Lippincott's Illustrated Reviews:

Pharmacology

You will have learned within, those are

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Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 1

Pharmacokinetics

I. Overview

The goal of drug therapy is to prevent, cure, or control various disease states. To achieve this goal, adequate drug doses must be delivered to the target tissues so that therapeutic yet nontoxic levels are obtained. Pharmacokinetics examines the movement of a drug over time through the body. Pharmacological as well as toxicological actions of drugs are primarily related to the plasma concentrations of drugs. Thus, the clinician must recognize that the speed of onset of drug action, the intensity of the drug's effect, and the duration of drug action are controlled by four fundamental pathways of drug movement and modification in the body (Figure 1.1). First, drug absorption from the site of administration (Absorption) permits entry of the therapeutic agent (either directly or indirectly) into plasma. Second, the drug may then reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids (Distribution). Third, the drug may be metabolized by the liver, kidney, or other tissues (Metabolism). Finally, the drug and its metabolites are removed from the body in urine, bile, or feces (Elimination). This chapter describes how knowledge of these four processes (Absorption, Distribution, Metabolism, and Elimination) influences the clinician's decision of the route of administration for a specific drug, the amount and frequency of each dose, and the dosing intervals.

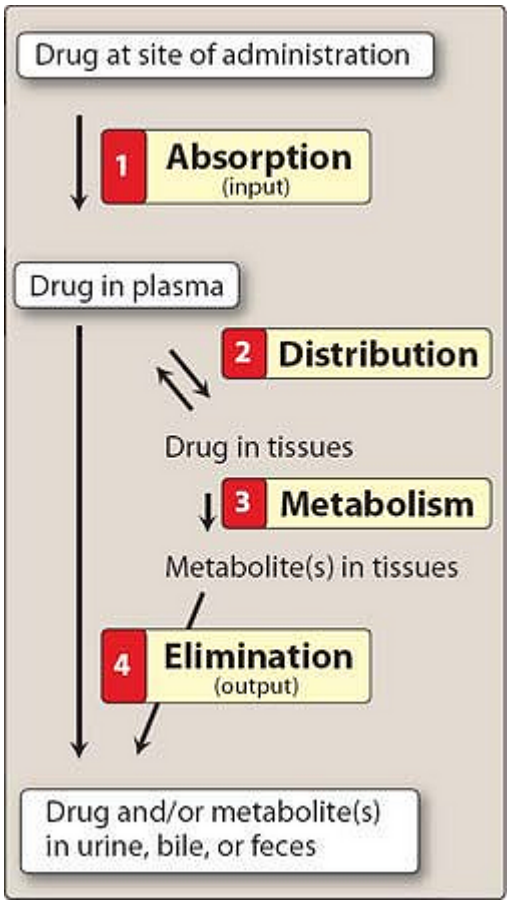


Figure 1.1 Schematic representation of drug absorption, distribution, metabolism, and elimination.

II. Routes of Drug Administration

The route of administration is determined primarily by the properties of the drug (for example, water or lipid solubility, ionization, etc.) and by the therapeutic objectives (for example, the desirability of a rapid onset of action or the need for long-term administration or restriction to a local site). There are two major routes of drug administration, enteral and parenteral. (Figure 1.2 illustrates the subcategories of these routes as well as other methods of drug administration.)

A. Enteral

Enteral administration, or administering a drug by mouth, is the simplest and most common means of administering drugs. When the drug is given in the mouth, it may be swallowed, allowing oral delivery, or it may be placed under the tongue, facilitating direct absorption into the bloodstream.

1. **Oral:** Giving a drug by mouth provides many advantages to the patient; oral drugs are easily self-administered and limit the number of systemic infections that could complicate treatment. Moreover, toxicities or overdose by the oral route may be overcome with antidotes such as activated charcoal. On the other hand, the pathways involved in drug absorption are the most complicated, and the drug is exposed to harsh gastrointestinal (GI) environments that may limit its absorption. Some drugs are absorbed from the stomach; however, the duodenum is a major site of entry to the systemic circulation because of its larger absorptive surface. Most drugs absorbed

from the GI tract enter the portal circulation and encounter the liver before they are distributed into the general circulation. These drugs undergo first-pass metabolism in the liver, where they may be extensively metabolized before entering the systemic circulation (Figure 1.3). [Note: First-pass metabolism by the intestine or liver limits the efficacy of many drugs when taken orally. For example, more than ninety percent of *nitroglycerin* is cleared during a single passage through the liver, which is the primary reason why this agent is not administered orally.] Drugs that exhibit high first-pass metabolism should be given in sufficient quantities to ensure that enough of the active drug reaches the target organ. Ingestion of drugs with food, or in combination with other drugs, can influence absorption. The presence of food in the stomach delays gastric emptying, so drugs that are destroyed by acid (for example, *penicillin*) become unavailable for absorption (see p. 364). [Note: Enteric coating of a drug protects it from the acidic environment; the coating may prevent gastric irritation, and depending on the formulation, the release of the drug may be prolonged, producing a sustained-release effect.]

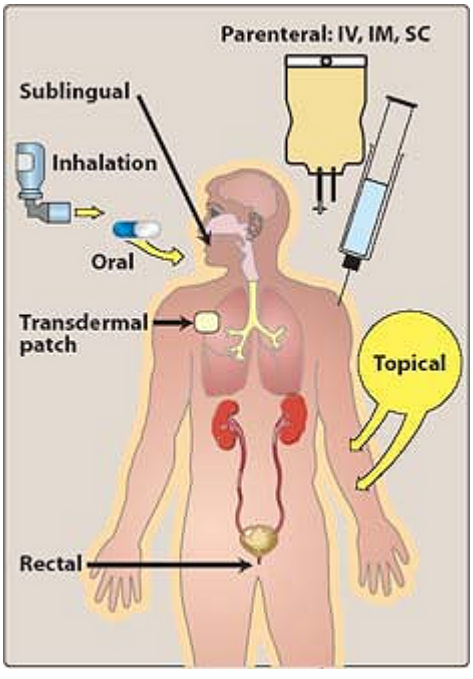


Figure 1.2 Commonly used routes of drug administration. IV = intravenous; IM = intramuscular; SC = subcutaneous.

2. **Sublingual:** Placement under the tongue allows a drug to diffuse into the capillary network and, therefore, to enter the systemic circulation directly. Administration of an agent, sublingually, has several advantages including rapid absorption, convenience of administration, low incidence of infection, avoidance of the harsh GI environment, and avoidance of first-pass metabolism.

B. Parenteral

The parenteral route introduces drugs directly across the body's barrier defenses into the systemic circulation or other vascular tissue. Parenteral administration is used for drugs that are poorly absorbed from the GI tract (for example *heparin*) and for agents that are unstable in the GI tract (for example, *insulin*). Parenteral administration is also used for treatment of unconscious patients and under circumstances that require a rapid onset of action. In addition, these routes have the highest bioavailability and are not subject to first-pass metabolism or harsh GI environments. Parenteral administration provides the most control over the actual dose of drug delivered to the

body. However, these routes are irreversible and may cause pain, fear, and infections. The three major parenteral routes are intravascular (intravenous or intra-arterial), intramuscular, and subcutaneous (see Figure 1.2). Each route has advantages and drawbacks.

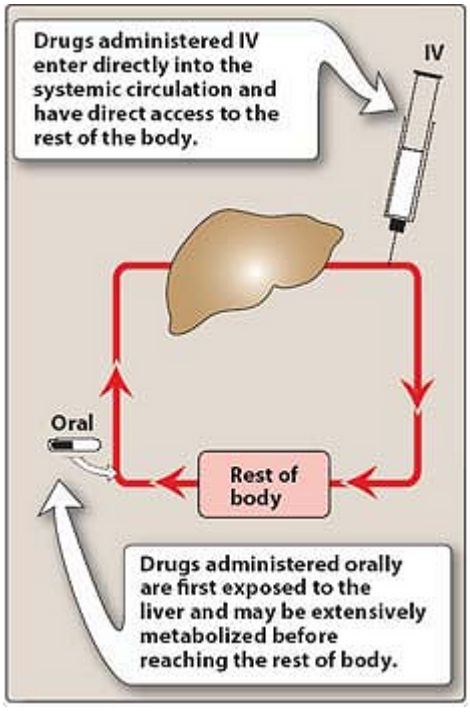


Figure 1.3 First-pass metabolism can occur with orally administered drugs. IV = intravenous.

1. **Intravenous (IV):** Injection is the most common parenteral route. For drugs that are not absorbed orally, such as the neuromuscular blocker *atracurium*, there is often no other choice. With IV administration,

the drug avoids the GI tract and therefore, first-pass metabolism by the liver. Intravenous delivery permits a rapid effect and a maximal degree of control over the circulating levels of the drug. However, unlike drugs in the GI tract, those that are injected cannot be recalled by strategies such as emesis or by binding to activated charcoal. Intravenous injection may inadvertently introduce bacteria through contamination at the site of injection. IV injection may also induce hemolysis or cause other adverse reactions by the too-rapid delivery of high concentrations of drug to the plasma and tissues. Therefore, the rate of infusion must be carefully controlled. Similar concerns apply to intra-arterially injected drugs.

2. **Intramuscular (IM):** Drugs administered IM can be aqueous solutions or specialized depot preparationsâ€"often a suspension of drug in a nonaqueous vehicle such as polyethylene glycol. Absorption of drugs in an aqueous solution is fast, whereas that from depot preparations is slow. As the vehicle diffuses out of the muscle, the drug precipitates at the site of injection. The drug then dissolves slowly, providing a sustained dose over an extended period of time. An example is sustained-release *haloperidol decanoate* (see p. 155), which slowly diffuses from the muscle and produces an extended neuroleptic effect.

3. **Subcutaneous (SC):** This route of administration, like that of IM injection, requires absorption and is somewhat slower than the IV route. Subcutaneous injection minimizes the risks associated with intravascular injection. [Note: Minute amounts of *epinephrine* are sometimes combined with a drug to restrict its area of action. *Epinephrine* acts as a local vasoconstrictor and decreases removal of a drug, such as *lidocaine*, from the site of administration.] Other examples of drugs utilizing SC administration include solids, such as a single rod

containing the contraceptive *etonogestrel* that is implanted for long-term activity (see p. 306), and also programmable mechanical pumps that can be implanted to deliver *insulin* in diabetic patients.

C. Other

1. **Inhalation:** Inhalation provides the rapid delivery of a drug across the large surface area of the mucous membranes of the respiratory tract and pulmonary epithelium, producing an effect almost as rapidly as with IV injection. This route of administration is used for drugs that are gases (for example, some anesthetics) or those that can be dispersed in an aerosol. This route is particularly effective and convenient for patients with respiratory complaints (such as asthma, or chronic obstructive pulmonary disease) because the drug is delivered directly to the site of action and systemic side effects are minimized. Examples of drugs administered via this route include *albuterol*, and corticosteroids, such as *fluticasone*.

2. **Intranasal:** This route involves administration of drugs directly into the nose. Agents include nasal decongestants such as the anti-inflammatory corticosteroid *mometasone furoate*. *Desmopressin* is administered intranasally in the treatment of diabetes insipidus; salmon *calcitonin*, a peptide hormone used in the treatment of osteoporosis, is also available as a nasal spray. The abused drug, *cocaine*, is generally taken by intranasal sniffing.

3. **Intrathecal/intraventricular:** It is sometimes necessary to introduce drugs directly into the cerebrospinal fluid. For example, *amphotericin B* is used in treating cryptococcal meningitis (see p. 408).

4. **Topical:** Topical application is used when a local effect of the drug is desired. For example, *clotrimazole* is applied as a cream directly to the skin in the treatment of dermatophytosis, and *tropicamide* or *cyclopentolate* are instilled (administered drop by drop) directly into the eye to dilate the pupil and permit measurement of refractive errors.

5. **Transdermal:** This route of administration achieves systemic effects by application of drugs to the skin, usually via a transdermal patch. The rate of absorption can vary markedly, depending on the physical characteristics of the skin at the site of application. This route is most often used for the sustained delivery of drugs, such as the antianginal drug *nitroglycerin*, the antiemetic *scopolamine*, and the once-a-week contraceptive patch (Ortho Evra) that has an efficacy similar to oral birth control pills.

6. **Rectal:** Fifty percent of the drainage of the rectal region bypasses the portal circulation; thus, the biotransformation of drugs by the liver is minimized. Like the sublingual route of administration, the rectal route of administration has the additional advantage of preventing the destruction of the drug by intestinal enzymes or by low pH in the stomach. The rectal route is also useful if the drug induces vomiting when given orally, if the patient is already vomiting, or if the patient is unconscious. [Note: The rectal route is commonly used to administer antiemetic agents.] On the other hand, rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa.

III. Absorption of Drugs

Absorption is the transfer of a drug from its site of administration to the bloodstream. The rate and efficiency of absorption depend on the route of administration. For IV delivery, absorption is complete; that is, the total dose of drug reaches the systemic circulation. Drug delivery by other routes may result in only partial absorption and, thus, lower bioavailability. For example, the oral route requires that a drug dissolve in the GI fluid and then penetrate the epithelial cells of the intestinal mucosa, yet disease states or the presence of food may affect this process.

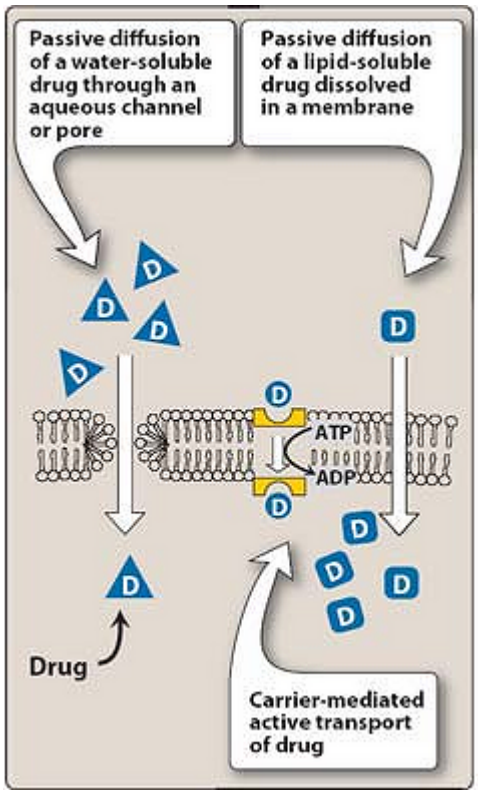


Figure 1.4 Schematic representation of drugs crossing a cell membrane of an epithelial cell of the gastrointestinal tract. ATP = adenosine triphosphate; ADP = adenosine diphosphate.

A. Transport of a drug from the GI tract

Depending on their chemical properties, drugs may be absorbed from the GI tract by either passive diffusion or active transport.

1. **Passive diffusion:** The driving force for passive absorption of a drug is the concentration gradient across a membrane separating two body compartments; that is, the drug moves from a region of high concentration to one of lower concentration. Passive diffusion does not involve a carrier, is not saturable, and shows a low structural specificity. The vast majority of drugs gain access to the body by this mechanism. Lipid-soluble drugs readily move across most biologic membranes due to their solubility in the membrane bilayers. Water-soluble drugs penetrate the cell membrane through aqueous

channels or pores (Figure 1.4). Other agents can enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules. These carrier proteins undergo conformational changes allowing the passage of drugs or endogenous molecules into the interior of cells, moving them from an area of high concentration to an area of low concentration. This process is known as facilitated diffusion. This type of diffusion does not require energy, can be saturated, and may be inhibited.

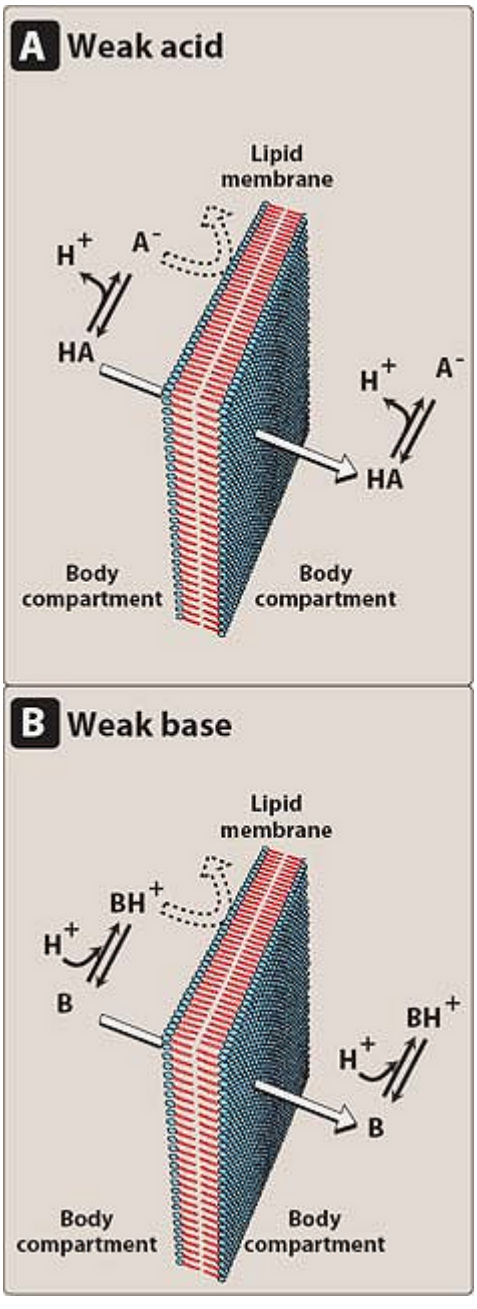


Figure 1.5 A. Diffusion of the non-ionized form of a weak acid through a lipid membrane. B. Diffusion of the nonionized form of a weak base through a lipid membrane.

2. **Active transport:** This mode of drug entry also involves specific carrier proteins that span the membrane. A few drugs that closely resemble the structure of naturally occurring metabolites are actively transported across cell membranes using these specific carrier proteins. Active transport is energy-dependent and is driven by the hydrolysis of adenosine triphosphate (see Figure 1.4). It is capable of moving drugs against a concentration gradientâ€"that is, from a region of low drug concentration to one of higher drug concentration. The process shows saturation kinetics for the carrier, much in the same way that an enzyme-catalyzed reaction shows a maximal velocity at high substrate levels where all the active sites are filled with substrate.[1]
3. **Endocytosis and exocytosis:** This type of drug delivery transports drugs of exceptionally large size across the

cell membrane. Endocytosis involves engulfment of a drug molecule by the cell membrane and transport into the cell by pinching off the drug-filled vesicle. Exocytosis is the reverse of endocytosis and is used by cells to secrete many substances by a similar vesicle formation process. For example, vitamin B_{12} is transported across the gut wall by endocytosis. Certain neurotransmitters (for example, norepinephrine) are stored in membrane-bound vesicles in the nerve terminal and are released by exocytosis.

B. Effect of pH on drug absorption

Most drugs are either weak acids or weak bases. Acidic drugs (HA) release an H^+ causing a charged anion (A^-) to form:[2]

$$HA \rightleftarrows H^+ + A^-$$

Weak bases (BH^+) can also release an H^+. However, the protonated form of basic drugs is usually charged, and loss of a proton produces the uncharged base (B):

$$BH^+ \rightleftarrows B + H^+$$

1. **Passage of an uncharged drug through a membrane:** A drug passes through membranes more readily if it is uncharged (Figure 1.5). Thus, for a weak acid, the uncharged HA can permeate through membranes, and A^- cannot. For a weak base, the uncharged form, B, penetrates through the cell membrane, but BH^+ does not. Therefore, the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms. The ratio between the two forms is, in turn, determined by the pH at the site of absorption and by the

strength of the weak acid or base, which is represented by the pK_a (Figure 1.6). [Note: The pK_a is a measure of the strength of the interaction of a compound with a proton. The lower the pK_a of a drug, the more acidic it is. Conversely, the higher the pK_a, the more basic is the drug.] Distribution equilibrium is achieved when the permeable form of a drug achieves an equal concentration in all body water spaces. [Note: Highly lipid-soluble drugs rapidly cross membranes and often enter tissues at a rate determined by blood flow.]

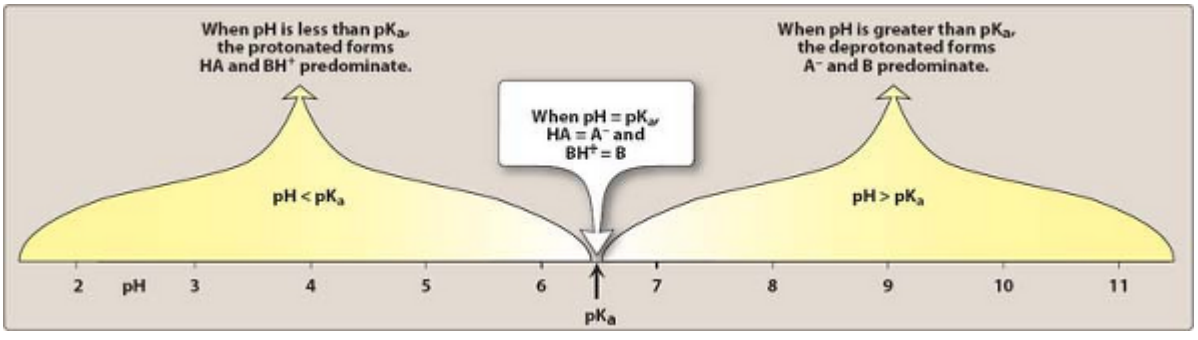


Figure 1.6 The distribution of a drug between its ionized and non-ionized forms depends on the ambient pH and pK_a of the drug. For illustrative purposes, the drug has been assigned a pK_a of 6.5.

2. **Determination of how much drug will be found on either side of a membrane:** The relationship of pK_a and the ratio of acid-base concentrations to pH is expressed by the Henderson-Hasselbalch equation:[3]

$$pH = pK_a + \log \frac{[\text{nonprotonated species}]}{[\text{protonated species}]}$$

For acids: $pH = pK_a + \log \frac{[A^-]}{[HA]}$

For bases: $pH = pK_a + \log \frac{[B]}{[BH^+]}$

This equation is useful in determining how much drug will be found on either side of a membrane that separates two compartments that differ in pHâ€"for example, stomach (pH 1.0â€“1.5) and blood plasma (pH 7.4). [Note: The lipid solubility of the non-ionized drug directly determines its rate of equilibration.]

C. Physical factors influencing absorption

1. **Blood flow to the absorption site:** Blood flow to the intestine is much greater than the flow to the stomach; thus, absorption from the intestine is favored over that from the stomach. [Note: Shock severely reduces blood flow to cutaneous tissues, thus minimizing the absorption from SC administration.]

2. **Total surface area available for absorption:** Because the intestine has a surface rich in microvilli, it has a surface area about 1000-fold that of the stomach; thus, absorption of the drug across the intestine is more efficient.

3. **Contact time at the absorption surface:** If a drug moves through the GI tract very quickly, as in severe diarrhea, it is not well absorbed. Conversely, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug. [Note: Parasympathetic input increases the rate of gastric emptying, whereas sympathetic input (prompted, for example, by exercise or stressful emotions), as well as anticholinergics (for example, *dicyclomine*), prolongs gastric emptying. Also, the presence of food in the stomach both dilutes the drug and slows gastric emptying. Therefore, a drug taken with a meal is generally absorbed more slowly.]

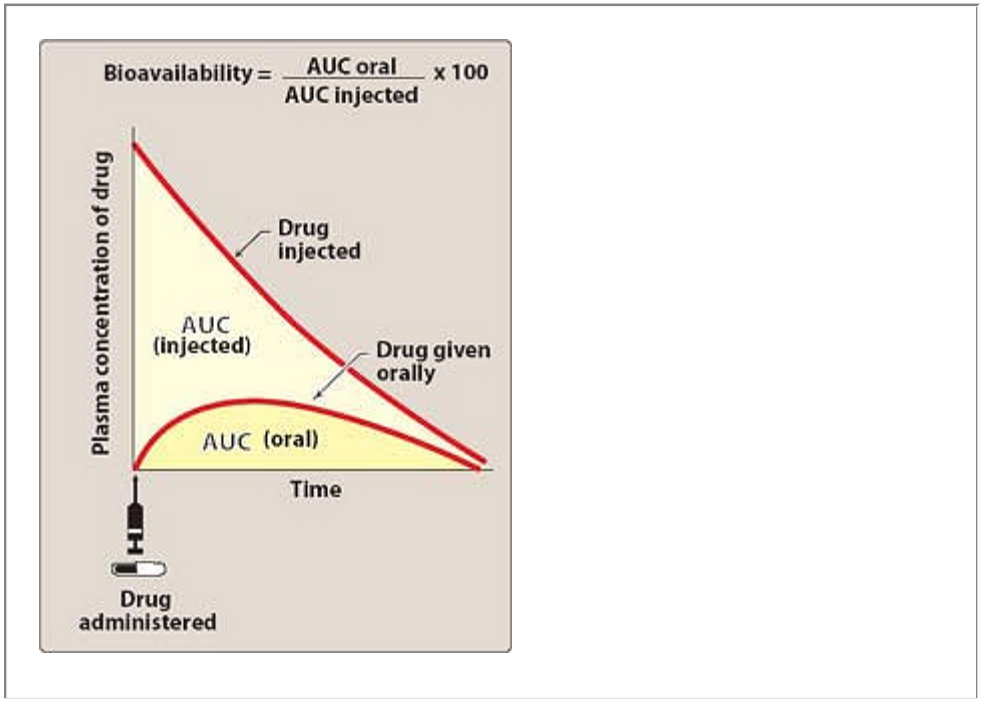


Figure 1.7 Determination of the bioavailability of a drug. (AUC = area under curve.)

IV. Bioavailability

Bioavailability is the fraction of administered drug that reaches the systemic circulation. Bioavailability is expressed as the fraction of administered drug that gains access to the systemic circulation in a chemically unchanged form. For example, if 100 mg of a drug are administered orally and 70 mg of this drug are absorbed unchanged, the bioavailability is 0.7 or seventy percent.

A. Determination of bioavailability

Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with plasma drug levels achieved by IV injectionâ€"in which all of the agent rapidly enters the circulation. When the drug is given orally, only part of the administered dose appears in the plasma. By plotting plasma concentrations of the drug versus time, one can measure the area under the curve (AUC). This curve reflects the extent of absorption of the drug. [Note: By definition, this is 100 percent for drugs delivered IV.] Bioavailability of a drug administered orally is the ratio of the area calculated for oral administration compared with the area calculated for IV injection (Figure 1.7).

B. Factors that influence bioavailability

1. **First-pass hepatic metabolism:** When a drug is absorbed across the GI tract, it enters the portal circulation before entering the systemic circulation (see Figure 1.3). If the drug is rapidly metabolized by the liver, the amount of unchanged drug that gains access to the systemic circulation is decreased. Many drugs, such as *propranolol* or *lidocaine*, undergo significant biotransformation during a single passage through the liver.
2. **Solubility of the drug:** Very hydrophilic drugs are poorly absorbed because of their inability to cross the lipid-rich cell membranes. Paradoxically, drugs that are extremely hydrophobic are also poorly absorbed, because they are totally insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells. For a drug to be readily absorbed, it must be largely hydrophobic, yet have some solubility in aqueous solutions. This is one reason why many drugs are weak acids or weak bases. There are some drugs that are highly lipid-soluble, and they are transported in the aqueous solutions of the body on carrier proteins such as albumin.

3. **Chemical instability:** Some drugs, such as *penicillin G*, are unstable in the pH of the gastric contents. Others, such as *insulin*, are destroyed in the GI tract by degradative enzymes.
4. **Nature of the drug formulation:** Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings and the presence of excipients (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

C. Bioequivalence

Two related drugs are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations. Two related drugs with a significant difference in bioavailability are said to be bioinequivalent.

D. Therapeutic equivalence

Two similar drugs are therapeutically equivalent if they have comparable efficacy and safety. [Note: Clinical effectiveness often depends on both the maximum serum drug concentrations and on the time required (after administration) to reach peak concentration. Therefore, two drugs that are bioequivalent may not be

therapeutically equivalent.]

V. Drug Distribution

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and/or the cells of the tissues. The delivery of a drug from the plasma to the interstitium primarily depends on blood flow, capillary permeability, the degree of binding of the drug to plasma and tissue proteins, and the relative hydrophobicity of the drug.

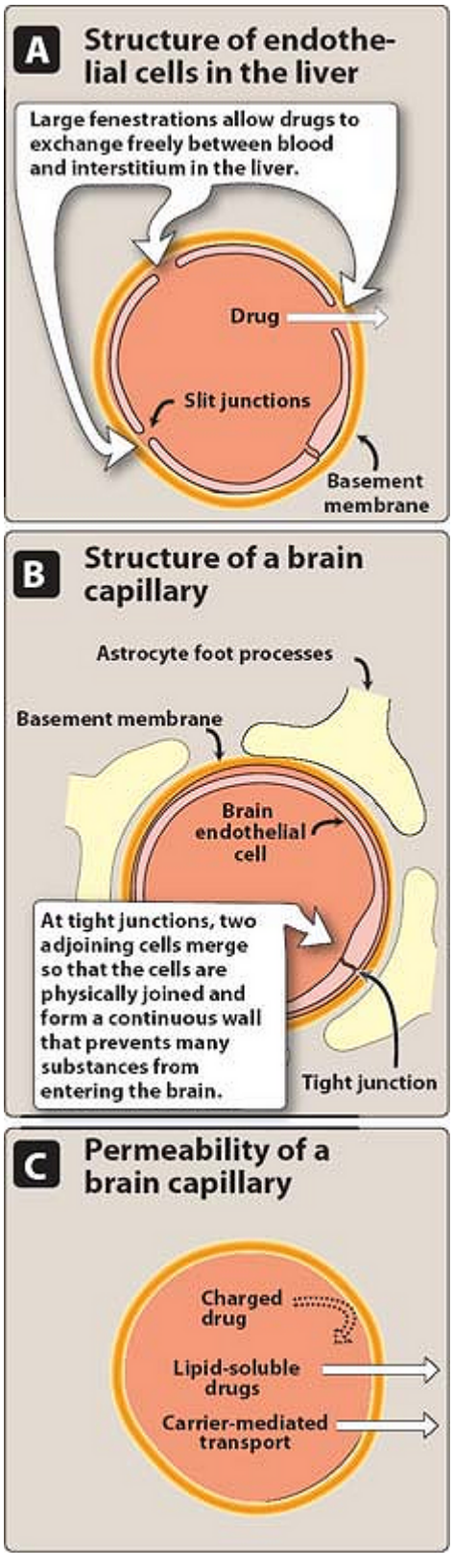


Figure 1.8 Cross-section of liver and brain capillaries.

A. Blood flow

The rate of blood flow to the tissue capillaries varies widely as a result of the unequal distribution of cardiac output to the various organs. Blood flow to the brain, liver, and kidney is greater than that to the skeletal muscles; adipose tissue has a still lower rate of blood flow. This differential blood flow partly explains the short duration of hypnosis produced by a bolus IV injection of *thiopental* (see p. 135). The high blood flow, together with the superior lipid solubility of *thiopental,* permit it to rapidly move into the central nervous system (CNS) and produce anesthesia. Slower distribution to skeletal muscle and adipose tissue lowers the plasma concentration sufficiently so that the higher concentrations within the CNS decrease, and consciousness is regained. Although this phenomenon occurs with all drugs to some extent, redistribution accounts for the extremely short duration of action of *thiopental* and compounds of similar chemical and pharmacologic properties.

B. Capillary permeability

Capillary permeability is determined by capillary structure and by the chemical nature of the drug.

1. **Capillary structure:** Capillary structure varies widely in terms of the fraction of the basement membrane that is exposed by slit junctions between endothelial cells. In the brain, the capillary structure is continuous, and there are no slit junctions (Figure 1.8). This contrasts

   with the liver and spleen, where a large part of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass.

   a. **Blood-brain barrier:** To enter the brain, drugs must pass through the endothelial cells of the capillaries of the CNS or be actively transported. For example, a specific transporter for the large neutral amino acid transporter carries *levodopa* into the brain. By contrast, lipid-soluble drugs readily penetrate into the CNS because they can dissolve in the membrane of the endothelial cells. Ionized or polar drugs generally fail to enter the CNS because they are unable to pass through the endothelial cells of the CNS, which have no slit junctions. These tightly juxtaposed cells form tight junctions that constitute the so-called blood-brain barrier.

2. **Drug structure:** The chemical nature of a drug strongly influences its ability to cross cell membranes. Hydrophobic drugs, which have a uniform distribution of electrons and no net charge, readily move across most biologic membranes. These drugs can dissolve in the lipid membranes and, therefore, permeate the entire cell's surface. The major factor influencing the hydrophobic drug's distribution is the blood flow to the area. By contrast, hydrophilic drugs, which have either a nonuniform distribution of electrons or a positive or negative charge, do not readily penetrate cell membranes, and therefore, must go through the slit junctions.

C. Binding of drugs to plasma proteins

Reversible binding to plasma proteins sequesters drugs in a nondiffusible form and slows their transfer out of the vascular compartment. Binding is relatively nonselective as to chemical structure and takes place at sites on the protein to which endogenous compounds, such as bilirubin, normally attach. Plasma albumin is the major drug-binding protein and may act as a drug reservoir; that is, as the concentration of the free drug decreases due to elimination by metabolism or excretion, the bound drug dissociates from the protein. This maintains the free-drug concentration as a constant fraction of the total drug in the plasma.

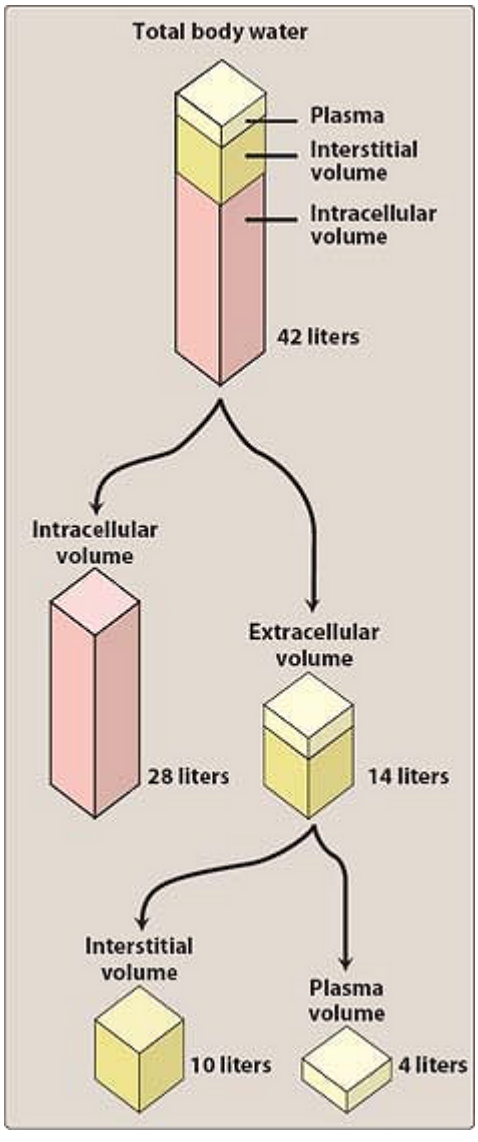


Figure 1.9 Relative size of various distribution volumes within a 70-kg individual.

VI. Volume of Distribution

The volume of distribution is a hypothetical volume of fluid into which a drug is dispersed. Although the volume of distribution has no physiologic or physical basis, it is sometimes useful to compare the distribution of a drug with the volumes of the water compartments in the body (Figure 1.9).

A. Water compartments in the body

Once a drug enters the body, from whatever route of administration, it has the potential to distribute into any one of three functionally distinct compartments of body water or to become sequestered in a cellular site.

1. **Plasma compartment:** If a drug has a very large molecular weight or binds extensively to plasma proteins, it is too large to move out through the endothelial slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment. As a consequence, the drug distributes in a volume (the plasma) that

is about six percent of the body weight or, in a 70-kg individual, about 4 L of body fluid. *Heparin* (see p. 236) shows this type of distribution.

2. **Extracellular fluid:** If a drug has a low molecular weight but is hydrophilic, it can move through the endothelial slit junctions of the capillaries into the interstitial fluid. However, hydrophilic drugs cannot move across the lipid membranes of cells to enter the water phase inside the cell. Therefore, these drugs distribute into a volume that is the sum of the plasma water and the interstitial fluid, which together constitute the extracellular fluid. This is about twenty percent of the body weight, or about 14 L in a 70-kg individual. Aminoglycoside antibiotics (see p. 377) show this type of distribution.
3. **Total body water:** If a drug has a low molecular weight and is hydrophobic, not only can it move into the interstitium through the slit junctions, but it can also move through the cell membranes into the intracellular fluid. The drug, therefore, distributes into a volume of about sixty percent of body weight, or about 42 L in a 70-kg individual. *Ethanol* exhibits this apparent volume of distribution (see below).
4. **Other sites:** In pregnancy, the fetus may take up drugs and thus increase the volume of distribution. Drugs that are extremely lipid-soluble, such as *thiopental* (see p. 135), may also have unusually high volumes of distribution.

B. Apparent volume of distribution

A drug rarely associates exclusively with only one of the water compartments of the body. Instead, the vast majority of drugs distribute into several compartments, often avidly binding cellular componentsâ€”for example, lipids (abundant in adipocytes and cell membranes), proteins (abundant in plasma and within cells), or nucleic acids (abundant in the nuclei of cells). Therefore, the volume into which drugs distribute is called the apparent volume of distribution, or V_d. Another useful way to think of this constant is as the partition coefficient of a drug between the plasma and the rest of the body.

1. **Determination of Vd**

   a. **Distribution of drug in the absence of elimination:** The apparent volume into which a drug distributes, V_d, is determined by injection of a standard dose of drug, which is initially contained entirely in the vascular system. The agent may then move from the plasma into the interstitium and into cells, causing the plasma concentration to decrease with time. Assume for simplicity that the drug is not eliminated from the body; the drug then achieves a uniform concentration that is sustained with time (Figure 1.10). The concentration within the vascular compartment is the total amount of drug administered, divided by the volume into which it distributes, V_d:

   $$C = D/V_d \text{ or } V_d = D/C$$

   where C = the plasma concentration of the drug and D = the total amount of drug in the body. For example, if 25 mg of a drug (D = 25 mg) are administered and the plasma concentration is 1 mg/L, then V_d = 25 mg/1 mg/L = 25 L.

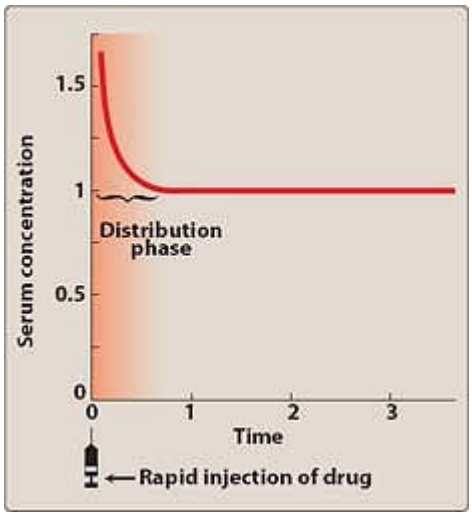


Figure 1.10 Drug concentrations in serum after a single injection of drug at time = 0. Assume that the drug distributes but is not eliminated.

b. **Distribution of drug when elimination is present:** In reality, drugs are eliminated from the body, and a plot of plasma

concentration versus time shows two phases. The initial decrease in plasma concentration is due to a rapid distribution phase in which the drug is transferred from the plasma into the interstitium and the intracellular water. This is followed by a slower elimination phase during which the drug leaves the plasma compartment and is lost from the bodyâ€"for example, by renal or biliary excretion or by hepatic biotransformation (Figure 1.11). The rate at which the drug is eliminated is usually proportional to the concentration of drug, C; that is, the rate for most drugs is first-order and shows a linear relationship with timeâ€"if lnC (where lnC is the natural log of C, rather than C) is plotted versus time (Figure 1.12). This is because the elimination processes are not saturated.

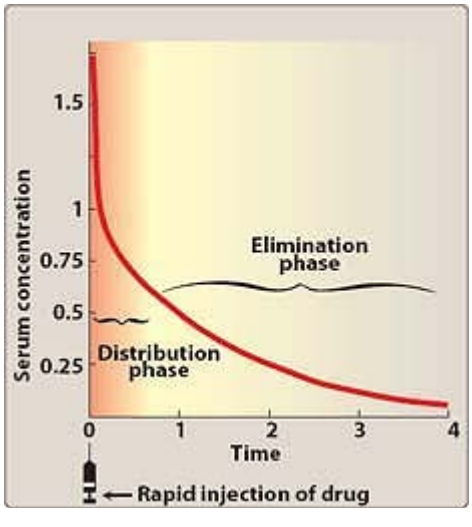


Figure 1.11 Drug concentrations in serum after a single injection of drug at time = 0. Assume that the drug distributes and is subsequently eliminated.

c. **Calculation of drug concentration if distribution is instantaneous:** Assume that the elimination process began at the time of injection and continued throughout the distribution phase. Then, the concentration of drug in the plasma, C, can be extrapolated back to time zero (the time of injection) to determine C_0, which is the concentration of drug that would have been achieved if the distribution phase had occurred instantly. For example, if 10 mg of drug are injected into a patient and the plasma concentration is extrapolated to time zero, the concentration is C_0 = 1 mg/L (from the graph shown in Figure 1.12), and then V_d = 10 mg/1 mg/L = 10 L.

d. **Uneven drug distribution between compartments:** The apparent volume of distribution assumes that the drug distributes uniformly, in a single compartment. However, most drugs distribute unevenly, in several compartments, and the volume of distribution does not describe a real, physical volume, but rather, reflects the ratio of drug in the extraplasmic spaces relative to the plasma space. Nonetheless, V_d is useful because it can be used to calculate the amount of drug needed to achieve a desired plasma concentration. For example, assume the arrhythmia of a cardiac patient is not well controlled due to inadequate plasma levels of *digitalis*. Suppose the concentration of the drug in the plasma is C_1 and the desired level of *digitalis* (known from clinical studies) is a higher concentration, C_2. The clinician needs to know how much additional drug should be administered to bring the circulating level of the drug from C_1 to C_2:

$(V_d)(C_1)$ = amount of drug initially in the body

$(V_d)(C_2)$ = amount of drug in the body needed to achieve the desired plasma concentration

The difference between the two values is the additional dosage needed, which equals $V_d(C_2$ â€“ $C_1)$.

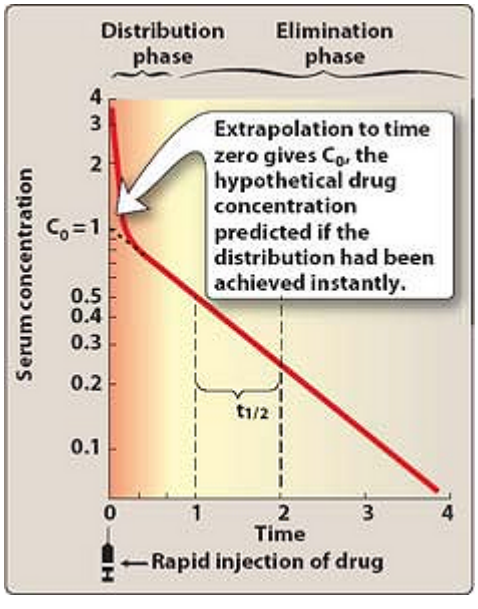


Figure 1.12 Drug concentrations in serum after a single injection of drug at time = 0. Data are plotted on a log scale.

2. **Effect of a large Vd on the half-life of a drug**

A large V_d has an important influence on the half-life of a drug, because drug elimination depends on the amount of drug delivered to the liver or kidney (or other organs where metabolism occurs) per unit of time. Delivery of drug to the organs of elimination depends not only on blood flow, but also on the fraction of the drug in the plasma. If the V_d for a drug is large, most of the drug is in the extraplasmic space and is unavailable to the excretory organs. Therefore,

any factor that increases the volume of distribution can lead to an increase in the half-life and extend the duration of action of the drug. [Note: An exceptionally large V_d indicates considerable sequestration of the drug in some organ or compartment.]

VII. Binding of Drugs to Plasma Proteins

Drug molecules may bind to plasma proteins (usually albumin). Bound drugs are pharmacologically inactive; only the free, unbound drug can act on target sites in the tissues, elicit a biologic response, and be available to the processes of elimination. [Note: Hypoalbuminemia may alter the level of free drug.]

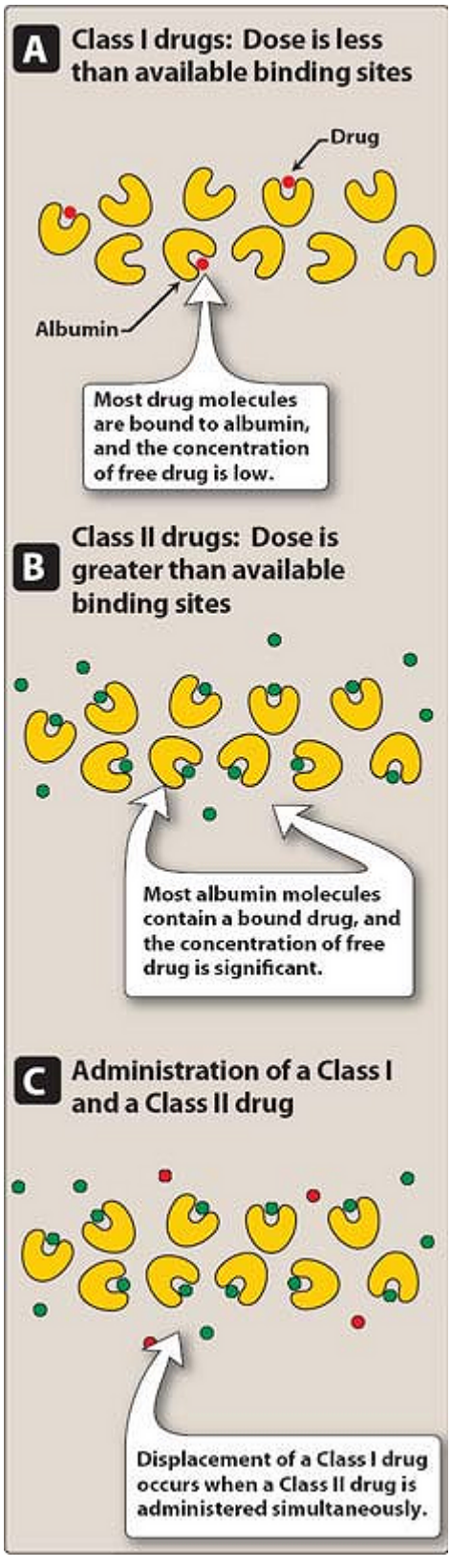


Figure 1.13 Binding of Class I and Class II drugs to albumin when drugs are administered alone (A and B) or together (C).

A. Binding capacity of albumin

The binding of drugs to albumin is reversible and may show low capacity (one drug molecule per albumin molecule) or high capacity (a number of drug molecules binding to a single albumin molecule). Drugs can also bind with varying affinities. Albumin has the strongest affinities for anionic drugs (weak acids) and hydrophobic drugs. Most hydrophilic drugs and neutral drugs do not bind to albumin. [Note: Many drugs are hydrophobic by design, because this property permits absorption after oral administration.]

B. Competition for binding between drugs

When two drugs are given, each with high affinity for albumin, they compete for the available binding sites. The drugs with high affinity for albumin can be divided into two classes, depending on whether the dose of drug (the amount of drug found in the body under conditions used clinically) is greater than, or less than, the binding capacity of albumin (quantified as the number of millimoles of albumin multiplied by the number of binding sites; Figure 1.13).

1. **Class I drugs:** If the dose of drug is less than the binding capacity of albumin, then the dose/capacity ratio is low. The binding sites are in excess of the available drug, and the bound-drug fraction is high. This is the case for Class I drugs, which include the majority of clinically useful agents.
2. **Class II drugs:** These drugs are given in doses that greatly exceed the number of albumin binding sites. The dose/capacity ratio is high, and a relatively high proportion of the drug exists in the free state, not bound to albumin.
3. **Clinical importance of drug displacement:** This assignment of drug classification assumes importance when a patient taking a Class I drug, such as *warfarin*, is given a Class II drug, such as a *sulfonamide antibiotic*. *Warfarin* is highly bound to albumin, and only a small fraction is free. This means that most of the drug is sequestered on albumin and is inert in terms of exerting pharmacologic actions. If a *sulfonamide* is administered, it displaces *warfarin* from albumin, leading to a rapid increase in the concentration of free *warfarin* in plasma, because almost 100 percent is now free, compared with the initial small percentage. [Note: The increase in *warfarin* concentration may lead to increased therapeutic effects, as well as increased toxic effects, such as bleeding.]

C. Relationship of drug displacement to Vd

The impact of drug displacement from albumin depends on both the V_d and the therapeutic index (see p. 33) of the drug. If the V_d is large, the drug displaced from the albumin distributes to the periphery, and the change in free-drug concentration in the plasma is not significant. If the V_d is small, the newly displaced drug does not move into the tissues as much, and the increase in free drug in the plasma is more profound. If the therapeutic index of the drug is small, this increase in drug concentration may have significant clinical consequences. [Note: Clinically, drug displacement from albumin is one of the most significant sources of drug interactions.]

VIII. Drug Metabolism

Drugs are most often eliminated by biotransformation and/or excretion into the urine or bile. The process of metabolism transforms lipophilic drugs into more polar readily excretable products. The liver is the major site for drug metabolism, but specific drugs may undergo biotransformation in other tissues, such as the kidney and the intestines. [Note: Some agents are initially administered as inactive compounds (pro-drugs) and must be metabolized to their active forms.]

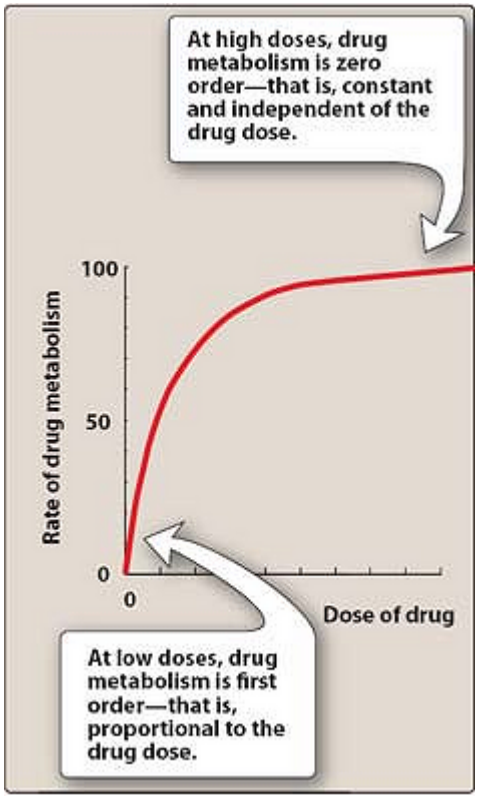


Figure 1.14 Effect of drug dose on the rate of metabolism.

A. Kinetics of metabolism

1. **First-order kinetics:** The metabolic transformation of drugs is catalyzed by enzymes, and most of the reactions obey Michaelis-Menten kinetics:[4]

$$v = \text{rate of drug metabolism} = \frac{V_{max}[C]}{K_m + [C]}$$

In most clinical situations, the concentration of the drug, [C], is much less than the Michaelis constant, K_m, and the Michaelis-Menten equation reduces to,

$$v = \text{rate of drug metabolism} = \frac{V_{max}[C]}{K_m}$$

That is, the rate of drug metabolism is directly proportional to the concentration of free drug, and first-order kinetics are observed (Figure 1.14). This means that a constant fraction of drug is metabolized per unit of time.

2. **Zero-order kinetics:** With a few drugs, such as *aspirin, ethanol,* and *phenytoin*, the doses are very large. Therefore [C] is much greater than K_m, and the velocity equation becomes

$$v = \text{rate of drug metabolism} = \frac{V_{max}[C]}{[C]} = V_{max}$$

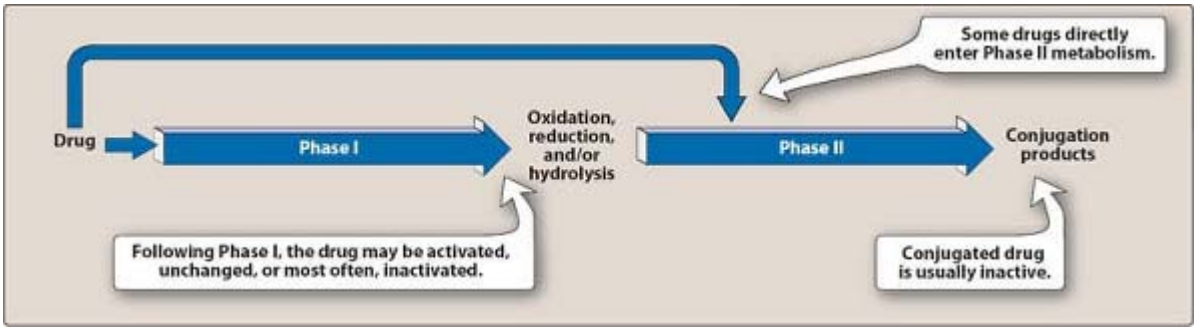


Figure 1.15 The biotransformation of drugs.

The enzyme is saturated by a high free-drug concentration, and the rate of metabolism remains constant over time. This is called zero-order kinetics (sometimes referred to clinically as nonlinear kinetics). A constant amount of drug is metabolized per unit of time.

B. Reactions of drug metabolism

The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal tubules. Therefore, lipid-soluble agents must first be metabolized in the liver using two general sets of reactions, called Phase I and Phase II (Figure 1.15).

1. **Phase I:** Phase I reactions function to convert lipophilic molecules into more polar molecules by introducing or unmasking a polar functional group, such as â€“OH or â€“NH_2. Phase I metabolism may increase, decrease, or leave unaltered the drug's pharmacologic activity.

   a. **Phase I reactions utilizing the P450 system:** The Phase I reactions most frequently involved in drug metabolism are catalyzed by the cytochrome P450 system (also called microsomal mixed function oxidase):

   $$\text{Drug} + O_2 + \text{NADPH} + H^+ \rightarrow \text{Drug}_{\text{modified}} + H_2O + \text{NADP}^+$$

   The oxidation proceeds by the drug binding to the oxidized form of cytochrome P450, and then oxygen is introduced through a reductive step, coupled to NADPH:cytochrome P450 oxidoreductase.

   b. **Summary of the P450 system:** The P450 system is important for the metabolism of many endogenous compounds (steroids, lipids, etc.) and for the biotransformation of exogenous substances (xenobiotics). Cytochrome P450, designated as CYP, is composed of many families of heme-containing isozymes that are located in most cells but are primarily found in the liver and GI tract. The family name is indicated by an arabic number followed by a capital letter for the subfamily (for example, CYP3A). Another number is added to indicate the specific isozyme (CYP3A4). There are many different genes, and many different enzymes; thus, the various P450s are known as isoforms. Six isozymes are responsible for the vast majority of P450-catalyzed reactions: CYP3A4, CYP2D6, CYP2C9/10, CYP2C19, CYP2E1, and CYP1A2. The percentages of currently available drugs that are substrates for these isozymes are

60, 25, 15, 15, 2, and 2 percent, respectively. [Note: An individual drug may be a substrate for more than one isozyme.] Considerable amounts of CYP3A4 are found in intestinal mucosa, accounting for first-pass metabolism of drugs such as *chlorpromazine* and *clonazepam.* As might be expected, these enzymes exhibit

considerable genetic variability, which has implications for individual dosing regimens, and even more importantly, as determinants of therapeutic responsiveness and the risk of adverse events. CYP2D6, in particular, has been shown to exhibit genetic polymorphism.[5] Mutations result in very low capacities to metabolize substrates. Some individuals, for example, obtain no benefit from the opioid analgesic *codeine* because they lack the enzyme that O-demethylates and activates the drug. This reaction is CYP2D6-dependent. The frequency of this polymorphism is in part racially determined, with a prevalence of five to ten percent in European Caucasians as compared to less than two percent of Southeast Asians. Similar polymorphisms have been characterized for the CYP2C subfamily of isozymes. Although CYP3A4 exhibits a greater than ten-fold interindividual variability, no polymorphisms have been identified for this P450 isozyme.

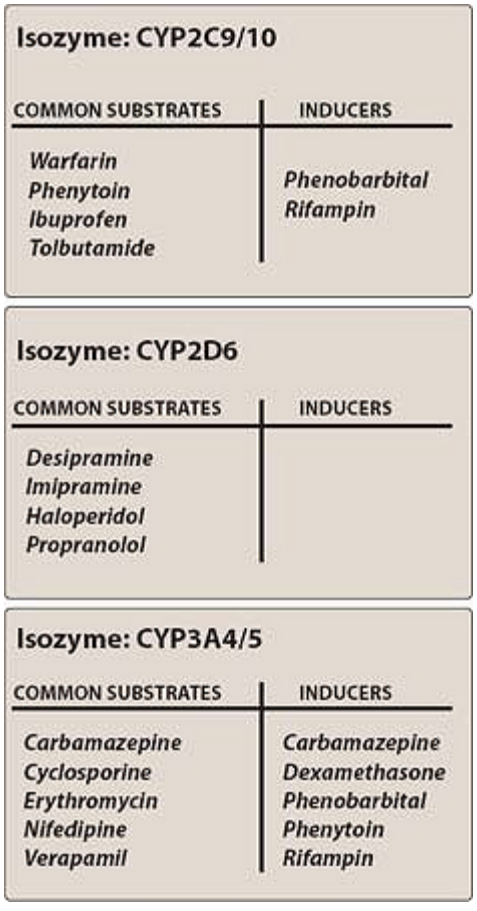


Figure 1.16 Some representative P450 isozymes.

c. **Inducers:** The cytochrome P450â€“dependent enzymes are an important target for pharmacokinetic drug interactions. One such interaction is the induction of selected CYP isozymes. Certain drugs, most notably *phenobarbital, rifampin*, and *carbamazepine*, are capable of increasing the synthesis of one or more CYP isozymes. This results in increased biotransformations of drugs and can lead to significant decreases in plasma concentrations of drugs metabolized by these CYP isozymes, as measured by AUC, with concurrent loss of pharmacologic effect. For example, *rifampin*, an antituberculosis drug (see p. 402), significantly decreases the plasma concentrations of human immunodeficiency virus (HIV) protease inhibitors,[6] diminishing their ability to suppress HIV virion maturation. Figure 1.16 lists some of the more important inducers for representative CYP isozymes. Consequences of increased drug metabolism include: 1)

decreased plasma drug concentrations, 2) decreased drug activity if metabolite is inactive, 3) increased drug activity if metabolite is active, and 4) decreased therapeutic drug effect. In addition to drugs, natural substances and pollutants can also induce CYP isozymes. For example, polycyclic aromatic hydrocarbons (found as air pollutants) can induce CYP1A. This has implications for certain drugs; for example, *amitriptyline* and *warfarin* are metabolized by P4501A2. Polycyclic hydrocarbons induce P4501A2, which decreases the therapeutic concentrations of these agents.

d. **Inhibitors:** Inhibition of CYP isozyme activity is an important source of drug interactions that leads to serious adverse events. The most common form of inhibition is through competition for the same isozyme. Some drugs, however, are capable of inhibiting reactions for which they are not substrates (for

example, *ketoconazole*), leading to drug interactions. Numerous drugs have been shown to inhibit one or more of the CYP-dependent biotransformation pathways of *warfarin*. For example, *omeprazole* is a potent inhibitor of three of the CYP isozymes responsible for *warfarin* metabolism. If the two drugs are taken together, plasma concentrations of *warfarin* increase, which leads to greater inhibition of coagulation and risk of hemorrhage and other serious bleeding reactions. [Note: The more important CYP inhibitors are *erythromycin, ketoconazole*, and *ritonavir*, because they each inhibit several CYP isozymes.] *Cimetidine* blocks the metabolism of *theophylline, clozapine,* and *warfarin*. Natural substances such as grapefruit juice may inhibit drug metabolism. Grapefruit juice inhibits CYP3A4 and, thus, drugs such as *amlodipine, clarithromycin*, and *indinavir,* which are metabolized by this system, have greater amounts in the systemic circulationâ€"leading to higher blood levels and the potential to increase therapeutic and/or toxic effects of the drugs. Inhibition of drug metabolism may lead to increased plasma levels over time with long-term medications, prolonged pharmacological drug effect, and increased drug-induced toxicities.

e. **Phase I reactions not involving the P450 system:** These include amine oxidation (for example, oxidation of catecholamines or histamine), alcohol dehydrogenation (for example, ethanol oxidation), esterases (for example, metabolism of *pravastatin* in liver), and hydrolysis (for example, of *procaine*).

2. **Phase II:** This phase consists of conjugation reactions. If the metabolite from Phase I metabolism is sufficiently polar, it can be excreted by the kidneys. However, many Phase I metabolites are too lipophilic to be retained in the kidney tubules. A subsequent conjugation reaction with an endogenous substrate, such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid, results in polar, usually more water-soluble compounds that are most often therapeutically inactive. A notable exception is *morphine-6-glucuronide*, which is more potent than *morphine*. Glucuronidation is the most common and the most important conjugation reaction. Neonates are deficient in this conjugating system, making them particularly vulnerable to drugs such as *chloramphenicol,* which is inactivated by the addition of glucuronic acid (see p. 382). [Note: Drugs already possessing an â€"OH, â€"HN_2, or â€"COOH group may enter Phase II directly and become conjugated without prior Phase I metabolism.] The highly polar drug conjugates may then be excreted by the kidney or bile.

3. **Reversal of order of the phases:** Not all drugs undergo Phase I and II reactions in that order. For example, *isoniazid* is first acetylated (a Phase II reaction) and then hydrolyzed to isonicotinic acid (a Phase I reaction).

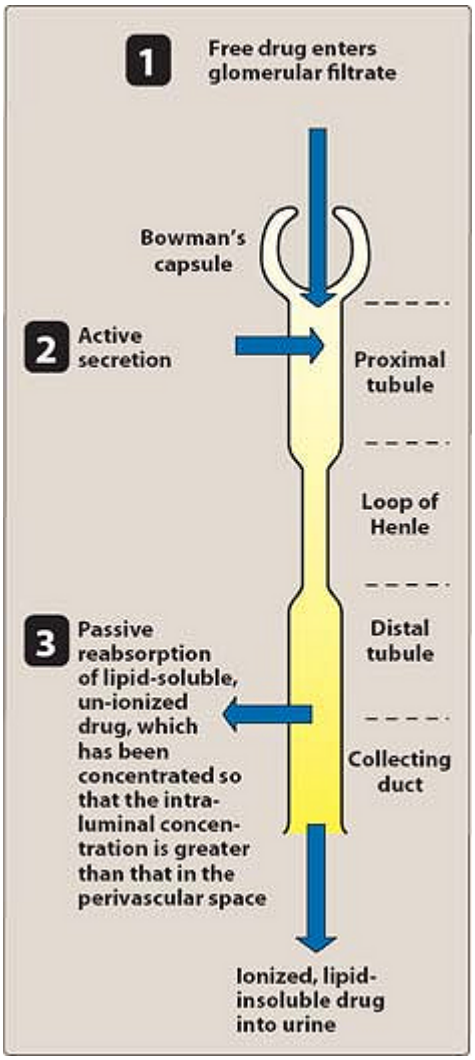


Figure 1.17 Drug elimination by the kidney.

IX. Drug Elimination

Removal of a drug from the body occurs via a number of routes, the most important being through the kidney into the urine. Other routes include the bile, intestine, lung, or milk in nursing mothers. A patient in renal failure may undergo extracorporeal dialysis, which removes small molecules such as drugs.

A. Renal elimination of a drug

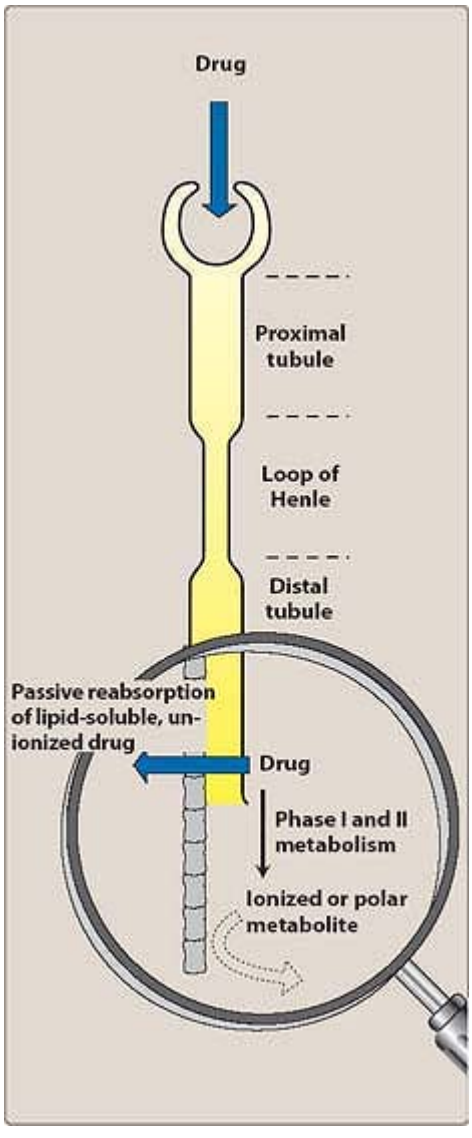


Figure 1.18 Effect of drug metabolism on reabsorption in the distal tubule.

1. **Glomerular filtration:** Drugs enter the kidney through renal arteries, which divide to form a glomerular capillary plexus. Free drug (not bound to albumin) flows through the capillary slits into Bowman's space as part of the glomerular filtrate (Figure 1.17). The glomerular filtration rate (125 mL/min) is normally about twenty percent of the renal plasma flow (600 mL/min). [Note: Lipid solubility and pH do not influence the passage of drugs into the glomerular filtrate]

2. **Proximal tubular secretion:** Drugs that were not transferred into the glomerular filtrate leave the glomeruli through efferent arterioles, which divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule. Secretion primarily occurs in the proximal tubules by two energy-requiring active transport (carrier-requiring) systems, one for anions (for example, deprotonated forms of weak acids) and one for cations (for example, protonated forms of weak bases). Each of these transport systems shows low specificity and can transport many compounds; thus, competition between drugs for these carriers can occur within each transport system (for example, see *probenecid*, p. 513). [Note: Premature infants and neonates have an incompletely developed tubular secretory mechanism and, thus, may retain certain drugs in the glomerular filtrate.]

3. **Distal tubular reabsorption:** As a drug moves toward the distal convoluted tubule, its concentration increases, and exceeds that of the perivascular space. The drug, if uncharged, may diffuse out of the nephric lumen, back into the systemic circulation. Manipulating the pH of the urine to increase the ionized form of the drug in the lumen may be used to minimize the amount of back-diffusion, and hence, increase the clearance of an undesirable drug. As a general rule, weak acids can be eliminated by alkalinization of the urine, whereas elimination of weak bases may be increased by acidification of the urine. This process is called â€œion trapping.â€ For example, a patient presenting with *phenobarbital* (weak acid) overdose can be given *bicarbonate*, which alkalinizes the urine and keeps the drug ionized, thereby decreasing its reabsorption. If overdose is with a weak base, such as *cocaine*, acidification of the urine with NH_4Cl leads to protonation of the drug and an increase in its clearance.

4. **Role of drug metabolism:** Most drugs are lipid soluble and without chemical modification would diffuse out of the kidney's tubular lumen when the drug concentration in the filtrate becomes greater than that in the perivascular space. To minimize this reabsorption, drugs are modified primarily in the liver into more polar substances using two types of reactions: Phase I reactions (see p. 14) that involve either the addition of hydroxyl groups or the removal of blocking groups from hydroxyl, carboxyl, or amino groups, and Phase II reactions (see p. 16) that use conjugation with sulfate, glycine, or glucuronic acid to increase drug polarity. The conjugates are ionized, and the charged molecules cannot back-diffuse out of the kidney lumen (Figure 1.18).

B. Quantitative aspects of renal drug elimination

Plasma clearance is expressed as the volume of plasma from which all drug appears to be removed in a given timeâ€”for example, as mL/min. Clearance equals the amount of renal plasma flow multiplied by the

extraction ratio, and because these are normally invariant over time, clearance is constant.

1. **Extraction ratio:** This ratio is the decline of drug concentration in the plasma from the arterial to the venous side of the kidney. The drugs enter the kidneys at concentration C_1 and exit the kidneys at concentration C_2. The extraction ratio = C_2/C_1.

2. **Excretion rate:** The excretion ratio is determined the equation:

$$\text{Excretion rate} = (\text{clearance})(\text{plasma concentration})$$

$$\text{mg/min} \qquad \text{mL/min} \qquad \text{mg/mL}$$

The elimination of a drug usually follows first-order kinetics, and the concentration of drug in plasma drops exponentially with time. This can be used to determine the half-life, Â½, of the drug (the time during which the concentration of a drug at equilibrium decreases from C to Â½C):

$$t_{1/2} = \ln 0.5/k_e = 0.693\ V_d/CL$$

where k_e = the first-order rate constant for drug elimination from the total body and CL = clearance.

C. Total body clearance

The total body (systemic) clearance, CL_{total} or CL_t, is the sum of the clearances from the various drug-metabolizing and drug-eliminating organs. The kidney is often the major organ of excretion; however, the liver also contributes to drug loss through metabolism and/or excretion into the bile. A patient in renal failure may sometimes benefit from a drug that is excreted by this pathway, into the intestine and feces, rather than through the kidney. Some drugs may also be reabsorbed through the enterohepatic circulation, thus prolonging their half-life. Total clearance can be calculated by using the following equation:

$$CL_{total} = CL_{hepatic} + CL_{renal} + CL_{pulmonary} + CL_{other}$$

It is not possible to measure and sum these individual clearances. How-ever, total clearance can be derived from the steady-state equation:

$$CL_{total} = k_e V_d$$

D. Clinical situations resulting in changes in drug half-life

When a patient has an abnormality that alters the half-life of a drug, adjustment in dosage is required. It is important to be able to predict in which patients a drug is likely to have a change in half-life. The half-life of a drug is increased by 1) diminished renal plasma flow or hepatic blood flowâ€"for example, in cardiogenic shock, heart failure, or hemorrhage; 2) decreased extraction ratioâ€"for example, as seen in renal disease; and 3) decreased metabolismâ€"for example, when another drug inhibits its biotransformation or in hepatic insufficiency, as with cirrhosis. On the other hand, the half-life of a drug may decrease by 1) increased hepatic blood flow, 2) decreased protein binding, and 3) increased metabolism.

X. Kinetics of Continuous Administration

The preceding discussion describes the pharmacokinetic processes that determine the rates of absorption, distribution, and elimination of a drug.

Pharmacokinetics also describes the quantitative, time-dependent changes of both the plasma drug concentration and the total amount of drug in the body, following the drug's administration by various routes, with the two most common being IV infusion and oral fixed-dose/fixed-time interval regimens (for example, â€œone tablet every 4 hoursâ€). The interactions of the processes previously described determine the pharmacokinetics profile of a drug. The significance of identifying the pharmacokinetics of a drug lies not only in defining the factors that influence its levels and persistence in the body, but also in tailoring the therapeutic use of drugs that have a high toxic potential. [Note: The following discussion assumes that the administered drug distributes into a single body compartment. In actuality, most drugs equilibrate between two or three compartments and, thus, display complex kinetic behavior. However, the simpler model suffices to demonstrate the concepts.]

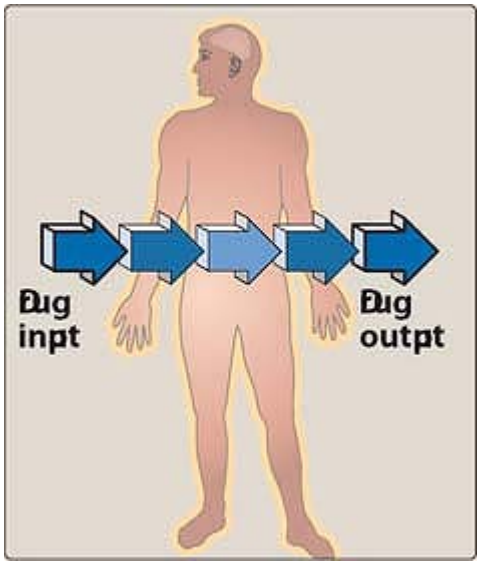


Figure 1.19 At steady state, input (rate of infusion) equals output (rate of elimination).

A. Kinetics of IV infusion

With continuous IV infusion, the rate of drug entry into the body is constant. In the majority of cases, the elimination of a drug is first order; that is, a constant fraction of the agent is cleared per unit of time. Therefore, the rate of drug exit from the body increases proportionately as the plasma concentration increases, and at every

point in time, it is proportional to the plasma concentration of the drug.

1. **Steady-state drug levels in blood:** Following the initiation of an IV infusion, the plasma concentration of drug rises until the rate of drug eliminated from the body precisely balances the input rate. Thus, a steady-state is achieved in which the plasma concentration of drug remains constant. [Note: The rate of drug elimination from the body = $(CL_t)(C)$, where CL_t = total body clearance (see p. 18) and C = the plasma concentration of drug.] Two questions can be asked about achieving the steady-state. First, what is the relationship between the rate of drug infusion and the plasma concentration of drug achieved at the plateau, or steady state? Second, what length of time is required to reach the steady state drug concentration?

2. **Influence of the rate of drug infusion on the steady state:** A steady-state plasma concentration of a drug occurs when the rate of drug elimination is equal to the rate of administration (Figure 1.19), as described by the following equation:

$$C_{ss} = R_o/k_eV_d = R_o/CL_t$$

where C_{ss} = the steady-state concentration of the drug, R_o = the infusion rate (for example, mg/min), k_e is the first-order elimination rate constant, and V_d = the volume of distribution. Because k_e, CL_t, and V_d are constant for most drugs showing first-order kinetics, C_{ss} is directly proportional to R_o; that is, the steady-state plasma concentration is directly proportional to the infusion rate. For example, if the infusion rate is doubled, the plasma concentration ultimately achieved at the steady state is doubled (Figure 1.20). Furthermore, the steady-state concentration is inversely proportional to the clearance of the drug, CL_t. Thus, any factor that decreases clearance, such as liver or kidney disease, increases the steady-state concentration of an infused drug (assuming V_d remains constant). Factors that increase clearance of a drug, such as increased metabolism, decrease the steady-state concentrations of an infused drug.

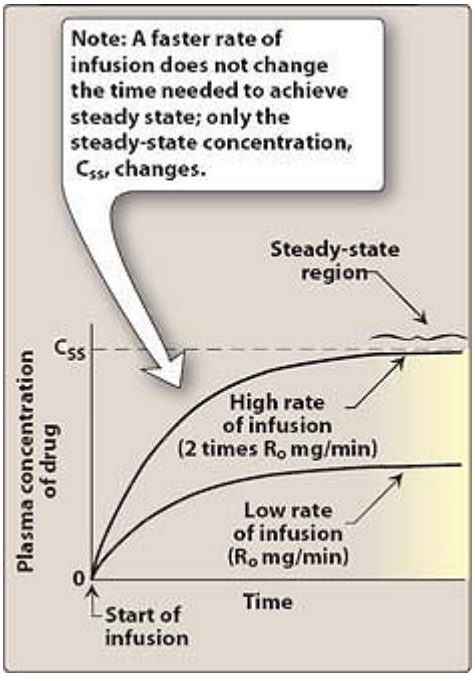


Figure 1.20 Effect of infusion rate on the steady-state concentration of drug in the plasma. (Ro = rate of infusion of a drug.)

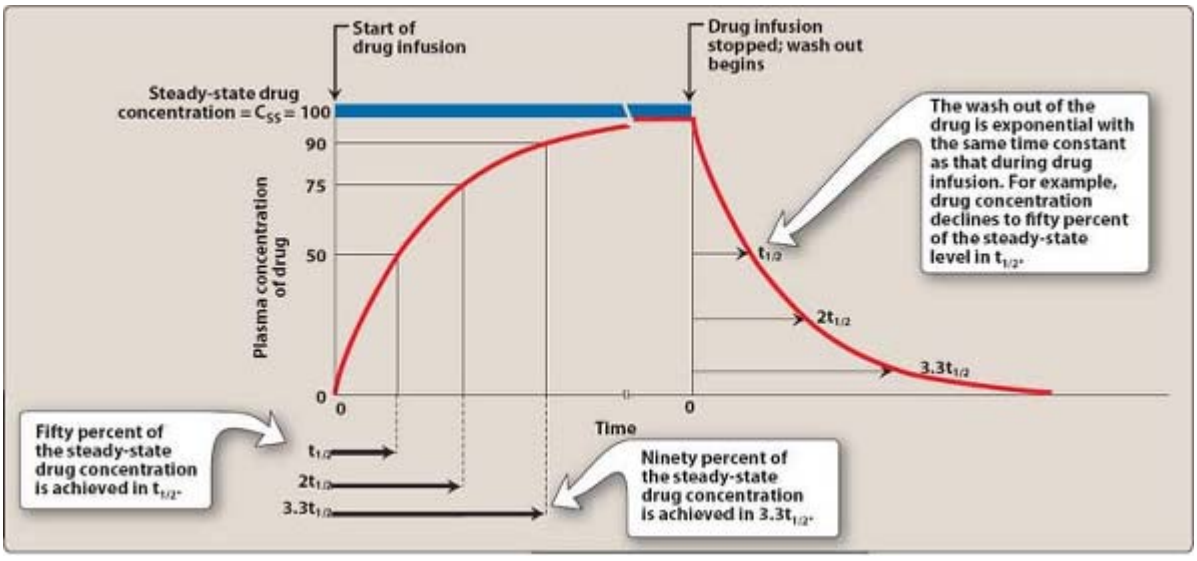


Figure 1.21 Rate of attainment of steady-state concentration of a drug in the plasma.

3. **Time required to reach the steady-state drug concentration:** The concentration of drug rises from zero at the start of the infusion to its ultimate steady-state level, C_{ss} (Figure 1.21). The fractional rate of approach to a steady state is achieved by a first-order process.

   a. **Exponential approach to steady state:** The rate constant for attainment of steady state is the rate constant for total body elimination of the drug, k_e. Thus, fifty percent of the final steady-state concentration of drug is observed after the time elapsed since the infusion, t, is equal to $t_{1/2}$, where $t_{1/2}$ (or half-life) is the time required for the drug concentration to change by fifty percent. Waiting another half-life allows the drug concentration to approach 75 percent of C_{ss} (see Figure 1.21). The drug concentration is ninety percent of the final steady-state concentration in 3.3 times $t_{1/2}$. For convenience, therefore, one can assume that a drug will reach steady-state in about four half-lives. The time required to reach a specific fraction of the steady-state is described by

   $$f = 1 - e^{-k_e t}$$

   where f = the fractional shift (for example, 0.9 if the time to reach ninety percent of the steady-state concentration was being calculated) and t = the time elapsed since the start of the infusion.

   b. **Effect of the rate of drug infusion:** The sole determinant of the rate that a drug approaches steady state is the $t_{1/2}$ or k_e, and this rate is influenced only by the factors that affect the half-life. The rate of approach to steady state is not affected by the rate of drug infusion. Although increasing the rate of infusion of a drug increases the rate at which any given concentration of drug in the plasma is achieved, it does not influence the time required

   to reach the ultimate steady-state concentration. This is because the steady-state concentration of drug rises directly with the infusion rate (see Figure 1.20).

   c. **Rate of drug decline when the infusion is stopped:** When the infusion is stopped, the plasma concentration of a drug declines (washes out) to zero with the same time course observed in approaching the steady state (see Figure 1.21). This relationship is expressed as

   $$C_t = C_0 - e^{-k_e t}$$

   where C_t i = the plasma concentration at any time, C_0 = the starting plasma concentration, k_e = the

first-order elimination rate constant, and t = the time elapsed.

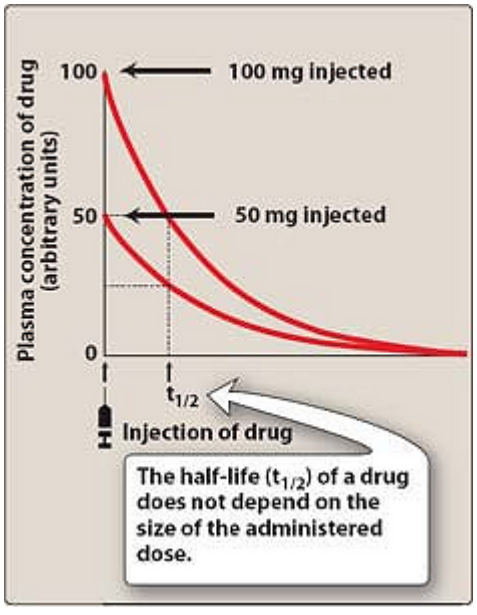


Figure 1.22 Effect of the dose of a single intravenous injection of drug on plasma levels

d. **Loading dose:** A delay in achieving the desired plasma levels of drug may be clinically unacceptable. Therefore, a â€œloading doseâ€ of drug can be injected as a single dose to achieve the desired plasma level rapidly, followed by an infusion to maintain the steady state (maintenance dose). In general, the loading dose can be calculated as

$$\text{Loading dose} = (V_d)(\text{desired steady-state plasma concentration})$$

B. Kinetics of fixed-dose/fixed-time-interval regimens

Administration of a drug by fixed doses rather than by continuous infusion is often more convenient. However, fixed doses, given at fixed-time intervals, result in time-dependent fluctuations in the circulating level of drug.

1. **Single IV injection:** For simplicity, assume the injected drug rapidly distributes into a single compartment. Because the rate of elimination is usually first order in regard to drug concentration, the circulating level of drug decreases exponentially with time (Figure 1.22). [Note: The $t_{1/2}$ does not depend on the dose of drug administered.]

2. **Multiple IV injections:** When a drug is given repeatedly at regular intervals, the plasma concentration increases until a steady state is reached (Figure 1.23). Because most drugs are given at intervals shorter than five half-lives and are eliminated exponentially with time, some drug from the first dose remains in the body at the time that the second dose is administered, and some from the second dose remains at the time that the third dose is given, and so forth. Therefore, the drug accumulates until, within the dosing interval, the rate of drug loss (driven by an elevated plasma concentration) exactly balances the rate of drug administrationâ€”that is, until a steady state is achieved.

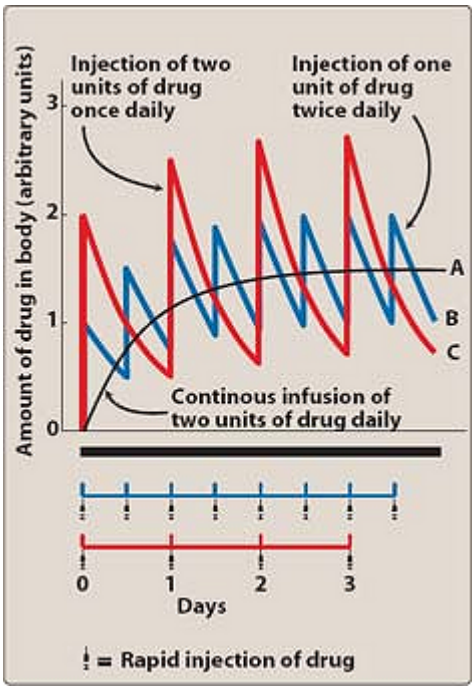


Figure 1.23 Predicted plasma concentrations of a drug given by infusion (A), twice-daily injection (B), or once-daily injection (C). Model assumes rapid mixing in a single body compartment and a half-life of twelve hours.

a. **Effect of dosing frequency:** The plasma concentration of a drug oscillates about a mean. Using smaller doses at shorter intervals reduces the amplitude of the swings in drug concentration. However, the steady-state concentration of the drug, and the rate at which the steady-state is approached, are not affected by the frequency of dosing.

b. **Example of achievement of steady state using different dosage regimens:** Curve B of Figure 1.23 shows the amount of drug in the body when 1 g of drug is administered IV to a patient and the dose is repeated at a time interval that corresponds to the half-life of the drug. At the end of the first dosing interval, 0.50 units of drug remain from the first dose when the second dose is administered. At the end of the second dosing interval, 0.75 units are present when the third dose is taken. The minimal amount of drug during the dosing interval progressively increases and approaches a value of 1.00 unit, whereas the maximal value immediately following drug administration progressively approaches 2.00 units. Therefore, at the steady state, 1.00 unit of drug is lost during the dosing interval, which is exactly matched by the rate at which the drug is administeredâ€"that is, the â€œrate inâ€ equals the â€œrate out.â€ As in the case for IV infusion, ninety percent of the steady-state value is achieved in 3.3 times $t_{1/2}$.

3. **Orally administered drugs:** Most drugs that are administered on an outpatient basis are taken orally on a fixed-dose/fixed-time-interval regimenâ€"for example, a specific dose taken one, two, or three times daily. In contrast to IV injection, orally administered drugs may be absorbed slowly, and the plasma concentration of the drug is influenced by both the rate of absorption and the rate of drug elimination (Figure 1.24). This relationship can be expressed as:

$$C_{ss} = \frac{1}{(k_e)(V_d)} \frac{(D)(F)}{T}$$

where D = the dose, F = the fraction absorbed (bioavailability), T = dosage interval, C_{ss} = the steady-state concentration of the drug, k_e = the first-order rate constant for drug elimination from the total body, and V_d = the volume of distribution.

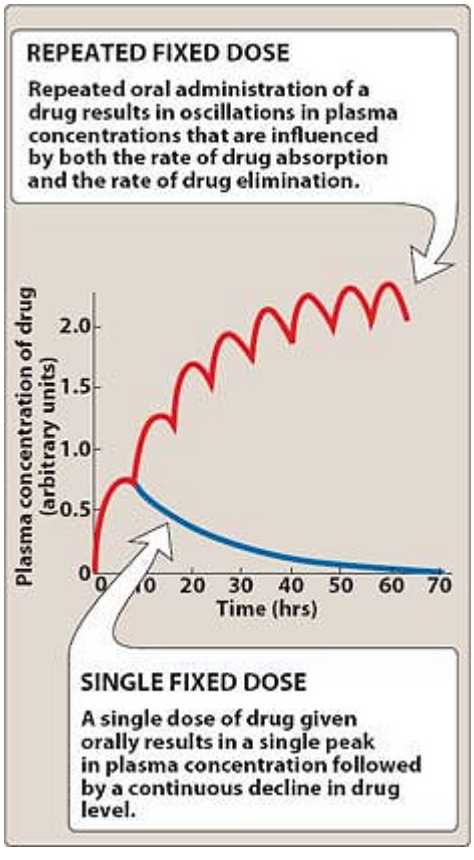


Figure 1.24 Predicted plasma concentrations of a drug given by repeated oral administrations.

Study Questions

Choose the ONE best answer.

1.1 Which one of the following statements is correct?

A. Weak bases are absorbed efficiently across the epithelial cells of the stomach.

B. Coadministration of atropine speeds the absorption of a second drug.

C. Drugs showing a large V_d can be efficiently removed by dialysis of the plasma.

D. Stressful emotions can lead to a slowing of drug absorption.

E. If the V_d for a drug is small, most of the drug is in the extraplasmic space.

View Answer

1.2 Which one of the following is true for a drug whose elimination from plasma shows first-order kinetics?

A. The half-life of the drug is proportional to the drug concentration in plasma.

B. The amount eliminated per unit of time is constant.

C. The rate of elimination is proportional to the plasma concentration.

D. Elimination involves a rate-limiting enzymic reaction operating at its maximal velocity (V_m).

E. A plot of drug concentration versus time is a straight line.

View Answer

1.3 A patient is treated with drug A, which has a high affinity for albumin and is administered in amounts that do not exceed the binding capacity of albumin. A second drug, B, is added to the treatment regimen. Drug B also has a high affinity for albumin but is administered in amounts that are 100 times the binding capacity of albumin. Which of the following occurs after administration of drug B?

A. An increase in the tissue concentrations of drug A.

B. A decrease in the tissue concentrations of drug A.

C. A decrease in the volume of distribution of drug A.

D. A decrease in the half-life of drug A.

E. Addition of more drug A significantly alters the serum concentration of unbound drug B.

View Answer

1.4 The addition of glucuronic acid to a drug:

A. Decreases its water solubility.

B. Usually leads to inactivation of the drug.

C. Is an example of a Phase I reaction.

D. Occurs at the same rate in adults and newborns.

E. Involves cytochrome P450.

View Answer

1.5 Drugs showing zero-order kinetics of elimination:

A. Are more common than those showing first-order kinetics.

B. Decrease in concentration exponentially with time.

C. Have a half-life independent of dose.

D. Show a plot of drug concentration versus time that is linear.

E. Show a constant fraction of the drug eliminated per unit of time.

View Answer

1.6 A drug, given as a 100-mg single dose, results in a peak plasma concentration of 20 Âµg/mL. The apparent volume of distribution is (assume a rapid distribution and negligible elimination prior to measuring the peak plasma level):

A. 0.5 L.

B. 1 L.

C. 2 L.

D. 5 L.

E. 10 L.

View Answer

1.7 A drug with a half-life of 12 hours is administered by continuous IV infusion. How long will it take for the drug to reach ninety percent of its final steady-state level?

A. 18 hours.

B. 24 hours.

C. 30 hours.

D. 40 hours.

E. 90 hours.

View Answer

1.8 Which of the following results in a doubling of the steady-state concentration of a drug?

A. Doubling the rate of infusion.

B. Maintaining the rate of infusion but doubling the loading dose.

C. Doubling the rate of infusion and doubling the concentration of the infused drug.

D. Tripling the rate of infusion.

E. Quadrupling the rate of infusion.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 2

Drugâ€“Receptor Interactions and Pharmacodynamics

I. Overview

Most drugs exert their effects, both beneficial and harmful, by interacting with receptorsâ€”that is, specialized target macromoleculesâ€”present on the cell surface or intracellularly. Receptors bind drugs and initiate events leading to alterations in biochemical and/or biophysical activity of a cell, and consequently, the function of an organ (Figure 2.1). Drugs may interact with receptors in many different ways. Drugs may bind to enzymes (for example, inhibition of dihydrofolate reductase by *trimethoprim,* see p. 394), nucleic acids (for example, blockade of transcription by *dactinomycin,* see p. 469), or membrane receptors (for example, alteration of membrane permeability by *pilocarpine*, see p. 49). In each case, the formation of the drugâ€“receptor complex leads to a biologic response. Most receptors are named to indicate the type of drug/chemical that interacts best with it; for example, the receptor for histamine is called a histamine receptor. Cells may have tens of thousands of receptors for certain ligands (drugs). Cells may also have different types of receptors, each of which is specific for a particular ligand. On the heart, for example, there are Î² receptors for norepinephrine, and muscarinic receptors for acetylcholine. These receptors dynamically interact to control vital functions of the heart. The magnitude of the response is proportional to the number of drugâ€“receptor complexes:

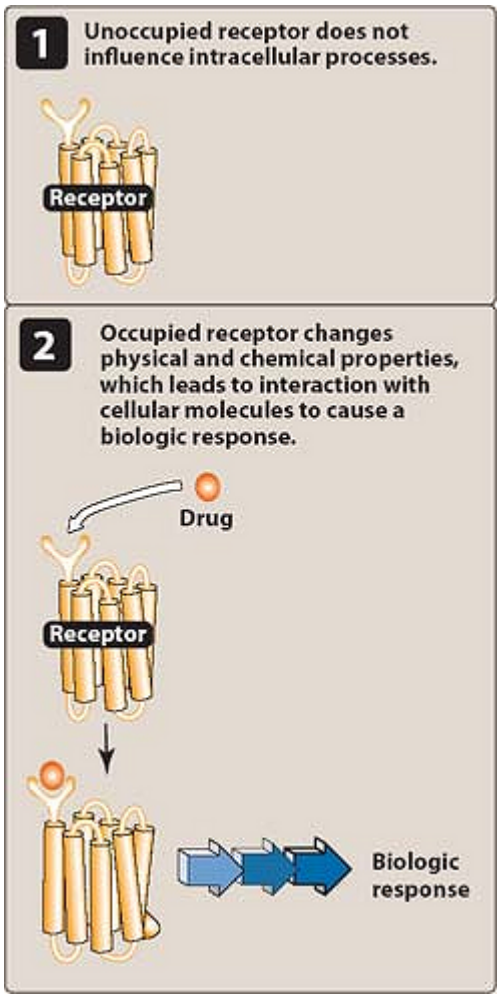


Figure 2.1 The recognition of a drug by a receptor triggers a biologic response.

$$\text{Drug} + \text{Receptor} \rightleftarrows \text{Drug–receptor complex} \rightarrow \text{Biologic effect}$$

This concept is closely related to the formation of complexes between enzyme and substrate,[1] or antigen and antibody; these interactions have many common features, perhaps the most noteworthy being specificity of the receptor for a given ligand. However, the receptor not only has the ability to recognize a ligand, but can also couple or transduce this binding into a response by causing a conformational change or a biochemical effect. Although much of this chapter will be centered on the interaction of drugs with specific receptors, it is important to be aware that not all drugs exert their effects by interacting with a receptor; for example, *antacids* chemically neutralize excess gastric acid, reducing the symptoms of â€œheartburn.â€ This chapter introduces the study of pharmacodynamicsâ€”the influence of drug concentrations on the magnitude of the response. It deals with the interaction of drugs with receptors, the molecular consequences of these interactions, and their effects in the patient.

A fundamental principle of pharmacodynamics is that drugs only modify underlying biochemical and physiological processes; they do not create effects de novo.

II. Chemistry of Receptors and Ligands

Interaction of receptors with ligands involves the formation of chemical bonds, most commonly electrostatic and

hydrogen bonds, as well as weak interactions involving van der Waals forces. These bonds are important in determining the selectivity of receptors, because the strength of these noncovalent bonds is related inversely to the distance between the interacting atoms. Therefore, the successful binding of a drug requires an exact fit of the ligand atoms with the complementary receptor atoms. The bonds are usually reversible, except for a handful of drugs (for example, the nonselective Î±-receptor blocker *phenoxybenzamine,* and acetylcholinesterase inhibitors in the organophosphate class) that covalently bond to their targets. The size, shape, and charge distribution of the drug molecule determines which of the myriad binding sites in the cells and tissues of the patient can interact with the ligand. The metaphor of the â€œlock and keyâ€ is a useful concept for understanding the interaction of receptors with their ligands. The precise fit required of the ligand echoes the characteristics of the â€œkey,â€ whereas the opening of the â€œlockâ€ reflects the activation of the receptor. The interaction of the ligand with its receptor thus exhibits a high degree of specificity. The induced-fit model has largely replaced the lock-and-key concept as the preferred model describing the interaction of a receptor and a ligand. In the presence of a ligand, the receptor undergoes a conformational change to bind the ligand. The change in conformation of the receptor caused by binding of the agonist activates the receptor, which leads to the pharmacologic effect. This model suggests that the receptor is flexible, not rigid as implied by the lock-and-key model.

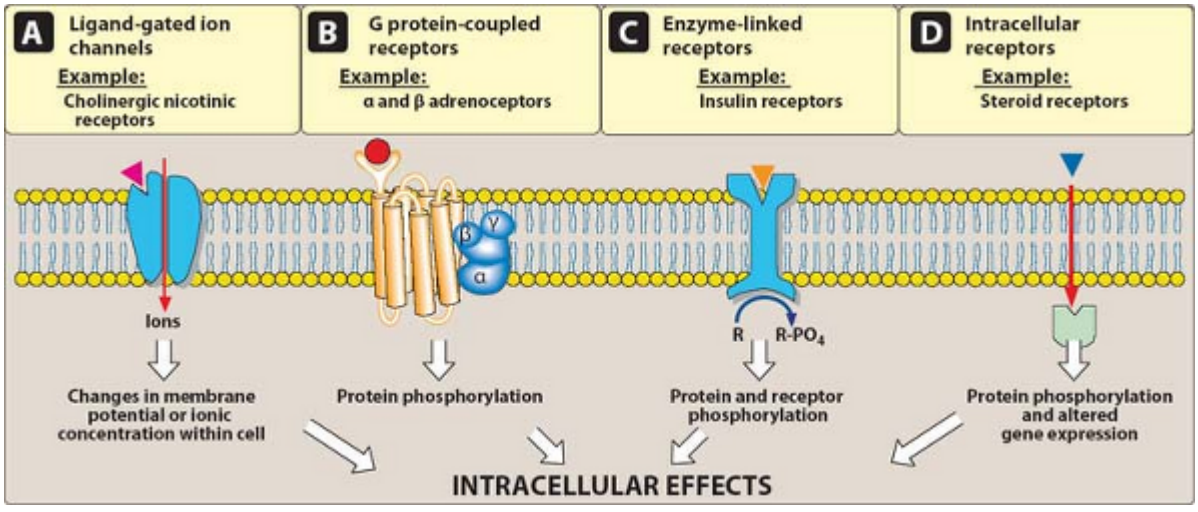


Figure 2.2 Transmembrane signaling mechanisms. A. Ligand binds to the extracellular domain of a ligand-gated channel. B. Ligand binds to a domain of a serpentine receptor, which is coupled to a G protein. C. Ligand binds to the extracellular domain of a receptor that activates a kinase enzyme. D. Lipid-soluble ligand diffuses across the membrane to interact with its intracellular receptor.

III. Major Receptor Families

Pharmacology defines a receptor as any biologic molecule to which a drug binds and produces a measurable response. Thus, enzymes and structural proteins can be considered to be pharmacologic receptors. However, the richest sources of therapeutically exploitable pharmacologic receptors are proteins that are responsible for transducing extracellular signals into intracellular responses. These receptors may be divided into four families: 1) ligand-gated ion channels, 2) G proteinâ€“coupled receptors, 3) enzyme-linked receptors, and 4) intracellular receptors (Figure 2.2). The type of receptor a ligand will interact with depends on the nature of the ligand. Hydrophobic ligands interact with receptors that are found on the cell surface (families 1, 2, and 3). In contrast, hydrophobic ligands can enter cells through the lipid bilayers of the cell membrane to interact with receptors found inside cells (family 4).

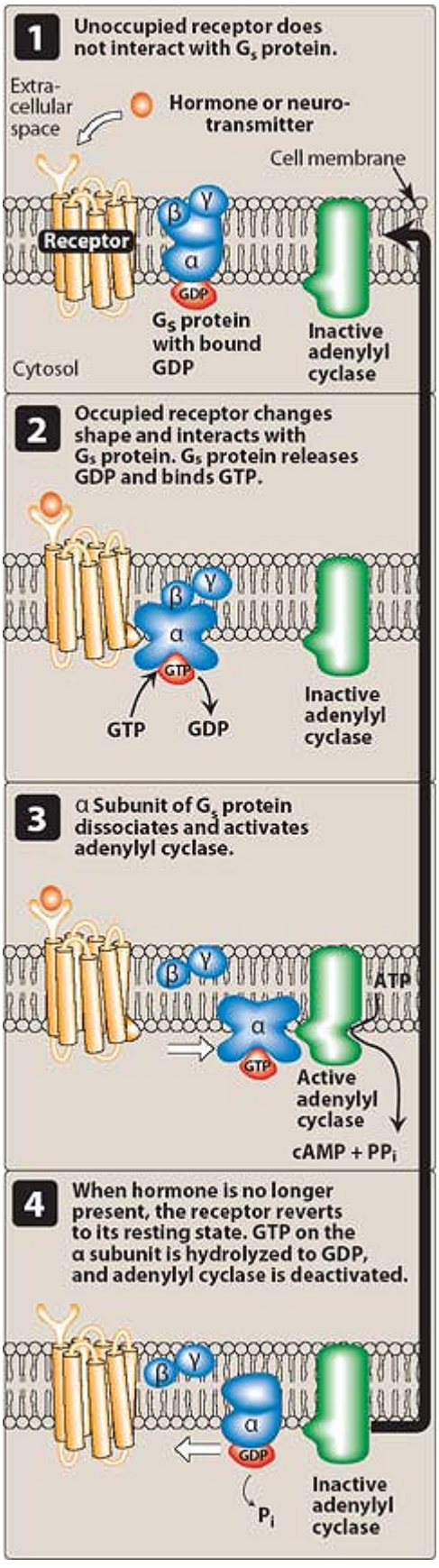

1
Unoccupied receptor does not interact with G_s protein.
Extra-cellular space
Hormone or neuro-transmitter
Cell membrane
Receptor
β
γ
α
GDP
G_S protein with bound GDP
Inactive adenylyl cyclase
Cytosol
2
Occupied receptor changes shape and interacts with G_s protein. G_s protein releases GDP and binds GTP.
β
γ
α
GTP
GTP
GDP
Inactive adenylyl cyclase
3
α Subunit of G_s protein dissociates and activates adenylyl cyclase.
β
γ
α
GTP
ATP
Active adenylyl cyclase
cAMP + PP_i
4
When hormone is no longer present, the receptor reverts to its resting state. GTP on the α subunit is hydrolyzed to GDP, and adenylyl cyclase is deactivated.
β
γ
α
GDP
P_i
Inactive adenylyl cyclase

Figure 2.3 The recognition of chemical signals by G protein-coupled membrane receptors triggers an increase (or, less often, a decrease) in the activity of adenylyl cyclase.

A. Ligand-gated ion channels

The first receptor family comprises ligand-gated ion channels that are responsible for regulation of the flow of ions across cell membranes (see Figure 2.2A). The activity of these channels is regulated by the binding of a ligand to the channel. Response to these receptors is very rapid, having durations of a few milliseconds. The nicotinic receptor and the Î³-aminobutyric acid (GABA) receptor are important examples of ligand-gated receptors, the functions of which are modified by numerous drugs. Stimulation of the nicotinic receptor by *acetylcholine* results in sodium influx, generation of an action potential, and activation of contraction in skeletal muscle. *Benzodiazepines*, on the other hand, enhance the stimulation of the GABA receptor by GABA, resulting in increased chloride influx and hyperpolarization of the respective cell. Although not ligand-gated, ion channels, such as the voltage-gated sodium channel, are important drug receptors for several drug classes, including local anesthetics.

B. G proteinâ€“coupled receptors

A second family of receptors consists of G proteinâ€“coupled receptors. These receptors are comprised of a single peptide that has seven membrane-spanning regions, and these receptors are linked to a G protein (G_s and others) having three subunits, an Î± subunit that binds guanosine triphosphate (GTP) and a Î²Î³ subunit (Figure 2.3). Binding of the appropriate ligand to the extracellular region of the receptor activates the G protein so that GTP replaces guanosine diphosphate (GDP) on the Îα subunit. Dissociation of the G protein occurs, and both the Îα-GTP subunit and the Î²Î³ subunit subsequently interact with other cellular effectors, usually an enzyme or ion channel. These effectors then change the concentrations of second messengers that are responsible for further actions within the cell. Stimulation of these receptors results in responses that last several seconds to minutes.

1. **Second messengers:** These are essential in conducting and amplifying signals coming from G proteinâ€“coupled receptors. A common pathway turned on by G_s, and other types of G proteins, is the activation of adenylyl cyclase by Îα-GTP subunits, which results in the production of cyclic adenosine monophosphate (cAMP)â€”a second messenger that regulates protein phosphorylation. G proteins also activate phospholipase C, which is responsible for the generation of two other second messengers, namely inositol-1,4,5-trisphosphate and diacylglycerol. These effectors are responsible for the regulation of

intracellular free calcium concentrations, and of other proteins as well. This family of receptors transduces signals derived from odors, light, and numerous neurotransmitters, including norepinephrine, dopa-mine, serotonin, and acetylcholine. G proteinâ€“coupled receptors also activate guanylyl cyclase, which converts (GTP) to cyclic guanosine monophosphate (cGMP), a fourth second messenger that stimulates cGMP-dependent protein kinase. cGMP signaling is important in only a few cells, for example, intestinal mucosa and vascular smooth muscle, where it causes relaxation of vascular smooth muscle cells. Some drugs such as *sildenafil* produce vasodilation by interfering with specific phosphodiesterases, the enzymes that metabolically break down cGMP.

C. Enzyme-linked receptors

A third major family of receptors consists of those having cytosolic enzyme activity as an integral component of their structure or function (see Figure 2.2C). Binding of a ligand to an extracellular domain activates or inhibits this cytosolic enzyme activity. Duration of responses to stimulation of these receptors is on the order of minutes to hours. The most common enzyme-linked receptors (epidermal growth factor, platelet-derived growth factor, *atrial natriuretic peptide, insulin,* and others) are those that have a tyrosine kinase activity as part of their structure. Typically, upon binding of the ligand to receptor subunits, the receptor undergoes conformational changes,

converting from its inactive form to an active kinase form. The activated receptor autophosphorylates, and phosphorylates tyrosine residues on specific proteins. The addition of a phosphate group can substantially modify the three-dimensional structure of the target protein, thereby acting as a molecular switch. For example, when the peptide hormone *insulin* binds to two of its receptor subunits, their intrinsic tyrosine kinase activity causes autophosphorylation of the receptor itself. In turn, the phosphorylated receptor phosphorylates target moleculesâ€"insulin-receptor substrate peptidesâ€"that subsequently activate other important cellular signals such as IP3 and the mitogen-activated protein kinase system. This cascade of activations results in a multiplication of the initial signal, much like that which occurs with G proteinâ€“coupled receptors.

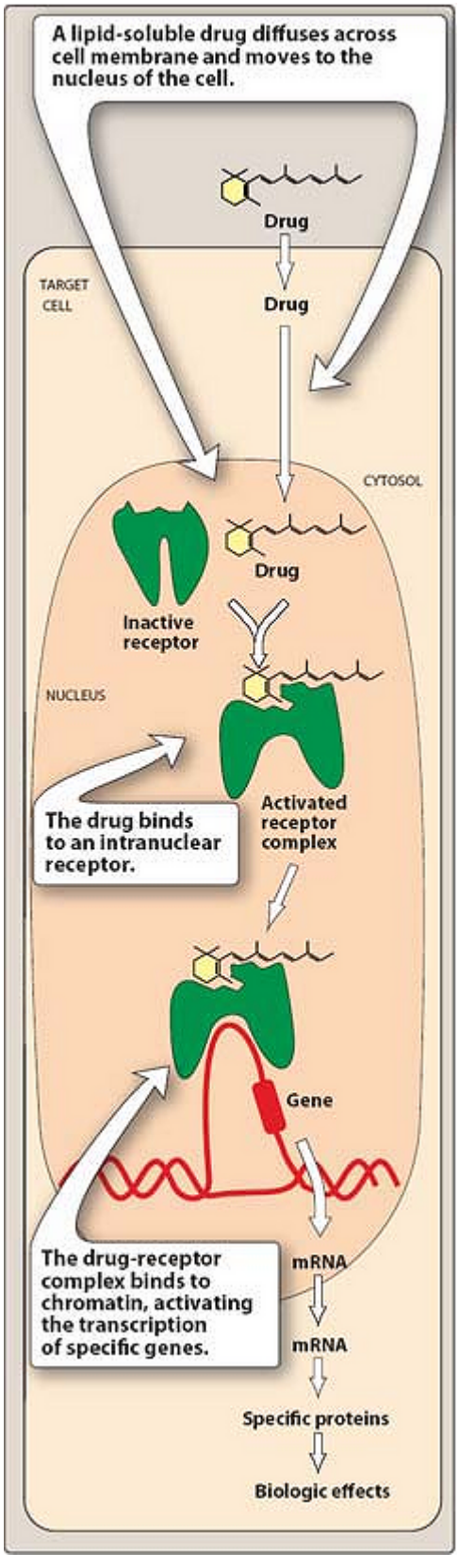


Figure 2.4 Mechanism of intracellular receptors.

D. Intracellular receptors

The fourth family of receptors differs considerably from the other three in that the receptor is entirely intracellular and, therefore, the ligand must diffuse into the cell to interact with the receptor (Figure 2.4). This places constraints on the physical and chemical properties of the ligand in that it must have sufficient lipid solubility to be able to move across the target cell membrane. Because these receptor ligands are lipid soluble, they are transported in the body attached to plasma proteins, such as albumin. For example, *steroid hormones* exert their action on target cells via this receptor mechanism. Binding of the ligand with its receptor follows a general pattern in which the receptor becomes activated because of the dissociation of a small repressor peptide. The activated ligandâ€“receptor complex migrates to the nucleus, where it binds to specific DNA sequences, resulting in the regulation of gene expression. The time course of activation and response of these receptors is much longer than that of the other mechanisms described above. Because gene expression and, therefore, protein synthesis is modified, cellular responses are not observed until considerable time has elapsed (thirty minutes or more), and the duration of the response (hours to days) is much greater than that of other receptor families.

IV. Some Characteristics of Receptors

A. Spare receptors

A characteristic of many receptors, particularly those that respond to hormones, neurotransmitters, and peptides, is their ability to amplify signal duration and intensity. The family of G proteinâ€“linked receptors exemplifies many of the possible responses initiated by ligand binding to a receptor. Specifically, two phenomena account for the amplification of the ligandâ€“receptor signal. First, a single ligandâ€“receptor complex can interact with many G proteins, thereby multiplying the original signal many-fold. Second, the activated G proteins persist for a longer duration than the original ligandâ€“receptor complex. The binding of *albuterol*, for example, may only exist for a few milliseconds, but the subsequent activated G proteins may last for hundreds of milliseconds. Further prolongation and amplification of the initial signal is mediated by the interaction between G proteins and their respective intracellular targets. Because of this amplification, only a fraction of the total receptors for a specific ligand may need to be occupied to elicit a maximal response from a cell. Systems that exhibit this behavior are said to have spare receptors. Spare receptors are exhibited by insulin receptors, where it has been estimated that 99 percent of the receptors are â€œspare.â€ This constitutes an immense functional reserve that ensures adequate amounts of glucose enter the cell. On the other end of the scale is the human heart, in which about five to ten percent of the total Î²-adrenoceptors are spare. An important implication of this observation is that little functional reserve exists in the failing heart; most receptors must be occupied to obtain maximum contractility.

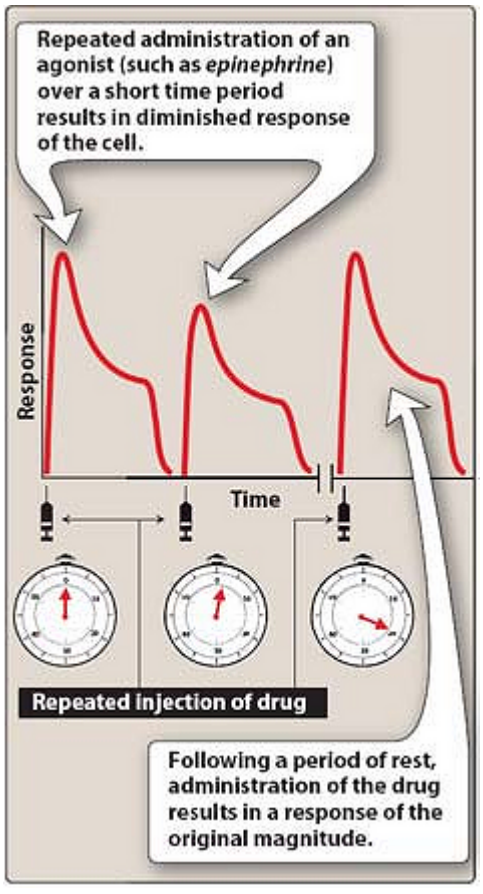


Figure 2.5 Desensitization of receptors.

B. Desensitization of receptors

Repeated or continuous administration of an agonist (or an antagonist) may lead to changes in the responsiveness of the receptor. To prevent potential damage to the cell (for example, high concentrations of calcium, initiating cell death), several mechanisms have evolved to protect a cell from excessive stimulation. When repeated administration of a drug results in a diminished effect, the phenomenon is called tachyphylaxis. The receptor becomes desensitized to the action of the drug (Figure 2.5). In this phenomenon, the receptors are still present on the cell surface but are unresponsive to the ligand. Other types of desensitization occur when receptors are down-regulated. Binding of the agonist results in molecular changes in the membrane-bound receptors, such that the receptor undergoes endocytosis and is sequestered from further agonist interaction. These receptors may be recycled to the cell surface, restoring sensitivity, or alternatively, may be further processed and degraded, decreasing the total number of receptors available. Some receptors, particularly voltage-gated channels, require a finite time (rest period) following stimulation before they can be activated again. During this recovery phase they are said to be â€œrefractoryâ€ or â€œunresponsive.â€

C. Importance of the receptor concept

It is important that we understand the roles and functions of receptors because most drugs interact with receptors that will determine selective therapeutic and toxic effects of the drug. Moreover, receptors largely determine the quantitative relations between dose of a drug and pharmacologic effect.

V. Doseâ€“Response Relationships

An agonist is defined as an agent that can bind to a receptor and elicit a biologic response. The magnitude of the drug effect depends on the drug concentration at the receptor site, which in turn is determined by the dose of drug administered and by factors characteristic of the drug pharmacokinetic profile, such as rate of absorption, distribution, and metabolism.

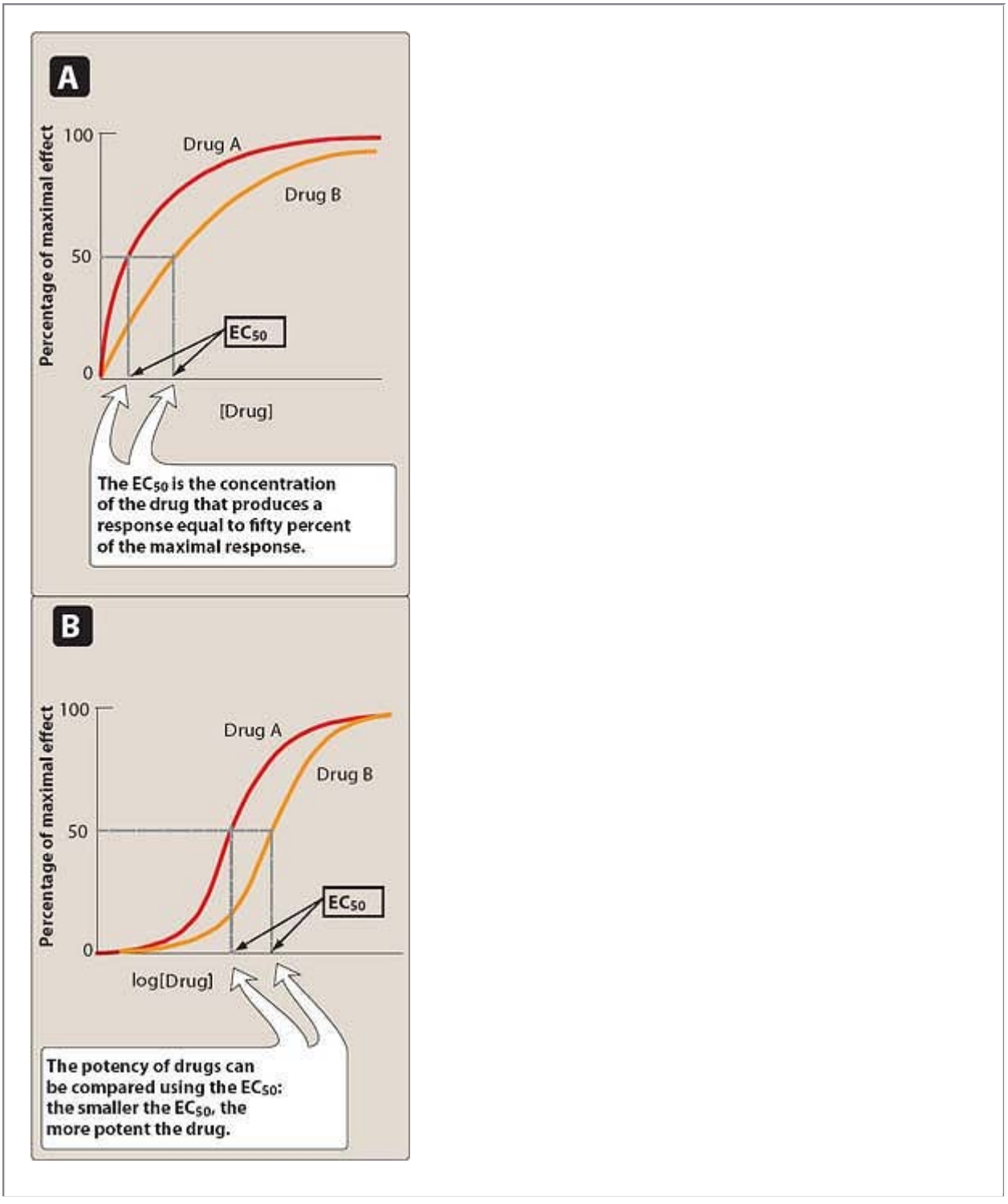


Figure 2.6 The effect of dose on the magnitude of pharmacologic response. Panel A is a linear graph. Panel B is a semilogarithmic plot of the same data. EC50 = drug dose that shows fifty percent of maximal response.

A. Graded doseâ€“response relations

As the concentration of a drug increases, the magnitude of its pharmacologic effect also increases. The relationship between dose and response is a continuous one, and it can be mathematically described for many systems by application of the law of mass action, assuming the simplest model of drug binding:

$$[\text{Drug}] + [\text{Receptor}] \rightleftarrows [\text{Drug–receptor complex}]$$

The response is a graded effect, meaning that the response is continuous and gradual. This contrasts with a quantal response, which describes an all-or-nothing response. A graph of this relationship is known as a graded doseâ€“response curve. Plotting the magnitude of the response against increasing doses of a drug produces a graph that has the general shape depicted in Figure 2.6A. The curve can be described as a rec-tangular hyperbolaâ€”a very familiar curve in biology, because it can be applied to diverse biological events, such as ligand binding, enzymatic activity, and responses to pharmacologic agents.

1. **Potency:** Two important properties of drugs can be determined by graded doseâ€“response curves. The first is potency, a measure of the amount of drug necessary to produce an effect of a given magnitude. For a number of reasons, the concentration producing an effect that is fifty percent of the maximum is used to determine potency; it commonly designated as the EC_{50}. In Figure 2.6, the EC_{50} for Drugs A and B are indicated. Drug A is more potent than Drug B because less Drug A is needed to obtain 50 percent effect. Thus, therapeutic preparations of drugs will reflect the potency. For example, *candesartan* and *irbesartan* are angiotensinâ€“receptor blockers that are used alone or in combination to treat hypertension. *Candesartan* is more potent than *irbesartan* because the dose range for *candesartan* is 4 to 32 mg, as compared to a dose range of 75 to 300 mg for *irbesartan*. *Candesartan* would be Drug A and *irbesartan* would be Drug B in Figure 2.6. An important contributing factor to the dimension of the EC_{50} is the affinity of the drug for the receptor. Semilogarithmic plots are often employed, because the range of doses (or concentrations) may span several orders of magnitude. By plotting the log of the concentration, the complete range of doses can be graphed. As shown in Figure 2.6B, the curves become sigmoidal in shape. It is also easier to visually estimate the EC_{50}.

2. **Efficacy [intrinsic activity]:** The second drug property that can be determined from graded doseâ€“response plots is the efficacy of the drug. This is the ability of a drug to illicit a physiologic response when it interacts with a receptor. Efficacy is dependent on the number of drugâ€“receptor complexes formed and the efficiency of the coupling of receptor activation to cellular responses. Analogous to the maximal velocity for enzyme-catalyzed reactions, the maximal response (E_{max}) or efficacy is more important than drug potency. A drug with

greater efficacy is more therapeutically beneficial than one that is more potent. Figure 2.7 shows the response to drugs of differing potency and efficacy.

3. **Drugâ€“receptor binding:** The quantitative relationship between drug concentration and receptor occupancy applies the law of mass action to the kinetics of the binding of drug and receptor molecules. By making the assumption that the binding of one drug molecule does not alter the binding of subsequent molecules, we can mathematically express the relationship between the percentage (or fraction) of bound receptors and the drug concentration:

$$\frac{[DR]}{[R_t]} = \frac{[D]}{K_d + [D]} \qquad (1)$$

where [D] = the concentration of free drug; [DR] = the concentration of bound drug; [R_t] = the total

concentration of receptors, and is equal to the sum of the concentrations of unbound (free) receptors and bound receptors and; $K_d = [D][R]/[DR]$, and is the dissociation constant for the drug from the receptor. The value of K_d can be used to determine the affinity of a drug for its receptor. Affinity describes the strength of the interaction (binding) between a ligand and its receptor. The higher the K_d value, the weaker the interaction and the lower the affinity. The converse occurs when a drug has a low K_d. The binding of the ligand to the receptor is strong, and the affinity is high. Equation (1) defines a curve that has the shape of a rectangular hyperbola (Figure 2.8). As the concentration of free drug increases, the ratio of the concentrations of bound receptors to total receptors approaches unity. Doses are often plotted on a logarithmic scale, because the range from lowest to highest concentrations of doses often spans several orders of magnitude. It is important to note the similarity between these curves and those representing the relationship between dose and effect.

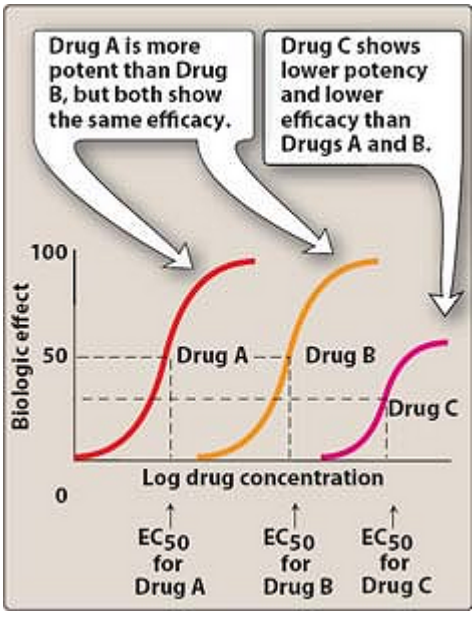


Figure 2.7 Typical dose-response curve for drugs showing differences in potency and efficacy. (EC_{50} = drug dose that shows fifty percent of maximal response.)

4. **Relationship of binding to effect:** The binding of the drug to its receptor initiates events that ultimately lead to a measurable biologic response. The mathematical model that describes drug concentration and receptor binding can be applied to dose (drug concentration) and response (or effect), providing the following assumptions are met: 1) The magnitude of the response is proportional to the amount of receptors bound or occupied, 2) the E_{max} occurs when all receptors are bound, and 3) binding of the drug to the receptor exhibits no cooperativity. In this case,

$$\frac{[E]}{[E_{max}]} = \frac{[D]}{K_d + [D]} \qquad (2)$$

where [E] = the effect of the drug at concentration [D] and [E_{max}] = the maximal effect of the drug.

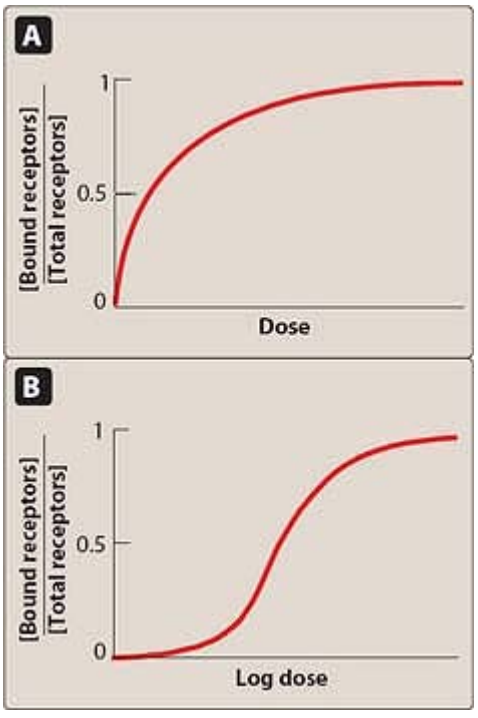


Figure 2.8 The effect of dose on the magnitude of drug binding.

5. **Agonists:** If a drug binds to a receptor and produces a biologic response that mimics the response to the endogenous ligand, it is known as an agonist. For example, *phenylephrine* is an agonist at Î±$_1$-adrenoceptors, because it produces effects that resemble the

action of the endogenous ligand, norepinephrine. Upon binding to Î±$_1$-adrenoceptors on the membranes of vascular smooth muscle, *phenylephrine* mobilizes intracellular Ca^{2+}, causing contraction of the actin and myosin filaments. The shortening of the muscle cells decreases the diameter of the arteriole, causing an increase in resistance to the flow of blood through the vessel. Blood pressure therefore rises to maintain the blood flow. As this brief description illustrates, an agonist may have many effects that can be measured, including actions on intracellular molecules, cells, tissues, and intact organisms. All of these actions are attributable to interaction of the drug molecule with the receptor molecule. In general, a full agonist has a strong affinity for its receptor and good efficacy.

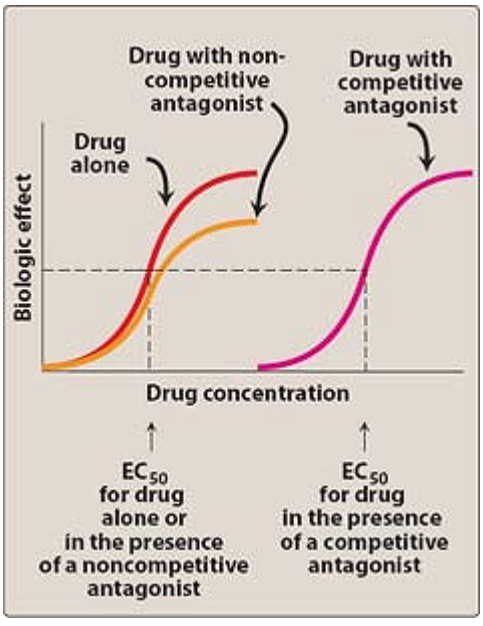


Figure 2.9 Effects of drug antagonists. EC_{50} = drug dose that shows fifty percent of maximal response.

6. **Antagonists:** Antagonists are drugs that decrease the actions of another drug or endogenous ligand. Antagonism may occur in several ways. Many antagonists act on the identical receptor macromolecule as the agonist. Antagonists, however, have no intrinsic activity and, therefore, produce no effect by themselves. Although antagonists have no intrinsic activity, they are able to bind avidly to target receptors because they possess strong affinity. If both the antagonist and the agonist bind to the same site on the receptor, they are said to be â€œcompetitive.â€ For example, the antihypertensive drug *prazosin* competes with the endogenous ligand, norepinephrine, at Î±$_1$-adrenoceptors, decreasing vascular smooth muscle tone and reducing blood pressure. Plotting the effect of the competitive antagonist characteristically causes a shift of the agonist doseâ€“response curve to the right. Competitive antagonists have no intrinsic activity. If the antagonist binds to a site other than where the agonist binds, the interaction is â€œnoncompetitiveâ€ or â€œallostericâ€ (Figure 2.9). [Note: A drug may also act as a chemical antagonist by combining with another drug and rendering it inactive. For example, *protamine* ionically binds to *heparin*, rendering it inactive and antagonizing *heparin's* anticoagulant effect.]

7. **Functional antagonism:** An antagonist may act at a completely separate receptor, initiating effects that are functionally opposite those of the agonist. A classic example is the antagonism by *epinephrine* to histamine-induced bronchoconstriction. Histamine binds to H_1 histamine receptors on bronchial smooth muscle, causing contraction and narrowing of the bronchial tree. *Epinephrine* is an agonist at Î²$_2$-adrenoceptors on bronchial smooth muscle, which causes the muscles to actively relax. This functional antagonism is also known as â€œphysiologic antagonism.â€

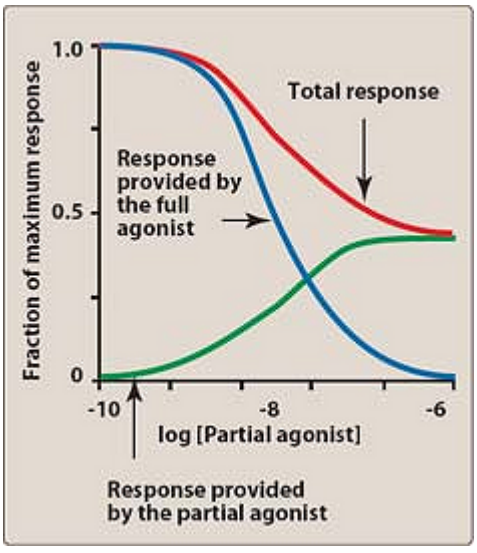


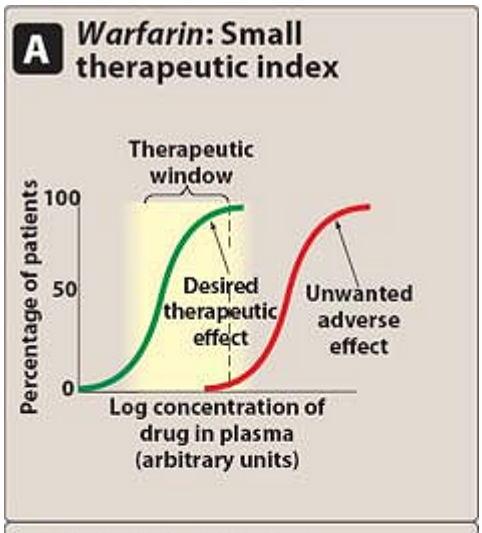
Figure 2.10 Effects of partial agonists.

8. **Partial agonists:** Partial agonists have efficacies (intrinsic activities) greater than zero, but less than that of a full agonist. Even if all the receptors are occupied, partial agonists cannot produce an E_{max} of as great a magnitude as that of a full agonist. However, a partial agonist may have an affinity that is greater than, less than, or equivalent to that of a full agonist. A unique feature of these drugs is that, under appropriate conditions, a partial agonist may act as an antagonist of a full agonist. Consider what would happen to the E_{max} of an agonist in the presence of increasing concentrations of a partial agonist (Figure 2.10). As the number of receptors occupied by the partial agonist increases, the E_{max} would decrease until it reached the E_{max} of the partial agonist. This potential of partial agonists to act both agonistically and antagonistically may be therapeutically exploited.

For example, *aripiprazole*, an atypical neuroleptic agent, is a partial agonist at selected dopamine receptors. Dopaminergic pathways that were overactive would tend to be inhibited by the partial agonist, whereas pathways that were underactive may be stimulated. This might explain the ability of *aripiprazole* to improve many of the symptoms of schizophrenia, with a small risk of causing extrapyramidal adverse effects (see p. 33).

VI. Quantal Doseâ€“Response Relationships

Another important doseâ€“response relationship is that of the influence of the magnitude of the dose on the proportion of a population that responds. These responses are known as quantal responses, because, for any individual, the effect either occurs or it does not. Even graded responses can be considered to be quantal if a predetermined level of the graded response is designated as the point at which a response occurs or not. For example, a quantal doseâ€“response relationship can be determined in a population for the antihypertensive drug *atenolol*. A positive response is defined as at least a 5 mm Hg fall in diastolic blood pressure. Quantal doseâ€“response curves are useful for determining doses to which most of the population responds.



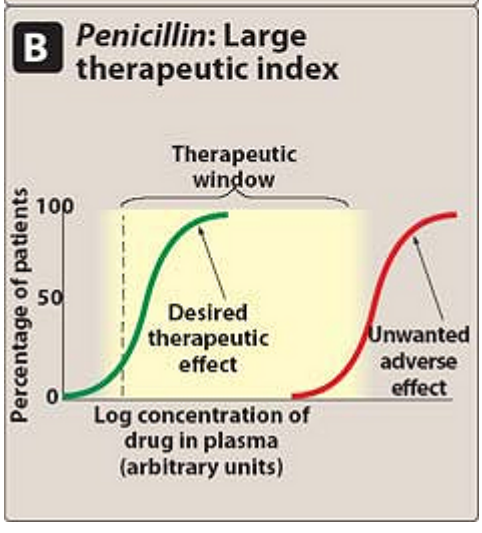


Figure 2.11 Cumulative percentage of patients responding to plasma levels of a drug.

A. Therapeutic index

The therapeutic index of a drug is the ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population of individuals:

$$C_t = C_0 - e^{-k_e t}$$

where TD_{50} = the drug dose that produces a toxic effect in half the population and ED_{50} = the drug dose that produces a therapeutic or desired response in half the population. The therapeutic index is a measure of a drug's safety, because a larger value indicates a wide margin between doses that are effective and doses that are toxic.

B. Determination of therapeutic index

The therapeutic index is determined by measuring the frequency of desired response, and toxic response, at various doses of drug. By convention, the doses that produce the therapeutic effect and the toxic effect in fifty percent of the population are employed; these are known as the ED_{50} and TD_{50}, respectively. In humans, the therapeutic index of a drug is determined using drug trials and accumulated clinical experience. These usually reveal a range of effective doses and a different (sometimes overlapping) range of toxic doses. Although some drugs have narrow

therapeutic indices, they are routinely used to treat certain diseases. Several lethal diseases, such as Hodgkin's lymphoma, are treated with narrow therapeutic index drugs; however, treatment of a simple headache, for example, with a narrow therapeutic index drug would be unacceptable. Figure 2.11 shows the responses to *warfarin*, an oral anti-coagulant with a narrow therapeutic index, and *penicillin*, an antimicrobial drug with a large therapeutic index.

1. **Warfarin (example of a drug with a small therapeutic index):** As the dose of *warfarin* is increased, a greater fraction of the patients respond (for this drug, the desired response is a two-fold increase in prothrombin time) until eventually, all patients respond (see Figure 2.11A). However, at higher doses of *warfarin*, a toxic response occurs,

   namely a high degree of anticoagulation that results in hemorrhage. [Note: that when the therapeutic index is low, it is possible to have a range of concentrations where the effective and toxic responses overlap. That is, some patients hemorrhage, whereas others achieve the desired two-fold prolongation of prothrombin time. Variation in patient response is, therefore, most likely to occur with a drug showing a narrow therapeutic index, because the effective and toxic concentrations are similar. Agents with a low therapeutic indexâ€"that is, drugs for which dose is critically importantâ€"are those drugs for which bioavailability critically alters the therapeutic effects (see p. 7).

2. **Penicillin (example of a drug with a large therapeutic index):** For drugs such as *penicillin* (see Figure 2.11B), it is safe and common to give doses in excess (often about ten-fold excess) of that which is minimally required to achieve a desired response. In this case, bioavailability does not critically alter the therapeutic effects.

Study Questions

Choose the ONE best answer.

2.1 Which of the following statements is correct?

A. If 10 mg of Drug A produces the same response as 100 mg of Drug B, Drug A is more efficacious than Drug B.

B. The greater the efficacy, the greater the potency of a drug.

C. In selecting a drug, potency is usually more important than efficacy.

D. A competitive antagonist increases the ED_{50}.

E. Variation in response to a drug among different individuals is most likely to occur with a drug showing a large therapeutic index.

View Answer

2.2 Variation in the sensitivity of a population of individuals to increasing doses of a drug is best determined by which of the following?

A. Efficacy.

B. Potency.

C. Therapeutic index.

D. Graded doseâ€"response curve.

E. Quantal doseâ€"response curve.

View Answer

2.3 Which of the following statements most accurately describes a system having spare receptors?

A. The number of spare receptors determines the maximum effect.

B. Spare receptors are sequestered in the cytosol.

C. A single drugâ€“receptor interaction results in many cellular response elements being activated.

D. Spare receptors are active even in the absence of agonist.

E. Agonist affinity for spare receptors is less than their affinity for nonspare receptors.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 3

The AutonomicNervous System

I. Overview

The autonomic nervous system, along with the endocrine system, coordinates the regulation and integration of bodily functions. The endocrine system sends signals to target tissues by varying the levels of blood-borne hormones. In contrast, the nervous system exerts its influence by the rapid transmission of electrical impulses over nerve fibers that terminate at effector cells, which specifically respond to the release of neuromediator substances. Drugs that produce their primary therapeutic effect by mimicking or altering the functions of the autonomic nervous system are called autonomic drugs and are discussed in the following four chapters. These autonomic agents act either by stimulating portions of the autonomic nervous system or by blocking the action of the autonomic nerves. This chapter outlines the fundamental physiology of the autonomic nervous system, and it describes the role of neurotransmitters in the communication between extracellular events and chemical changes within the cell.

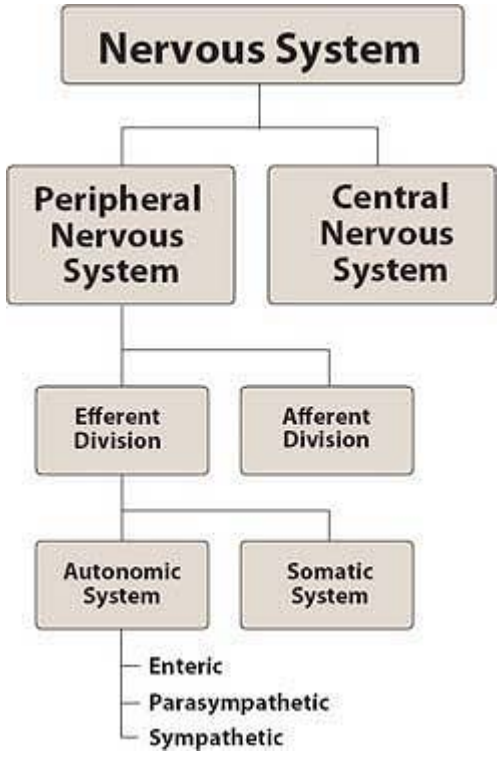


Figure 3.1 Organization of the nervous system.

II. Introduction to the Nervous System

The nervous system is divided into two anatomical divisions: the central nervous system (CNS), which is composed of the brain and spinal cord, and the peripheral nervous system, which includes neurons located outside the brain and spinal cordâ€"that is, any nerves that enter or leave the CNS (Figure 3.1). The peripheral nervous system is subdivided into the efferent division, the neurons of which carry signals away from the brain and spinal cord to the peripheral tissues, and the afferent division, the neurons of which bring information from the periphery to the CNS. Afferent neurons provide sensory input to modulate the function of the efferent division through reflex arcs, that is, neural pathways that mediate a reflex action.

A. Functional divisions within the nervous system

The efferent portion of the peripheral nervous system is further divided into two major functional subdivisions, the somatic and the autonomic systems (see Figure 3.1). The somatic efferent neurons are involved in the voluntary control of functions such as contraction of the skeletal muscles essential for locomotion. On the other hand, the autonomic system regulates the everyday requirements of vital bodily functions without the conscious participation of the mind. It is composed of efferent neurons that innervate smooth muscle of the viscera,

cardiac muscle, vasculature, and the exocrine glands, thereby controlling digestion, cardiac output, blood flow, and glandular secretions.

B. Anatomy of the autonomic nervous system

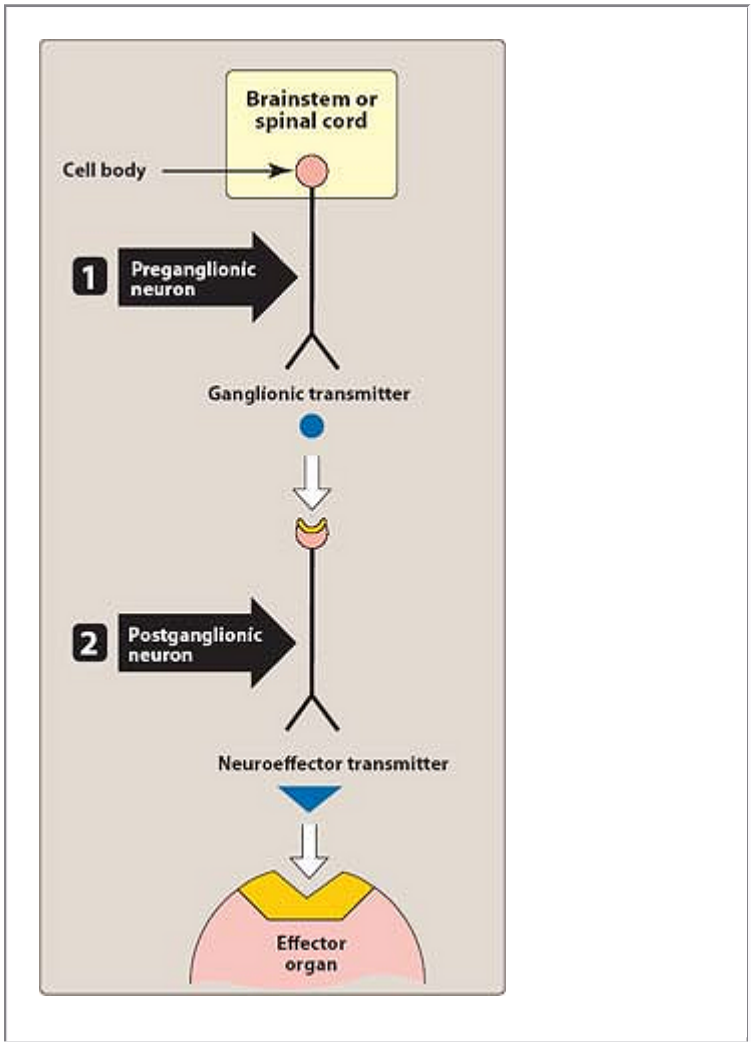


Figure 3.2 Efferent neurons of the autonomic nervous system.

1. **Efferent neurons:** The autonomic nervous system carries nerve impulses from the CNS to the effector organs by way of two types of efferent neurons (Figure 3.2). The first nerve cell is called a preganglionic neuron, and its cell body is located within the CNS. Preganglionic neurons emerge from the brainstem or spinal cord and make a synaptic connection in ganglia (an aggregation of nerve cell bodies located in the peripheral nervous system). These ganglia function as relay stations between a preganglionic neuron and a second nerve cell, the postganglionic neuron. The latter neuron has a cell body originating in the ganglion. It is generally nonmyelinated and terminates on effector organs, such as smooth muscles of the viscera, cardiac muscle, and the exocrine glands.
2. **Afferent neurons:** The afferent neurons (fibers) of the autonomic nervous system are important in the reflex regulation of this system (for example, by sensing pressure in the carotid sinus and aortic arch) and signaling the CNS to influence the efferent branch of the system to respond (see below).
3. **Sympathetic neurons:** The efferent autonomic nervous system is divided into the sympathetic and the parasympathetic nervous systems, as well as the enteric nervous system (see Figure 3.1). Anatomically, they originate in the CNS and emerge from two different spinal cord regions. The preganglionic neurons of the sympathetic system come from thoracic and lumbar regions of the spinal cord, and they synapse in two cord-like chains of ganglia that run in parallel on each side of the spinal cord. The preganglionic neurons are short in comparison to the postganglionic ones. Axons of the postganglionic neuron extend from these ganglia to the tissues that they innervate and regulate (see Chapter 6). [Note: The adrenal medulla, like the sympathetic ganglia, receives preganglionic fibers from the sympathetic system. Lacking axons, the adrenal medulla, in response to stimulation by the ganglionic neurotransmitter acetylcholine, influences other organs by secreting the hormone epinephrine, also known as adrenaline, and lesser amounts of norepinephrine into the blood.]
4. **Parasympathetic neurons:** The parasympathetic preganglionic fibers arise from the cranium (from cranial nerves III, VII, IX, and X) and from the sacral region of the spinal cord and synapse in ganglia near or on the effector organs. Thus, in contrast to the sympathetic system, the preganglionic fibers are long, and the postganglionic ones are short, with the ganglia close to or within the organ innervated. In most instances there is a one-to-one connection between the preganglionic and postganglionic neurons, enabling the discrete response of this division.
5. **Enteric neurons:** The enteric nervous system is the third division of the autonomic nervous system. It is a collection of nerve fibers that innervate the gastrointestinal tract, pancreas, and gallbladder, and it constitutes the â€œbrain of the gut.â€ This system functions independently of the CNS and controls the motility, exocrine and endocrine secretions, and microcirculation of the gastrointestinal tract. It is modulated by both the sympathetic and parasympathetic nervous systems.

C. Functions of the sympathetic nervous system

Although continually active to some degree (for example, in maintaining the tone of vascular beds), the sympathetic division has the property of adjusting in response to stressful situations, such as trauma, fear, hypoglycemia, cold, or exercise.

1. **Effects of stimulation of the sympathetic division:** The effect of sympathetic output is to increase heart rate and blood pressure, to mobilize energy stores of the body, and to increase blood flow to skeletal muscles and the heart while diverting flow from the skin and internal organs. Sympathetic stimulation results in dilation of the pupils and the bronchioles (Figure 3.3). It also affects gastrointestinal motility and the function of the bladder and sexual organs.
2. **Fight or flight response:** The changes experienced by the body during emergencies have been referred to as

the â€œfight or flightâ€ response (Figure 3.4). These reactions are triggered both by direct sympathetic activation of the effector organs and by stimulation of the adrenal medulla to release epinephrine and lesser amounts of norepinephrine. These hormones enter the bloodstream and promote responses in effector organs that contain adrenergic receptors (see Figure 6.6). The sympathetic nervous system tends to function as a unit, and it

often discharges as a complete systemâ€”for example, during severe exercise or in reactions to fear (see Figure 3.4). This system, with its diffuse distribution of postganglionic fibers, is involved in a wide array of physiologic activities, but it is not essential for life.

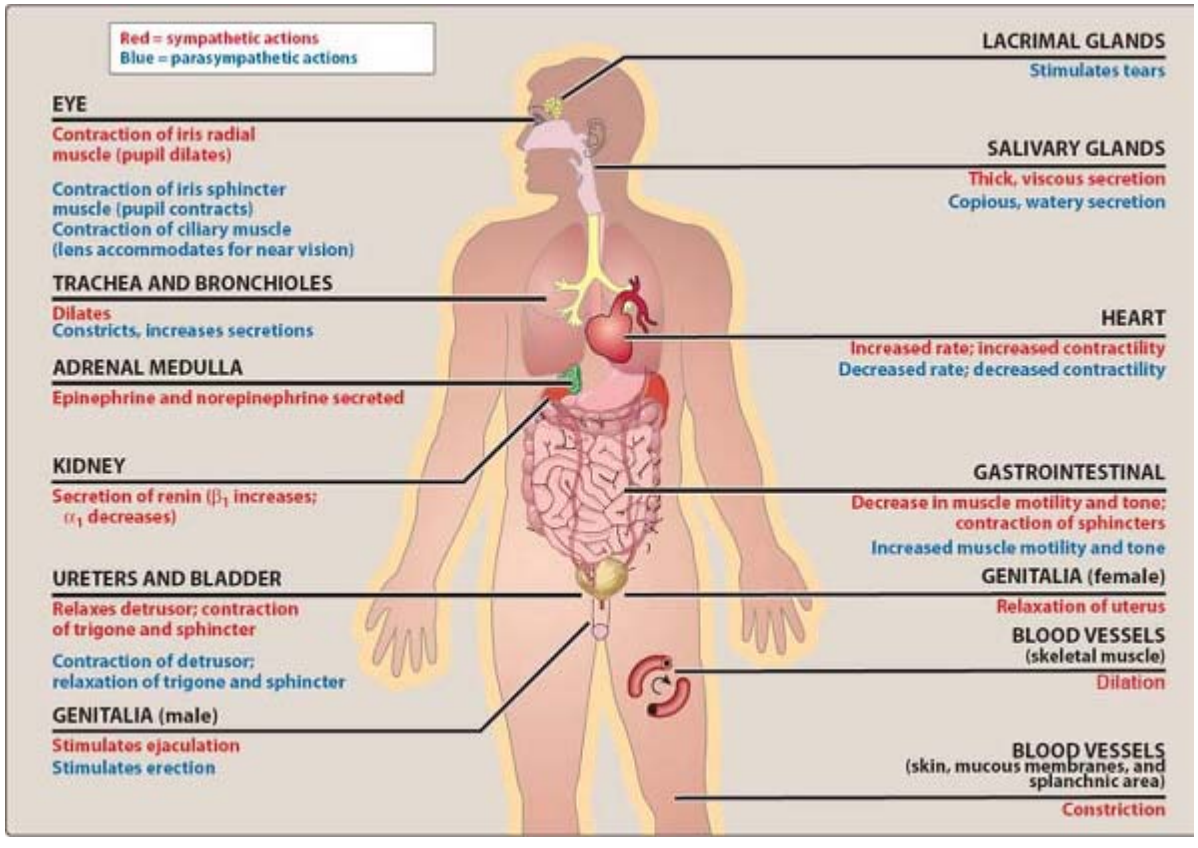


Figure 3.3 Action of sympathetic and parasympathetic nervous systems on effector organs.

D. Functions of the parasympathetic nervous system

The parasympathetic division maintains essential bodily functions, such as digestive processes and elimination of wastes, and is required for life. It usually acts to oppose or balance the actions of the sympathetic division and is generally dominant over the sympathetic system in â€œrest and digestâ€ situations. The parasympathetic system is not a functional entity as such, and it never discharges as a complete system. If it did, it would produce massive, undesirable, and unpleasant symptoms. Instead, discrete parasympathetic fibers are activated separately, and the system functions to affect specific organs, such as the stomach or eye.

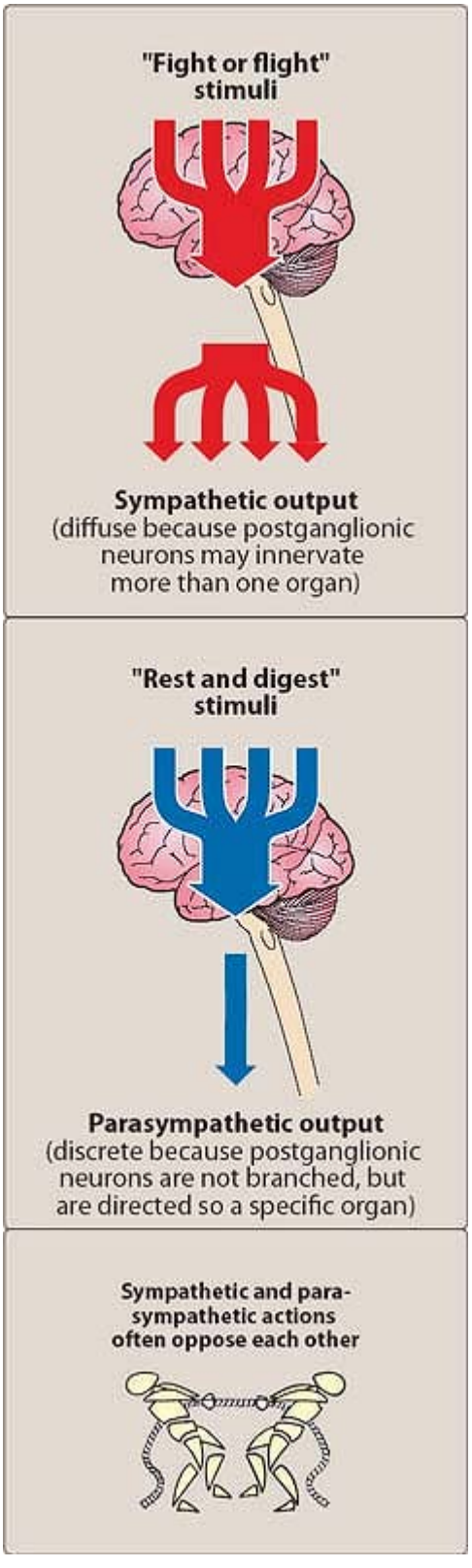


Figure 3.4 Sympathetic and parasympathetic actions are elicited by different stimuli.

E. Role of the CNS in autonomic control functions

Although the autonomic nervous system is a motor system, it does require sensory input from peripheral structures to provide information on the state of affairs in the body. This feedback is provided by streams of afferent impulses, originating in the viscera and other autonomically innervated structures, that travel to integrating centers in the CNSâ€"that is, the hypothalamus, medulla oblongata, and spinal cord. These centers respond to the stimuli by sending out efferent reflex impulses via the autonomic nervous system (Figure 3.5).

1. **Reflex arcs:** Most of the afferent impulses are translated into reflex responses without involving consciousness. For example, a fall in blood pressure causes pressure-sensitive neurons (baroreceptors in the heart, vena cava, aortic arch, and carotid sinuses) to send fewer impulses to cardiovascular centers in the brain. This prompts a reflex response of increased sympathetic output to the heart and vasculature and decreased parasympathetic output to the heart, which results in a compensatory rise in blood pressure and tachycardia (see Figure 3.5). [Note: In each case, the reflex arcs of the autonomic nervsous system comprise a sensory (or afferent) arm, and a motor (or efferent, or effector) arm.]
2. **Emotions and the autonomic nervous system:** Stimuli that evoke feelings of strong emotion, such as rage, fear, or pleasure, can modify the activity of the autonomic nervous system.

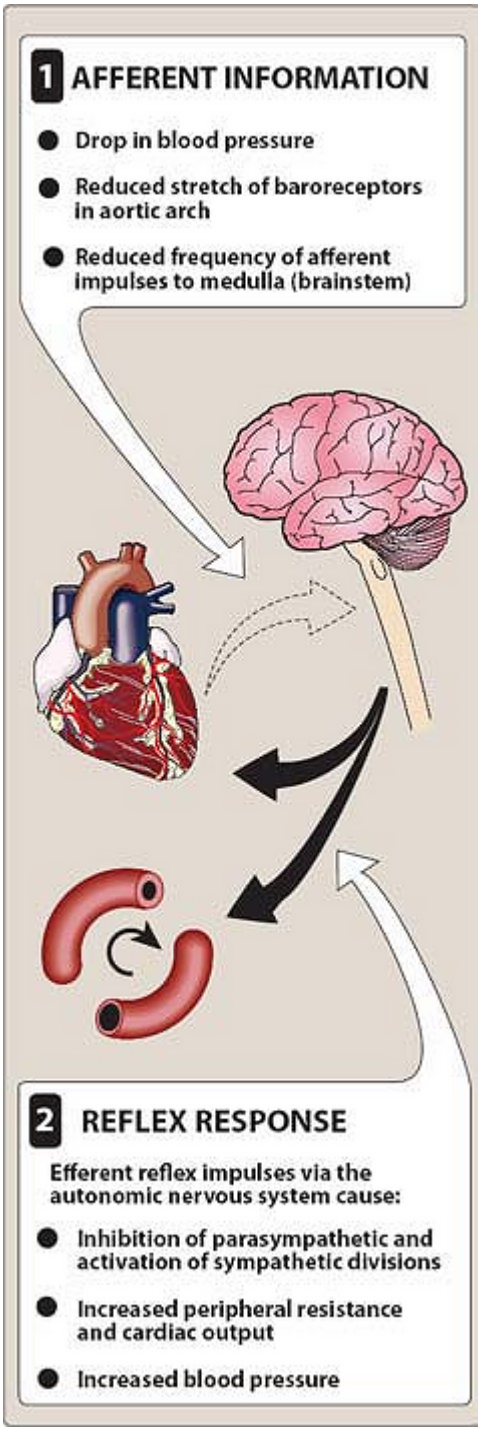


Figure 3.5 Baroreceptor reflex arc responds to a decrease in blood pressure.

F. Innervation by the autonomic nervous system

1. **Dual innervation:** Most organs in the body are innervated by both divisions of the autonomic nervous system. Thus, vagal parasympathetic innervation slows the heart rate, and sympathetic innervation increases the heart rate. Despite this dual innervation, one system usually predominates in controlling the activity of a given organ.

For example, in the heart, the vagus nerve is the predominant factor for controlling rate. This type of antagonism is considered to be dynamic and is fine-tuned at any given time to control homeostatic organ functions.

2. **Organs receiving only sympathetic innervation:** Although most tissues receive dual innervation, some effector organs, such as the

adrenal medulla, kidney, pilomotor muscles, and sweat glands, receive innervation only from the sympathetic system. The control of blood pressure is also mainly a sympathetic activity, with essentially no participation by the parasympathetic system.

G. Somatic nervous system

The efferent somatic nervous system differs from the autonomic system in that a single myelinated motor neuron, originating in the CNS, travels directly to skeletal muscle without the mediation of ganglia. As noted earlier, the somatic nervous system is under voluntary control, whereas the autonomic is an involuntary system.

III. Chemical Signaling Between Cells

Neurotransmission in the autonomic nervous system is an example of the more general process of chemical signaling between cells. In addition to neurotransmission, other types of chemical signaling are the release of local mediators and the secretion of hormones.

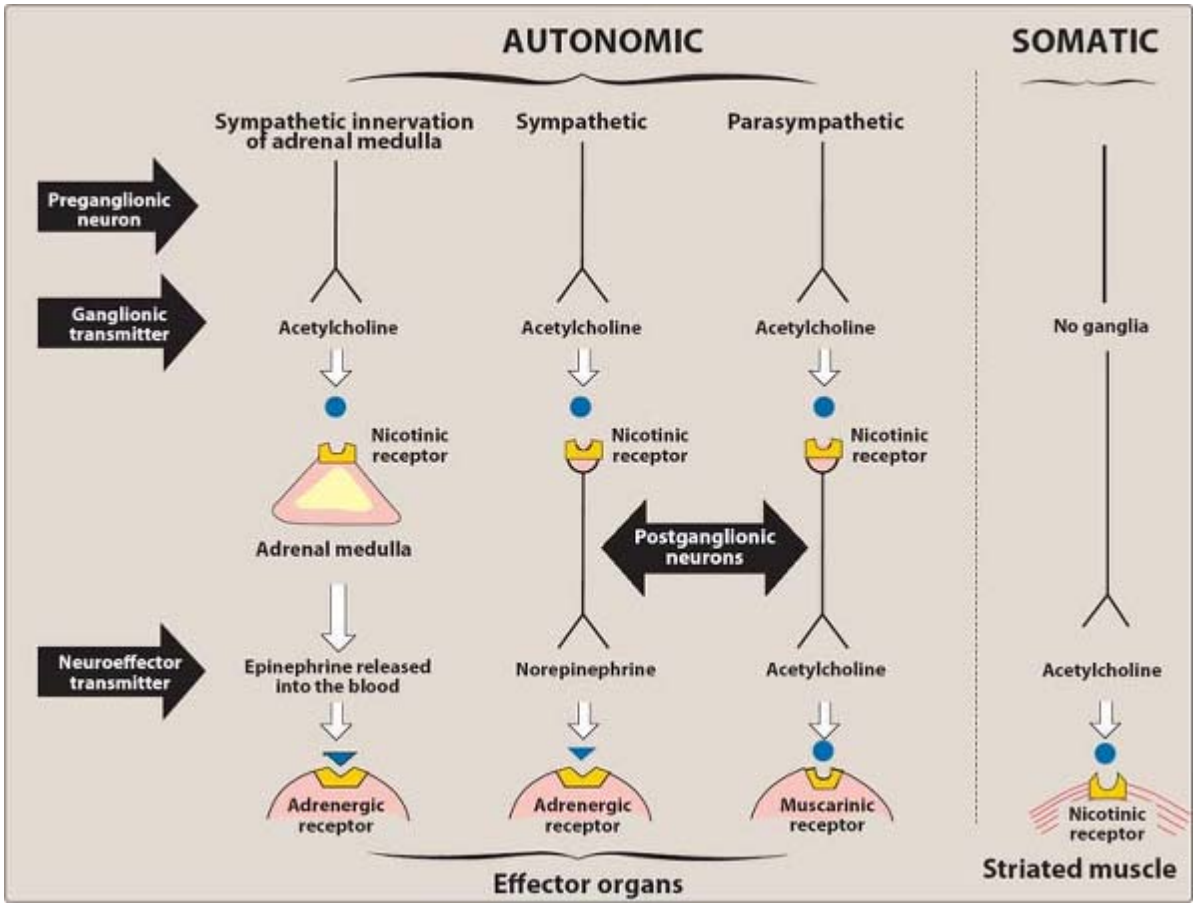


Figure 3.6 Summary of the neurotransmitters released and the types of receptors found within the autonomic

and somatic nervous systems. [Note: This schematic diagram does not show that the parasympathetic ganglia are close to or on the surface of the effector organs and that the postganglionic fibers are usually shorter than the preganglionic fibers. By contrast, the ganglia of the sympathetic nervous system are close to the spinal cord. The postganglionic fibers are long, allowing extensive branching to innervate more than one organ system. This allows the sympathetic nervous system to discharge as a unit.]

A. Local mediators

Most cells in the body secrete chemicals that act locallyâ€"that is, on cells in their immediate environment. These chemical signals are rapidly destroyed or removed; therefore, they do not enter the blood and are not distributed throughout the body. Histamine (see p. 520) and the prostaglandins (see p. 519) are examples of local mediators.

B. Hormones

Specialized endocrine cells secrete hormones into the bloodstream, where they travel throughout the body exerting effects on broadly distributed target cells in the body. (Hormones are described in Chapters 23 through 26.)

C. Neurotransmitters

All neurons are distinct anatomic units, and no structural continuity exists between most neurons. Communication between nerve cellsâ€"and between nerve cells and effector organsâ€"occurs through the release of specific chemical signals, called neurotransmitters, from the nerve terminals. This release is triggered by the arrival of the action potential at the nerve ending, leading to depolarization. Uptake of Ca^{2+} initiates fusion of the synaptic vesicles with the presynaptic membrane and release of their contents. The neurotransmitters rapidly diffuse across the synaptic cleft or space (synapse) between neurons and combine with specific receptors on the postsynaptic (target) cell (Figure 3.6 and see Chapter 2).

1. **Membrane receptors:** All neurotransmitters and most hormones and local mediators are too hydrophilic to penetrate the lipid bilayer of target-cell plasma membranes. Instead, their signal is mediated by binding to specific receptors on the cell surface of target organs. [Note: A receptor is defined as a recognition site for a substance. It has a binding specificity, and it is coupled to processes that eventually evoke a response. Most receptors are proteins. They need not be located in the membrane (see Chapter 2).]

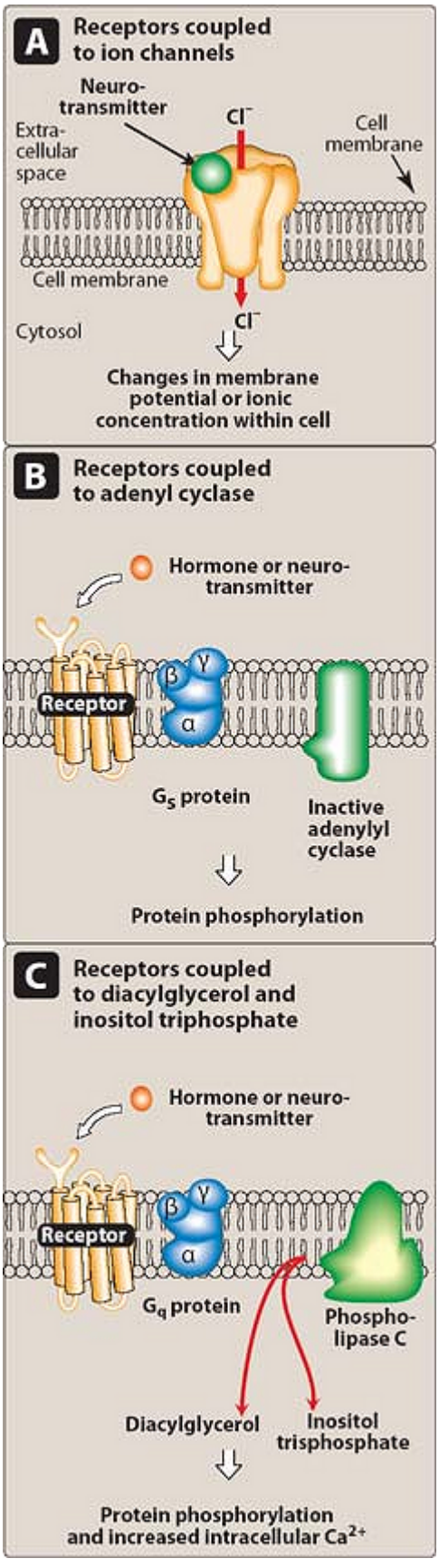

A
Receptors coupled to ion channels
Neuro-transmitter
Extra-cellular space
Cl⁻
Cell membrane
Cell membrane
Cytosol
Cl⁻
Changes in membrane potential or ionic concentration within cell
B
Receptors coupled to adenyl cyclase
Hormone or neuro-transmitter
Receptor
β
γ
α
Gs protein
Inactive adenylyl cyclase
Protein phosphorylation
C
Receptors coupled to diacylglycerol and inositol triphosphate
Hormone or neuro-transmitter
Receptor
β
γ
α
Gq protein
Phospho-lipase C
Diacylglycerol
Inositol trisphosphate
Protein phosphorylation and increased intracellular Ca2+

Figure 3.7 Three mechanisms whereby binding of a neurotransmitter leads to a cellular effect.

2. **Types of neurotransmitters:** Although over fifty signal molecules in the nervous system have tentatively been identified, six signal compoundsâ€"norepinephrine (and the closely related epinephrine), acetylcholine, dopamine, serotonin, histamine, and Î³-aminobutyric acidâ€"are most commonly involved in the actions of therapeutically useful drugs. Each of these chemical signals binds to a specific family of receptors. Acetylcholine and norepinephrine are the primary chemical signals in the autonomic nervous system, whereas a wide variety of neurotransmitters function in the CNS. Not only are these neurotransmitters released on nerve stimulation, cotransmitters, such as adenosine, often accompany them and modulate the transmission process.

   a. **Acetylcholine:** The autonomic nerve fibers can be divided into two groups based on the chemical nature of the neurotransmitter released. If transmission is mediated by acetylcholine, the neuron

   is termed cholinergic (see Chapters 4 and 5). Acetylcholine mediates the transmission of nerve impulses across autonomic ganglia in both the sympathetic and parasympathetic nervous systems. It is the neurotransmitter at the adrenal medulla. Transmission from the autonomic postganglionic nerves to the effector organs in the parasympathetic system and a few sympathetic system organs also involves the release of acetylcholine. In the somatic nervous system, transmission at the neuromuscular junction (that is, between nerve fibers and voluntary muscles) is also cholinergic (see Figure 3.6).

   b. **Norepinephrine and epinephrine:** When norepinephrine or epinephrine is the transmitter, the fiber is termed adrenergic (adrenaline being another name for epinephrine). In the sympathetic system, norepinephrine mediates the transmission of nerve impulses from autonomic postganglionic nerves to effector organs. Norepinephrine and adrenergic receptors are discussed in Chapters 6 and 7. A summary of the neuromediators released and the type of receptors within the peripheral nervous system is shown in Figure 3.6. [Note: A few sympathetic fibers, such as those involved in sweating, are cholinergic; for simplicity, they are not shown in the figure.]

IV. Secondâ€"Messenger Systems in Intracellular Response

The binding of chemical signals to receptors activates enzymatic processes within the cell membrane that ultimately result in a cellular response, such as the phosphorylation of intracellular proteins or changes in the conductivity of ion channels. A neurotransmitter can be thought of as a signal and a receptor as a signal detector and transducer. Second-messenger molecules, produced in response to neurotransmitter binding to a receptor, translate the extracellular signal into a response that may be further propagated or amplified within the cell. Each component serves as a link in the communication between extracellular events and chemical changes within the cell (see Chapter 2).

A. Membrane receptors affecting ion permeability

Neurotransmitter receptors are membrane proteins that provide a binding site that recognizes and responds to neurotransmitter molecules. Some receptors, such as the postsynaptic receptors of nerve or muscle, are directly linked to membrane ion channels; thus, binding of the neurotransmitter occurs rapidly (within fractions of a millisecond) and directly affects ion permeability (Figure 3.7A). [Note: The effect of acetylcholine on these chemically gated ion channels is discussed on p. 27.]

B. Regulation involving second-messenger molecules

Many receptors are not directly coupled to ion gates. Rather, the receptor signals its recognition of a bound neurotransmitter by initiating a series of reactions, which ultimately results in a specific intracellular response. Second-messenger moleculesâ€"so named because they intervene between the original message (the

neurotransmitter or hormone) and the ultimate effect on the cellâ€”are part of the cascade of events that translates neurotransmitter binding into a cellular response, usually through the intervention of a G protein. The two most widely recognized

second messengers are the adenylyl cyclase system and the calcium/phosphatidylinositol system (Figure 3.7B and C). [Note: G_s is the protein involved in the activation of adenylyl cyclase, and G_q is the subunit that activates phospholipase C to release diacylglycerol and inositol trisphosphate (see p. 27).]

Study Questions

Choose the ONE best answer.

3.1 Which one of the following statements concerning the parasympathetic nervous system is correct?

A. The parasympathetic system uses norepinephrine as a neurotransmitter.

B. The parasympathetic system often discharges as a single, functional system.

C. The parasympathetic division is involved in accommodation of near vision, movement of food, and urination.

D. The postganglionic fibers of the parasympathetic division are long compared to those of the sympathetic nervous system.

E. The parasympathetic system controls the secretion of the adrenal medulla.

View Answer

3.2 Which one of the following is characteristic of parasympathetic stimulation?

A. Decrease in intestinal motility.

B. Inhibition of bronchial secretion.

C. Contraction of sphincter muscle in the iris of the eye (miosis).

D. Contraction of sphincter of urinary bladder.

E. Increase in heart rate.

View Answer

3.3 Which of the following is characteristic of the sympathetic nervous system.

A. A discrete response to activation

B. Actions mediated by muscarinic and nicotinic receptors

C. Effects only mediated by norepinephrine

D. Responses predominate during physical activity or when one is frightened

E. Subjected to voluntary control

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 4

Cholinergic Agonists

I. Overview

Drugs affecting the autonomic nervous system are divided into two groups according to the type of neuron involved in their mechanism of action. The cholinergic drugs, which are described in this and the following chapter, act on receptors that are activated by acetylcholine. The second groupâ€"the adrenergic drugs (discussed in Chapters 6 and 7)â€"act on receptors that are stimulated by norepinephrine or epinephrine. Cholinergic and adrenergic drugs both act by either stimulating or blocking receptors of the autonomic nervous system. Figure 4.1 summarizes the cholinergic agonists discussed in this chapter.

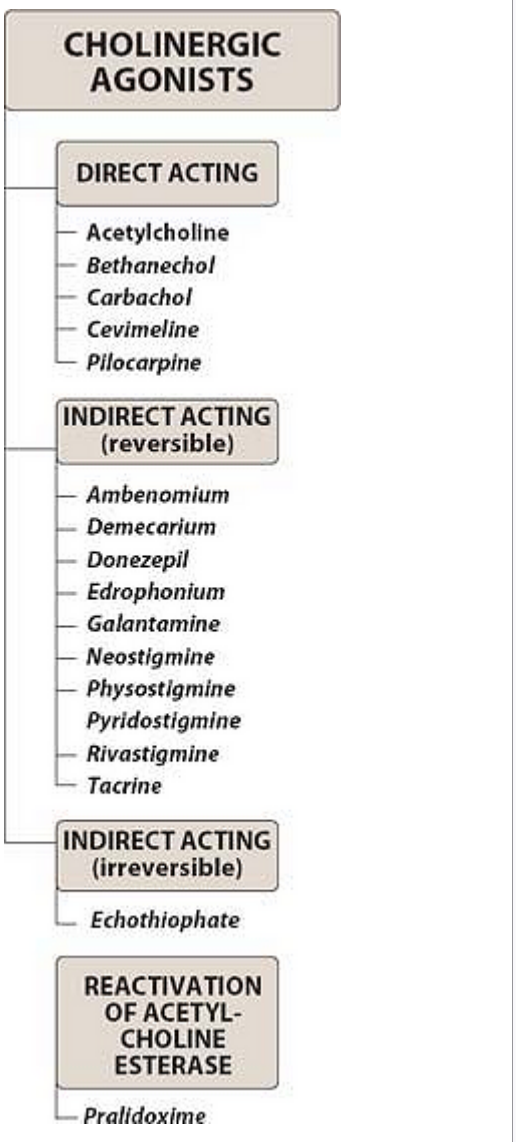


Figure 4.1 Summary of cholinergic agonists.

II. The Cholinergic Neuron

The preganglionic fibers terminating in the adrenal medulla, the autonomic ganglia (both parasympathetic and sympathetic), and the postganglionic fibers of the parasympathetic division use acetylcholine as a neurotransmitter (Figure 4.2). In addition, cholinergic neurons innervate the muscles of the somatic system and also play an important role in the central nervous system (CNS). [Note: Patients with Alzheimer's disease have a significant loss of cholinergic neurons in the temporal lobe and entorhinal cortex. Most of the drugs available to treat the disease are acetylcholinesterase inhibitors (see p. 102).]

A. Neurotransmission at cholinergic neurons

Neurotransmission in cholinergic neurons involves sequential six steps. The first fourâ€"synthesis, storage, release, and binding of acetylcholine to a receptorâ€"are followed by the fifth step, degradation of the neurotransmitter in the synaptic gap (that is, the space between the nerve endings and adjacent receptors located on nerves or

effector organs), and the sixth step, the recycling of choline (Figure 4.3).

1. **Synthesis of acetylcholine:** Choline is transported from the extra-cellular fluid into the cytoplasm of the cholinergic neuron by an energy-dependent carrier system that cotransports sodium and that can be inhibited by the drug *hemicholinium*. [Note: Choline has a quaternary nitrogen and carries a permanent positive charge, and thus, cannot diffuse through the membrane.] The uptake of choline is the rate-limiting step in acetylcholine synthesis. Choline acetyltransferase catalyzes the reaction of choline with acetyl coenzyme A (CoA) to form acetylcholineâ€"an esterâ€"in the cytosol. Acetyl CoA is derived from the mitochondria and is produced by the Krebs cycle and fatty acid oxidation.

2. **Storage of acetylcholine in vesicles:** The acetylcholine is packaged into presynaptic vesicles by an active transport process coupled to the efflux of protons. The mature vesicle contains not only acetylcholine but also adenosine triphosphate (ATP) and proteoglycan. [Note: ATP has been suggested to be a cotransmitter acting at prejunctional purinergic receptors to inhibit the release of acetylcholine or norepinephrine.] Cotransmission from autonomic neurons is the rule rather than the exception. This means that most synaptic vesicles will contain the primary neurotransmitter, here acetylcholine, as well as a cotransmitter that will increase or decrease the effect of the primary neurotransmitter. The neurotransmitters in vesicles will appear as bead-like structures, known as varicosities, along the nerve terminal of the presynaptic neuron.
3. **Release of acetylcholine:** When an action potential propagated by the action of voltage-sensitive sodium channels arrives at a nerve ending, voltage-sensitive calcium channels on the presynaptic membrane open, causing an increase in the concentration of intracellular calcium. Elevated calcium levels promote the fusion of synaptic vesicles with the cell membrane and release of their contents into the synaptic space. This release can be blocked by botulinum toxin. In

contrast, the toxin in black widow spider venom causes all the acetylcholine stored in synaptic vesicles to empty into the synaptic gap.

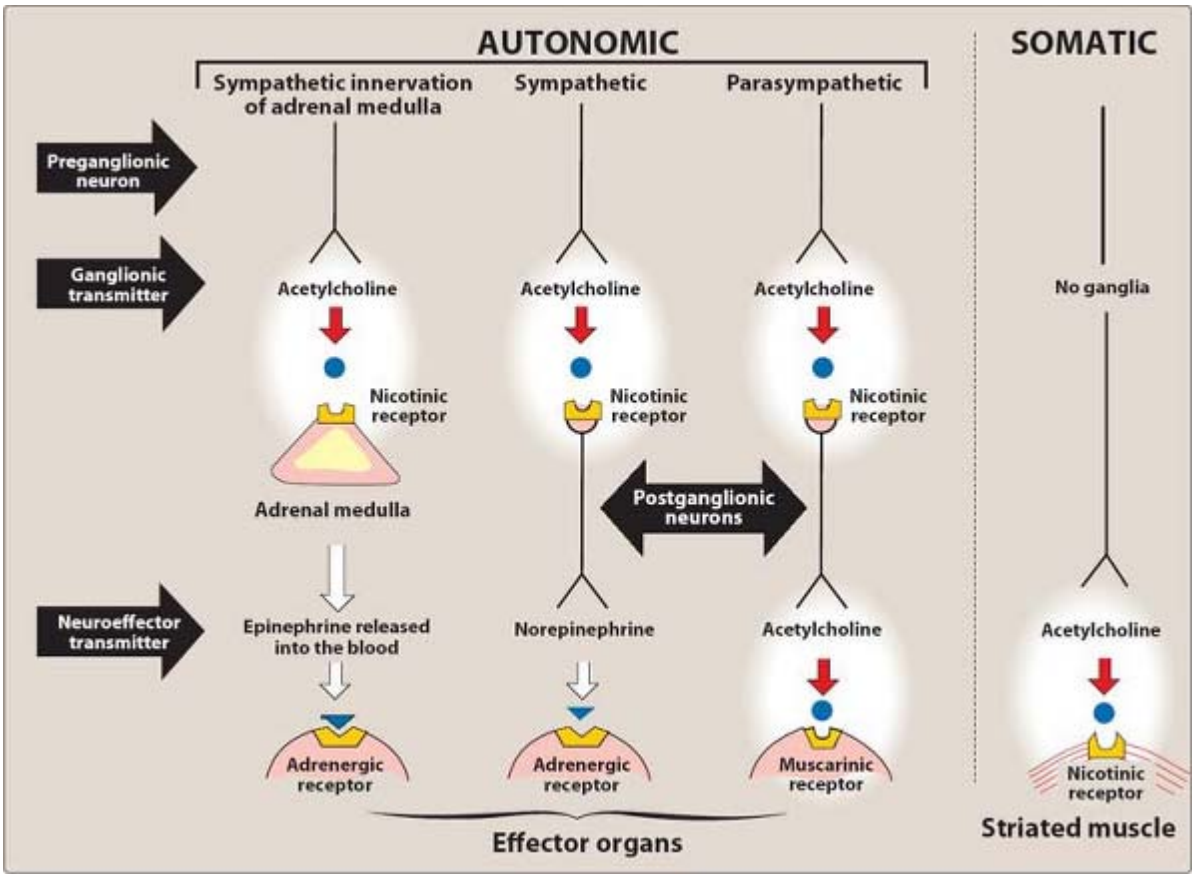


Figure 4.2 Sites of actions of cholinergic agonists in the autonomic and somatic nervous systems.

4. **Binding to the receptor:** Acetylcholine released from the synaptic vesicles diffuses across the synaptic space, and it binds to either of two postsynaptic receptors on the target cell or to presynaptic receptors in the membrane of the neuron that released the acetylcholine. The postsynaptic cholinergic receptors on the surface of the effector organs are divided into two classesâ€"muscarinic and nicotinic. (see Figure 4.2 and p. 46). Binding to a receptor leads to a biologic response within the cell, such as the initiation of a nerve impulse in a postganglionic fiber or activation of specific enzymes in effector cells as mediated by second-messenger molecules (see p. 27 and below).

5. **Degradation of acetylcholine:** The signal at the postjunctional effector site is rapidly terminated, because acetylcholinesterase cleaves acetylcholine to choline and acetate in the synaptic cleft (see Figure 4.3). [Note: Butyrylcholinesterase, sometimes called pseudocholinesterase,

is found in the plasma, but it does not play a significant role in termination of acetylcholine's effect in the synapse.]

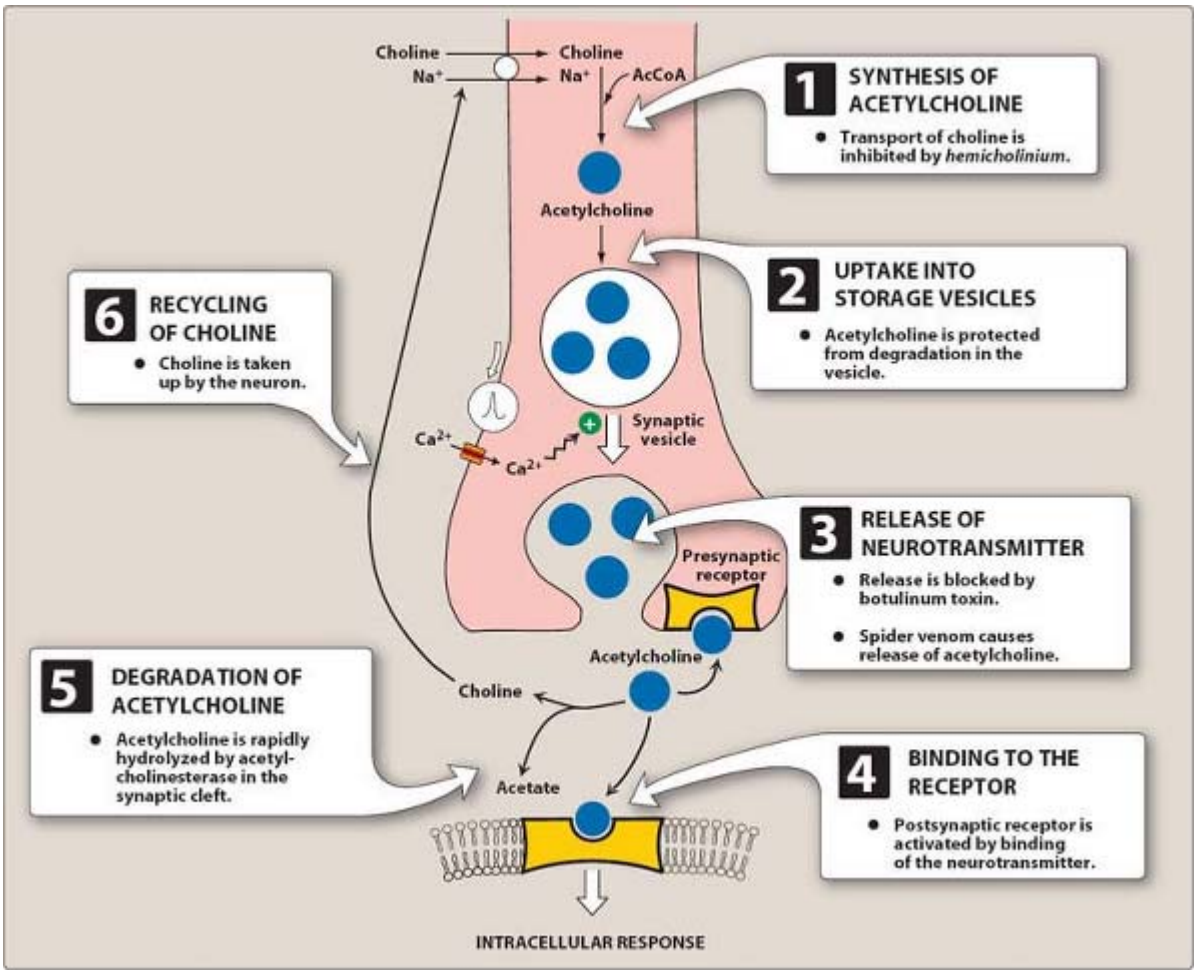


Figure 4.3 Synthesis and release of acetylcholine from the cholinergic neuron. AcCoA = acetyl coenzyme A.

6. **Recycling of choline:** Choline may be recaptured by a sodium-coupled, high-affinity uptake system that transports the molecule back into the neuron, where it is acetylated into acetylcholine that is stored until released by a subsequent action potential.

III. Cholinergic Receptors (Cholinoceptors)

Two families of cholinoceptors, designated muscarinic and nicotinic receptors, can be distinguished from each other on the basis of their different affinities for agents that mimic the action of acetylcholine (cholinomimetic agents or parasympathomimetics).

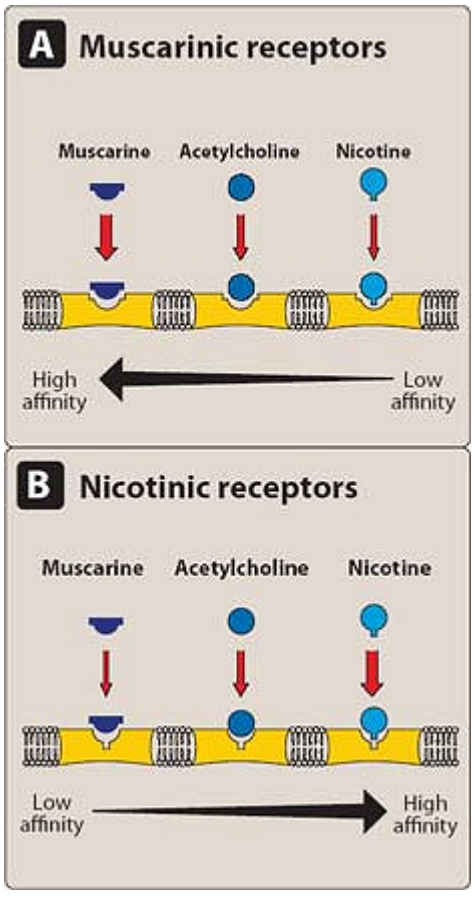


Figure 4.4 Types of cholinergic receptors.

A. Muscarinic receptors

These receptors, in addition to binding acetylcholine, also recognize muscarine, an alkaloid that is present in certain poisonous mushrooms. By contrast, the muscarinic receptors show only a weak affinity for nicotine (Figure 4.4A). Binding studies and specific inhibitors, as well as cDNA characterization, have distinguished five subclasses of muscarinic receptors: M_1, M_2, M_3, M_4, and M_5. Although five muscarinic receptors have been identified by gene cloning, only M_1, M_2 and M_3, receptors have been functionally characterized.

1. **Locations of muscarinic receptors:** These receptors have been found on ganglia of the peripheral nervous system and on the autonomic effector organs, such as the heart, smooth muscle, brain, and exocrine glands (see Figure 3.3, p. 37). Specifically, although all five subtypes have been found on neurons, M_1 receptors are also found on gastric parietal cells, M_2 receptors on cardiac cells and smooth muscle, and M_3 receptors on the bladder, exocrine glands, and smooth muscle. [Note: Drugs with muscarinic actions preferentially stimulate muscarinic receptors on these tissues, but at high concentration they may show some activity at nicotinic receptors.]

2. **Mechanisms of acetylcholine signal transduction:** A number of different molecular mechanisms transmit the signal generated by acetylcholine occupation of the receptor. For example, when the M_1 or M_3 receptors are activated, the receptor undergoes a conformational change and interacts with a G protein, designated G_q, which in turn activates phospholipase C.[1] This leads to the hydrolysis of phosphatidylinositol-(4,5)-bisphosphate-P_2 to yield diacylglycerol and inositol (1,4,5)-trisphosphate (formerly

called inositol (1,4,5)-triphosphate), which cause an increase in intracellular Ca^{2+} (see Figure 3.7C, p. 41). This cation can then interact to stimulate or inhibit enzymes, or cause hyperpolarization, secretion, or contraction. In contrast, activation of the M_2 subtype on the cardiac muscle stimulates a G protein, designated G_i, that inhibits adenylyl cyclase[2] and increases K^+ conductance (see Figure 3.7B, p. 41), to which the heart responds with a decrease in rate and force of contraction.

3. **Muscarinic agonists and antagonists:** Attempts are currently underway to develop muscarinic agonists and antagonists that are directed against specific receptor subtypes. For example, *pirenzepine*, a tricyclic anticholinergic drug, has a greater selectivity for inhibiting M_1 muscarinic receptors, such as in the gastric mucosa. At therapeutic doses, *pirenzepine* does not cause many of the side effects seen with the non-subtype-specific drugs; however, it does produce a reflex tachycardia on rapid infusion due to blockade of M_2 receptors in the heart. Therefore, the usefulness of *pirenzepine* as an alternative to proton pump inhibitors in the treatment of gastric and duodenal ulcers is questionable. *Darifenacin* is a competitive muscarinic receptor antagonist with a greater affinity for the M_3 receptor than for the other muscarinic receptors. The drug is used in the treatment of overactive bladder. [Note: At present, no clinically important agents interact solely with the M_4 and M_5 receptors.]

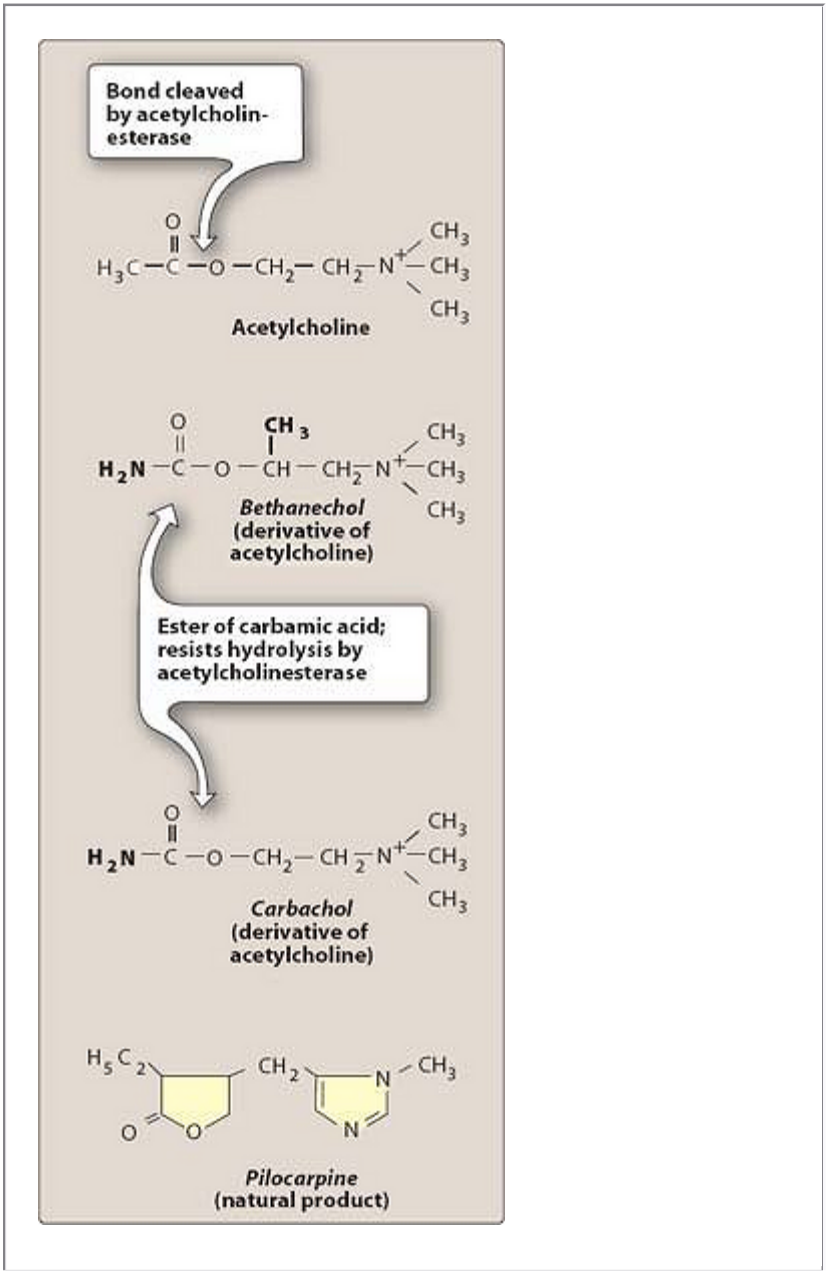


Figure 4.5 Comparison of the structures of some cholinergic agonists.

4. **Nicotinic receptors:** These receptors, in addition to binding acetylcholine, also recognize nicotine but show only a weak affinity for muscarine (see Figure 4.4B). The nicotinic receptor is composed of five subunits, and it functions as a ligand-gated ion channel (see Figure 3.7A). Binding of two acetylcholine molecules elicits a conformational change that allows the entry of sodium ions, resulting in the depolarization of the effector cell. Nicotine (or acetylcholine) initially stimulates and then blocks the receptor. Nicotinic receptors are located in the CNS, adrenal medulla, autonomic ganglia, and the neuromuscular junction. Those at the neuromuscular junction are sometimes designated N_M and the others N_N. The nicotinic receptors of autonomic ganglia differ from those of the neuromuscular junction. For example, ganglionic receptors are selectively blocked by *hexamethonium*, whereas neuromuscular junction receptors are specifically blocked by *tubocurarine.*

IV. Direct-Acting Cholinergic Agonists

Cholinergic agonists (also known as parasympathomimetics) mimic the effects of acetylcholine by binding directly to cholinoceptors. These agents may be broadly classified into two groups: choline esters, which include acetylcholine and synthetic esters of choline, such as *carbachol* and *bethanechol*.Naturally occurring alkaloids, such as *pilocarpine* constitue the second group (Figure 4.5). All of the direct-acting cholinergic drugs have longer durations of action than acetylcholine. Some of the more therapeutically useful drugs (*pilocarpine* and *bethanechol*) preferentially bind to muscarinic receptors and are sometimes referred to as muscarinic agents. [Note: Muscarinic receptors are located primarily, but not exclusively, at the neuroeffector junction of the parasympathetic nervous system.] However, as a group, the direct-acting agonists show little specificity in their actions, which limits their clinical usefulness.

A. Acetylcholine

Acetylcholine [a-se-teel-KOE-leen] is a quaternary ammonium compound that cannot penetrate membranes. Although it is the neurotransmitter of parasympathetic and somatic nerves as well as autonomic ganglia, it is therapeutically of no importance because of its multiplicity of actions and its rapid inactivation by the cholinesterases. Acetylcholine has both muscarinic and nicotinic activity. Its actions include:

1. **Decrease in heart rate and cardiac output:** The actions of acetylcholine on the heart mimic the effects of vagal stimulation. For example, acetylcholine, if injected intravenously, produces a brief decrease in cardiac rate (negative chronotropy) and stroke volume as a result of a reduction in the rate of firing at the sinoatrial (SA) node. [Note: It should be remembered that normal vagal activity regulates the heart by the release of acetylcholine at the SA node.]

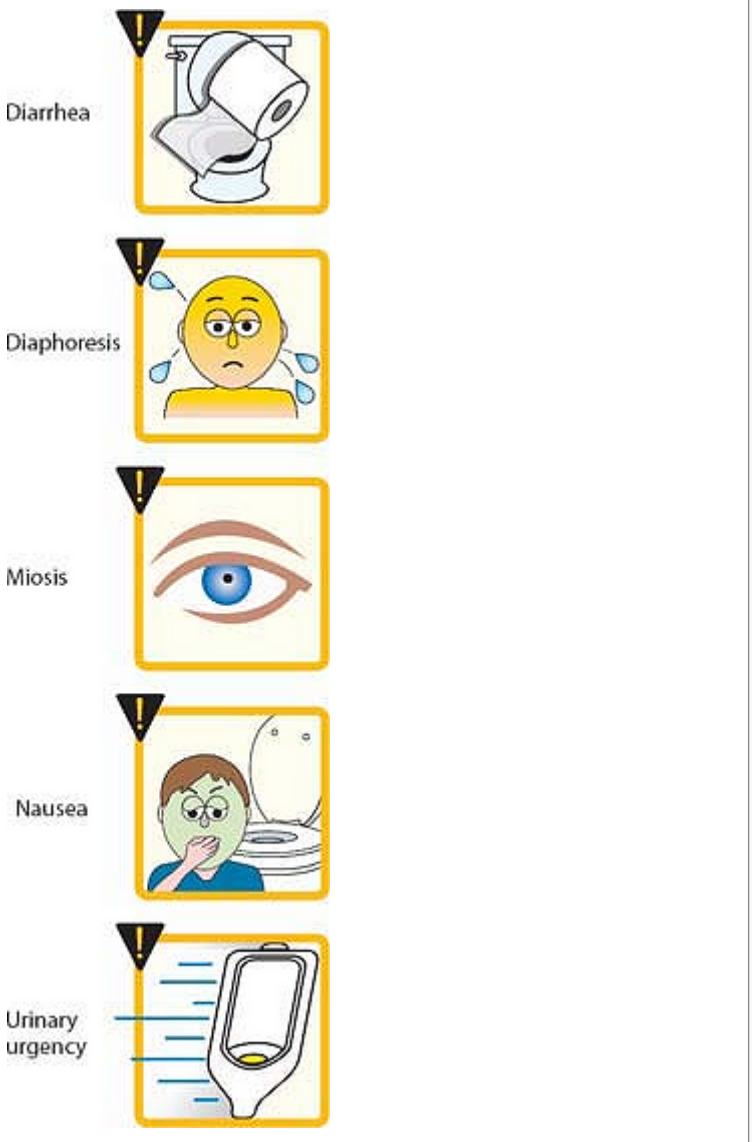


Figure 4.6 Some adverse effects observed with cholinergic drugs.

2. **Decrease in blood pressure:** Injection of acetylcholine causes vasodilation and lowering of blood pressure by an indirect mechanism of action. Acetylcholine activates M_3 receptors found on endothelial cells lining the smooth muscles of blood vessels. This results in the production of nitric oxide from arginine.[3] [Note: nitric oxide is also known as endothelium-derived relaxing factor.] (See p. 341 for more detail on nitric oxide.) Nitric oxide then diffuses to vascular smooth muscle cells to stimulate protein kinase G production, leading to hyperpolarization and smooth muscle relaxation. In the absence of administered cholinergic agents, the vascular receptors have no known function, because acetylcholine is never released into the blood in any significant quantities. *Atropine* blocks these muscarinic receptors and prevents acetylcholine from producing vasodilation.

3. **Other actions:** In the gastrointestinal tract, acetylcholine increases salivary secretion and stimulates intestinal secretions and motility. Bronchiolar secretions are also enhanced. In the genitourinary tract, the tone of the detrusor urinae muscle is increased, causing expulsion of urine. In the eye, acetylcholine is involved in stimulating ciliary muscle contraction for near vision and in the constriction of the pupillae sphincter muscle, causing miosis (marked constriction of the pupil). Acetylcholine (1% solution) is instilled into the anterior

chamber of the eye to produce miosis during ophthalmic surgery.

B. Bethanechol

Bethanechol [be-THAN-e-kole] is structurally related to acetylcholine, in which the acetate is replaced by carbamate and the choline is methylated (see Figure 4.5). Hence, it is not hydrolyzed by acetylcholinesterase (due to the addition of carbonic acid), although it is inactivated through hydrolysis by other esterases. It lacks nicotinic actions (due to the addition of the methyl group) but does have strong muscarinic activity. Its major actions are on the smooth musculature of the bladder and gastrointestinal tract. It has a duration of action of about 1 hour.

1. **Actions:** *Bethanechol* directly stimulates muscarinic receptors, causing increased intestinal motility and tone. It also stimulates the detrusor muscles of the bladder whereas the trigone and sphincter are relaxed, causing expulsion of urine.
2. **Therapeutic applications:** In urologic treatment, *bethanechol* is used to stimulate the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention. *Bethanechol* may also be used to treat neurogenic atony as well as megacolon.

3. **Adverse effects:** *Bethanechol* causes the effects of generalized cholinergic stimulation (Figure 4.6). These include sweating, salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm.

C. Carbachol (carbamylcholine)

Carbachol [KAR-ba-kole] has both muscarinic as well as nicotinic actions (lacks a methyl group present in *bethanechol*; see Figure 4.5). Like *bethanechol, carbachol* is an ester of carbamic acid and a poor substrate for acetylcholinesterase (see Figure 4.5). It is biotransformed by other esterases, but at a much slower rate. A single administration can last as long as 1 hour.

1. **Actions:** *Carbachol* has profound effects on both the cardiovascular system and the gastrointestinal system because of its ganglion-stimulating activity, and it may first stimulate and then depress these systems. It can cause release of epinephrine from the adrenal medulla by its nicotinic action. Locally instilled into the eye, it mimics the effects of acetylcholine, causing miosis and a spasm of accommodation in which the ciliary muscle of the eye remains in a constant state of contraction
2. **Therapeutic uses:** Because of its high potency, receptor nonselectivity, and relatively long duration of action, *carbachol* is rarely used therapeutically except in the eye as a miotic agent to treat glaucoma by causing pupillary contraction and a decrease in intraocular pressure.
3. **Adverse effects:** At doses used ophthalmologically, little or no side effects occur due to lack of systemic penetration (quaternary amine).

D. Pilocarpine

The alkaloid *pilocarpine* [pye-loe-KAR-peen] is a tertiary amine and is stable to hydrolysis by acetylcholinesterase (see Figure 4.5). Compared with acetylcholine and its derivatives, it is far less potent, but it is uncharged and will penetrate the CNS at therapeutic doses. *Pilocarpine* exhibits muscarinic activity and is used primarily in ophthalmology.

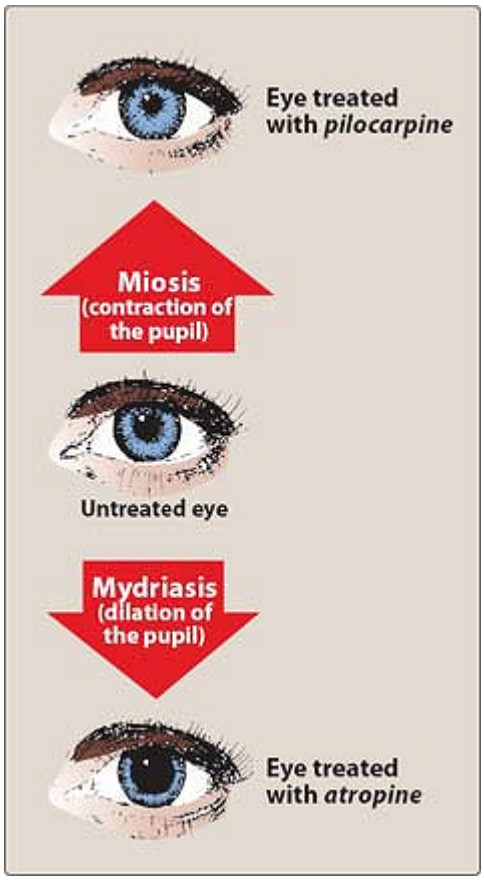


Figure 4.7 Actions of *pilocarpine* and *atropine* on the iris and ciliary muscle of the eye.

1. **Actions:** Applied topically to the cornea, *pilocarpine* produces a rapid miosis and contraction of the ciliary muscle. The eye undergoes miosis and a spasm of accommodation; the vision is fixed at some particular distance, making it impossible to focus (Figure 4.7). [Note the opposing effects of *atropine*, a muscarinic blocker, on the eye (see p. 57).] *Pilocarpine* is one of the most potent stimulators of secretions (secretagogue) such as sweat, tears, and saliva, but its use for producing these effects has been limited due to its lack of selectivity. The drug is beneficial in promoting salivation in patients with xerostomia resulting from irradiation of the head and neck. SjÃ¶gren's syndrome, which is characterized by dry mouth and lack of tears, is treated with oral *pilocarpime* tablets and *cevimeline*, a cholinergic drug that also has the drawback of being nonspecific.

2. **Therapeutic use in glaucoma:** *Pilocarpine* is the drug of choice in the emergency lowering of intraocular pressure of both narrow-angle (also called closed-angle) and wide-angle (also called open-angle) glaucoma. *Pilocarpine* is extremely effective in opening the trabecular meshwork around Schlemm's canal, causing an immediate drop

in intraocular pressure as a result of the increased drainage of aqueous humor. This action lasts up to 8 hours and can be repeated. The organophosphate *echothiophate* inhibits acetylcholinesterase and exerts the same effect for a longer duration. [Note: Carbonic anhydrase inhibitors, such as *acetazolamide*, as well as the Î²-adrenergic blocker *timolol*, are effective in treating glaucoma chronically but are not used for emergency lowering of intraocular pressure.]

3. **Adverse effects:** *Pilocarpine* can enter the brain and cause CNS disturbances. It stimulates profuse sweating and salivation.

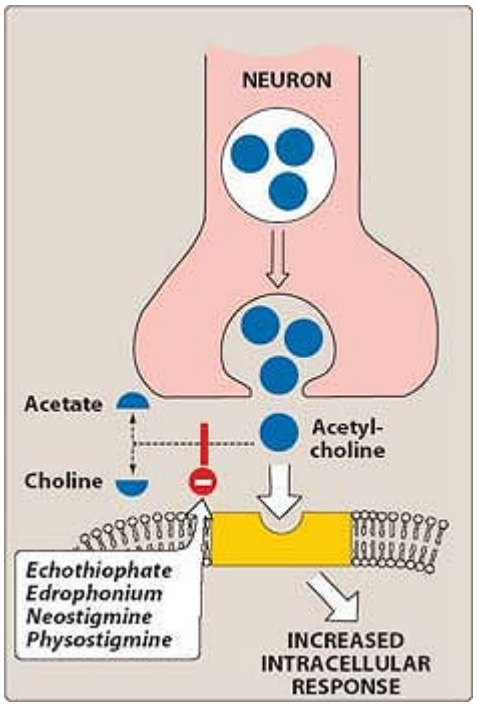


Figure 4.8 Mechanisms of action of indirect (reversible) cholinergic agonists.

V. Indirect-Acting Cholinergic Agonsists: Anticholinesterases (Reversible)

Acetylcholinesterase is an enzyme that specifically cleaves acetylcholine to acetate and choline and, thus, terminates its actions. It is located both pre- and postsynaptically in the nerve terminal, where it is membrane bound. Inhibitors of acetylcholinesterase indirectly provide a cholinergic action by prolonging the lifetime of acetylcholine produced endogenously at the cholinergic nerve endings. This results in the accumulation of acetylcholine in the synaptic space (Figure 4.8). These drugs can thus provoke a response at all cholinoceptors in the body, including both muscarinic and nicotinic receptors of the autonomic nervous system, as well as at neuromuscular junctions and in the brain.

A. Physostigmine

Physostigmine [fi-zoe-STIG-meen] is a nitrogenous carbamic acid ester found naturally in plants and is a tertiary amine. It is a substrate for acetylcholinesterase, and it forms a relatively stable carbamoylated intermediate with the enzyme, which then becomes reversibly inactivated. The result is potentiation of cholinergic activity throughout the body.

1. **Actions:** *Physostigmine* has a wide range of effects as a result of its action, and not only the muscarinic and nicotinic sites of the autonomic nervous system but also the nicotinic receptors of the neuromuscular junction are stimulated. Its duration of action is about 2 to 4 hours, and it is considered to be an intermediate-acting agent. *Physostigmine* can enter and stimulate the cholinergic sites in the CNS.

2. **Therapeutic uses**: The drug increases intestinal and bladder motility, which serve as its therapeutic action in atony of either organ (Figure 4.9). Placed topically in the eye, it produces miosis and spasm of accommodation, as well as a lowering of intraocular pressure. It is used to treat glaucoma, but *pilocarpine* is more effective. *Physostigmine* is also used in the treatment of overdoses of drugs with anticholinergic actions, such as *atropine,*

phenothiazines, and tricyclic antidepressants.

3. **Adverse effects:** The effects of *physostigmine* on the CNS may lead to convulsions when high doses are used. Bradycardia and a fall in cardiac output may also occur. Inhibition of acetylcholinesterase at the skeletal neuromuscular junction causes the accumulation of acetylcholine and, ultimately, results in paralysis of skeletal muscle. However, these effects are rarely seen with therapeutic doses.

B. Neostigmine

Neostigmine [nee-oh-STIG-meen] is a synthetic compound that is also a carbamic acid ester, and it reversibly inhibits acetylcholinesterase in a manner similar to that of *physostigmine*. Unlike *physostigmine, neostigmine* has a quaternary nitrogen; hence, it is more polar and does not enter the CNS. Its effect on skeletal muscle is greater than that of *physostigmine*, and it can stimulate contractility before it paralyzes. *Neostigmine* has a moderate duration of action, usually 30 minutes to 2 hours. It is used to stimulate the bladder and GI tract, and it is also used as an antidote for *tubocurarine* and other competitive neuromuscular blocking agents (see p. 60). *Neostigmine* has found use in symptomatic treatment of myasthenia gravis, an autoimmune disease caused by antibodies to the nicotinic receptor at neuromuscular junctions. This causes their degradation and, thus, makes fewer receptors available for interaction with the neurotransmitter. Adverse effects of *neostigmine* include those of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm. *Neostigmine* does not cause CNS side effects and is not used to overcome toxicity of central-acting antimuscarinic agents such as atropine.

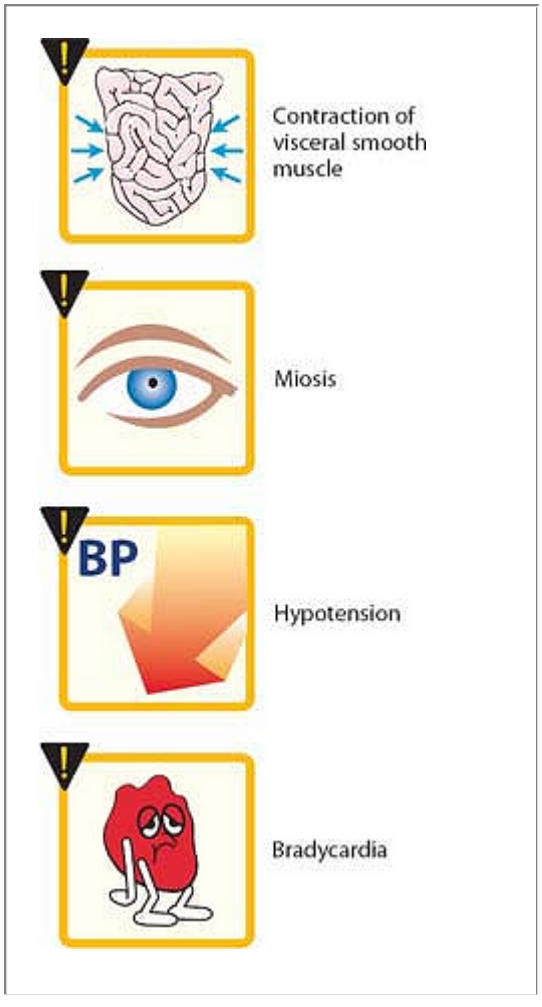


Figure 4.9 Some actions of *physostigmine*.

C. Pyridostigmine and ambenomium

Pyridostigmine [peer-id-oh-STIG-meen] and *ambenomium* [am-be-NOE-mee-um] are other cholinesterase inhibitors that are used in the chronic management of myasthenia gravis. Their durations of action are intermediate (3 to 6 hours and 4 to 8 hours, respectively), but longer than that of *neostigmine*. Adverse effects of these agents are similar to those of *neostigmine*.

D. Demecarium

Demecarium [dem-e-KARE-ee-um] is another cholinesterase inhibitor used to treat chronic open-angle glaucoma (primarily in patients refractory to other agents) closed-angle glaucoma after irredectomy. It is also used for the diagnosis and treatment of accommodative esotropia. *Demecarium* is a quaternary amine that is structurally related to *neostigmine.* Mechanisms of actions and side effects are similar to those of *neostigmine.*

E. Edrophonium

The actions of *edrophonium* [ed-row-FOE-nee-um] are similar to those of *neostigmine*, except that it is more rapidly absorbed and has a short duration of action of 10 to 20 minutes (prototype short-acting agent). *Edrophonium* is a quaternary amine and is used in the diagnosis of myasthenia gravis. Intravenous injection of *edrophonium* leads to a rapid increase in muscle strength. Care must be taken, because excess drug may provoke a cholinergic crisis. *Atropine* is the antidote.

F. Tacrine, donepezil, rivastigmine, and galantamine

As mentioned above, patients with Alzheimer's disease have a deficiency of cholinergic neurons in the CNS. This observation led to the development of anticholinesterases as possible remedies for the loss of cognitive function. *Tacrine* [TAK-reen] was the first to become available, but it has been replaced by the others because of its hepatotoxicity. Despite the ability of *donepezil* [doe-NEP-e-zil], *rivastigmine* [ri-va-STIG-meen], and

galantamine [gaa-LAN-ta-meen] to delay the progression of the disease, none can stop its progression. Gastrointestinal distress is their primary adverse effect (see p. 102).

VI. Indirect-Acting Cholinergic Agonsists: Anticholinesterases (Irreversible)

A number of synthetic organophosphate compounds have the capacity to bind covalently to acetylcholinesterase. The result is a long-lasting increase in acetylcholine at all sites where it is released. Many of these drugs are extremely toxic and were developed by the military as nerve agents. Related compounds, such as *parathion*, are employed as insecticides.

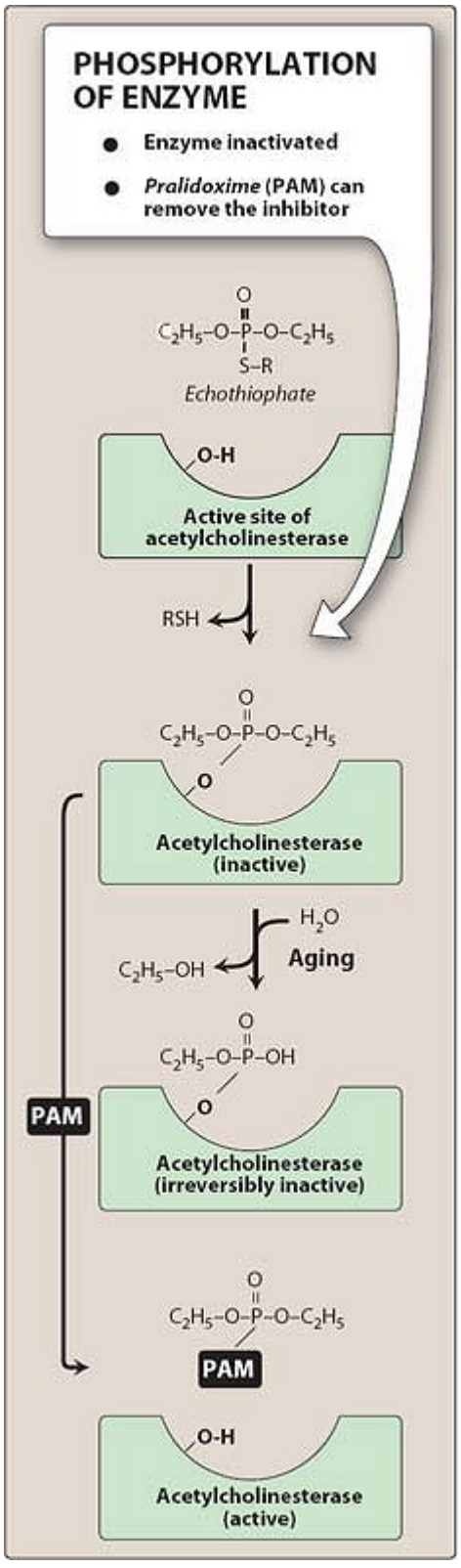


Figure 4.10 Covalent modification of acetylcholinesterase by *echothiophate*; also shown is the reactivation of the enzyme with *pralidoxime*. R = (CH3)3N+-CH2-CH2-

A. Echothiophate

1. **Mechanism of action:** *Echothiophate* [ek-oe-THI-oh-fate] is an organophosphate that covalently binds via its phosphate group to the serine-OH group at the active site of acetylcholinesterase (Figure 4.10). Once this occurs, the enzyme is permanently inactivated, and restoration of acetylcholinesterase activity requires the synthesis of new enzyme molecules. Following covalent modification of acetylcholinesterase, the phosphorylated enzyme slowly releases one of its ethyl groups (see Figure 4.10). The loss of an alkyl group, which is called aging, makes it impossible for chemical reactivators, such as *pralidoxime* (see below), to break the bond between the remaining drug and the enzyme.

2. **Actions:** Actions include generalized cholinergic stimulation, paralysis of motor function (causing breathing difficulties), and convulsions. *Echothiophate* produces intense miosis and, thus, has found therapeutic use. *Atropine* in high dosage can reverse many of the muscarinic and some of the central effects of *echothiophate*.

3. **Therapeutic uses:** An ophthalmic solution of the drug is used directly in the eye for the chronic treatment of open-angle glaucoma. The effects may last for up to one week after a single administration. *Echothiophate* is not a first-line agent in the treatment of glaucoma. In addition to its other side effects, the potential risk for causing cataracts limits the use of *echothiophate*.

4. **Reactivation of acetylcholinesterase:** *Pralidoxime* can reactivate inhibited acetylcholinesterase. However, it is unable to penetrate into the CNS. The presence of a charged group allows it to approach an anionic site on the enzyme, where it essentially displaces the phosphate group of the organophosphate and regenerates the enzyme. If given before aging of the alkylated enzyme occurs, it can reverse the effects of *echothiophate*, except for those in the CNS. With the newer nerve agents, which produce aging of the enzyme complex within seconds, *pralidoxime* is less effective. *Pralidoxime* is a weak acetylcholinesterase inhibitor and, at higher doses, may cause side effects similar to other acetylcholinsterase inhibitors (Figures 4.6 and 4.9).

A summary of the actions of some of the cholinergic agonists is presented in Figure 4.11.

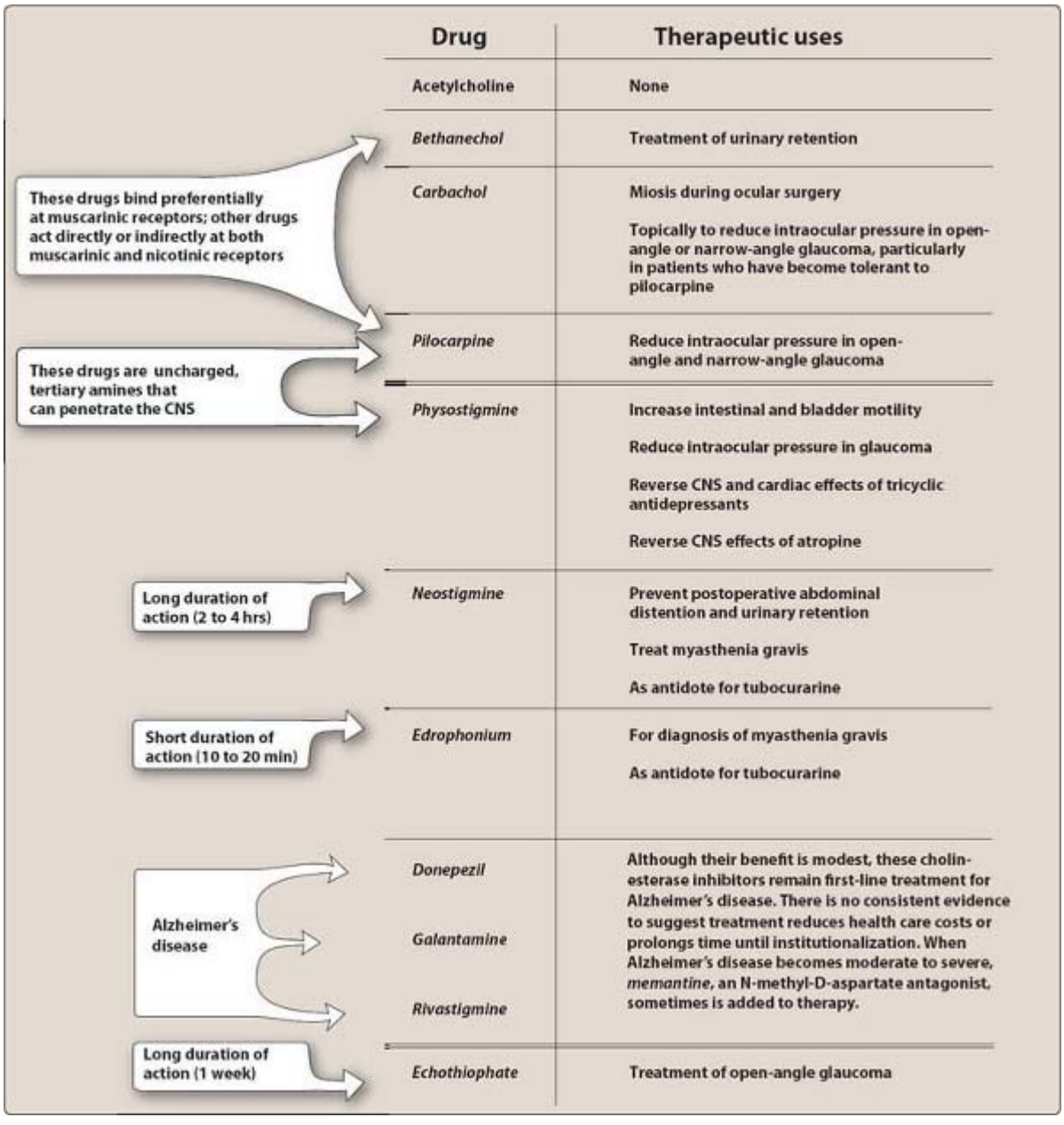


Figure 4.11 Summary of actions of some cholinergic agonists.

Study Questions

Choose the ONE best answer.

4.1 A patient with an acute attack of glaucoma is treated with pilocarpine. The primary reason for its effectiveness in this condition is its:

A. Action to terminate acetylcholinesterase.

B. Selectivity for nicotinic receptors.

C. Ability to inhibit secretions, such as tears, saliva, and sweat.

D. Ability to lower intraocular pressure.

E. Inability to enter the brain.

View Answer

4.2 A soldier's unit has come under attack with a nerve agent. The symptoms exhibited are skeletal muscle paralysis, profuse bronchial secretions, miosis, bradycardia, and convulsions. The alarm indicates exposure to an organophosphate. What is the correct treatment?

A. Do nothing until you can confirm the nature of the nerve agent.

B. Administer atropine, and attempt to confirm the nature of the nerve agent.

C. Administer atropine and 2-PAM (pralidoxime).

D. Administer 2-PAM.

View Answer

4.3 A patient being diagnosed for myasthenia gravis would be expected to have improved neuromuscular function after being treated with:

A. Donepezil.

B. Edrophonium.

C. Atropine.

D. Echothiophate.

E. Neostigmine.

View Answer

4.4 The drug of choice for treating decreased salivation accompanying head and neck irradiation is:

A. Physostigmine.

B. Scopolamine.

C. Carbachol.

D. Acetylcholine.

E. Pilocarpine.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 5

Cholinergic Antagonists

I. Overview

The cholinergic antagonists (also called cholinergic blockers, parasympatholytics or anticholinergic drugs) bind to cholinoceptors, but they do not trigger the usual receptor-mediated intracellular effects. The most useful of these agents selectively block muscarinic synapses of the parasympathetic nerves. The effects of parasympathetic innervation are thus interrupted, and the actions of sympathetic stimulation are left unopposed. A second group of drugs, the ganglionic blockers, show a preference for the nicotinic receptors of the sympathetic and parasympathetic ganglia. Clinically, they are the least important of the anticholinergic drugs. A third family of compounds, the neuromuscular blocking agents, interfere with transmission of efferent impulses to skeletal muscles. These agent are used as adjuvants in anesthesia during surgery. Figure 5.1 summarizes the cholinergic antagonists discussed in this chapter.

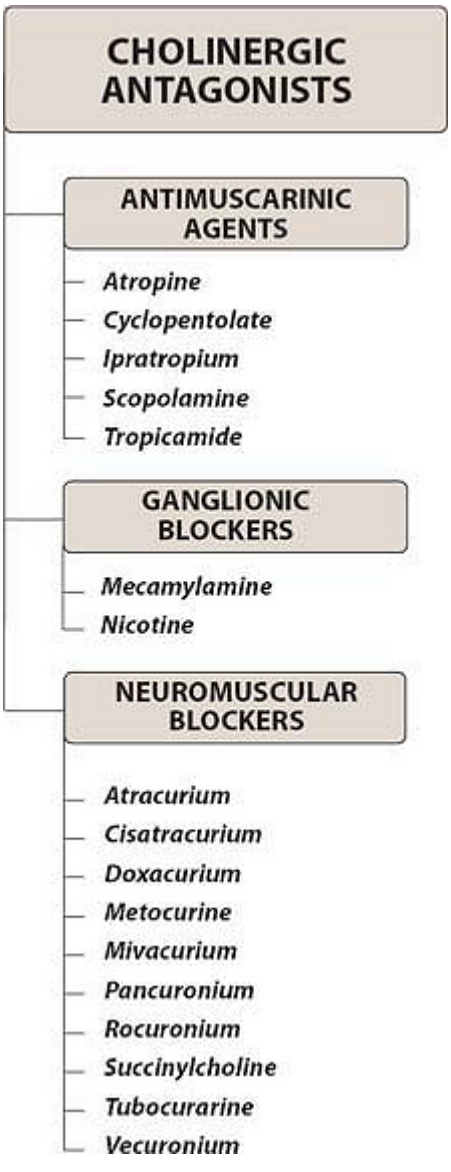


Figure 5.1 Summary of cholinergic antagonists.

II. Antimuscarinic Agents

Commonly known as antimuscarinics, these agents (for example, *atropine* and *scopolamine*) block muscarinic receptors (Figure 5.2), causing inhibition of all muscarinic functions. In addition, these drugs block the few exceptional sympathetic neurons that are cholinergic, such as those innervating salivary and sweat glands. In contrast to the cholinergic agonists, which have limited usefulness therapeutically, the cholinergic blockers are beneficial in a variety of clinical situations. Because they do not block nicotinic receptors, the antimuscarinic drugs have little or no action at skeletal neuromuscular junctions or autonomic ganglia. [Note: A number of antihistaminic and antidepressant drugs also have antimuscarinic activity.]

A. Atropine

Atropine [A-troe-peen], a tertiary amine belladonna alkaloid, has a high affinity for muscarinic receptors, where it

binds competitively, preventing acetylcholine from binding to those sites (Figure 5.3). *Atropine* acts both centrally and peripherally. Its general actions last about 4 hours except when placed topically in the eye, where the action may last for days.

1. **Actions:**

   a. **Eye:** *Atropine* blocks all cholinergic activity on the eye, resulting in persistent mydriasis (dilation of the pupil, see Figure 4.6, p. 46), unresponsiveness to light, and cycloplegia (inability to focus for near vision). In patients with narrow-angle glaucoma,

   intraocular pressure may rise dangerously. Shorter-acting agents, such as the antimuscarinic *tropicamide*, or an Î±-adrenergic drug, like *phenylephrine*, are generally favored for producing mydriasis in ophthalmic examinations.

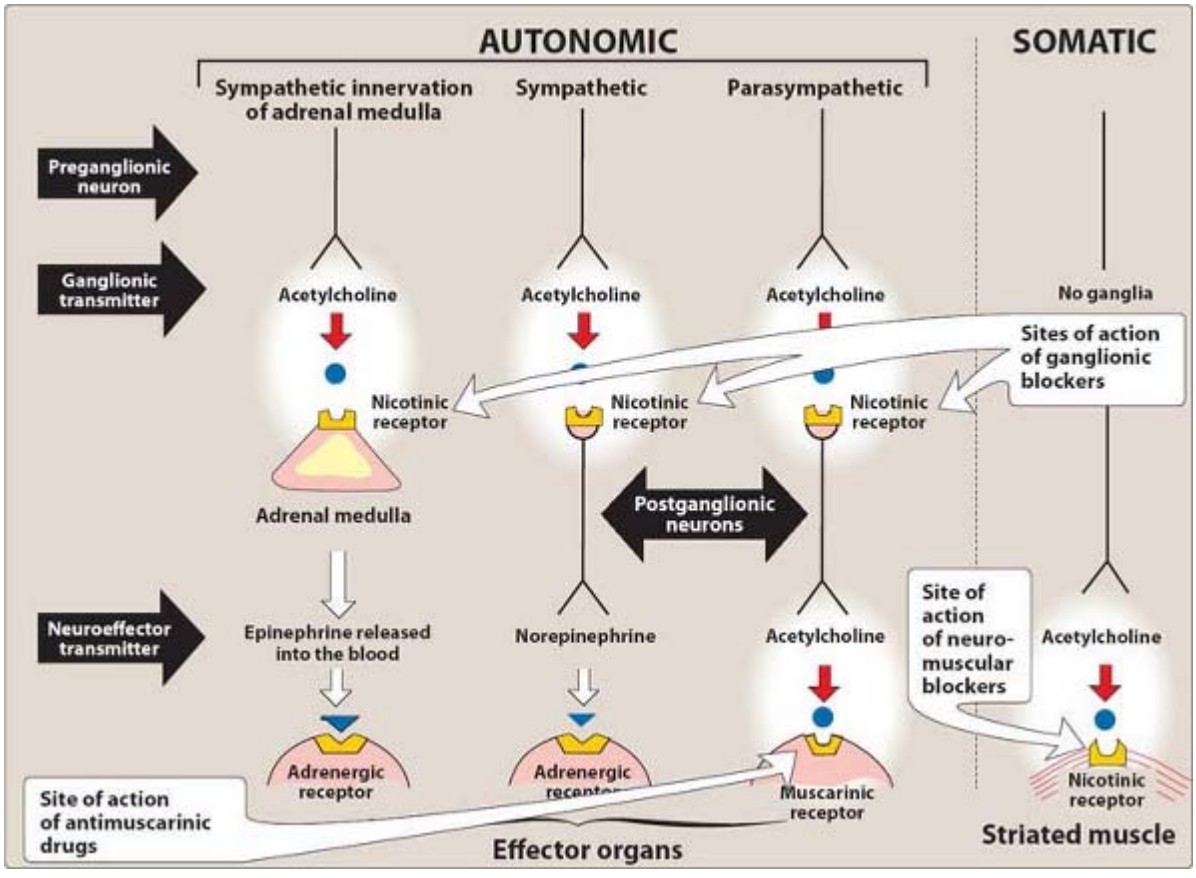


Figure 5.2 Sites of actions of cholinergic antagonists.

   b. **Gastrointestinal (GI):** *Atropine* can be used as an antispasmodic to reduce activity of the GI tract. *Atropine* and *scopolamine* (which is discussed below) are probably the most potent drugs available that produce this effect. Although gastric motility is reduced, hydrochloric acid production is not significantly affected. Thus, the drug is not effective in promoting healing of peptic ulcer. [Note: *Pirenzepine* (see p. 47), an M_1-muscarinic antagonist, does reduce gastric acid secretion at doses that do not antagonize other systems.]

   c. **Urinary system:** *Atropine* is also employed to reduce hypermotility states of the urinary bladder. It is still occasionally used in enuresis (involuntary voiding of urine) among children, but Î±-adrenergic agonists with

fewer side effects may be more effective.

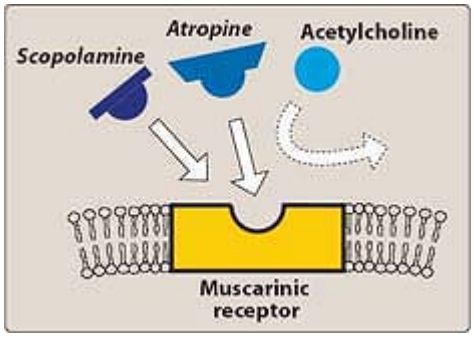


Figure 5.3 Competition of *atropine* and *scopolamine* with acetylcholine for the muscarinic receptor.

d. **Cardiovascular:** *Atropine* produces divergent effects on the cardiovascular system, depending on the dose (Figure 5.4). At

low doses, the predominant effect is a decreased cardiac rate (bradycardia). Originally thought to be due to central activation of vagal efferent outflow, the effect is now known to result from blockade of the M_1 receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased acetylcholine release. With higher doses of *atropin*e, the M_2 receptors on the sinoatrial node are blocked, and the cardiac rate increases modestly. This generally requires at least 1 mg of *atropine*, which is a higher dose than ordinarily given. Arterial blood pressure is unaffected, but at toxic levels, *atropine* will dilate the cutaneous vasculature.

e. **Secretions:** *Atropine* blocks the salivary glands, producing a drying effect on the oral mucous membranes (xerostomia). The salivary glands are exquisitely sensitive to *atropine*. Sweat and lacrimal glands are also affected. [Note: Inhibition of secretions by sweat glands can cause elevated body temperature.]

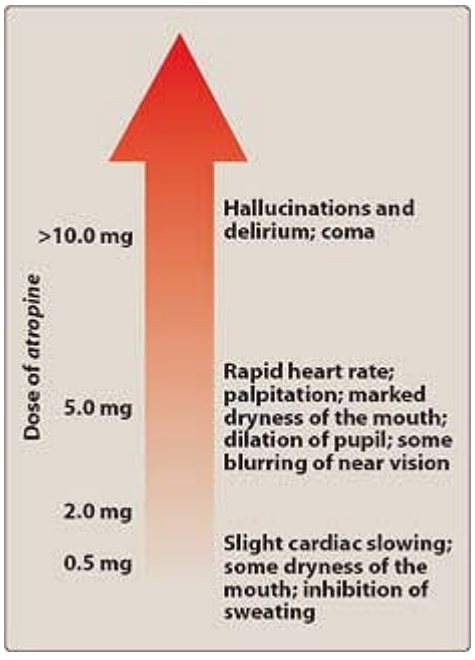


Figure 5.4 Dose-dependent effects of *atropine*.

2. **Therapeutic uses:**

   a. **Ophthalmic:** In the eye, topical *atropine* exerts both mydriatic and cycloplegic effects, and it permits the measurement of refractive errors without interference by the accommodative capacity of the eye. [Note: *Phenylephrine* or similar Î±-adrenergic drugs are preferred for pupillary dilation if cycloplegia is not required. Also, individuals 40 years of age and older have decreased ability to accommodate, and drugs are not necessary for an accurate refraction.] Shorter-acting antimuscarinics (*cyclopentolante* and *tropicamide*) have largely replaced *atropine* due to prolonged mydriasis observed with *atropine* (7â€“14 days versus 6â€“24 hours with other agents). *Atropine* may induce an acute attack of eye pain due to sudden increases in eye pressure in individuals with narrow-angle glaucoma.

   b. **Antispasmodic:** *Atropine* is used as an antispasmodic agent to relax the GI tract and bladder.

   c. **Antidote for cholinergic agonists:** *Atropine* is used for the treatment of overdoses of cholinesterase inhibitor insecticides and some types of mushroom poisoning (certain mushrooms contain cholinergic substances that block cholinesterases). Massive doses of the antagonist may be required over a long period of time to counteract the poisons. The ability of *atropine* to enter the central nervous system (CNS) is of particular importance. The drug also blocks the effects of excess acetylcholine resulting from acetylcholinesterase inhibitors, such as *physostigmine*.

   d. **Antisecretory:** The drug is sometimes used as an antisecretory agent to block secretions in the upper and lower respiratory tracts prior to surgery.

3. **Pharmacokinetics:** *Atropine* is readily absorbed, partially metabolized by the liver, and eliminated primarily in the urine. It has a half-life of about 4 hours.

4. **Adverse effects:** Depending on the dose, *atropine* may cause dry mouth, blurred vision, â€œsandy eyes,â€ tachycardia, and constipation.

Effects on the CNS include restlessness, confusion, hallucinations, and delirium, which may progress to depression, collapse of the circulatory and respiratory systems, and death. Low doses of cholinesterase inhibitors such as *physostigmine* may be used to overcome *atropine* toxicity. In older individuals, the use of *atropine* to induce mydriasis and cycloplegia is considered to be too risky, because it may exacerbate an attack of glaucoma in someone with a latent condition. In other older individuals, *atropine* may induce urinary retention that is troublesome. Children are sensitive to effects of *atropine*â€"in particular, the rapid increases in body temperature that it may elicit. This may be dangerous in children.

B. Scopolamine

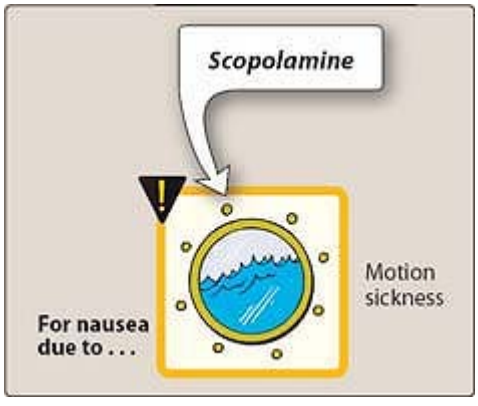


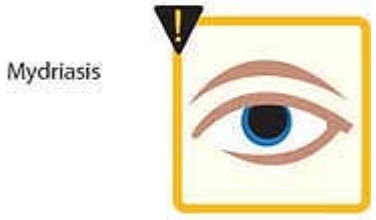
Figure 5.5 *Scopolamine* is an effective antimotion sickness agent.

Scopolamine [skoe-POL-a-meen], another tertiary amine belladonna alkaloid, produces peripheral effects similar to those of *atropine*. However, *scopolamin*e has greater action on the CNS (unlike with *atropine*, CNS effects are observed at therapeutic doses) and a longer duration of action in comparison to those of *atropine*. It has some special actions as indicated below.

1. **Actions:** *Scopolamine* is one of the most effective antiâ€"motion sickness drugs available (Figure 5.5). *Scopolamine* also has the unusual effect of blocking short-term memory. In contrast to *atropine, scopolamine* produces sedation, but at higher doses it can produce excitement instead. *Scopolamine* may produce euphoria and is subject to abuse.
2. **Therapeutic uses:** Although similar to *atropine*, therapeutic use of *scopolamine* is limited to prevention of motion sickness (for which it is particularly effective) and to blocking short-term memory. [Note: As with all such drugs used for motion sickness, it is much more effective prophylactically than for treating motion sickness once it occurs. The amnesic action of *scopolamine* makes it an important adjunct drug in anesthetic procedures.]
3. **Pharmacokinetics and adverse effects:** These aspects are similar to those of *atropine*.

C. Ipratropium

Inhaled *ipratropium* [i-pra-TROE-pee-um], a quaternary derivative of *atropine*, is useful in treating asthma in patients who are unable to take adrenergic agonists. *Ipratropium* is also beneficial in the management of chronic obstructive pulmonary disease. It is inhaled for these conditions. Because of its positive charge, it does not enter the systemic circulation or the CNS, isolating its effects to the pulmonary system. Important characteristics of the muscarinic antagonists are summarized in Figures 5.6 and 5.7.



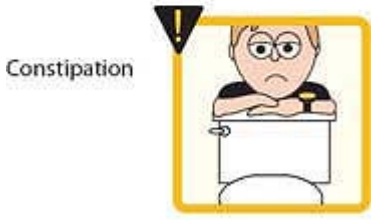


Figure 5.6 Adverse effects commonly observed with cholinergic antagonists.

D. Tropicamide and cyclopentolate

These agents are used as ophthalmic solutions for similar conditions as *atropine* (mydriasis and cyclopegia). Their duration of action is shorter than that of *atropine*; *tropicamide* produces mydriasis for 6 hours and *cyclopentolate* for 24 hours.

III. Ganglionic Blockers

Ganglionic blockers specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia. Some also block the ion channels of the autonomic ganglia. These drugs show no selectivity toward the parasympathetic or sympathetic ganglia and are not effective as neuromuscular antagonists. Thus, these drugs block

the entire output of the autonomic nervous system at the nicotinic receptor. Except for nicotine, the other drugs mentioned in this category are nondepolarizing, competitive antagonists. The responses observed are complex and unpredictable, making it impossible to achieve selective actions. Therefore, ganglionic blockade is rarely used therapeutically. However, ganglionic blockers often serve as tools in experimental pharmacology.

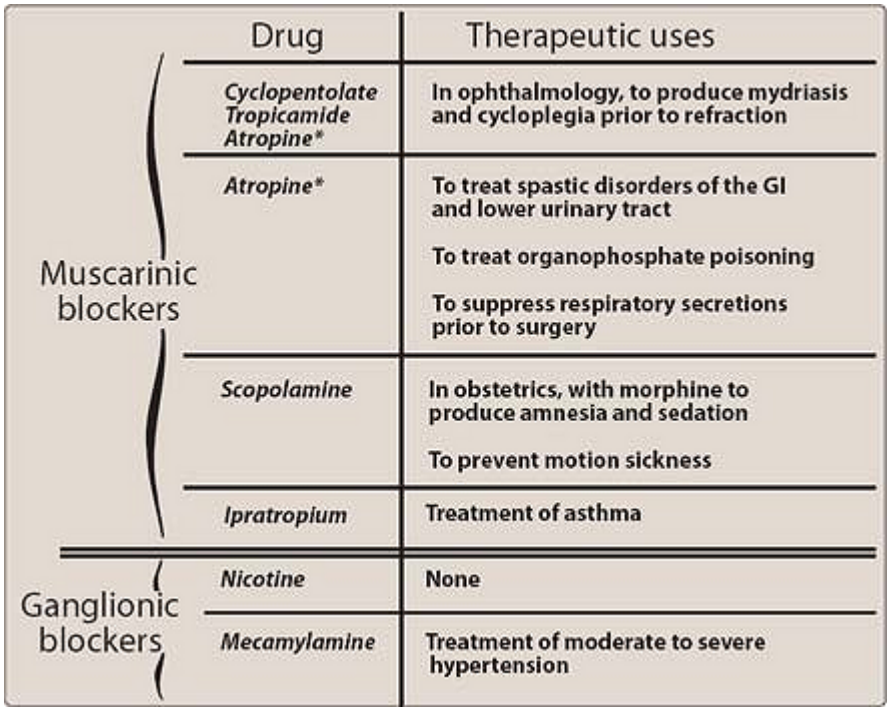


Figure 5.7 Summary of cholinergic antagonists. *Contraindicated in narrowangle glaucoma. GI = gastrointestinal.

A. Nicotine

A component of cigarette smoke, nicotine [NIC-oh-teen] is a poison with many undesirable actions. It is without therapeutic benefit and is deleterious to health. [Note: Nicotine is available as patches, lozenges, gums, and other forms. Patches are available for application to the skin. The drug is absorbed and is effective in reducing the craving for nicotine in people who wish to stop smoking.] Depending on the dose, nicotine depolarizes autonomic ganglia, resulting first in stimulation and then in paralysis of all ganglia. The stimulatory effects are complex due to effects on both sympathetic and parasympathetic ganglia. The effects include increased blood pressure and cardiac rate (due to release of transmitter from adrenergic terminals and from the adrenal medulla) and increased peristalsis and secretions. At higher doses, the blood pressure falls because of ganglionic blockade, and activity both in the GI tract and bladder musculature ceases. (See p. 118 for a full discussion of nicotine.)

B. Mecamylamine

Mecamylamine [mek-a-MILL-a-meen] produces a competitive nicotinic blockade of the ganglia. The duration of action is about 10 hours after a single administration. The uptake of the drug via oral absorption is good, in contrast to that of *trimethaphan*. As with *trimethaphan*, it is primarily used to lower blood pressure in emergency situations.

IV. Neuromuscular Blocking Drugs

These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on the neuromuscular end plate of skeletal muscle (see Figure 5.2). These neuromuscular blockers are structural analogs of acetylcholine, and they act either as antagonists (nondepolarizing type) or agonists (depolarizing type) at the receptors on the end plate of the neuromuscular junction. Neuromuscular blockers are clinically useful during surgery for producing complete muscle relaxation, without having to employ higher anesthetic doses to achieve comparable muscular relaxation. Agents are also useful in facilitating intubation as well. A second group of muscle

relaxants, the central muscle relaxants, are used to control spastic muscle tone. These drugs include *diazepam*, which binds at Î³-aminobutyric acid (GABA) receptors; *dantrolen*e, which acts directly on muscles by interfering with the release of calcium from the sarcoplasmic reticulum; and *baclofen*, which probably acts at GABA receptors in the CNS.

A. Nondepolarizing (competitive) blockers

The first drug that was found to be capable of blocking the skeletal neuromuscular junction was curare, which the native hunters of the Amazon in South America used to paralyze game. The drug *tubocurarine* [too-boe-kyoo-AR-een] was ultimately purified and introduced into clinical practice in the early 1940s. Although *tubocurarine* is considered to be the prototype agent in this class, it has been largely replaced by other agents due to side effects (see Figure 5.10). The neuromuscular blocking agents have significantly increased the safety of anesthesia, because less anesthetic is required to produce muscle relaxation, allowing patients to recover quickly and completely after surgery. Note: Higher doses of anesthesia may produce respiratory paralysis and cardiac depression, increasing recovery time after surgery.]

1. **Mechanism of action:**

   a. **At low doses:** Nondepolarizing neuromuscular blocking drugs interact with the nicotinic receptors to prevent the binding of acetylcholine (Figure 5.8). These drugs thus prevent depolarization of the muscle cell membrane and inhibit muscular contraction. Because these agents compete with acetylcholine at the receptor without stimulating the receptor, they are called competitive blockers. Their action can be overcome by increasing the concentration of acetylcholine in the synaptic gapâ€"for example, by administration of cholinesterase inhibitors, such as *neostigmine, pyridostigmine*, or *edrophonium*. Anesthesiologists often employ this strategy to shorten the duration of the neuromuscular blockade.

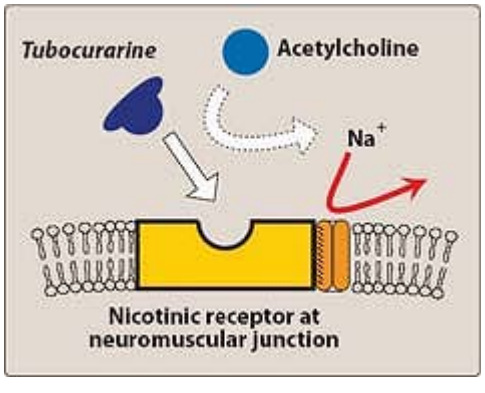


Figure 5.8 Mechanism of action of competitive neuromuscular blocking drugs.

   b. **At high doses:** Nondepolarizing blockers can block the ion channels of the end plate. This leads to further

weakening of neuromuscular transmission, and it reduces the ability of acetylcholinesterase inhibitors to reverse the actions of nondepolarizing muscle relaxants.

2. **Actions:** Not all muscles are equally sensitive to blockade by competitive blockers. Small, rapidly contracting muscles of the face and eye are most susceptible and are paralyzed first, followed by the fingers. Thereafter, the limbs, neck, and trunk muscles are paralyzed. Then the intercostal muscles are affected, and lastly, the diaphragm muscles are paralyzed. Those agents (for example, *tubocurarine, mivacurium*, and *atracurium*), which release histamine, can produce a fall in blood pressure, flushing, and bronchoconstriction.

3. **Therapeutic uses:** These blockers are used therapeutically as adjuvant drugs in anesthesia during surgery to relax skeletal muscle. These agents are also used to facilitate intubation as well as during orthopedic surgery.

4. **Pharmacokinetics:** All neuromuscular blocking agents are injected intravenously, because their uptake via oral absorption is minimal.

These agents possess two or more quaternary amines in their bulky ring structure, making them orally ineffective. They penetrate membranes very poorly and do not enter cells or cross the blood-brain barrier. Many of the drugs are not metabolized; their actions are terminated by redistribution (Figure 5.9). For example, *tubocurarine, pancuronium, mivacurium, metocurin*e, and *doxacurium* are excreted in the urine unchanged. *Atracurium* is degraded spontaneously in the plasma and by ester hydrolysis. [Note: *Atracurium* has been replaced by its isomer, *cisatracurium. Atracurium* releases histamine and is metabolized to laudanosine, which can provoke seizures. *Cisatracurium*, which has the same pharmacokinetic properties as *atracurium,* is less likely to have these effects.] The aminosteroid drugs (*vecuronium* and *rocuronium*) are deacetylated in the liver, and their clearance may be prolonged in patients with hepatic disease. These drugs are also excreted unchanged in the bile. The choice of an agent will depend on how quickly muscle relaxation is needed and on the duration of the muscle relaxation. The onset and duration of action as well as other characteristics of the neuromuscular blocking drugs are shown in Figure 5.10.

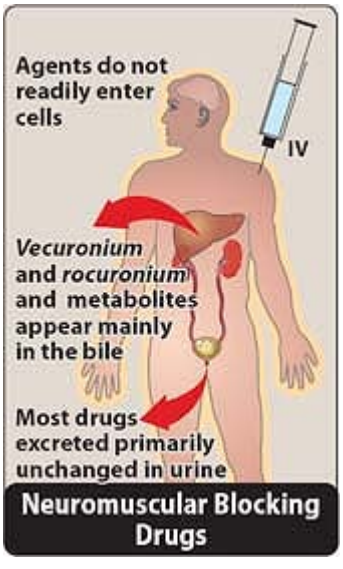


Figure 5.9 Pharmacokinetics of the neuromuscular blocking drugs. IV = intravenous.

5. **Adverse effects:** In general, agents are safe with minimal side effects. The adverse effects of the specific neuromuscular blocking drugs are shown in Figure 5.10.

6. **Drug interactions:**

a. **Cholinesterase inhibitors:** Drugs such as *neostigmine, physostigmine, pyridostigmine*, and *edrophonium* can overcome the action of nondepolarizing neuromuscular blockers, but with increased dosage, cholinesterase inhibitors can cause a depolarizing block as a result of elevated acetylcholine concentrations at the end-plate membrane. If the neuromuscular blocker has entered the ion channel, cholinesterase inhibitors are not as effective in overcoming blockade.

b. **Halogenated hydrocarbon anesthetics:** Drugs such as *halothane* act to enhance neuromuscular blockade by exerting a stabilizing action at the neuromuscular junction. These agents sensitize the neuromusclular junction to the effects of neuromuscular blockers.

c. **Aminoglycoside antibiotics:** Drugs such as *gentamicin* or *tobramycin* inhibit acetylcholine release from cholinergic nerves by competing with calcium ions. They synergize with *tubocurarine* and other competitive blockers, enhancing the blockade.

d. **Calcium-channel blockers:** These agents may increase the neuromuscular block of *tubocurarine* and other competitive blockers as well as depolarizing blockers.

B. Depolarizing agents

1. **Mechanism of action:** The depolarizing neuromuscular blocking drug *succinylcholine* [suk-sin-ill-KOE-leen] attaches to the nicotinic receptor and acts like acetylcholine to depolarize the junction (Figure 5.11). Unlike acetylcholine, which is instantly destroyed by acetylcholinesterase, the depolarizing agent persists at high concentrations in the synaptic cleft, remaining attached to the receptor for a relatively

longer time and providing a constant stimulation of the receptor. [Note: The duration of action of *succinylcholine* is dependent on diffusion from the motor end plate and hydrolysis by plasma cholinesterase.] The depolarizing agent first causes the opening of the sodium channel associated with the nicotinic receptors, which results in depolarization of the receptor (Phase I). This leads to a transient twitching of the muscle (fasciculations). Continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses. With time, continuous depolarization gives way to gradual repolarization as the sodium channel closes or is blocked. This causes a resistance to depolarization (Phase II) and a flaccid paralysis.

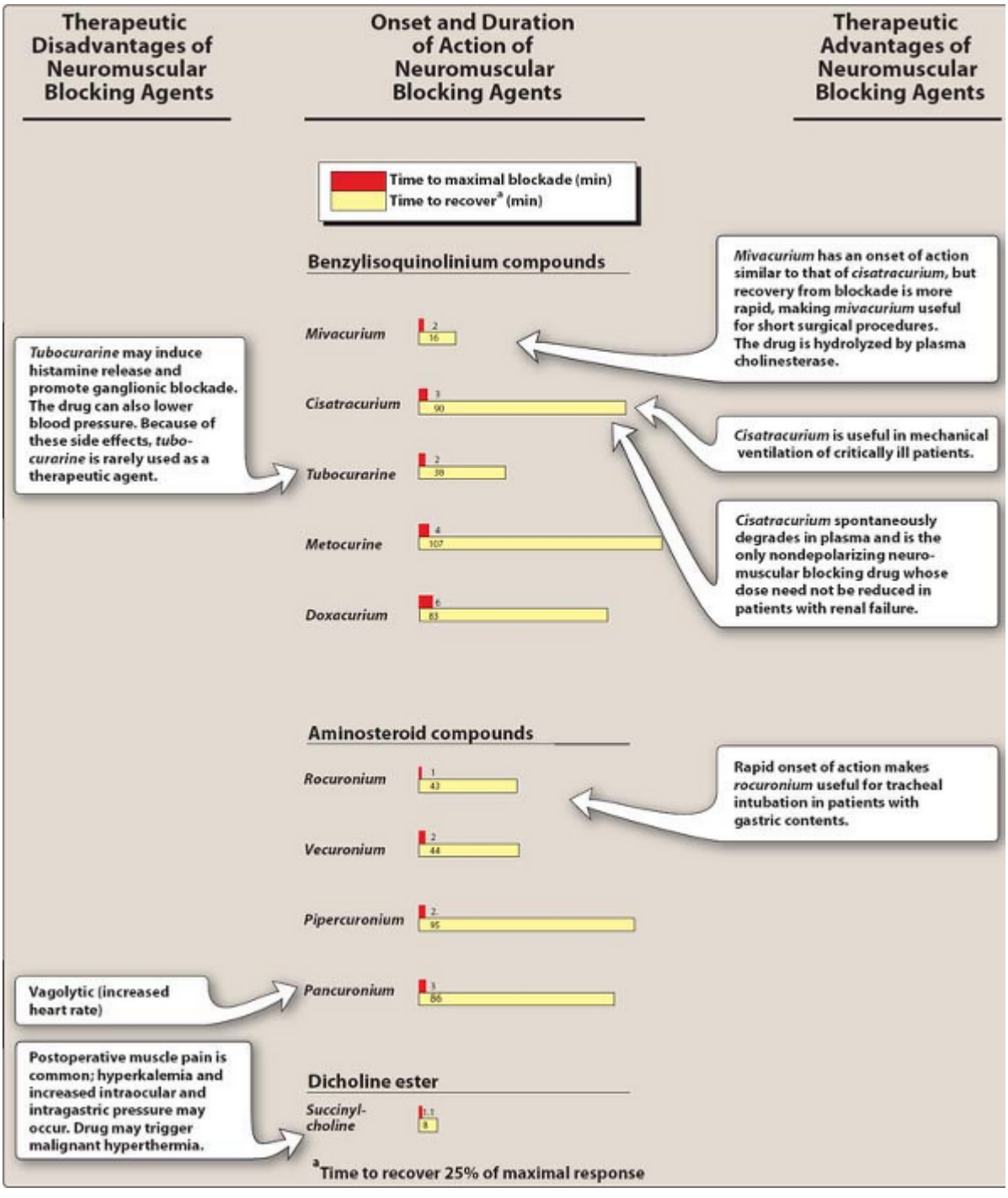


Figure 5.10 Onset and duration of action of neuromuscular blocking drugs (center column), with a summary of therapeutic considerations.

2. **Actions:** The sequence of paralysis may be slightly different, but as with the competitive blockers, the respiratory muscles are paralyzed last. *Succinylcholine* initially produces short-lasting muscle fasciculations, followed within a few minutes by paralysis. The drug does not produce a ganglionic block except at high doses, but it does have weak histamine-releasing action. Normally, the duration of action of *succinylcholine* is extremely short, because this drug is rapidly broken down by plasma cholinesterase. However, *succinylcholine*

that gets to the neuromusclular junction is not metabolized by acetylcholinesterase, allowing the agent to bind to nicotinic receptors, and redistribution to plasma is necessary for metabolism (therapeutic benefits last only for a few minutes). [Note: Genetic variants in which plasma cholinesterase levels are low or absent leads to prolonged neuromuscular paralysis.]

3. **Therapeutic uses:** Because of its rapid onset and short duration of action, *succinylcholine* is useful when rapid endotracheal intubation is required during the induction of anesthesia (a rapid action is essential if aspiration of gastric contents is to be avoided during intubation). It is also employed during electroconvulsive shock treatment.

4. **Pharmacokinetics:** *Succinylcholine* is injected intravenously. Its brief duration of action (several minutes) results from redistribution and rapid hydrolysis by plasma cholinesterase. It therefore is usually given by continuous infusion.

5. **Adverse effects:**

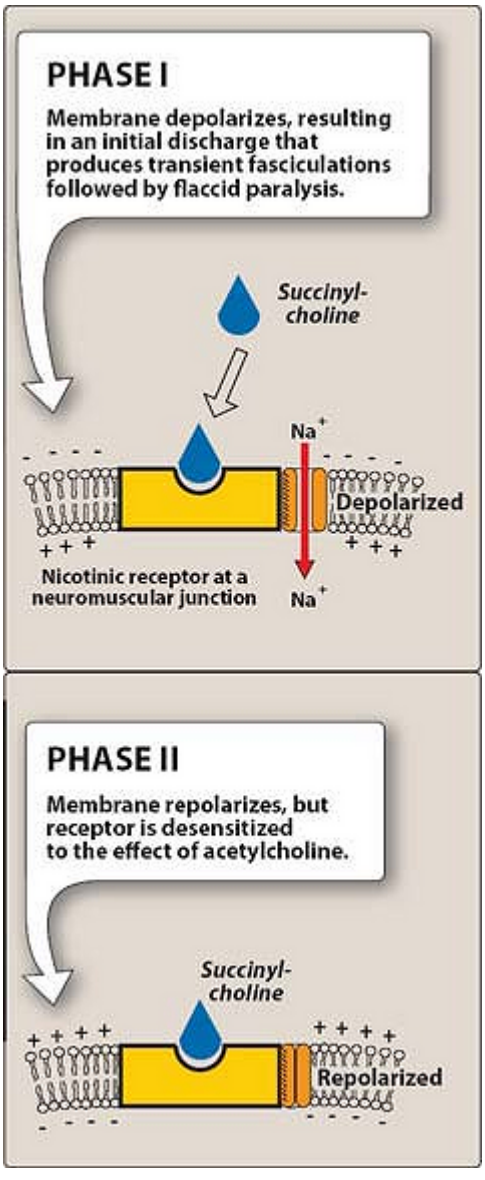


Figure 5.11 Mechanism of action of depolarizing neuromuscular blocking drugs.

a. **Hyperthermia:** When *halothane* (see p. 133) is used as an anesthetic, administration of *succinylcholine* has occasionally caused malignant hyperthermia (with muscular rigidity and hyperpyrexia) in genetically susceptible people (see Figure 5.10). This is treated by rapidly cooling the patient and by administration of *dantrolene*, which blocks release of Ca^{2+} from the sarcoplasmic reticulum of muscle cells, thus reducing heat production and relaxing muscle tone.

b. **Apnea:** Administration of *succinylcholine* to a patient who is genetically deficient in plasma cholinesterase or has an atypical form of the enzyme can lead to prolonged apnea due to paralysis of the diaphragm.

c. **Hyperkalemia:** *Succinylcholine* increases potassium release from intracellular stores. This may be particularly dangerous in burn patients or patients with massive tissue damage in which postassium is been rapidly lost from within cells.

Study Questions

Choose the ONE best answer.

5.1 A 75-year-old man who was a smoker is diagnosed with chronic obstructive pulmonary disease and suffers from occasional bronchospasm. Which of the following would be effective in treating him?

A. Ipratropium aerosol.

B. Scopolamine patches.

C. Mecamylamine.

D. Oxygen.

View Answer

5.2 Which of the following may precipitate an attack of open-angle glaucoma if instilled into the eye?

A. Physostigmine.

B. Atropine.

C. Pilocarpine.

D. Echothiophate.

View Answer

5.3 The prolonged apnea sometimes seen in patients who have undergone an operation in which *succinylcholine* was employed as a muscle relaxant has been shown to be due to:

A. Urinary atony.

B. Depressed levels of plasma cholinesterase.

C. A mutation in acetylcholinesterase.

D. A mutation in the nicotinic receptor at the neuromuscular junction.

View Answer

5.4 A 50-year-old male farm worker is brought to the emergency room. He was found confused in the orchard and since then has lost consciousness. His heart rate is 45, and his blood pressure is 80/40 mm Hg. He is sweating and salivating profusely. Which of the following treatments is indicated?

A. Physostigmine.

B. Norepinephrine.

C. Trimethaphan.

D. Atropine.

E. Edrophonium.

View Answer