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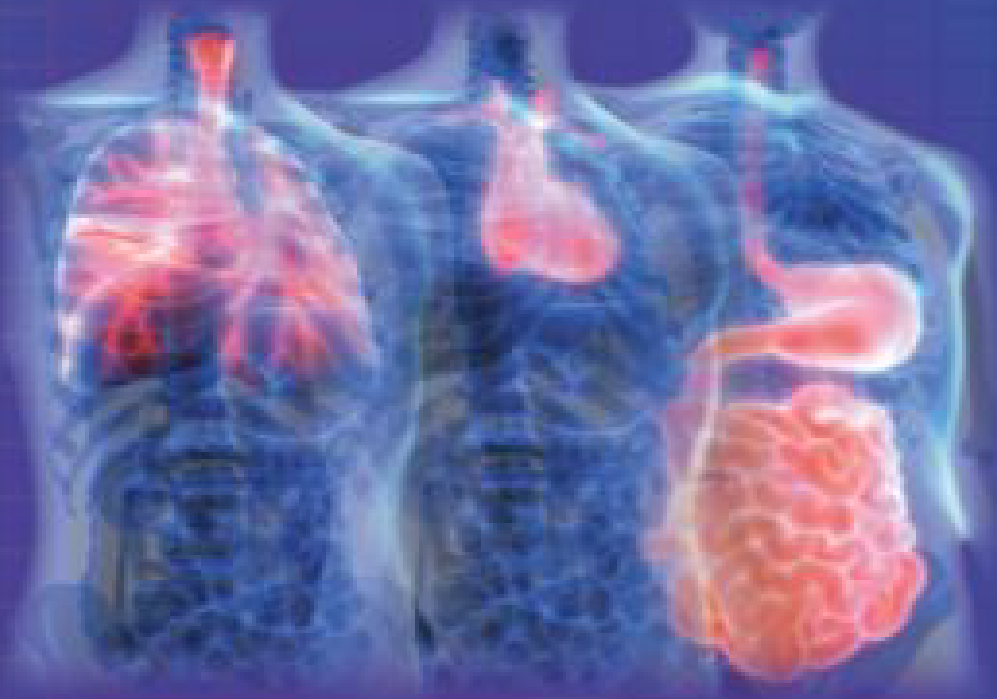
Physiology

SEVENTH EDITION

Linda S. Costanzo



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For Richard
And
for Dan, Rebecca, and Sheila
And
for Elise and Max

Preface

The subject matter of physiology is the foundation of the practice of medicine, and a firm grasp of its principles is essential for the physician. This book is intended to aid the student preparing for the United States Medical Licensing Examination (USMLE) Step 1. It is a concise review of key physiologic principles and is intended to help the student recall material taught during the first and second years of medical school. It is not intended to substitute for comprehensive textbooks or for course syllabi, although the student may find it a useful adjunct to physiology and pathophysiology courses.

The material is organized by organ system into seven chapters. The first chapter reviews general principles of cellular physiology. The remaining six chapters review the major organ systems—neurophysiology, cardiovascular, respiratory, renal and acid–base, gastrointestinal, and endocrine physiology.

Difficult concepts are explained stepwise, concisely, and clearly, with appropriate illustrative examples and sample problems. Numerous clinical correlations are included so that the student can understand physiology in relation to medicine. An integrative approach is used, when possible, to demonstrate how the organ systems work together to maintain homeostasis. More than 130 full-color illustrations and flow diagrams and more than 50 tables help the student visualize the material quickly and aid in long-term retention. Appendices contain “Key Physiology Topics for USMLE Step 1,” “Key Physiology Equations for USMLE Step 1,” and “Normal Blood Values.”

Questions reflecting the content and format of USMLE Step 1 are included at the end of each chapter and in a Comprehensive Examination at the end of the book. These questions, many with clinical relevance, require problem-solving skills rather than straight recall. Clear, concise explanations accompany the questions and guide the student through the correct steps of reasoning. The questions can be used as a pretest to identify areas of weakness or as a posttest to determine mastery. Special attention should be given to the Comprehensive Examination, because its questions integrate several areas of physiology and related concepts of pathophysiology and pharmacology.

New to this edition:

- Addition of new full-color figures
- Updated organization and text
- Expanded coverage of neurophysiology, and respiratory, renal, gastrointestinal, and endocrine physiology
- Addition of new multi-step questions

Best of luck in your preparation for USMLE Step 1!

Linda S. Costanzo, Ph.D.

Acknowledgments

It has been a pleasure to be a part of the Board Review Series and to work with the staff at Wolters Kluwer. Crystal Taylor and Andrea Vosburgh provided expert editorial assistance.

My sincere thanks to students in the School of Medicine at Virginia Commonwealth University/Medical College of Virginia, who have provided so many helpful suggestions for *BRS Physiology.* Thanks also to the many students from other medical schools who have taken the time to write to me about their experiences with this book.

Linda S. Costanzo, Ph.D.

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Chapter 1 Cell Physiology

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I. CELL MEMBRANES

- are composed primarily of phospholipids and proteins.

A. Lipid bilayer

1. **Phospholipids** have a **glycerol backbone,** which is the hydrophilic (water soluble) head, and two **fatty acid tails,** which are hydrophobic (water insoluble). The hydrophobic tails face each other and form a bilayer.
2. **Lipid-soluble substances** (e.g., O_2, CO_2, steroid hormones) cross cell membranes because they can dissolve in the hydrophobic lipid bilayer.
3. **Water-soluble substances** (e.g., Na^+, Cl^-, glucose, H_2O) cannot dissolve in the lipid of the membrane, but may cross through water-filled channels, or pores, or may be transported by carriers.

B. Proteins

1. Integral proteins

- are anchored to, and imbedded in, the cell membrane through **hydrophobic** interactions.
- may span the cell membrane.
- include ion channels, transport proteins, receptors, and guanosine 5′-triphosphate (GTP)–binding proteins (G proteins).

2. Peripheral proteins

- are *not* imbedded in the cell membrane.
- are *not* covalently bound to membrane components.
- are loosely attached to the cell membrane by **electrostatic** interactions.

C. Intercellular connections

1. Tight junctions (zonula occludens)

- are the attachments between cells (often epithelial cells).
- may be an intercellular pathway for solutes, depending on the size, charge, and characteristics of the tight junction.
- may be **"tight"** (impermeable), as in the renal distal tubule, or **"leaky"** (permeable), as in the renal proximal tubule and gallbladder.

2. Gap junctions

- are the attachments between cells that permit intercellular communication.
- for example, permit current flow and electrical **coupling between myocardial cells.**

II. TRANSPORT ACROSS CELL MEMBRANES (TABLE 1.1)

table **1.1** Characteristics of Different Types of Transport

Type	Electrochemical Gradient	Carrier-Mediated	Metabolic Energy	Na^+ Gradient	Inhibition of Na^+–K^+ Pump
Simple diffusion	Downhill	No	No	No	—
Facilitated diffusion	Downhill	Yes	No	No	—
Primary active transport	Uphill	Yes	Yes	—	Inhibits (if Na^+–K^+ pump)
Cotransport	Uphill*	Yes	Indirect	Yes, same direction	Inhibits (by abolishing Na^+ gradient)
Countertransport	Uphill*	Yes	Indirect	Yes, opposite direction	Inhibits (by abolishing Na^+ gradient)

*One or more solutes are transported uphill; Na^+ is transported downhill.

A. Simple diffusion

1. Characteristics of simple diffusion

- is the only form of transport that is **not carrier mediated.**

- occurs **down an electrochemical gradient** ("downhill").
- does not require metabolic energy and therefore is passive.

2. Diffusion can be measured using the following equation:

$J = -PA(C_1 - C_2)$

where:

J = flux (flow) (mmol/sec)

P = permeability (cm/sec)

A = area (cm^2)

C_1 = concentration$_1$ (mmol/L)

C_2 = concentration$_2$ (mmol/L)

3. Sample calculation for diffusion

- The urea concentration of blood is 10 mg/100 mL. The urea concentration of proximal tubular fluid is 20 mg/100 mL. If the permeability to urea is 1×10^{-5} cm/sec and the surface area is 100 cm^2, what are the magnitude and direction of the urea flux?

$$\text{Flux} = \left(\frac{1\times10^{-5}\ \text{cm}}{\text{sec}}\right)\left(100\ \text{cm}^2\right)\left(\frac{20\ \text{mg}}{100\ \text{mL}} - \frac{10\ \text{mg}}{100\ \text{mL}}\right)$$

$$= \left(\frac{1\times10^{-5}\ \text{cm}}{\text{sec}}\right)\left(100\ \text{cm}^2\right)\left(\frac{10\ \text{mg}}{100\ \text{mL}}\right)$$

$$= \left(\frac{1\times10^{-5}\ \text{cm}}{\text{sec}}\right)\left(100\ \text{cm}^2\right)\left(\frac{0.1\ \text{mg}}{\text{cm}^3}\right)$$

$$= 1\times10^{-4}\ \text{mg/sec from lumen to blood (high to low concentration)}$$

Note: The minus sign preceding the diffusion equation indicates that the direction of flux, or flow, is from high to low concentration. It can be ignored if the higher concentration is called C_1 and the lower concentration is called C_2.

Also note: 1 mL = 1 cm^3.

4. Permeability

- is the P in the equation for diffusion.
- describes the ease with which a solute diffuses through a membrane.
- depends on the characteristics of the solute and the membrane.

a. Factors that increase permeability:

- ↑ **Oil/water partition coefficient** of the solute increases solubility in the lipid of the membrane.

- ↓ **Radius (size) of the solute** increases the diffusion coefficient and speed of diffusion.
- ↓ **Membrane thickness** decreases the diffusion distance.

b. Small hydrophobic solutes (e.g., O_2, CO_2) have the highest permeabilities in lipid membranes.

c. Hydrophilic solutes (e.g., Na^+, K^+) must cross cell membranes through water-filled channels, or pores, or via transporters. If the solute is an ion (is charged), then its flux will depend on both the concentration difference and the potential difference across the membrane.

B. Carrier-mediated transport

- includes facilitated diffusion and primary and secondary active transport.
- The **characteristics** of carrier-mediated transport are

1. **Stereospecificity.** For example, D-glucose (the natural isomer) is transported by facilitated diffusion, but the L-isomer is not. Simple diffusion, in contrast, would not distinguish between the two isomers because it does not involve a carrier.
2. **Saturation.** The transport rate increases as the concentration of the solute increases, until the carriers are saturated. The **transport maximum (T_m)** is analogous to the maximum velocity **(V_{max})** in enzyme kinetics.
3. **Competition.** Structurally related solutes compete for transport sites on carrier molecules. For example, galactose is a competitive inhibitor of glucose transport in the small intestine.

C. Facilitated diffusion

1. Characteristics of facilitated diffusion

- occurs **down an electrochemical gradient** ("downhill"), similar to simple diffusion.
- does not require metabolic energy and therefore is **passive.**
- is more **rapid** than simple diffusion.
- is **carrier mediated** and therefore exhibits stereospecificity, saturation, and competition.

2. Example of facilitated diffusion

- Glucose transport in muscle and adipose cells is "downhill," is carrier mediated, and is inhibited by sugars such as galactose; therefore, it is

categorized as facilitated diffusion. In **diabetes mellitus,** glucose uptake by muscle and adipose cells is impaired because the carriers for facilitated diffusion of glucose require **insulin.**

D. Primary active transport

1. Characteristics of primary active transport

- occurs **against an electrochemical gradient** ("uphill").
- requires **direct input of metabolic energy** in the form of adenosine triphosphate **(ATP)** and therefore is **active.**
- is **carrier mediated** and therefore exhibits stereospecificity, saturation, and competition.

2. Examples of primary active transport

a. Na^+, K^+-ATPase (or Na^+–K^+ pump) in cell membranes transports Na^+ from intracellular to extracellular fluid and K^+ from extracellular to intracellular fluid; it maintains low intracellular [Na^+] and high intracellular [K^+].

- Both **Na^+ and K^+ are transported against their electrochemical gradients.**
- Energy is provided from the terminal phosphate bond of ATP.
- The **usual stoichiometry is 3 Na^+/2 K^+**.
- Specific inhibitors of Na^+, K^+-ATPase are the cardiac glycoside drugs ouabain and **digitalis.**

b. Ca^{2+}-ATPase (or Ca^{2+} pump) in the sarcoplasmic reticulum (SR) or cell membranes transports Ca^{2+} against an electrochemical gradient.

- Sarcoplasmic and endoplasmic reticulum Ca^{2+}-ATPase is called **SERCA.**

c. H^+, K^+-ATPase (or proton pump) in gastric parietal cells and renal α-intercalated cells transports H^+ into the lumen (of the stomach or renal tubule) against its electrochemical gradient.

- It is inhibited by proton pump inhibitors, such as **omeprazole.**

E. Secondary active transport

1. Characteristics of secondary active transport

a. The transport of two or more solutes is **coupled.**

b. One of the solutes (usually Na^+) is transported "downhill" and provides

energy for the "uphill" transport of the other solute(s).

c. Metabolic energy is not provided directly but indirectly from the **Na^+ gradient** that is maintained across cell membranes. Thus, inhibition of Na^+, K^+-ATPase will decrease transport of Na^+ out of the cell, decrease the transmembrane Na^+ gradient, and eventually inhibit secondary active transport.

d. If the solutes move in the same direction across the cell membrane, it is called **cotransport** or **symport.**

- Examples are **Na^+-glucose cotransport** in the small intestine and renal early proximal tubule and **Na^+–K^+–2Cl^-** cotransport in the renal thick ascending limb.

e. If the solutes move in opposite directions across the cell membranes, it is called **countertransport, exchange,** or **antiport.**

- Examples are **Na^+-Ca^{2+} exchange** and **Na^+–H^+ exchange.**

2. Example of Na^+–glucose cotransport (Figure 1.1)

a. The carrier for Na^+–glucose cotransport is located in the luminal membrane of intestinal mucosal and renal proximal tubule cells.

b. Glucose is transported "uphill"; Na^+ is transported "downhill."

c. Energy is derived from the "downhill" movement of Na^+. The inwardly directed Na^+ gradient is maintained by the Na^+–K^+ pump on the basolateral (blood side) membrane. Poisoning the Na^+–K^+ pump decreases the transmembrane Na^+ gradient and consequently inhibits Na^+–glucose cotransport.

3. Example of Na^+–Ca^{2+} countertransport or exchange (Figure 1.2)

a. Many cell membranes contain a Na^+–Ca^{2+} exchanger that transports Ca^{2+} "uphill" from low intracellular [Ca^{2+}] to high extracellular [Ca^{2+}]. Ca^{2+} and Na^+ move in opposite directions across the cell membrane.

b. The energy is derived from the "downhill" movement of Na^+. As with cotransport, the inwardly directed Na^+ gradient is maintained by the Na^+–K^+ pump. Poisoning the Na^+–K^+ pump therefore inhibits Na^+–Ca^{2+} exchange.

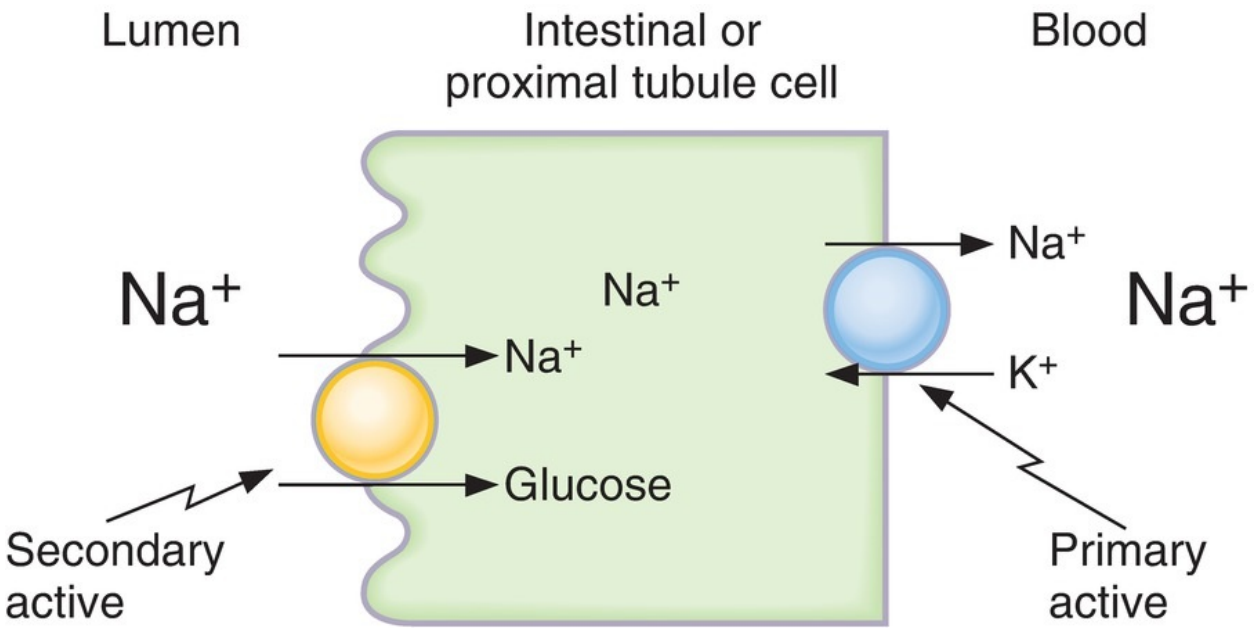

FIGURE 1.1 Na^+–glucose cotransport (symport) in intestinal or proximal tubule epithelial cell.

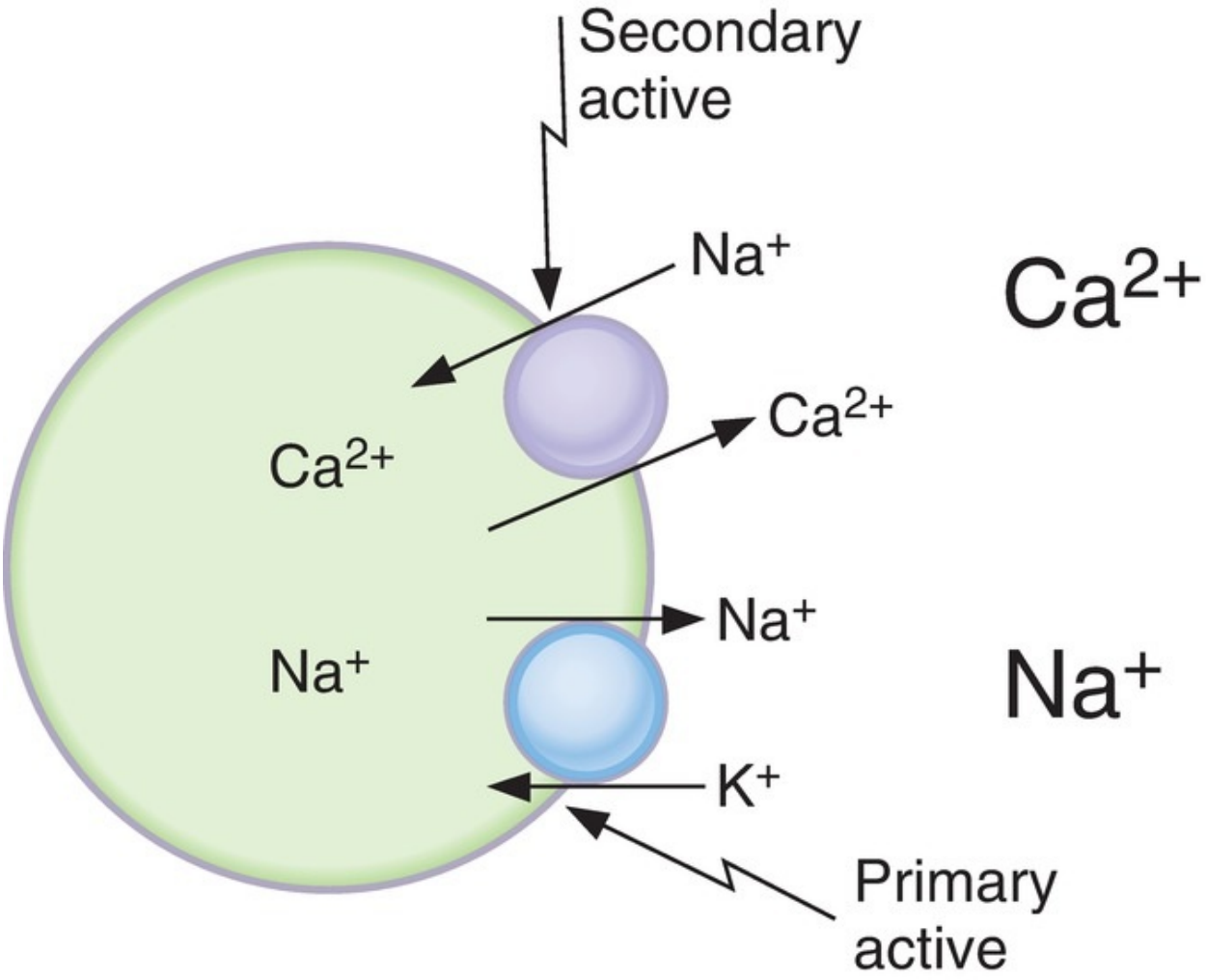

FIGURE 1.2 Na^+–Ca^{2+} countertransport (antiport).

III. OSMOSIS

A. Osmolarity

- is the concentration of osmotically active particles in a solution.
- is a colligative property that can be measured by freezing point depression.
- can be calculated using the following **equation:**
  Osmolarity = **g** × **C**
  where:
  Osmolarity = concentration of particles (Osm/L)

g = number of particles in solution (Osm/mol)
[e.g., $g_{NaCl} = 2$; $g_{glucose} = 1$]
C = concentration (mol/L)

- Two solutions that have the same calculated osmolarity are **isosmotic.** If two solutions have different calculated osmolarities, the solution with the higher osmolarity is **hyperosmotic** and the solution with the lower osmolarity is **hyposmotic.**
- **Sample calculation:** What is the osmolarity of a 1 M NaCl solution?

$$E = -2.3\frac{RT}{zF}\log_{10}\frac{[C_i]}{[C_e]}$$

B. Osmosis and osmotic pressure

- **Osmosis** is the **flow of water** across a semipermeable membrane from a solution with low solute concentration to a solution with high solute concentration.

1. Example of osmosis (Figure 1.3)

a. Solutions 1 and 2 are separated by a semipermeable membrane. Solution 1 contains a solute that is too large to cross the membrane. Solution 2 is pure water. The presence of the solute in solution 1 produces an **osmotic pressure.**

b. The osmotic pressure difference across the membrane causes water to flow from solution 2 (which has no solute and the lower osmotic pressure) to solution 1 (which has the solute and the higher osmotic pressure).

c. With time, the volume of solution 1 increases and the volume of solution 2 decreases.

2. Calculating osmotic pressure (van't Hoff's law)

a. The **osmotic pressure** of solution 1 (see Figure 1.3) can be calculated by van't Hoff's law, which states that osmotic pressure depends on the concentration of osmotically active particles. The concentration of particles is converted to pressure according to the following **equation:**
$\boldsymbol{\pi = g \times C \times RT}$
where:
π = osmotic pressure (mm Hg or atm)
g = number of particles in solution (osm/mol)
C = concentration (mol/L)

R = gas constant (0.082 L—atm/mol—K)
T = absolute temperature (K)

b. The osmotic pressure increases when the solute concentration increases. A solution of 1 M $CaCl_2$ has a higher osmotic pressure than does a solution of 1 M KCl because, for a given volume, the number of osmotically active particles is higher.

c. The higher the osmotic pressure of a solution, the greater the water flow into it.

d. Two solutions having the same effective osmotic pressure are **isotonic** because no water flows across a semipermeable membrane separating them. If two solutions separated by a semipermeable membrane have different effective osmotic pressures, the solution with the higher effective osmotic pressure is **hypertonic** and the solution with the lower effective osmotic pressure is **hypotonic.** Water flows from the hypotonic to the hypertonic solution.

e. Colloid osmotic pressure, or **oncotic pressure,** is the osmotic pressure created by proteins (e.g., plasma proteins).

3. Reflection coefficient (σ)

- is a number between zero and one that describes the ease with which a solute permeates a membrane.

a. If the reflection coefficient is one, the solute is impermeable. Therefore, it is retained in the original solution, it creates an osmotic pressure, and it causes water flow. **Serum albumin** (a large solute) has a reflection coefficient of nearly one.

b. If the reflection coefficient is zero, the solute is completely permeable. Therefore, it will not exert any osmotic effect, and it will not cause water flow. **Urea** (a small solute) usually has a reflection coefficient of close to zero and it is, therefore, an **ineffective osmole.**

4. Calculating effective osmotic pressure

- Effective osmotic pressure is the osmotic pressure (calculated by van’t Hoff’s law) multiplied by the reflection coefficient.
- If the reflection coefficient is one, the solute will exert maximal effective osmotic pressure. If the reflection coefficient is zero, the solute will exert no osmotic pressure.

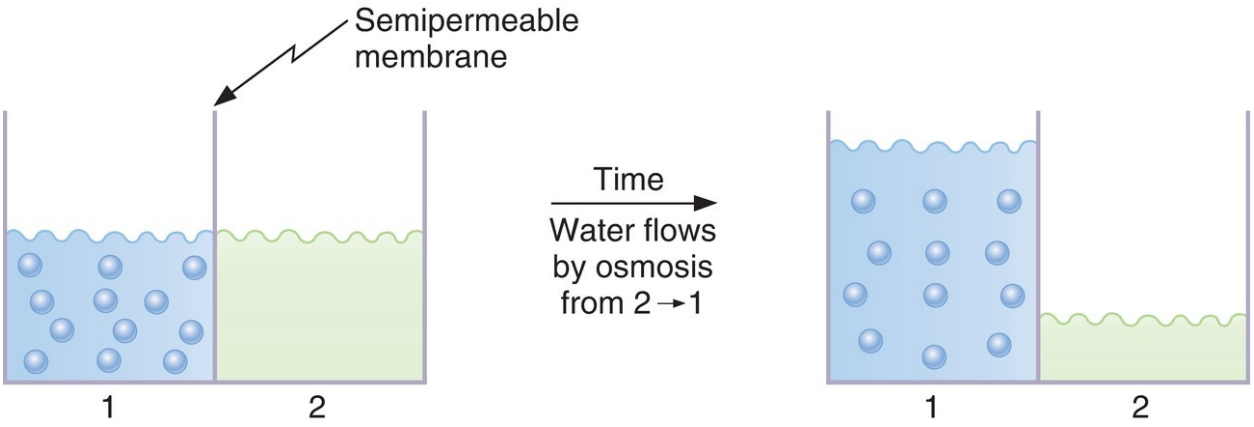

FIGURE 1.3 Osmosis of H_2O across a semipermeable membrane.

IV. DIFFUSION POTENTIAL, RESTING MEMBRANE POTENTIAL, AND ACTION POTENTIAL

A. Ion channels

- are **integral proteins** that span the membrane and, when open, permit the passage of certain ions.

1. **Ion channels are selective;** they permit the passage of some ions, but not others. Selectivity is based on the size of the channel and the distribution of charges that line it.
    - For example, a small channel lined with negatively charged groups will be selective for small cations and exclude large solutes and anions. Conversely, a small channel lined with positively charged groups will be selective for small anions and exclude large solutes and cations.
2. **Ion channels may be open or closed.** When the channel is open, the ion(s) for which it is selective can flow through. When the channel is closed, ions cannot flow through.
3. **The conductance of a channel** depends on the probability that the channel is open. The higher the probability that a channel is open, the higher the conductance, or **permeability.** Opening and closing of channels are controlled by **gates.**

a. Voltage-gated channels are opened or closed by changes in membrane potential.

- The **activation gate of the Na^+ channel** in nerve is opened by depolarization.
- The **inactivation gate of the Na^+ channel** in nerve is closed by depolarization.
- When both the activation and inactivation gates on Na^+ channels are open, the channels are open and permeable to Na^+ (e.g., during the upstroke of the nerve action potential).
- If either the activation or inactivation gate on the Na^+ channel is closed, the channel is closed and impermeable to Na^+. For example, at the resting potential, the activation gates are closed and thus the Na^+ channels are closed.

b. Ligand-gated channels are opened or closed by hormones, second messengers, or neurotransmitters.

- For example, the **nicotinic receptor** for acetylcholine (ACh) at the motor end plate is an ion channel that opens when ACh binds to it. When open, it is permeable to Na^+ and K^+, causing the motor end plate to depolarize.

B. Diffusion and equilibrium potentials

- A **diffusion potential** is the potential difference generated across a membrane because of a concentration difference of an ion.
- A diffusion potential can be generated only if the membrane is permeable to the ion.
- The **size of the diffusion potential** depends on the size of the concentration gradient.
- The **sign of the diffusion potential** depends on whether the diffusing ion is positively or negatively charged.
- Diffusion potentials are created by the diffusion of **very few ions** and, therefore, do not result in changes in concentration of the diffusing ions.
- The **equilibrium potential** is the potential difference that would exactly balance (oppose) the tendency for diffusion down a concentration difference. At **electrochemical equilibrium,** the chemical and electrical driving forces that act on an ion are equal and opposite, and no further net diffusion of the ion occurs.

1. Example of a Na^+ diffusion potential (Figure 1.4)

a. Two solutions of NaCl are separated by a membrane that is permeable to Na^+ but not to Cl^-. The NaCl concentration of solution 1 is higher than that of solution 2.

b. Because the membrane is permeable to Na^+, Na^+ will diffuse from solution 1 to solution 2 down its concentration gradient. Cl^- is impermeable and therefore will not accompany Na^+.

c. As a result, a **diffusion potential** will develop at the membrane and solution 1 will become negative with respect to solution 2.

d. Eventually, the potential difference will become large enough to oppose further net diffusion of Na^+. The potential difference that exactly counterbalances the diffusion of Na^+ down its concentration gradient is the **Na^+ equilibrium potential.** At electrochemical equilibrium, the chemical and electrical driving forces on Na^+ are equal and opposite, and there is no net diffusion of Na^+.

2. Example of a Cl^- diffusion potential (Figure 1.5)

a. Two solutions identical to those shown in Figure 1.4 are now separated by a membrane that is permeable to Cl^- rather than to Na^+.

b. Cl^- will diffuse from solution 1 to solution 2 down its concentration gradient. Na^+ is impermeable and therefore will not accompany Cl^-.

c. A **diffusion potential** will be established at the membrane such that solution 1 will become positive with respect to solution 2. The potential difference that exactly counterbalances the diffusion of Cl^- down its concentration gradient is the **Cl^- equilibrium potential.** At electrochemical equilibrium, the chemical and electrical driving forces on Cl^- are equal and opposite, and there is no net diffusion of Cl^-.

3. Using the Nernst equation to calculate equilibrium potentials

a. The **Nernst equation** is used to calculate the equilibrium potential at a given concentration difference of a permeable ion across a cell membrane. It tells us what potential would exactly balance the tendency for diffusion down the concentration gradient; in other words, **at what potential would the ion be at electrochemical equilibrium?**

$$2.3\frac{RT}{zF} = \frac{60\,mV}{z} \text{ at } 37°C$$

where:

$$E_{Na^+} = \frac{-60\ mV}{z} \log_{10} \frac{[C_i]}{[C_e]}$$
$$= \frac{-60\ mV}{+1} \log_{10} \frac{15\ mM}{150\ mM}$$
$$= -60\ mV \log_{10} 0.1$$
$$= +60\ mV$$

E = equilibrium potential (mV) z = charge on the ion (+1 for Na^+, +2 for Ca^{2+}, −1 for Cl^-)
C_i = intracellular concentration (mM)
C_e = extracellular concentration (mM)

b. Sample calculation with the Nernst equation

- If the intracellular [Na^+] is 15 mM and the extracellular [Na^+] is 150 mM, what is the equilibrium potential for Na^+? E_{Na^+} **Note:** You need not remember which concentration goes in the numerator. Because it is a log function, perform the calculation either way to get the absolute value of 60 mV. Then use an "intuitive approach" to determine the correct sign. (Intuitive approach: The [Na^+] is higher in extracellular fluid than in intracellular fluid, so Na^+ ions will diffuse from extracellular to intracellular, making the inside of the cell positive [i.e., +60 mV at equilibrium].)

c. Approximate values for equilibrium potentials in nerve and skeletal muscle

E_{Na^+}	+65 mV
$E_{Ca^{2+}}$	+120 mV
E_{K^+}	−85 mV
E_{Cl^-}	−85 mV

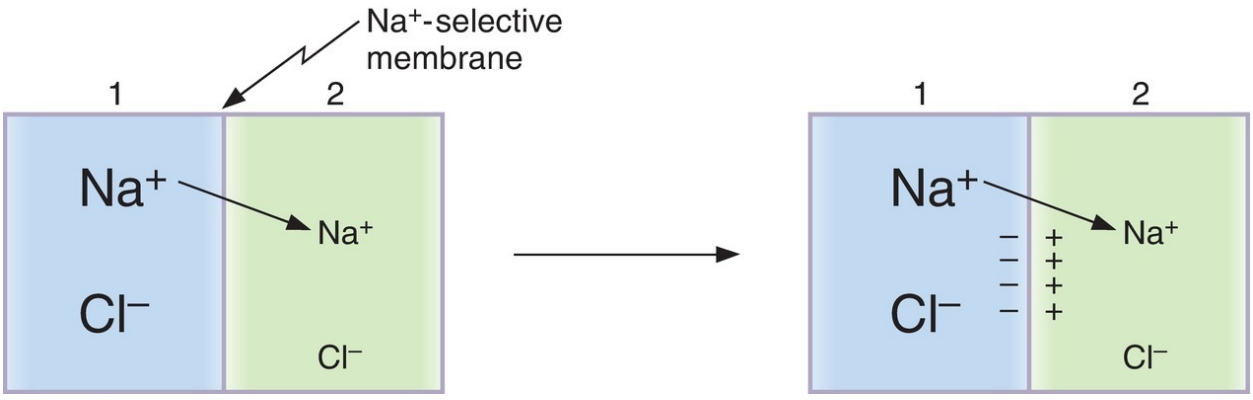

FIGURE 1.4 Generation of an Na^+ diffusion potential across a Na^+-selective membrane.

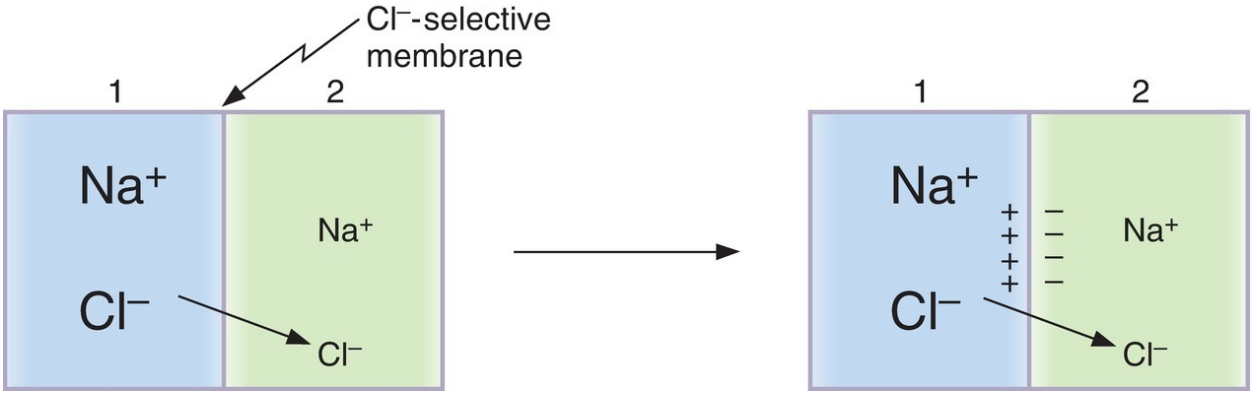

FIGURE 1.5 Generation of a Cl^- diffusion potential across a Cl^--selective membrane.

C. Driving force and current flow

- The **driving force** on an ion is the difference between the actual membrane potential (E_m) and the ion's equilibrium potential (calculated with the Nernst equation). In other words, the driving force is the difference between the actual membrane potential and what the ion would "like" the membrane potential to be; the ion would "like" the membrane potential to be its equilibrium potential, as calculated by the Nernst equation.
- **Current flow** occurs if there is a driving force on the ion and the membrane is permeable to the ion. The *direction* of current flow is in

the same direction as the driving force. The *magnitude* of current flow is determined by the size of the driving force and the permeability (or conductance) of the ion. If there is no driving force on the ion, no current flow can occur. If the membrane is impermeable to the ion, no current flow can occur.

D. Resting membrane potential

- is expressed as the measured potential difference across the cell membrane in millivolts (mV).
- is, by convention, expressed as the intracellular potential relative to the extracellular potential. Thus, a resting membrane potential of −70 mV means **70 mV, cell negative.**

1. **The resting membrane potential is established by diffusion potentials** that result from concentration differences of permeant ions.
2. **Each permeable ion attempts to drive the membrane potential toward its equilibrium potential.** Ions with the highest permeabilities, or conductances, will make the greatest contributions to the resting membrane potential, and those with the lowest permeabilities will make little or no contribution.
3. **For example,** the resting membrane potential of nerve is −70 mV, which is close to the calculated K^+ equilibrium potential of −85 mV, but far from the calculated Na^+ equilibrium potential of +65 mV. **At rest, the nerve membrane is far more permeable to K^+ than to Na^+**.
4. **The Na^+–K^+ pump contributes only indirectly** to the resting membrane potential by maintaining, across the cell membrane, the Na^+ and K^+ concentration gradients that then produce diffusion potentials. The direct **electrogenic** contribution of the pump (3 Na^+ pumped out of the cell for every 2 K^+ pumped into the cell) is small.

E. Action potentials

1. Definitions

a. Depolarization makes the membrane potential **less negative** (the cell interior becomes less negative).

b. Hyperpolarization makes the membrane potential **more negative** (the cell interior becomes more negative).

c. Inward current is the flow of positive charge into the cell. Inward

current **depolarizes** the membrane potential.

d. Outward current is the flow of positive charge out of the cell. Outward current **hyperpolarizes** the membrane potential.

e. Action potential is a property of excitablecells (i.e., nerve, muscle) that consists of a rapid depolarization, or upstroke, followed by repolarization of the membrane potential. Action potentials have **stereotypical size and shape,** are **propagating,** and are **all-or-none.**

f. Threshold is the membrane potential at which the action potential is inevitable. At threshold potential, net inward current becomes larger than net outward current. The resulting depolarization becomes self-sustaining and gives rise to the upstroke of the action potential. If net inward current is less than net outward current, no action potential will occur (i.e., all-or-none response).

2. Ionic basis of the nerve action potential (Figure 1.6)

a. Resting membrane potential

- is approximately −70 mV, cell negative.
- is the result of the **high resting conductance to K^+**, which drives the membrane potential toward the K^+ equilibrium potential.
- At rest, although the inactivation gates on Na^+ channels are open (having been opened by repolarization from the preceding action potential), the activation gates on Na^+ channels are closed and thus the Na^+ channels are closed and Na^+ conductance is low.

b. Upstroke of the action potential

1. Inward current depolarizes the membrane potential to threshold.

2. Depolarization causes rapid opening of the activation gates of the Na^+ channels. Now, both activation and inactivation gates are open and the Na^+ conductance of the membrane promptly increases.

3. The Na^+ conductance becomes higher than the K^+ conductance, and the membrane potential is driven toward (but does not quite reach) the Na^+ equilibrium potential of +65 mV. Thus, the rapid depolarization during the upstroke is caused by an **inward Na^+ current.**

4. The **overshoot** is the brief portion at the peak of the action potential when the membrane potential is positive.

5. Tetrodotoxin (TTX) and **lidocaine** block these voltage-sensitive Na^+ channels and abolish action potentials.

c. Repolarization of the action potential

1. **Depolarization also closes the inactivation gates of the Na^+ channels** (but more slowly than it opens the activation gates). Closure of the inactivation gates results in closure of the Na^+ channels, and the Na^+ conductance returns toward zero.
2. **Depolarization slowly opens K^+ channels and increases K^+ conductance** to even higher levels than at rest. **Tetraethylammonium (TEA)** blocks these voltage-gated K^+ channels.
3. The combined effect of closing the Na^+ channels and greater opening of the K^+ channels makes the K^+ conductance higher than the Na^+ conductance, and the membrane potential is repolarized. Thus, repolarization is caused by an **outward K^+ current.**

d. Undershoot (hyperpolarizing afterpotential)

- The K^+ conductance remains higher than at rest for some time after closure of the Na^+ channels. During this period, the membrane potential is driven very close to the K^+ equilibrium potential.

3. **Refractory periods** (see Figure 1.6)

a. Absolute refractory period

- is the period during which another action potential cannot be elicited, no matter how large the stimulus.
- coincides with almost the entire duration of the action potential.
- **Explanation:** Recall that the inactivation gates of the Na^+ channels are closed when the membrane potential is depolarized. They remain closed until repolarization occurs. No action potential can occur until the inactivation gates open.

b. Relative refractory period

- begins at the end of the absolute refractory period and continues until the membrane potential returns to the resting level.
- An action potential can be elicited during this period only if a larger than usual inward current is provided.
- **Explanation:** The K^+ conductance is higher than at rest, and the membrane potential is closer to the K^+ equilibrium potential and, therefore, farther from threshold; more inward current is required to bring the membrane to threshold.

c. Accommodation

- occurs when the cell membrane is held at a depolarized level such that the threshold potential is passed without firing an action potential.
- occurs because depolarization closes inactivation gates on the Na^+ channels.
- is demonstrated in **hyperkalemia,** in which skeletal muscle membranes are depolarized by the high serum K^+ concentration. Although the membrane potential is closer to threshold, action potentials do not occur because inactivation gates on Na^+ channels are closed by depolarization, causing **muscle weakness.**

4. Propagation of action potentials (Figure 1.7)

- occurs by the spread of **local currents** to adjacent areas of membrane, which are then depolarized to threshold and generate action potentials.
- **Conduction velocity is increased by:**

a. ↑ **fiber size.** Increasing the diameter of a nerve fiber results in decreased internal resistance; thus, conduction velocity down the nerve is faster.

b. Myelination. Myelin acts as an insulator around nerve axons and increases conduction velocity. Myelinated nerves exhibit **saltatory conduction** because action potentials can be generated only at the **nodes of Ranvier,** where there are gaps in the myelin sheath (Figure 1.8).

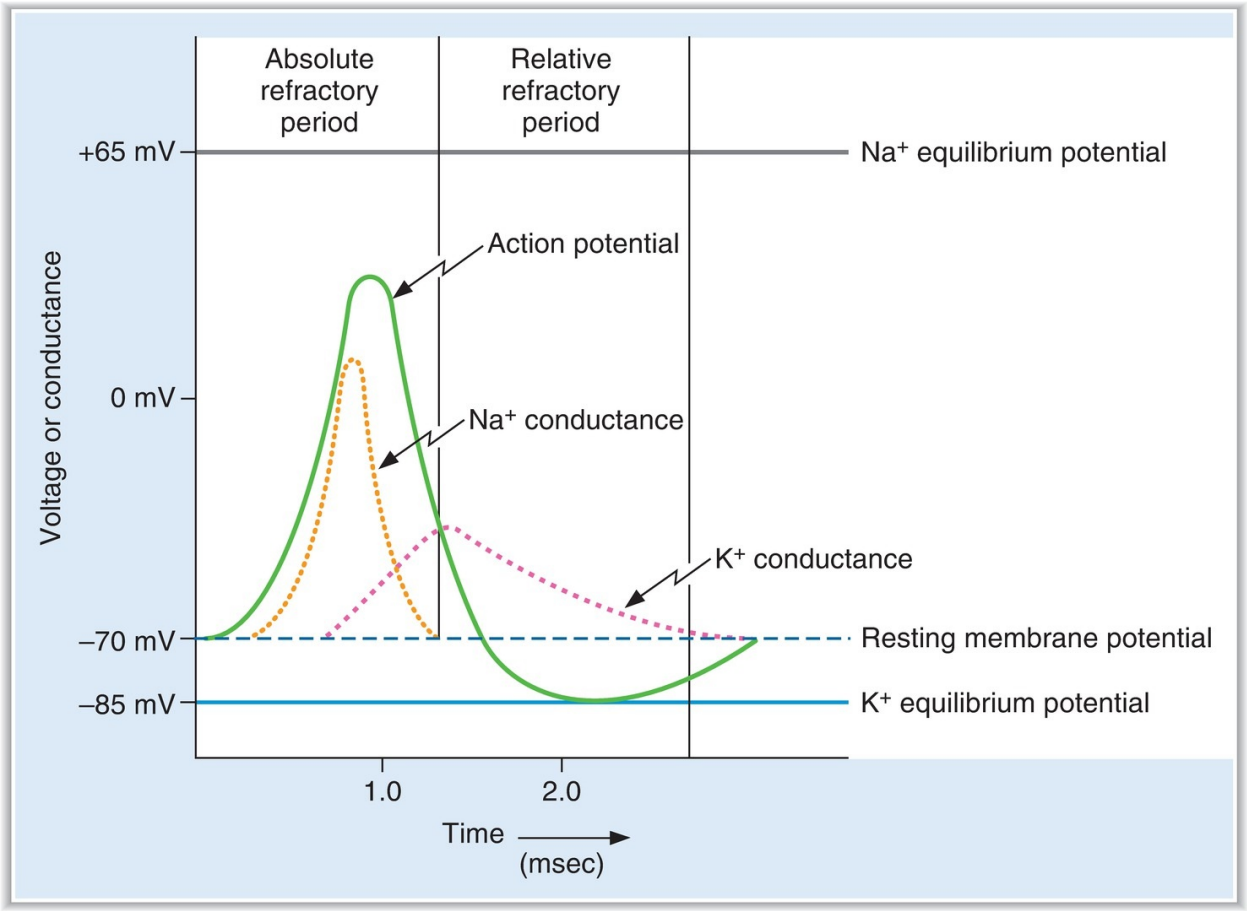

FIGURE 1.6 Nerve action potential and associated changes in Na^+ and K^+ conductance.

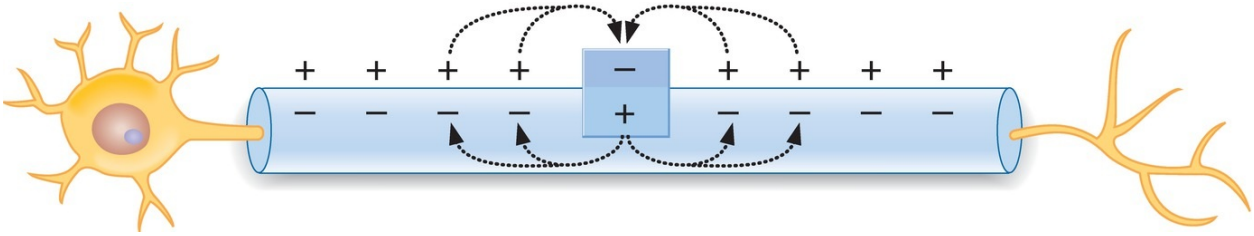

FIGURE 1.7 Unmyelinated axon showing spread of depolarization by local current flow. *Box* shows active zone where action potential had reversed the polarity.

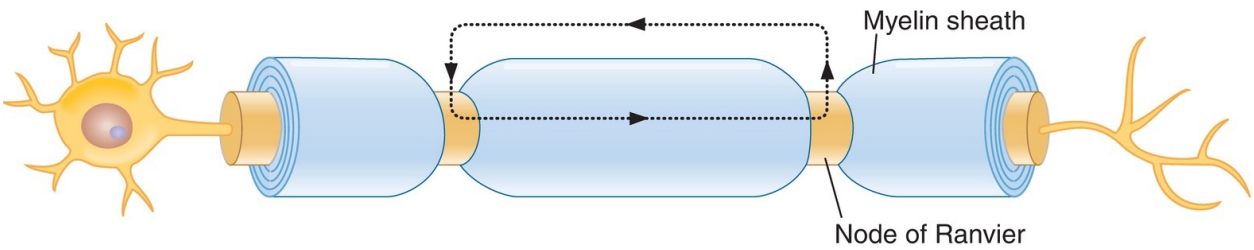

FIGURE 1.8 Myelinated axon. Action potentials can occur at nodes of Ranvier.

V. NEUROMUSCULAR AND SYNAPTIC TRANSMISSION

A. General characteristics of chemical synapses

1. **An action potential in the presynaptic cell** causes depolarization of the presynaptic terminal.
2. As a result of the depolarization, **Ca^{2+} enters the presynaptic terminal,** causing **release of neurotransmitter** into the synaptic cleft.
3. Neurotransmitter diffuses across the synaptic cleft and combines with **receptors on the postsynaptic cell membrane,** causing a change in its permeability to ions and, consequently, a change in its membrane potential.
4. **Inhibitory neurotransmitters** hyperpolarize the postsynaptic membrane: **excitatory neurotransmitters** depolarize the postsynaptic membrane.

B. Neuromuscular junction (Figure 1.9 and Table 1.2)

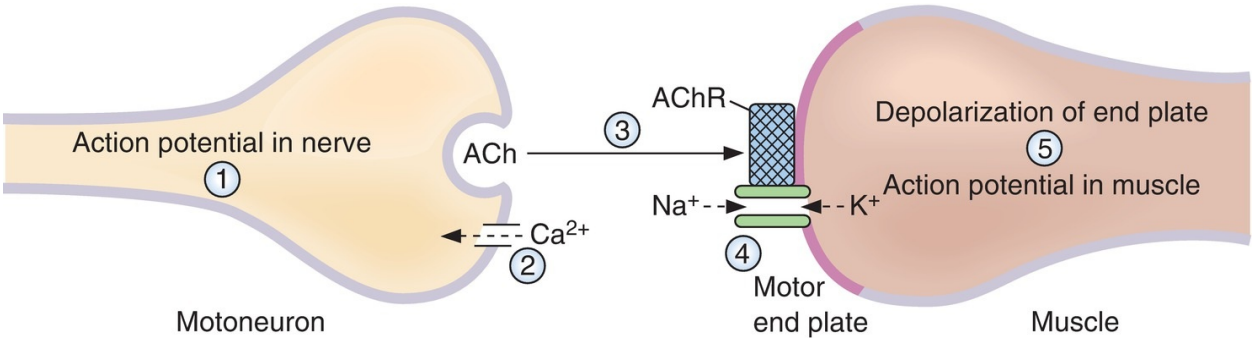

FIGURE 1.9 Neuromuscular junction. ACh = acetylcholine; AChR = acetylcholine receptor.

- is the synapse between axons of motoneurons and skeletal muscle.
- The neurotransmitter released from the presynaptic terminal is **ACh,** and the postsynaptic membrane contains a **nicotinic receptor.**

1. Synthesis and storage of ACh in the presynaptic terminal

- **Choline acetyltransferase** catalyzes the formation of ACh from acetyl coenzyme A (CoA) and choline in the presynaptic terminal.
- ACh is stored in **synaptic vesicles** with ATP and proteoglycan for later release.

2. Depolarization of the presynaptic terminal and Ca^{2+} uptake

- Action potentials are conducted down the motoneuron. Depolarization of the presynaptic terminal **opens Ca^{2+} channels.**
- When Ca^{2+} permeability increases, Ca^{2+} rushes into the presynaptic terminal down its electrochemical gradient.

3. Ca^{2+} uptake causes release of ACh into the synaptic cleft

- The synaptic vesicles fuse with the plasma membrane and empty their contents into the cleft by **exocytosis.**

4. Diffusion of ACh to the postsynaptic membrane (muscle end plate) and binding of ACh to nicotinic receptors

- The nicotinic ACh receptor is also a **Na^+ and K^+ ion channel.**
- Binding of ACh to α subunits of the receptor causes a conformational change that opens the central core of the channel and increases its conductance to Na^+ and K^+. These are examples of **ligand-gated channels.**

5. End plate potential (EPP) in the postsynaptic membrane

- Because the channels opened by ACh conduct both Na^+ and K^+ ions, the postsynaptic membrane potential is depolarized to a value halfway between the Na^+ and K^+ equilibrium potentials (approximately 0 mV).
- The contents of one synaptic vesicle (one quantum) produce a **miniature end plate potential** (MEPP), the smallest possible EPP.
- MEPPs summate to produce a full-fledged EPP. **The EPP is not an action potential,** but simply a depolarization of the specialized muscle end plate.

6. Depolarization of adjacent muscle membrane to threshold

- Once the end plate region is depolarized, local currents cause depolarization and action potentials in the adjacent muscle tissue. Action potentials in the muscle are followed by contraction.

7. Degradation of ACh

- The EPP is transient because ACh is degraded to acetyl CoA and choline by **acetylcholinesterase** (AChE) on the muscle end plate.
- One-half of the choline is taken back into the presynaptic ending by Na^+-choline cotransport and used to synthesize new ACh.
- **AChE inhibitors (neostigmine)** block the degradation of ACh, prolong its action at the muscle end plate, and increase the size of the EPP.
- **Hemicholinium** blocks choline reuptake and depletes the presynaptic endings of ACh stores.

8. Disease—myasthenia gravis

- is caused by the presence of antibodies to the ACh receptor.
- is characterized by skeletal muscle weakness and fatigability resulting from a **reduced number of ACh receptors** on the muscle end plate.
- The size of the EPP is reduced; therefore, it is more difficult to depolarize the muscle membrane to threshold and to produce action potentials.
- **Treatment with AChE inhibitors (e.g., neostigmine)** prevents the degradation of ACh and prolongs the action of ACh at the muscle end plate, partially compensating for the reduced number of receptors.

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table 1.2 Agents Affecting Neuromuscular Transmission

Example	Action	Effect on Neuromuscular Transmission
Botulinum toxin	Blocks release of ACh from presynaptic terminals	Total blockade
Curare	Competes with ACh for receptors on motor end plate	Decreases size of EPP; maximal doses produce paralysis of respiratory muscles and death
Neostigmine	Inhibits acetylcholinesterase	Prolongs and enhances action of ACh at muscle end plate
Hemicholinium	Blocks reuptake of choline into presynaptic terminal	Depletes ACh stores from presynaptic terminal

ACh = acetylcholine; EPP = end plate potential.