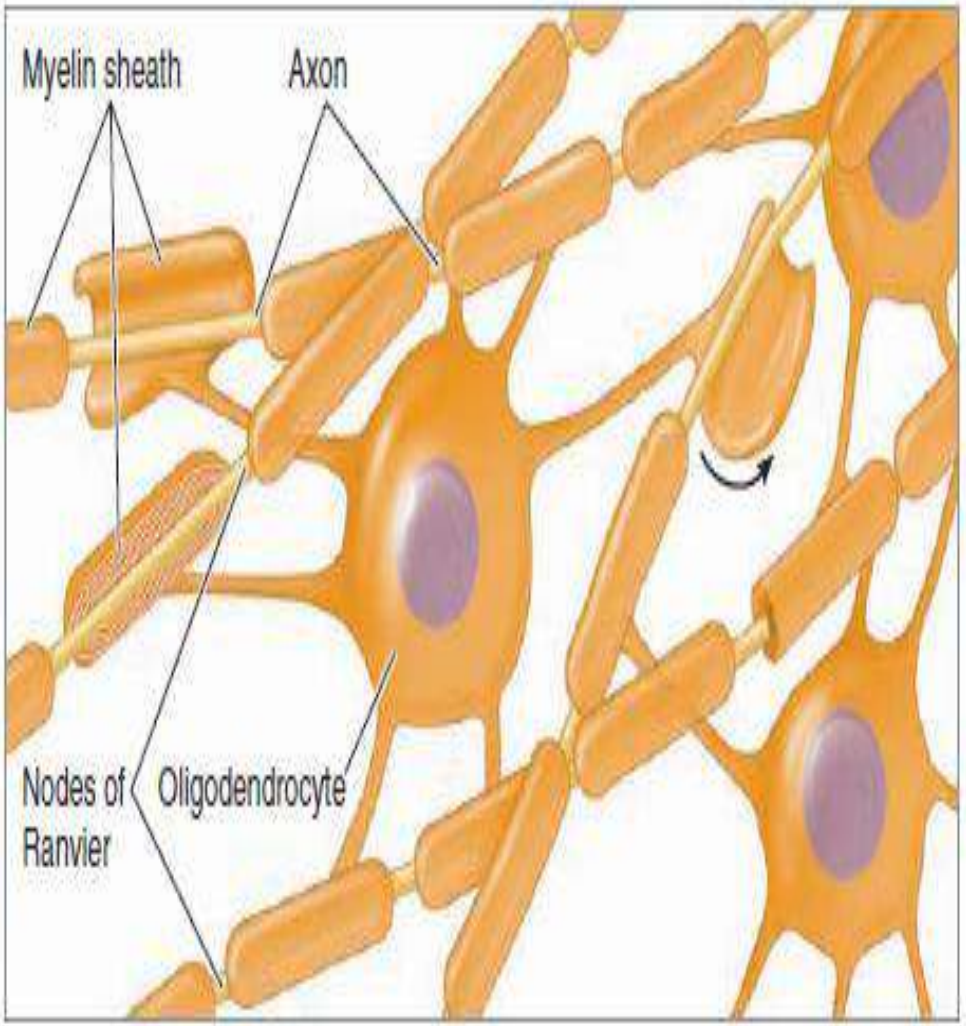
Neuronal physiology



Neuronal physiology



(b) Schwann cells in peripheral nervous system



(c) Oligodendrocytes in central nervous system

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Neuronal physiology

■ When an **action potential** occurs at **one node**, local current flow between this node and **the oppositely charged adjacent node** reduces the adjacent node's potential to **threshold** so that it undergoes an action potential, and so on. Consequently, in a **myelinated** fiber, the **impulse "jumps"** from node to node, skipping over the **myelinated sections** of the axon; this process is called **saltatory conduction.**

Neuronal physiology

■ **Saltatory** conduction **propagates action potentials more rapidly** than **contiguous** conduction does, because the **action potential does not** have to be **regenerated** at **myelinated sections** but must be regenerated within **every section** of **an unmyelinated** axonal membrane from beginning to end. In **myelinated** fibers, **local current generated** at **an active node travels a longer distance**, **depolarizing** the **next node** instead of the **next section** (myelin).

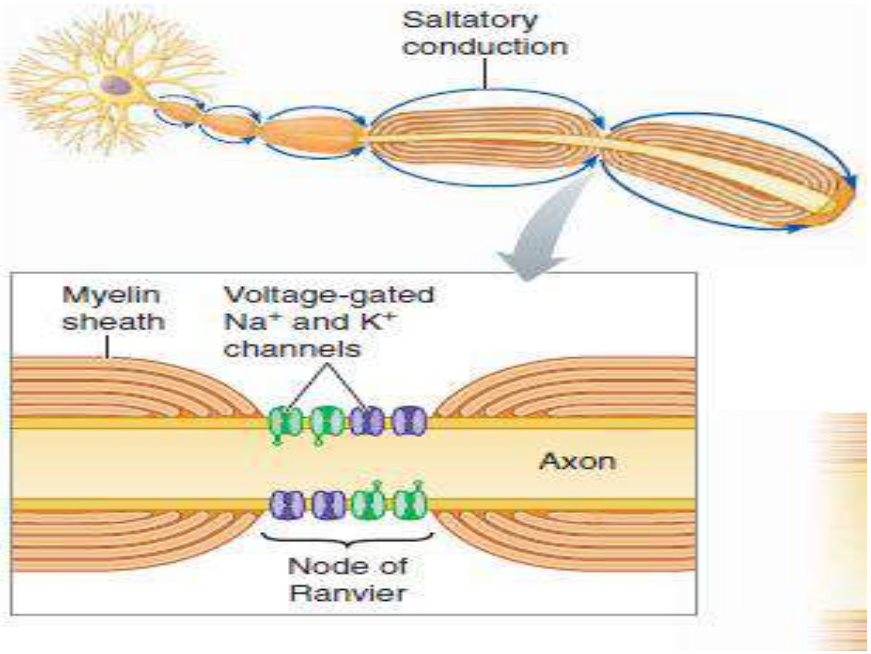
■ **Myelinated fibers conduct impulses** about **50 times faster** than **unmyelinated fibers** of **comparable size**. Thus, the **most urgent types** of **information** are **transmitted** via **myelinated fibers**, whereas nerve pathways carrying **less** In addition, **urgent information** are **unmyelinated. myelination** also **conserves energy**. Because the **ion fluxes** associated with **action potentials** are **confined** to **the nodal regions**, the **energy-consuming Na^+–K^+ pump** must restore **fewer ions** to their respective sides of the membrane following propagation of an action potential.

■ **Fiber diameter** also **influences the velocity** of **action potential propagation:**

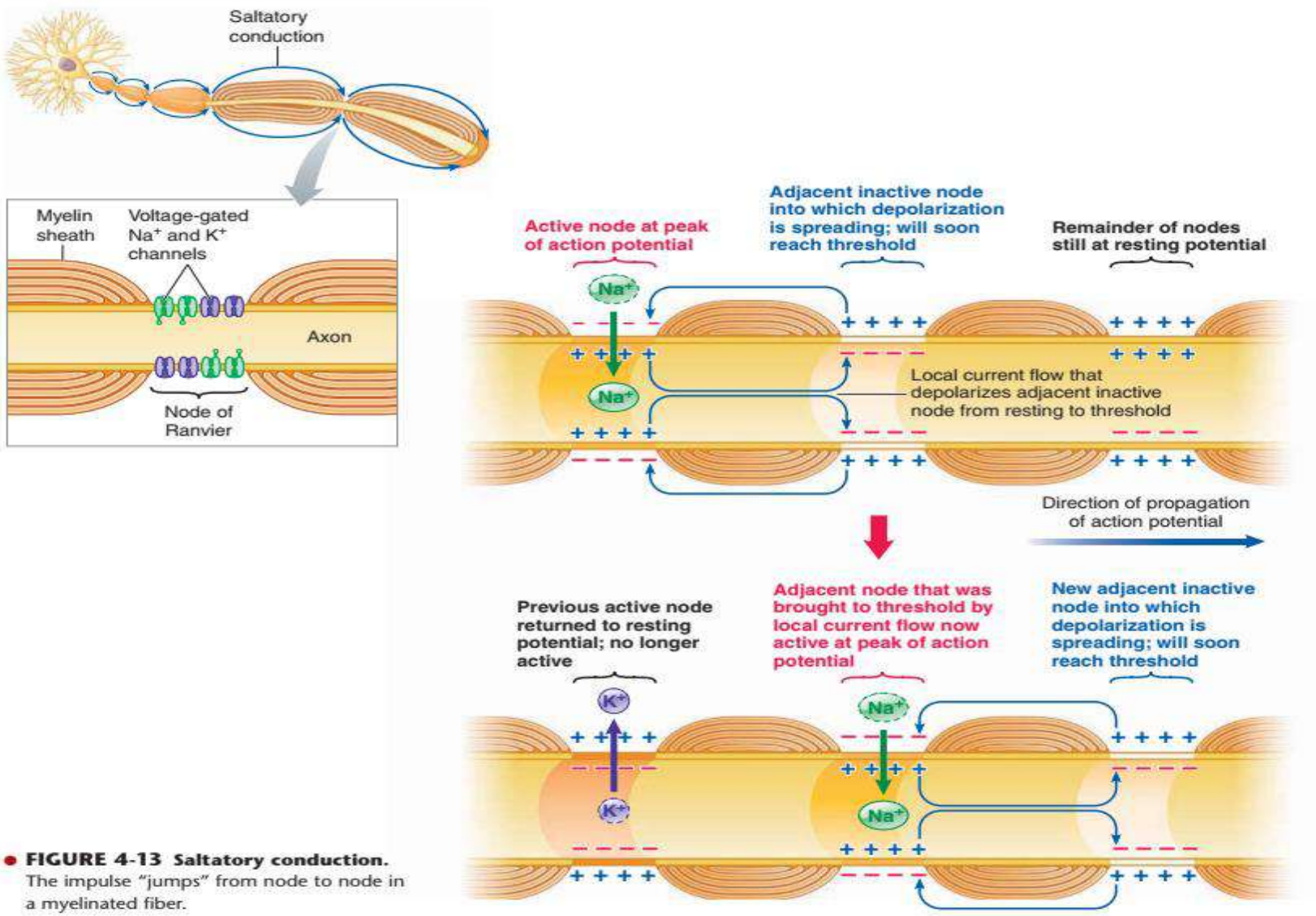
■ Fiber **diameter influences** the **speed** with which an axon can **conduct** action potentials. When **fiber diameter increases**, the **resistance** to local current **decreases**. Thus, the **larger** the fiber **diameter**, the **faster** action potentials can be propagated.

■ **Large myelinated** fibers (such as those supplying skeletal muscles) can **conduct** action potentials at **a velocity** of up to 120 m/sec (268 mile/hr), **compared** with a conduction velocity of 0.7 m/sec (2 mile/hr) in **small unmyelinated** fibers (such as those supplying the digestive tract). This **difference** in **speed** of **propagation** is related to the **urgency** of the information being conveyed. A signal to **skeletal muscles** to execute a particular movement must be transmitted **more rapidly** than a signal to modify **a slow-acting digestive process.**

- **Without myelination**, **axon diameters** within **urgent nerve pathways** would have to be **very large** and **cumbersome** to **achieve** the **necessary conduction velocities.**

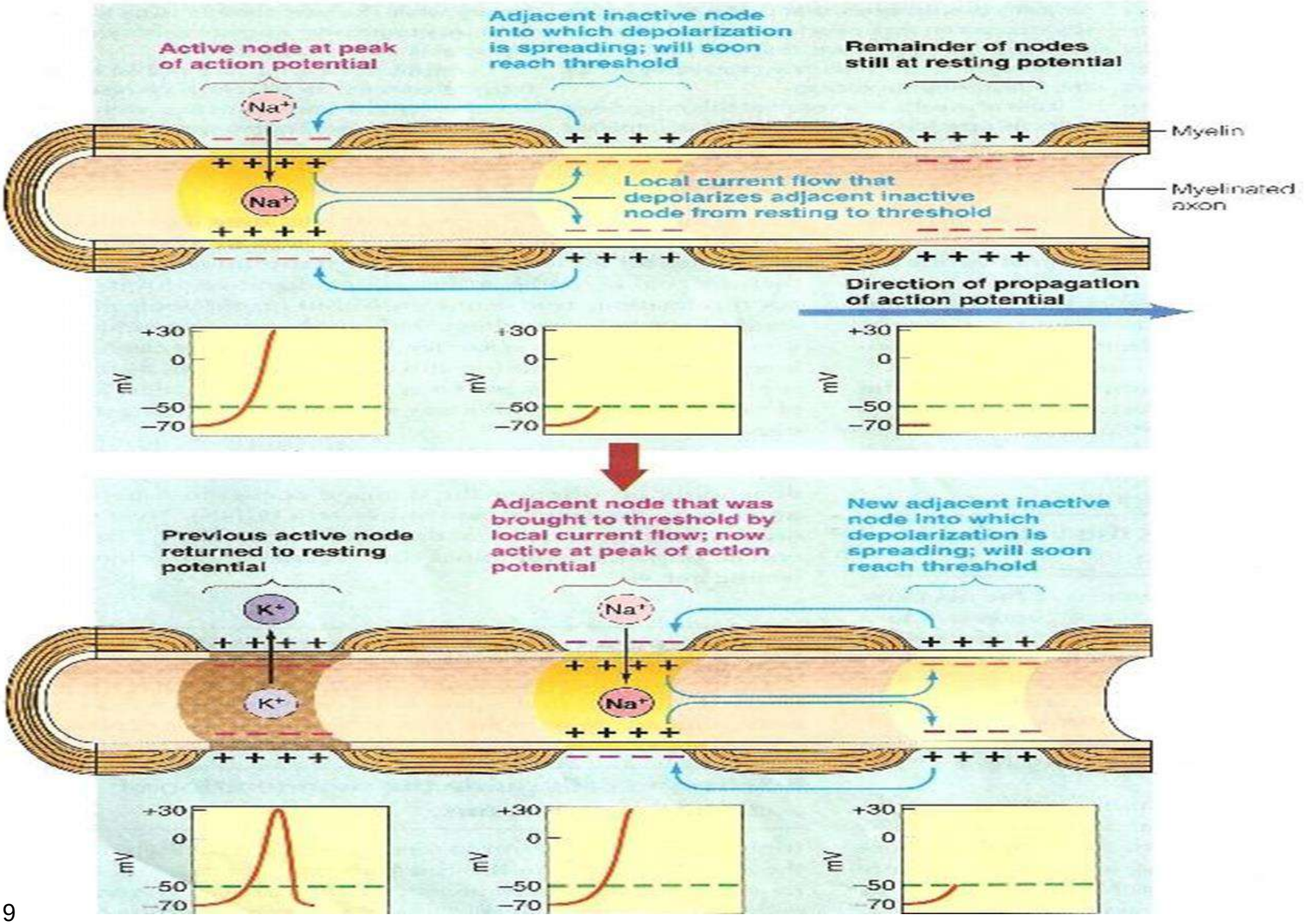


Neuronal physiology



● **FIGURE 4-13 Saltatory conduction.** The impulse "jumps" from node to node in a myelinated fiber.

Neuronal physiology



■ **The presence** of **myelinating cells** can be **either a tremendous benefit** or **a tremendous detriment** when an **axon** is **cut**, **depending on** whether **the damage** occurs in a **peripheral nerve** or in **the CNS.**

■ **Regeneration of nerve fibers:**

■ Whether or not **a severed axon regenerates depends on** its **location** in **CNS** or in **PNS.**

■ **Schwann cells** guide **the regeneration** of **cut peripheral axons:** In case of **a cut axon** in **a peripheral nerve**, the portion of the axon **farthest from** the cell body **degenerates**, and the surrounding Schwann cells phagocytize the debris. The Schwann cells **remain** and **form** a regeneration tube, to guide the regenerating nerve fiber to its proper destination. The remaining portion of the axon connected to the cell body starts to grow and move **forward** within the Schwann cell column by amoeboid movement.

■ **Oligodendrocytes inhibit regeneration of cut central axons: CNS fibers**, which are **myelinated** by **oligodendrocytes do not** have **regenerative ability.** Actually, **the axons** have **the ability** to **regenerate**, but the **oligodendrocytes surrounding them synthesize certain proteins** that **inhibit axonal growth. Nerve growth** in **CNS** controlled by: **Nerve-growth-enhancing proteins** (during fetal development) and **Nerve-growth-inhibiting proteins** (afterward).

Neuronal physiology

TABLE 4-1 Comparison of Graded Potentials and Action Potentials

Property	Graded Potentials	Action Potentials
Triggering Events	Triggered by stimulus, by combination of neurotransmitter with receptor, or by inherent shifts in channel permeability	Triggered by depolarization to threshold, usually through passive spread of depolarization from adjacent area undergoing graded potential or action potential
Ion Movement Producing Change in Potential	Produced by net movement of Na^+, K^+, Cl^-, or Ca^{2+} across plasma membrane by various means	Produced by sequential movement of Na^+ into and K^+ out of cell through voltage-gated channels
Coding of Magnitude of Triggering Event	Graded potential change; magnitude varies with magnitude of triggering event	All-or-none membrane response; magnitude of triggering event coded in frequency rather than amplitude of action potentials
Duration	Varies with duration of triggering event	Constant
Magnitude of Potential Change with Distance from Initial Site	Decremental conduction; magnitude diminishes with distance from initial site	Propagated throughout membrane in undiminishing fashion; self-regenerated in neighboring inactive areas of membrane
Refractory Period	None	Relative, absolute
Summation	Temporal, spatial	None
Direction of Potential Change	Can be depolarization or hyperpolarization	Always depolarization and reversal of charges
Location	Occurs in specialized regions of membrane designed to respond to triggering event	Occurs in regions of membrane with abundance of voltage-gated Na^+ channels

Action Potentials

▲ TABLE 4-1
Comparison of Graded Potentials and Action Potentials

Graded Potentials	Action Potentials
Graded potential change; magnitude varies with magnitude of triggering event	All-or-none membrane response; magnitude of triggering event coded in frequency rather than amplitude of action potentials
Duration varies with duration of triggering event	Constant duration
Decremental conduction; magnitude diminishes with distance from initial site	Propagated throughout membrane in undiminishing fashion
Passive spread to neighboring inactive areas of membrane	Self-regeneration in neighboring inactive areas of membrane
No refractory period	Refractory period
Can be summed	Summation impossible
Can be depolarization or hyperpolarization	Always depolarization and reversal of charges
Triggered by stimulus, by combination of neurotransmitter with receptor, or by spontaneous shifts in leak–pump cycle	Triggered by depolarization to threshold, usually through spread of graded potential
Occurs in specialized regions of membrane designed to respond to triggering event	Occurs in regions of membrane with abundance of voltage-gated Na^+ channels

The End

Part 4B

Human Physiology I

Second Year Pharmacy Students

Chapter 4: Neuronal Physiology

Part 5A

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First Semester 2020/2021

Synapses and Neuronal Integration

■ A neuron may terminate on one of **3** structures: a muscle, a gland, or another neuron. Therefore, **depending on** where a neuron **terminates**, it can **cause** a muscle cell to **contract**, a gland cell to **secrete**, another neuron to **convey** an electrical message along a nerve pathway, or some other function. When a neuron **terminates** on a muscle or a gland, the neuron is said to **innervate**, (or supply) the structure (muscle or gland).

■ The **junction** between 2 **neurons**, **a synapse** (synapsis means "juncture").

Synapses and Neuronal Integration

■ The vast majority of synapses in the human nervous system are c**hemical** synapses at which a chemical messenger **transmits** information **one way** across a space **separating** the two neurons. A chemical synapse involves a junction **between** an axon terminal of one neuron, known as **the presynaptic neuron**, and the dendrites or cell body of a second neuron, known as **the postsynaptic neuron**. The **presynaptic** neuron **lies before** the synapse, and the **postsynaptic** neuron **lies after** the synapse.

Synapses and Neuronal Integration

■ The dendrites and (to a lesser extent, the cell body) of most neurons **receiv**e thousands of **synaptic inputs** (which are **axon terminals** from many other neurons). Some neurons in the CNS **receive** as many as 100,000 synaptic inputs. The anatomy of **one** of these thousands of chemical synapses is as follows: The axon terminal of the **presynaptic** neuron (which **conducts** its action potentials **toward** the synapse) **ends in** a **slight swelling**, the **synaptic knob.**

Synapses and Neuronal Integration

■ The **synaptic knob** contains synaptic vesicles, which **store** a specific chemical messenger (**a neurotransmitter)** that has been **synthesized** and **packaged** by the **presynaptic** neuron. T**he synaptic knob** comes into **close proximity** to, but **does not actually** touch, the **postsynaptic** neuron (the neuron whose action potentials are propagated away from the synapse). **The space between** the **presynaptic** and **postsynaptic** neurons is called the **synaptic cleft. Current does not** spread **directly** from the **presynaptic** to the **postsynaptic** neuron at **a chemical synapse**.

Synapses and Neuronal Integration

■ Instead, an action potential in the **presynaptic** neuron **alters** the **postsynaptic** neuron's potential by **chemical means** (via the neurotransmitter-receptor combination). **Synapses operate** in **one direction only**; that is, the **presynaptic** neuron brings about changes in the membrane potential of the **postsynaptic** neuron, but the **postsynaptic** neuron **does not directly** influence the potential of the **presynaptic** neuron. The reason for this becomes apparent when the events that occur at a synapse are examined.

Synapses and Neuronal Integration

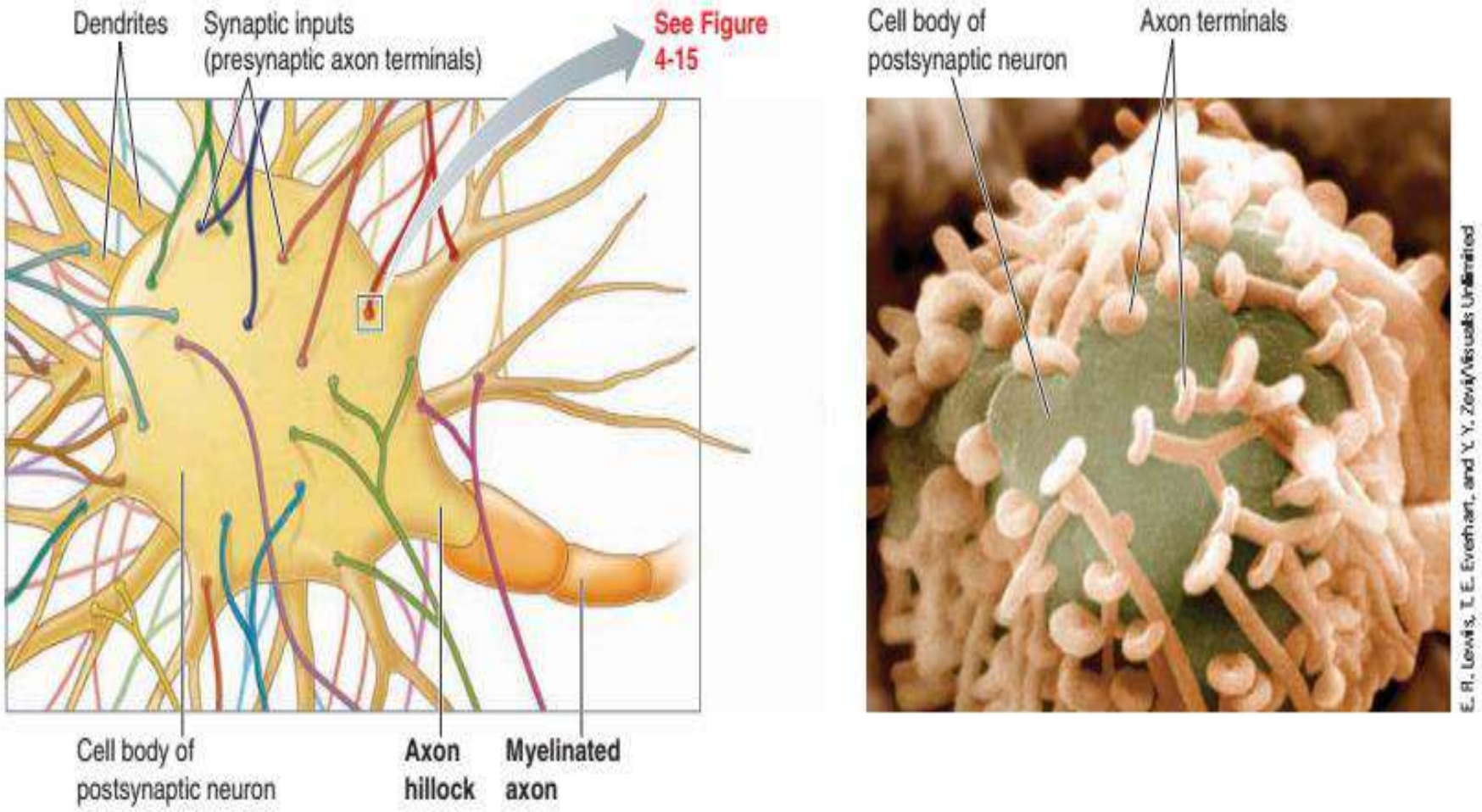
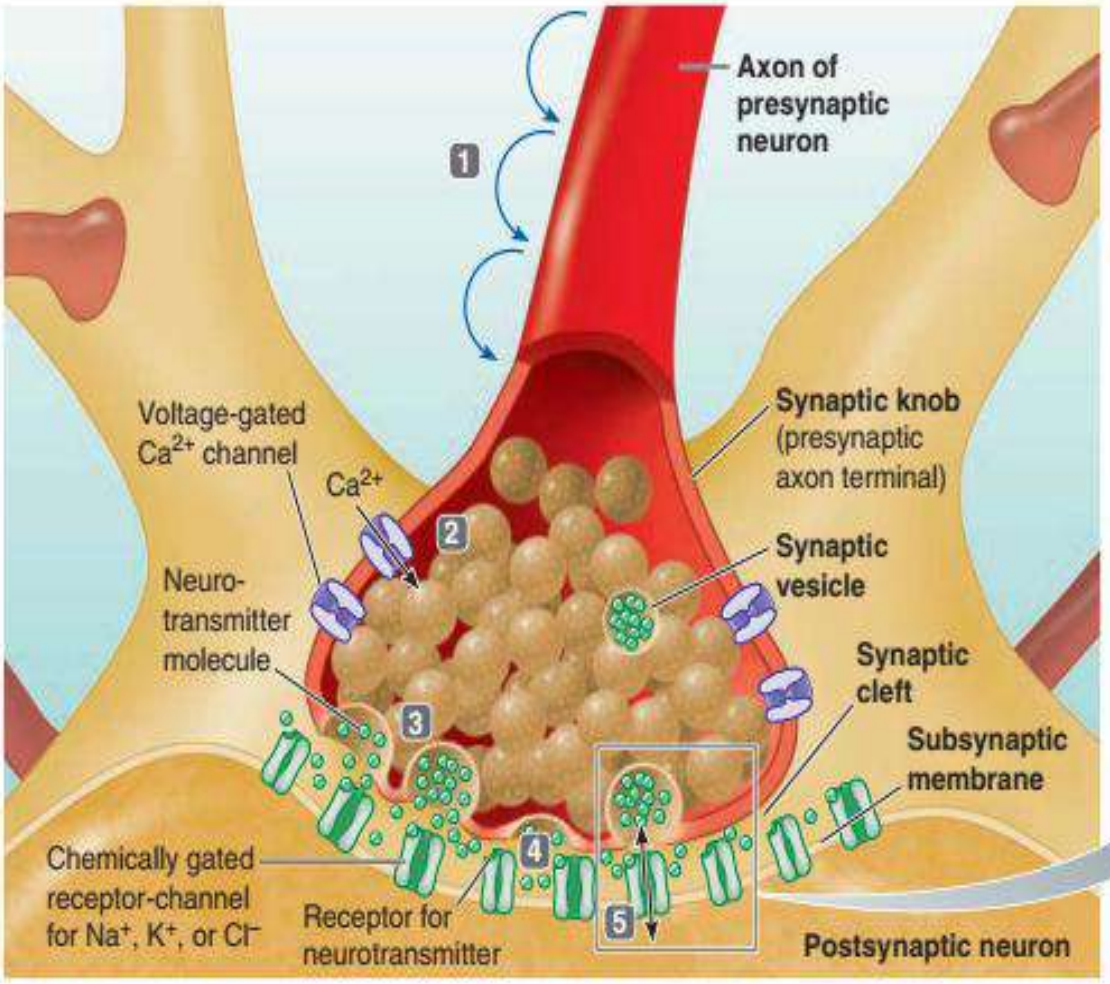


FIGURE 4-14 Synaptic inputs (presynaptic axon terminals) to the cell body and dendrites of a single postsynaptic neuron. The drying process used to prepare the neuron for the electron micrograph has toppled the presynaptic axon terminals and pulled them away from the postsynaptic cell body.

Synapse and Neuronal integration
A structure and a function of a single synapse:



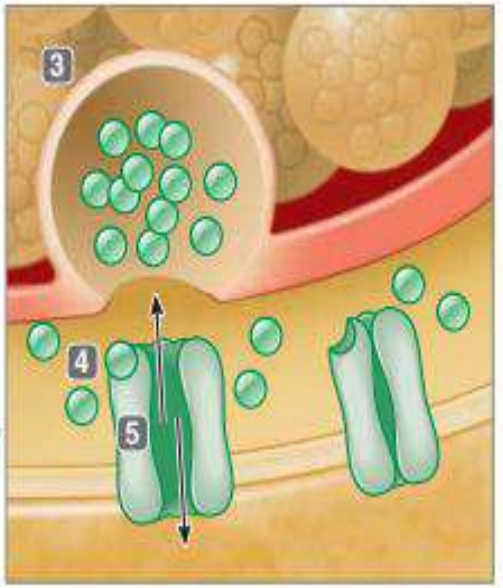
1 Action potential reaches axon terminal of presynaptic neuron.

2 Ca^{2+} enters synaptic knob (presynaptic axon terminal).

3 Neurotransmitter is released by exocytosis into synaptic cleft.

4 Neurotransmitter binds to receptors that are an integral part of chemically gated channels on subsynaptic membrane of postsynaptic neuron.

5 Binding of neurotransmitter to receptor opens that specific channel.



Synapses and Neuronal Integration

■ **synaptic delay:** Conversion of **the electrical signal** in the **presynaptic** neuron to **an electrical signal** in the **postsynaptic** neuron by **chemical means takes time.** This synaptic delay is usually about **0.5-1 msec**. In a neural pathway, chains of neurons often must be traversed.

■ The **more complex the pathway** is, the **more synaptic delays** and **the longer the total reaction time** (the time required to respond to a particular event).

■ **Some synapses excite whereas others inhibit the postsynaptic potential:**

■ **Each presynaptic** neuron typically **releases only one neurotransmitter**; however, different neurons v**ary** in the neurotransmitter they release. On binding with their sub-synaptic receptor-channels, different neurotransmitters cause different ion permeability changes.

Synapses and Neuronal Integration

■ There are **2 types** of synapses, **depending on** the permeability changes **induced** in the **postsynaptic** neuron by the combination of a specific neurotransmitter with its receptor-channels: **excitatory synapses** and **inhibitory synapses.**

■ **Excitatory Synapses:** At an excitatory synapse, **the response** to the binding of a neurotransmitter to the receptor-channel is **the opening** of **nonspecific cation channels** in **the sub-synaptic membrane** that **permit simultaneous passage** of **Na^+** and **K^+** through **them** (These are a different type of channel from voltage-gated channels.) Thus, **permeability** to **both these ions** is **increased** at **the same time**, which **depends on their electrochemical gradients.**

■ At **resting potential**, **both** the concentration and electrical gradients for **Na^+ favor** its movement into **the postsynaptic neuron**, whereas **only the concentration gradient** for **K^+ favors its movement outward.** Therefore, the permeability change induced at an excitatory synapse **results in** the movement of **a few K^+ ions out** of the **postsynaptic** neuron, while **a larger number** of **Na^+ ions simultaneously** enter this neuron. The result is **net movement** of **positive ions into** the cell.

■ This **makes the inside** of the membrane **slightly** less negative than at resting potential, thus **producing a small depolarization** of the **postsynaptic** neuron.

■ Activation of one excitatory synapse can **rarely depolarize** the **postsynaptic** neuron enough to **bring it** to **threshold.** Too few channels are involved at a single sub-synaptic membrane to permit **adequate** ion flow to **reduce** the **potential** to **threshold.**

■ This small depolarization, however, brings the membrane of the postsynaptic neuron **closer** to **threshold**, **increasing** the likelihood that **threshold** will be reached (in response to further excitatory input) and that an action potential will occur. That is, the membrane is now more excitable (easier to bring to threshold) than when **at rest**. Accordingly, the change in **postsynaptic** potential occurring at an **excitatory synapse** is called **an excitatory postsynaptic potential**, or **EPSP.**

■ **Inhibitory Synapses:** At an inhibitory synapse, the binding of a different released neurotransmitter with its receptor-channels **increases the permeability** of the sub-synaptic membrane to **either** K^+ or Cl^-. The resulting ion movements bring about **a small hyperpolarization** of the **postsynaptic** neuron (the inside of the neuron becomes slightly more negative). In the case of **increased P_{K+}, more positive charges leave** the cell via **K^+ efflux**, leaving **more negative charges** behind on **the inside.**

■ In the case of **increased P_{Cl^-}**, **more negative charges enter** the cell in the form of Cl^- ions than are **driven out** by the opposing electrical gradient established by the resting membrane potential. In **either** case, this small hyperpolarization moves the membrane potential even **farther away** from **threshold**, **lessening** the likelihood that the **postsynaptic** neuron will reach **threshold** and undergo an action potential. That is, the membrane is now less excitable (harder to bring to threshold by excitatory input) than when it is **at resting potential.**

■ The membrane is said to be **inhibited** under these circumstances, and the **small hyperpolarization** of the **postsynaptic** cell is called **an inhibitory postsynaptic potential**, or **IPSP.**

■ In cells where the equilibrium potential for Cl^- exactly equals the resting potential, an increased P_{Cl^-} **does not** result in a hyperpolarization because there is **no** driving force to produce Cl^- movement. Opening of Cl^- channels in these cells tends to hold the membrane at resting potential, reducing the likelihood that threshold will be reached.

The End

Part 5A

Human Physiology I

Second Year Pharmacy Students

Chapter 4: Neuronal Physiology

Part 5B

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First Semester 2020/2021

■ **Each neurotransmitter–receptor combination always produces the same response:**

■ Even though neurotransmitters **vary** from synapse to synapse, the **same** neurotransmitter is **always** released at **a particular synapse**. Furthermore, at a given synapse, **binding** of a neurotransmitter with its sub-synaptic receptor-channels **always** leads to the **same** change in **permeability** and **resultant change** in **potential** of the **postsynaptic** membrane.

■ That is, the response to a given neurotransmitter-receptor combination is **always** the **same**; the combination **does not** generate an **EPSP** under **one** circumstance and an **IPSP** under **another.**

■ **Some neurotransmitters** (for e.g., glutamate, the most common excitatory neurotransmitter in the brain) bring about **EPSPs**, whereas **others** (for e.g., glycine, and gamma-aminobutyric acid (GABA), the brain's main **inhibitory** neurotransmitter) **always** cause **IPSPs.**

■ Still other neurotransmitters (for e.g.,, norepinephrine) are **quite variable**, producing **EPSPs** at **one** synapse and **IPSPs** at **a different** synapse; that is, **different** permeability changes in the **postsynaptic** neuron can occur in response to the binding of the **same** neurotransmitter to the sub-synaptic receptor-channels of **different postsynaptic** neurons.

■ **Most** of the time, **each** axon terminal **releases only** one neurotransmitter. However, that in **some** cases **2** different neurotransmitters can be **released simultaneously** from **a single** axon terminal. For e.g., glycine and GABA, **both** of which produce **inhibitory** responses, can be packaged and released from **the same** synaptic vesicles. It is proposed that **the fast-acting** glycine and **more slowly acting** GABA may **complement** each other in the control of activities that **depend on** precise timing, for e.g., coordination of complex movements.

Synapses and Neuronal Integration

TABLE 4-2 Some Common Neurotransmitters

Acetylcholine	Histamine
Dopamine	Glycine
Norepinephrine	Glutamate
Epinephrine	Aspartate
Serotonin	Gamma-aminobutyric acid (GABA)

Synapses and Neuronal Integration

TABLE 4-2
Some Known or Suspected Neurotransmitters and Neuropeptides

Classical Neurotransmitters (small, rapid-acting molecules)	
Acetylcholine	Histamine
Dopamine	Glycine
Norepinephrine	Glutamate
Epinephrine	Aspartate
Serotonin	Gamma-aminobutyric acid (GABA)

Neuropeptides (large, slow-acting molecules)	
β-endorpin	Motilin
Adrenocorticotropic hormone (ACTH)	Insulin
α-melancoyte-stimulating hormone (MSH)	Glucagon
Thyrotropin-releasing hormone (TRH)	Angiotensin II
Gonadotropin-releasing hormone (GnRH)	Bradykinin
Somatostatin	Vasopressin
Vasoactive intestinal polypeptide (VIP)	Oxytocin
Cholecystokinin (CCK)	Carnosine
Gastrin	Bombesin
Substance P	Neurotensin

■ **Neurotransmitters are quickly removed from the synaptic cleft:**

■ As long as the neurotransmitter **remains** bound to the receptor- channels, the alteration in membrane permeability responsible for the **EPSP** or **IPSP continues**. For the **postsynaptic** neuron to be ready to **receive** additional messages from the same (or other presynaptic inputs), the neurotransmitter **must** be **inactivated** or **removed** from **the postsynaptic cleft after** it has **produced** the appropriate response in the **postsynaptic** neuron.

■ That is, the postsynaptic **"slate"** must be **"wiped clean."** Thus, **after** combining with the **postsynaptic** receptor-channel, chemical transmitters are **removed** and the response is **terminated.**

■ Several mechanisms can **remove the neurotransmitter:**

(1) It may diffuse away from the synaptic cleft.

(2) Be **inactivated** by **specific enzymes** within **the sub-synaptic membrane**.

(3) Be **actively taken back up** into the axon terminal by transport mechanisms in the **presynaptic** membrane. Once the neurotransmitter is taken back up, it can be **stored** and **released** another time (recycled) in response to a subsequent action potential or **destroyed** by **enzymes within** the synaptic knob.

■ **Some neurotransmitters function through intracellular second-messenger systems:**

■ **Most**, but **not all**, neurotransmitters **function** by **changing** the **conformation** of **chemically** gated channels (altering membrane permeability and ion fluxes across the postsynaptic membrane). **Synapses** involving these **rapid** responses are considered **"fast"** synapse.

■ **Another mode** of **synaptic transmission** used by other neurotransmitters (e.g., serotonin) involves the activation of intracellular second messengers, such as cyclic AMP (cAMP), within the **postsynaptic** neuron. **Synapses** that lead to **responses** mediated by **second messengers** are known as **"slow"** synapse, because **these responses take longer** and often **last longer** than those accomplished by **fast** synapses.

■ Activation of cAMP can induce **both short**-and **long**-term **effects:** In the **short term**, cAMP can lead to **opening** of **specific** ionic gates (a task that other neurotransmitter-receptor combinations do directly and more rapidly). The gating effect can be **either** EPSP or IPSP. cAMP may trigger more **long-term** changes in the **postsynaptic** cell, even to the extent of altering the cell's genetic expression. These long-term cellular changes are linked to neuronal growth and development and they may play a role in learning and memory.

Activation of cAMP second-messenger system

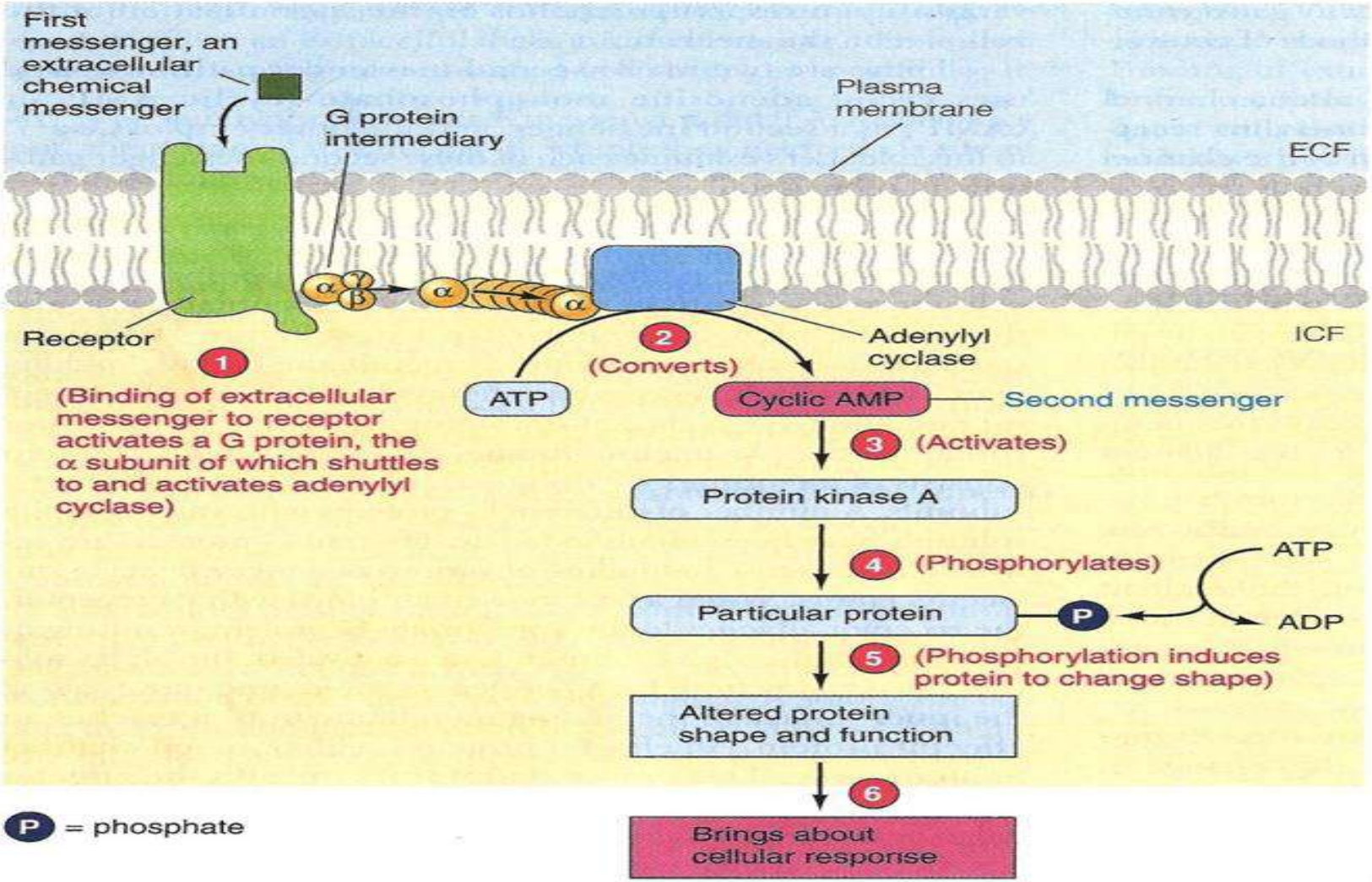


FIGURE 3-8

Activation of the cyclic AMP second-messenger system by an extracellular messenger

■ **The grand postsynaptic potential depends on the sum of the activities of all presynaptic inputs:**

■ The events that occur at **a single** synapse **result in either** an EPSP or an IPSP at the **postsynaptic** neuron. But if **a single** EPSP is **inadequate** to bring the **postsynaptic** neuron to threshold and an IPSP moves it even farther from **threshold**, how can **an action potential** be **initiated** in the **postsynaptic** neuron**?** The answer lies in the thousands of **presynaptic** inputs that a typical neuronal cell body receives from many other neurons.

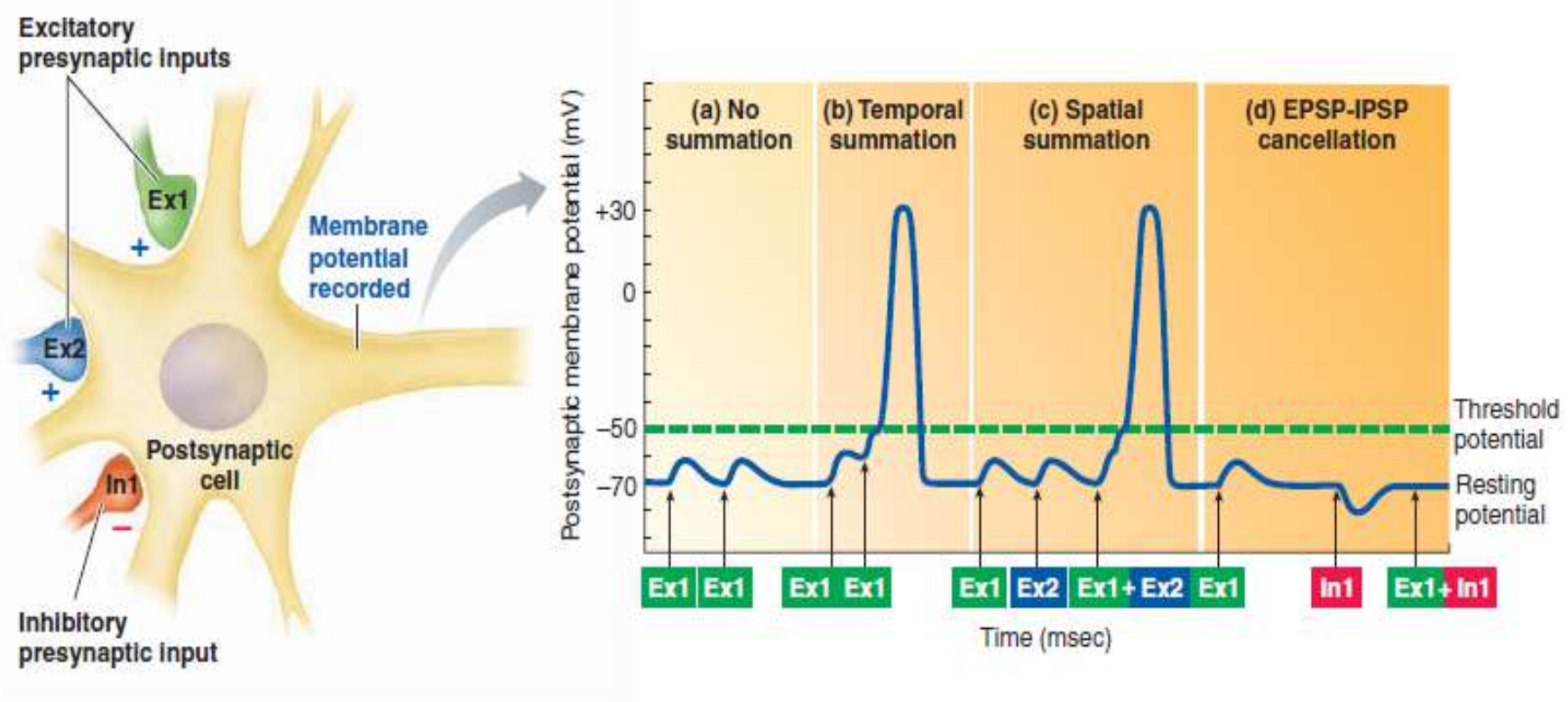
■ **Some** of these **presynaptic** inputs may be carrying **sensory** information from the environment; **some** may be **signaling internal changes** in homeostatic balance; **others** may be **transmitting signals** from control centers in the brain; and still **others** may arrive carrying **other types** of information. At any given time, any number of these **presynaptic** neurons (probably hundreds) may be firing and thus **influencing** the **postsynaptic** neuron's level of activity.

Synapses and Neuronal Integration

■ The **total potential** in the **postsynaptic** neuron, **the grand postsynaptic potential** (GPSP), is a composite of **all** EPSPs and IPSPs occurring at **approximately** the same time.

■ The postsynaptic neuron can be brought to threshold by **either temporal** summation (the summation of several EPSPs occurring very close together in time because of successive firing of a single presynaptic neuron) or **spatial** summation (the summation of EPSPs originating simultaneously from several different presynaptic inputs). Similarly, IPSPs can undergo temporal and spatial summation.

Synapses and Neuronal Integration



(a) If an excitatory presynaptic input (Ex1) is stimulated a second time after the first EPSP in the postsynaptic cell has died off, a second EPSP of the same magnitude will occur.

(b) If, however, Ex1 is stimulated a second time before the first EPSP has died off, the second EPSP will add onto, or sum with, the first EPSP, resulting in *temporal summation*, which may bring the postsynaptic cell to threshold.

(c) The postsynaptic cell may also be brought to threshold by *spatial summation* of EPSPs that are initiated by simultaneous activation of two (Ex1 and Ex2) or more excitatory presynaptic inputs.

(d) Simultaneous activation of an excitatory (Ex1) and inhibitory (In1) presynaptic input does not change the postsynaptic potential, because the resultant EPSP and IPSP cancel each other out.

■ **Cancellation of concurrent EPSPS and IPSPS:**

■ If an **excitatory** and an **inhibitory** input are **simultaneously** activated, **the concurrent** EPSP and IPSP **more** or **less cancel each other out**.

■ The extent of **cancellation** depends on **their respective magnitudes.** In **most** cases, the **postsynaptic** membrane potential **remains close** to **resting.**

Human Physiology I

Second Year Pharmacy Students

Chapter 4: Neuronal Physiology

Part 5 C

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First Semester 2020/2021

Synapses and Neuronal Integration

■ **Importance of postsynaptic neuronal integration:**

■ The magnitude of the GPSP depends on the sum of activity in **all** the presynaptic inputs and, in turn, determines whether or **not** the postsynaptic neuron will undergo an action potential to pass information on to the cells on which the neuron **terminates** (muscle, gland cell, or other neurons).

■ Each postsynaptic neuron "**computes**" **all** the input it receives and makes a "decision" about whether to pass the information on (that is, whether threshold is reached and an action potential

Synapses and Neuronal Integration

■ In this way, neurons serve as complex computational devices (integrators). The dendrites function as the primary processors of incoming information. They receive and tally the signals from **all** the presynaptic neurons. Each neuron's output in the form of frequency of action potentials to other cells reflects the balance of activity in the inputs it receives via EPSPs or IPSPs from the thousands of other neurons that terminate on it. Each postsynaptic neuron **filters out** information that is **not** significant enough to bring it to threshold and **does not** pass it on.

Synapses and Neuronal Integration

■ If **every** action potential in **every** presynaptic neuron were to cause an action potential in the postsynaptic neuron, the neuronal pathways would be overwhelmed with trivia. **Only** if an excitatory presynaptic signal is reinforced by other supporting signals through summation will the information be passed on. Furthermore, interaction of EPSPs and IPSPs provides a way for one set of signals to offset another, allowing a fine degree of discrimination and control in determining what information will be passed on.

Synapses and Neuronal Integration

■ Thus, **a chemical synapse** is **more** than a simple on-off switch because many factors can influence the generation of a new action potential in the postsynaptic cell. Whether or **not** the postsynaptic neuron has an action potential **depends on** the relative balance of information coming in **via** presynaptic neurons at **all** of its excitatory and inhibitory synapses.

■ **Action potentials are initiated at the axon hillock because it has the lowest threshold:**

■ Threshold potential is **not** uniform throughout the postsynaptic neuron. The axon hillock has the **lowest** threshold, because it has a much higher density of voltage-gated Na^+ channels than anywhere else in the neuron. So, it is **more** responsive than the dendrites or the cell body to changes in potential. Because of local current flow, EPSPs or IPSPs occurring on the dendrites or cell body **spread** throughout the dendrites, cell body, and axon hillock.

Synapses and Neuronal Integration

■ When summation of EPSPs takes place, the **lower** threshold of the axon hillock is reached **first**, whereas the dendrites and cell body are still below their much **higher** thresholds. Therefore, an action potential originates in the axon hillock and is propagated from there to the end of the axon.

■ **Neuropeptides act primarily as neuromodulators:**

■ In addition to the **classical neurotransmitters**, **some neurons** also **release neuropeptides.**

■ **Neuromodulators** are **chemical messengers** that **do not** cause the formation of EPSPs or IPSPs but rather bring about long-term changes that **modulate** (depress or enhance) the action of the synapse. For e.g., cholecystokinin (CCK), has been found in axon terminal vesicles in the brain, it is believed to cause the feeling of no longer being hungry.

Synapses and Neuronal Integration

■ **Neuropeptides** differ from **classical neurotransmitters** in several important ways (see the table):

▲ TABLE 4-3 Comparison of Classical Neurotransmitters and Neuropeptides

Characteristic	Classical Neurotransmitters	Neuropeptides
Size	Small (one amino acid or similar chemical)	Large (2 to 40 amino acids)
Site of Synthesis	Cytosol of synaptic knob	Endoplasmic reticulum and Golgi complex in cell body; moved to synaptic knob by axonal transport
Site of Storage	Small synaptic vesicles in axon terminal	Large dense-core vesicles in axon terminal
Site of Release	Axon terminal	Axon terminal; may be co-secreted with neurotransmitter
Amount of Release	Variable, depending on synapse	Much lower concentration than classical neurotransmitter
Speed and Duration of Action	Rapid, brief response	Slow, prolonged response
Site of Action	Subsynaptic membrane of postsynaptic cell	Nonsynaptic sites on either presynaptic or postsynaptic cell
Effect	Usually alter potential of postsynaptic cell by opening specific ion channels	Modulate synaptic effectiveness by long-term changes in neurotransmitter synthesis or postsynaptic receptors

■ **Presynaptic inhibition or facilitation can selectively alter the effectiveness of a presynaptic input:**

■ Another means of **depressing** or enhancing **synaptic effectiveness** is **presynaptic inhibition** or **facilitation.**

Sometimes, **a third** neuron influences activity between a presynaptic ending and a postsynaptic neuron.

■ The presynaptic axon terminal may be **innervated** by another axon terminal (modulatory axon terminal).

Synapses and Neuronal Integration

■ The neurotransmitter **released** from modulatory axon terminal **binds** with receptors on the presynaptic axon terminal. This binding **alters** the amount of neurotransmitter **released** from presynaptic axon terminal in response to action potentials. If the amount of neurotransmitter **released** from presynaptic terminal axon is **reduced**, the phenomenon is known as **presynaptic inhibition**. If the release of neurotransmitter is **enhanced**, the effect is called **presynaptic facilitation.**

Synapses and Neuronal Integration

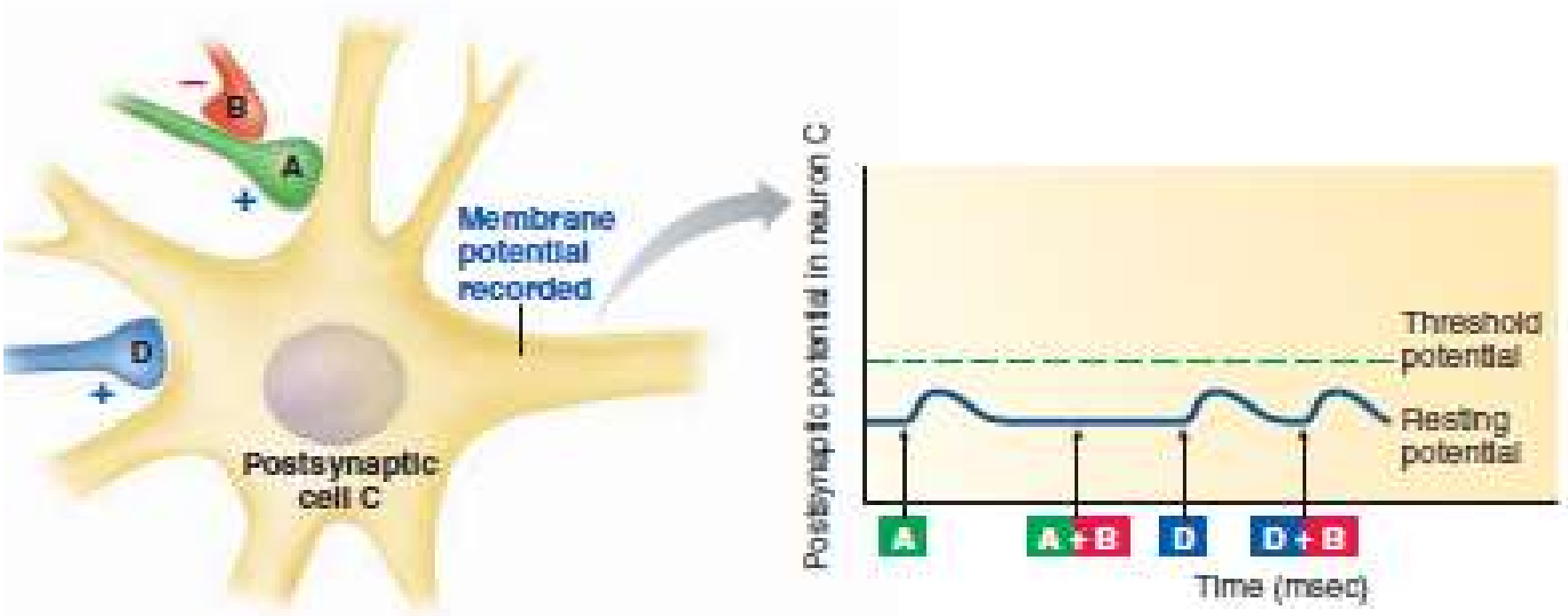


FIGURE 4-18 Presynaptic inhibition. A, an excitatory terminal ending on postsynaptic cell C, is itself innervated by inhibitory terminal B. Stimulation of terminal A alone produces an EPSP in cell C, but simultaneous stimulation of terminal B prevents the release of excitatory neurotransmitter from terminal A. Consequently, no EPSP is produced in cell C despite the fact that terminal A has been stimulated. Such presynaptic inhibition selectively depresses activity from terminal A without suppressing any other excitatory input to cell C. Stimulation of excitatory terminal D produces an EPSP in cell C even though inhibitory terminal B is simultaneously stimulated because terminal B only inhibits terminal A.

Synapses and Neuronal Integration

■ **Neurons are linked through complex converging and diverging pathways:**

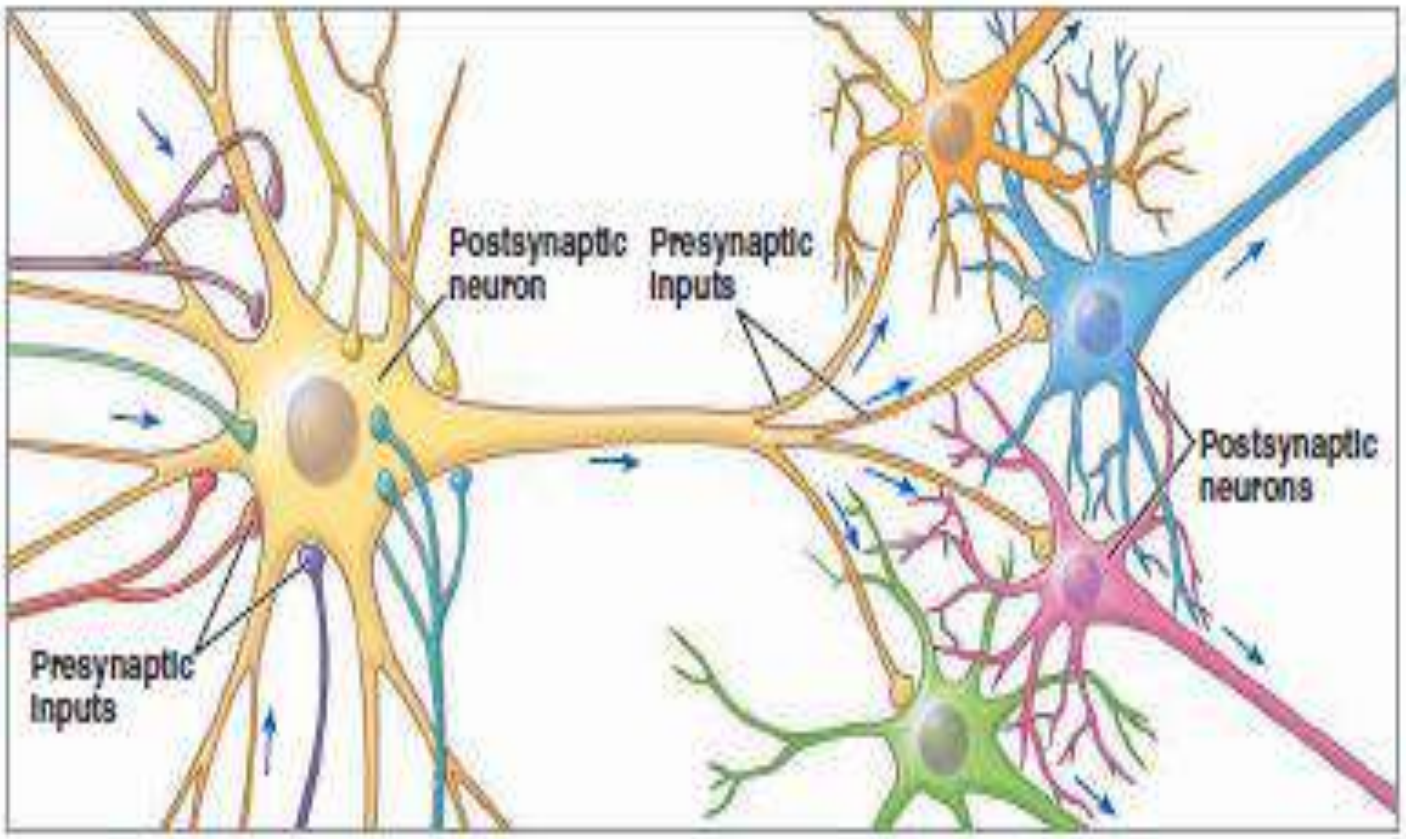
■ **2 important relationships** exist between **neurons:**

convergence and **divergence.** A given neuron may have many other neurons **synapsing** on it. Such a relationship is known as **convergence**. Through converging input, a single cell is influenced by thousands of other cells. This single cell, in turn, **influences** the level of activity in many other cells by **divergence** of output.

Synapses and Neuronal Integration

■ The term **divergence** refers to the branching of axon terminals so that a single cell **synapses with** and **influences** many other cells.

Synapses and Neuronal Integration



● **FIGURE 4-19 Convergence and divergence.** Arrows indicate the direction in which information is being conveyed.