UNIT I:
Introduction to Pharmacology

# Absorption, Distribution, and Elimination of Drugs

# 1

## I. OVERVIEW

The aim 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. The clinician must recognize that the speed of onset of drug action, the intensity of the drug's effect, and the duration of the 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 permits entry of the therapeutic agent (either directly or indirectly) into plasma (input). Second, the drug may then reversibly leave the blood stream and distribute into the interstitial and intracellular fluids (distribution). Third, the drug may be metabolized by the liver, kidney, or other tissues. Finally, the drug and its metabolites are eliminated from the body (output) in urine, bile, or feces. Chapters 1 and 2 describe how knowledge of these processes influences the clinician's decision as to the route of administration, drug loading, and dosing interval.

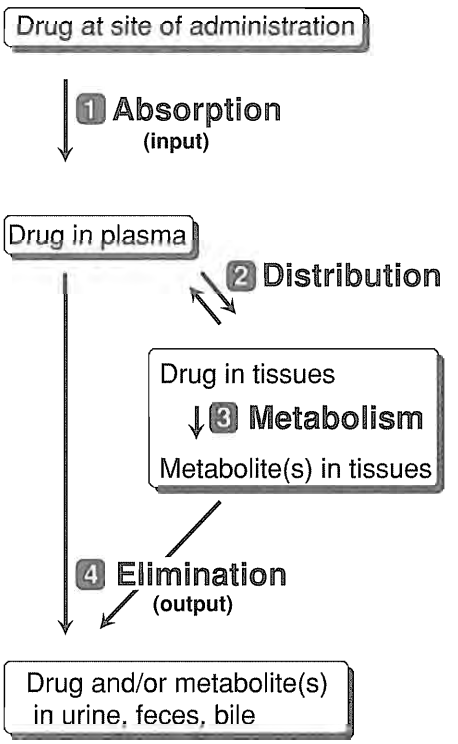


**Figure 1.1**
Schematic representation of drug absorption, distribution, metabolism and elimination.

## II. ROUTES OF DRUG ADMINISTRATION

The route of administration is determined primarily by the properties of the drug (such as 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.)

*Lippincott's Illustrated Reviews: Pharmacology, Second Edition.*
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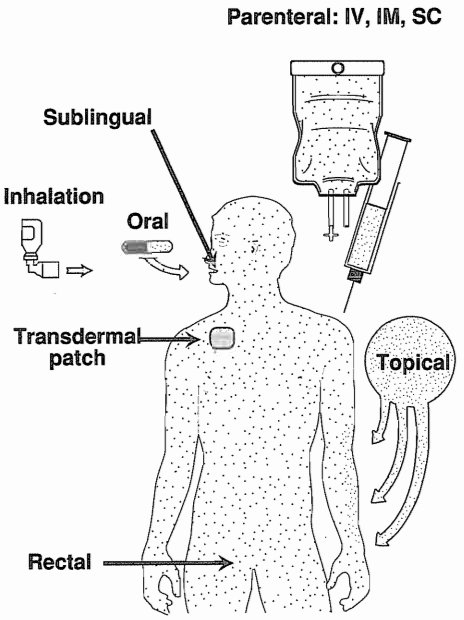



**Figure 1.2**
Commonly used routes of drug administration. (IV=intravenous; IM=intramuscular; SC= subcutaneous).

## A. Enteral

1. **Oral:** Giving a drug by mouth is the most common route of administration, but it is also the most variable, and requires the most complicated pathway to the tissues. Some drugs are absorbed from the stomach; however, the duodenum is often the major site of entry to the systemic circulation because of its larger absorptive surface. [Note: Most drugs absorbed from the gastrointestinal (GI) tract enter the portal circulation and encounter the liver before they are distributed in the general circulation (Figure 1.3). First-pass metabolism by the intestine or liver limits the efficacy of many drugs when taken orally. For example, more than 90% of *nitroglycerin* is cleared during a single passage through the liver.] Ingestion of drugs with food can influence absorption. The presence of food in the stomach delays gastric emptying time so that drugs that are destroyed by acid, for example, *penicillin*, become unavailable for absorption (see p. 302). [Note: Enteric coating of a drug protects it from the acidic environment and may prevent gastric irritation. Depending on the formulation, the release of the drug may be prolonged, producing a sustained-release preparation.]

2. **Sublingual:** Placement under the tongue allows the drug to diffuse into the capillary network and therefore to enter the systemic circulation directly. Administration of an agent by this route has the advantage that the drug bypasses the intestine and liver and is not inactivated by metabolism.

3. **Rectal:** Fifty percent of the drainage of the rectal region bypasses the portal circulation; thus the biotransformation of drugs by the liver is minimized. Both the sublingual and the rectal routes of administration have the additional advantage that they prevent 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 or if the patient is already vomiting. [Note: The rectal route also is commonly used to administer antiemetic agents.]

## B. Parenteral

Parenteral administration is used for drugs that are poorly absorbed from the gastrointestinal (GI) tract, and for agents such as *insulin* that are unstable in the GI tract. Parenteral administration is also used for treatment of unconscious patients and under circumstances that require a rapid onset of action. Parenteral administration provides the most control over the actual dose of drug delivered to the body. The three major parenteral routes are intravascular (intravenous or intra-arterial), intramuscular, and subcutaneous (see Figure 1.2). Each has its advantages and drawbacks.

1. **Intravascular:** Intravenous (IV) injection is the most common parenteral route. For drugs that are not absorbed orally, there is often no other choice. With IV administration, the drug avoids the GI tract and, therefore, first-pass metabolism by the liver. This route permits a rapid effect and a maximal degree of control over the circulating levels of the drug. However, unlike drugs present in the GI tract, those that are injected cannot be recalled by

strategies such as emesis or binding to activated charcoal. Intravenous injection of some drugs may introduce bacteria through contamination, 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 (IA) injected drugs.

2. **Intramuscular (IM):** Drugs administered intramuscularly can be aqueous solutions or specialized depot preparations—often a suspension of drug in a nonaqueous vehicle, such as ethylene glycol or peanut oil. Absorption of drugs in 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. 130), whose slow diffusion from the muscle 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. SC 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 silastic capsules containing the contraceptive *levonorgestrel* that are implanted for long-term activity (see p. 268), and also programmable mechanical pumps that can be implanted to deliver *insulin* in some diabetics.

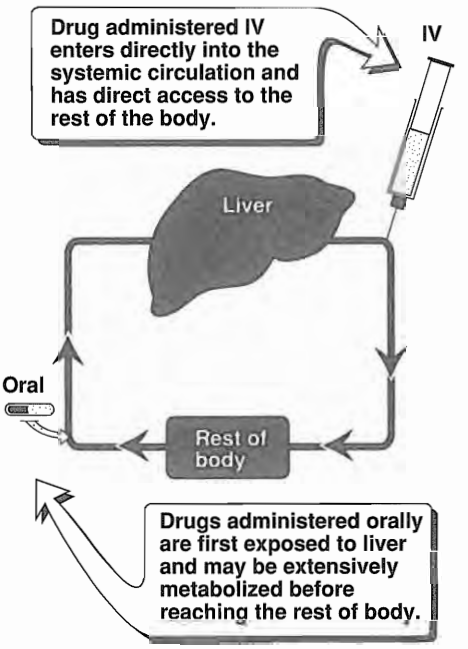



**Figure 1.3**
First-pass metabolism can occur with orally administered drugs. (IV = intravenous).

### 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 by intravenous 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. The route is particularly effective and convenient for patients with respiratory complaints (for example, asthma or chronic obstructive pulmonary disease) as drug is delivered directly to the site of action and systemic side effects are minimized (see p. 219).

2. **Intranasal:** *Desmopressin* is administered intranasally in the treatment of diabetes insipidus; salmon *calcitonin*, a peptide hormone used in the treatment of of osteoporosis, is available as a nasal spray. The abused drug, *cocaine*, is generally taken by sniffing.

3. **Intrathecal/Intraventricular:** It is sometimes necessary to introduce drugs directly into the cerebrospinal fluid (CSF), such as *methotrexate* in acute lymphocytic leukemia (see p. 379).

4. **Topical:** Topical application is used when a local effect of the drug is desired. For example, *clotrimazole* (see p. 343) is applied as a

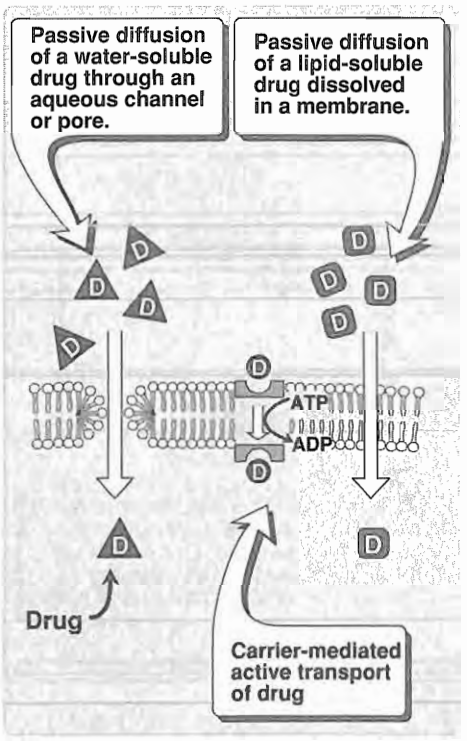



**Figure 1.4**
Schematic representation of drugs crossing cell membrane of epithelial cell of gastrointestinal tract.

cream directly to the skin in the treatment of dermatophytosis, and *atropine* (see p. 47) is instilled 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 upon 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* (see p. 175).

## III. ABSORPTION OF DRUGS

Absorption is the transfer of a drug from its site of administration to the blood stream. The rate and efficiency of absorption depend on the route of administration. For intravenous 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 gastrointestinal fluid and then penetrate the epithelial cells of the intestinal mucosa; disease states or the presence of food may affect this process.

### A. Transport of 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 biological membranes, whereas water-soluble drugs penetrate the cell membrane through aqueous channels (Figure 1.4).

2. **Active transport:** This mode of drug entry 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 gradient, 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 when binding to the enzyme is maximal.[1]

### B. Effect of pH on drug absorption

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

[1,2]See p. 16 for Infolink references to other books in this series.

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

Weak bases ($BH^+$) can also release a $H^+$; 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 stronger the acid. Conversely, the higher the $pK_a$, the stronger the base.] Distribution equilibrium is achieved when the permeable form of drug achieves an equal concentration in all body water spaces. Highly lipid-soluble drugs rapidly cross membranes and often enter tissues at a rate determined by blood flow.

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]:

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

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

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

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 pH, for example, stomach (pH 1.0 to 1.5) and blood plasma (pH 7.4). [Note: The lipid solubility of the nonionized drug directly determines its rate of equilibration.]

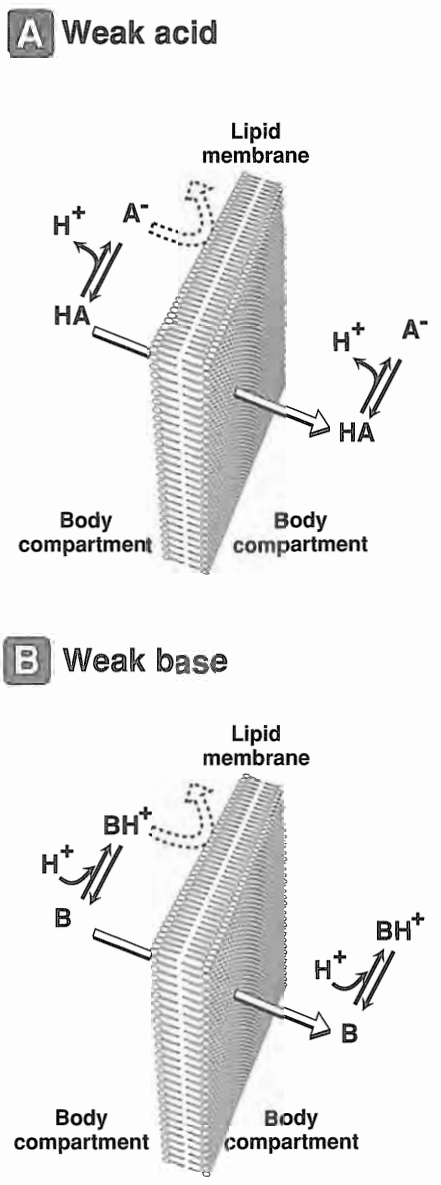



**Figure 1.5**
A. Diffusion of non-ionized form of a weak acid through lipid membrane; B. Diffusion of non-ionized form of a weak base through lipid membrane.

### 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

[3]See p. 16 for Infolink references to other books in this series.

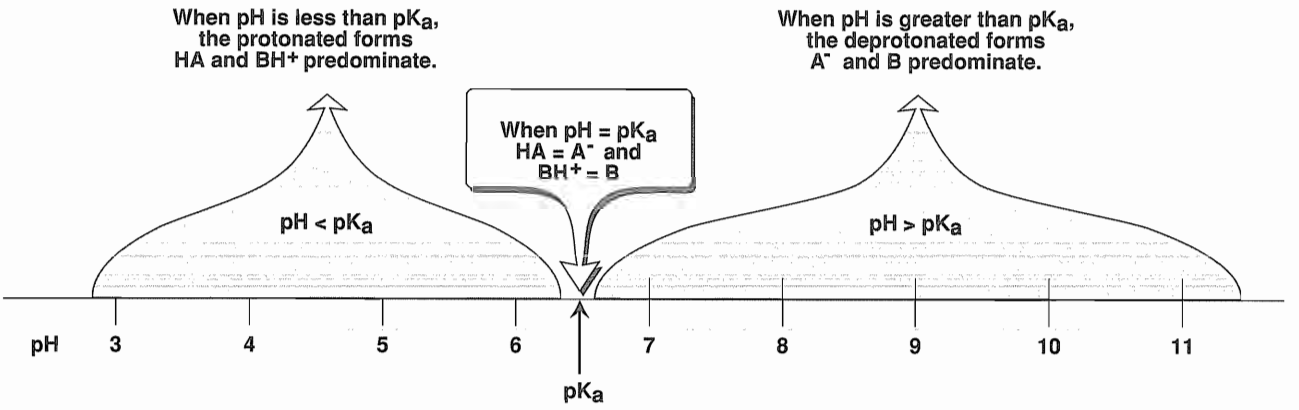



**Figure 1.6**
The distribution of a drug between its ionized and un-ionized form depends on the ambient pH and $pK_a$ of the drug. For illustrative purposes, the drug has been assigned a $pK_a$ of 6.5.

severely reduces blood flow to cutaneous tissues, thus minimizing the absorption from subcutaneous administration.]

2. **Total surface area available for absorption:** Because the intestine has a surface rich in microvilli, it has a surface area about 1,000 times 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) 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.]

## 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 is administered orally and 70 mg of this drug is absorbed unchanged, the bioavailability is 70%.

### 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 injection, in which all of the agent enters the circulation. When the drug is given orally, only part of the administered dose appears in the plasma. By plot-

ting 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% for drugs delivered intravenously.] 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).

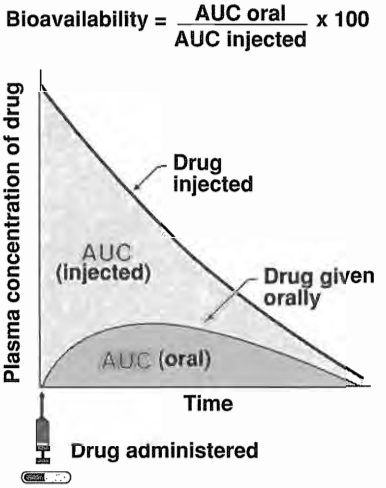



**Figure 1.7**
Determination of the bioavailability of a drug. (AUC = area under curve.)

### 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 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 the 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.

3. **Chemical instability:** Some drugs, such as *penicillin G* (see p. 302), are unstable in the pH of the gastric contents. Others, such as *insulin* (see p. 258), may be 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, 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 both on maximum serum drug concentrations and the time after administration required 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 blood stream and enters the interstitium (extracellular fluid) and/or the cells of the tissues. The delivery of a drug from the plasma to the inter-

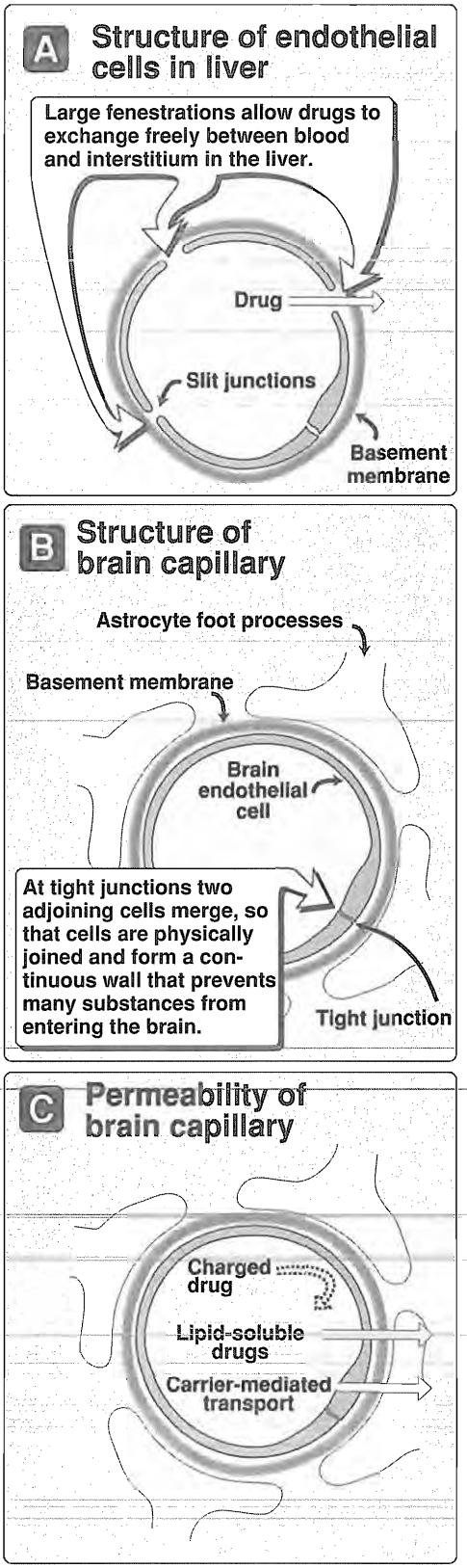



**Figure 1.8**
Cross section of liver and brain capillaries.

stitium 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.

### 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, whereas adipose tissue has a still lower rate of blood flow.

### 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 (tight) 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:** In order to enter the brain, drugs must pass through the endothelial cells of the capillaries of the central nervous system (CNS) or be actively transported. For example, the large neutral amino acid carrier transports *levodopa* into the brain. Lipid-soluble drugs readily penetrate into the CNS, since they can dissolve in the membrane of the endothelial cells. Ionized or polar drugs generally fail to enter the CNS, since 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 (Figure 1.8).

2. **Drug structure:** The chemical nature of the 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 biological 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 must go through the slit junctions (see Figure 1.8).

### C. Binding of drugs to proteins

Reversible binding to plasma proteins sequesters drugs in a non-diffusible form and slows their transfer out of the vascular compartment. Binding is relatively non-selective 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, for example, 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. (See p. 11 for further discussion of drug binding by proteins.)

## VI. VOLUME OF DISTRIBUTION

The volume of distribution ($V_d$) is a hypothetical volume of fluid into which the drug is disseminated. Although the volume of distribution has no physiological 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 some 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 6% of the body weight or, in a 70-kg individual, about 4 L of body fluid. Aminoglycoside antibiotics (see p. 314) show this type of distribution.

2. **Extracellular fluid:** If the 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 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 20% of the body weight, or about 14 L in a 70-kg individual.

3. **Total body water:** If the drug has a low molecular weight and is hydrophobic, it can not only move into the interstitium through the slit junctions, but can also move through the cell membranes into the intracellular fluid. The drug therefore distributes into a volume of about 60% of body weight, or about 42 L in a 70-kg individual.

4. **Other sites:** In pregnancy, the fetus may take up drugs and thus increase the $V_d$. Drugs such as *thiopental* (see p. 115), which are stored in fat, may also have unusually high volumes of distribution.

### B. The 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 components, for example, lipids (abundant in adipocytes and cell membranes),

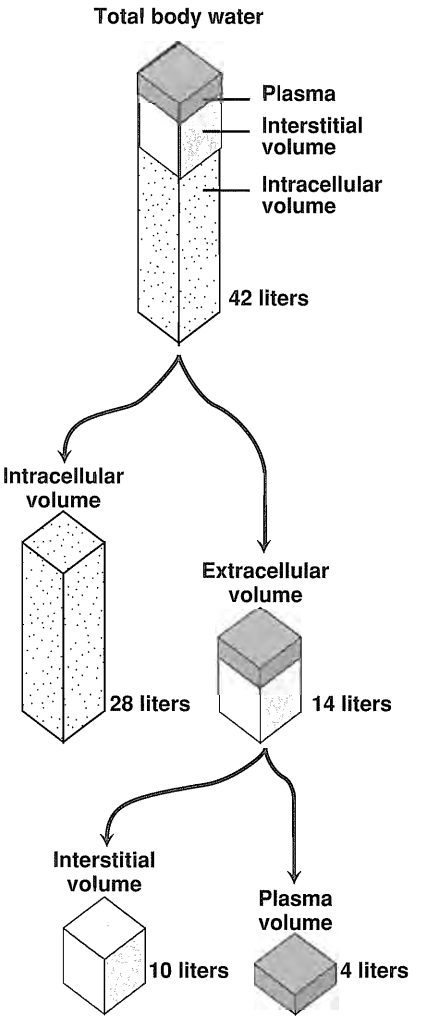



**Figure 1.9**
Relative size of various distribution volumes within a 70-kg individual.

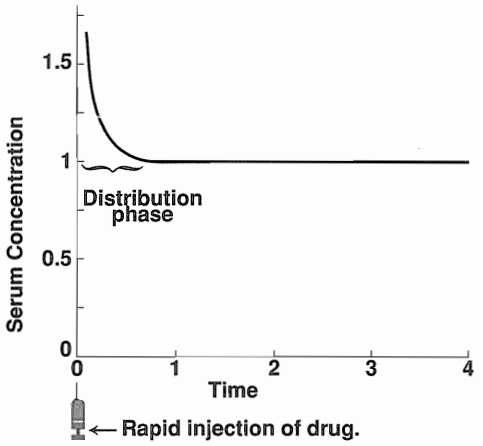



**Figure 1.10**
Drug concentrations in serum after a single injection of drug at time = 0. Assume that drug distributes but is not eliminated.

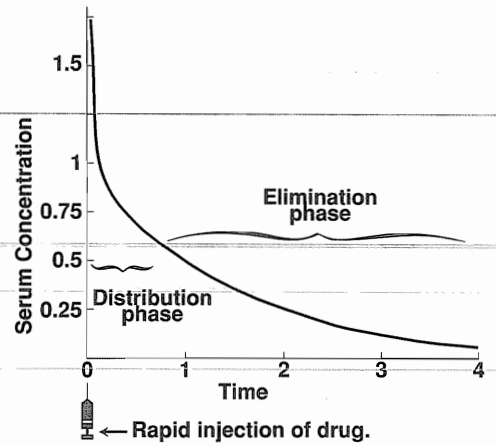



**Figure 1.11**
Drug concentrations in serum after a single injection of drug at time = 0. Assume that drug distributes and is subsequently eliminated.

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 $V_d$.

**1. Determination of $V_d$**

**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, $V_d$:

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

C = Plasma concentration of drug
D = Total amount of drug in the body

For example, if 25 mg of a drug (D = 25 mg) is administered, and the plasma concentration is 1.0 mg/L, then the $V_d$ = 25 mg/1.0 mg/L = 25 L.

**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 body, for example, by renal or biliary elimination or 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 with most drugs is first order and shows a linear relationship with time if ln C (rather than C) is plotted versus time (Figure 1.12).

**c. Calculation of drug concentration if distribution were 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 zero time (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 is injected into a patient and the plasma concentration extrapolated to zero time concentration is $C_0$ = 1.0 mg/L (from graph shown in Figure 1.12), then $V_d$ = 10 mg/1.0 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 since 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 drug from $C_1$ to $C_2$.

$V_d \cdot C_1$ = amount of drug initially in body

$V_d \cdot C_2$ = 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 $V_d(C_2–C_1)$.

2. **Effect of a large $V_d$ on the half-life of a drug:** A large $V_d$ has an important influence on the half-life of a drug, since 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.]

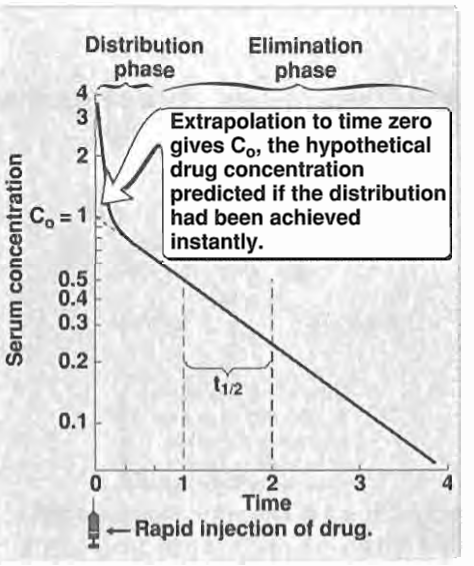



**Figure 1.12**
Drug concentrations in serum after a single injection of drug at time = 0. Data plotted on log scale.

## 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 and elicit a biological response. Thus, by binding to plasma proteins, drugs become "trapped" and, in effect, inactive. [Note: Hypoalbuminemia may alter the level of free drug.]

### 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 affinity 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, since 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

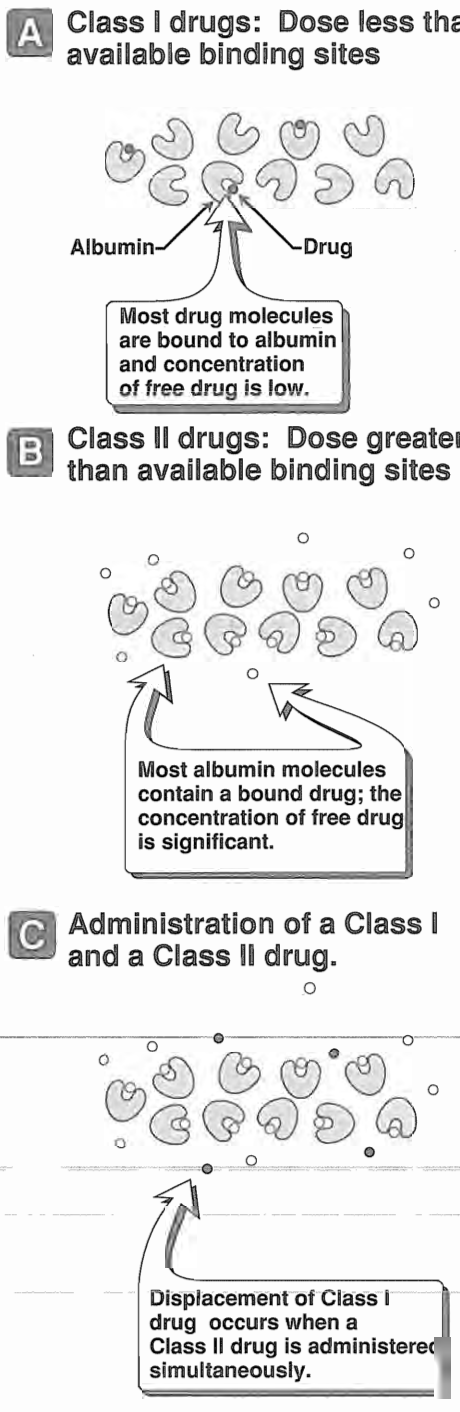



**Figure 1.13**
Binding of Class I and Class II drugs to albumin when drugs are administered alone (A,B), or together (C).

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 (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 drug fraction bound is high. This is the case for Class I drugs, which includes 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 who is taking a Class I drug, such as *tolbutamide*, is given a Class II drug, such as a sulfonamide antibiotic. The *tolbutamide* is normally 95% bound, and only 5% 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 *tolbutamide* from albumin, leading to a rapid increase in the concentration of free *tolbutamide* in plasma, because almost 100% is now free compared with the initial 5%. [Note: The *tolbutamide* concentration does not remain elevated since the drug moves out of the plasma into the interstitial fluid and achieves a new equilibrium.]

### C. Relationship of drug displacement to $V_d$

The impact of drug displacement from albumin depends on both $V_d$ and the therapeutic index 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 (see p. 22) 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 liver is the major site for drug metabolism, but specific drugs may undergo biotransformation in other tissues. [Note: Some agents are initially administered as inactive compounds (prodrugs) and must be metabolized to their active forms.]

## 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 time.

2. **Zero-order kinetics:** With a few drugs, such as *aspirin* (see p. 407), *ethanol* and *phenytoin* (see p. 146), the doses are very large, so the [C] is much greater than $K_m$, and the velocity equation becomes:

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

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 (or sometimes referred to clinically as non-linear kinetics). A constant amount of drug is metabolized per unit time.

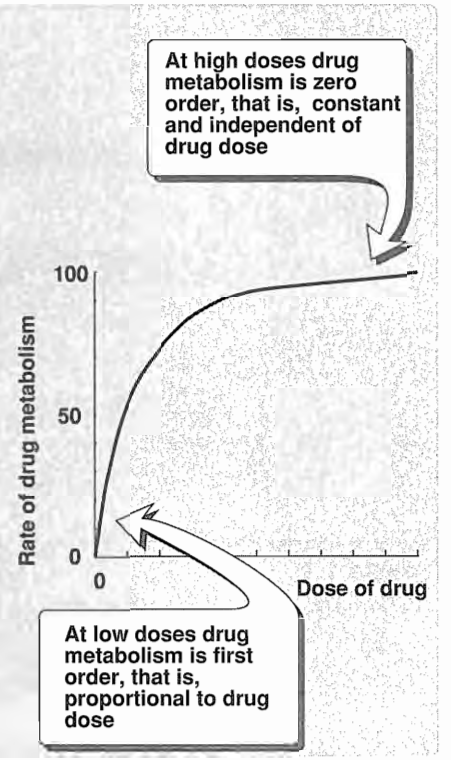



**Figure 1.14**
Effect of drug dose on the rate of metabolism.

## B. Reactions of drug metabolism

The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal tubules (see p. 23). 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 –OH, or $–NH_2$. Phase I metabolism may increase, decrease, or leave unaltered the drug's pharmacologic activity.

   a. **Phase I reactions utilizing the P-450 system:** The Phase I reactions most frequently involved in drug metabolism are catalyzed by the cytochrome P-450 system (also called microsomal mixed function oxidase).

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

[4]See p. 16 for Infolink references to other books in this series.

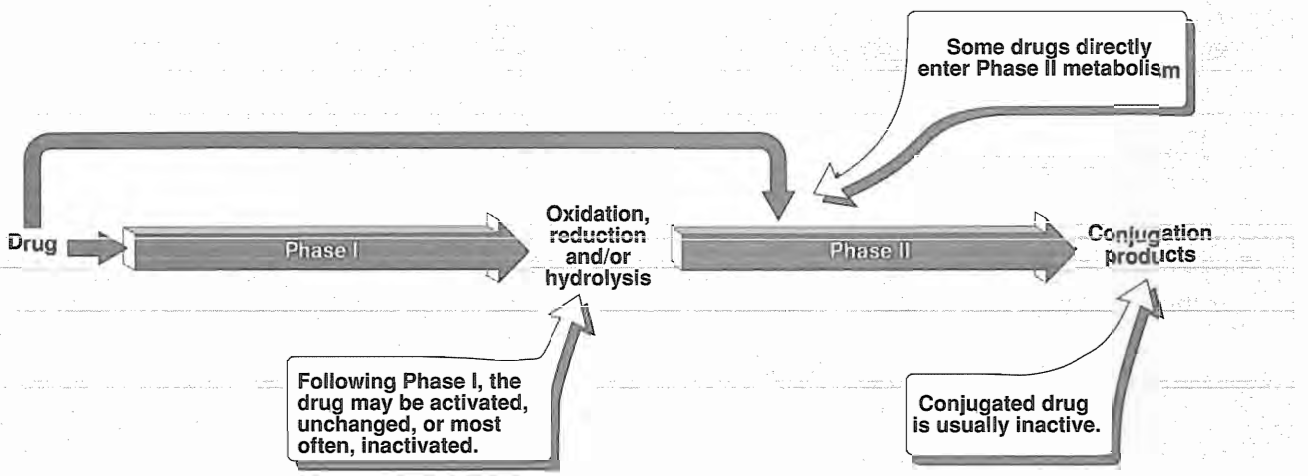



**Figure 1.15**
The biotransformations of drugs.

The oxidation proceeds by the drug binding to the oxidized form of cytochrome P-450, and then oxygen is introduced through a reductive step coupled to NADPH:cytochrome P-450 oxidoreductase.

b. **Summary of the P-450 system:** P-450 is a family of enzymes (isozymes) that occur in most cells, but that are particularly abundant in the liver. [Note: The name P-450 is derived from the spectrophotometric peak observed when the enzyme is treated with carbon monoxide (which inhibits mixed function oxidase activity). Some of the isozymes have peaks at 448 nm, etc.] Each of the enzymes has a broad and, therefore, sometimes overlapping specificity. Many drugs are able to induce elevated levels of cytochrome P-450, resulting in an increased rate of metabolism of the inducing drug, as well as other drugs biotransformed by the P-450 system. This enzyme induction is indicated in Figure 1.16. Many drugs inhibit the P-450 system and may potentiate the actions of other drugs that are metabolized by cytochrome enzymes.

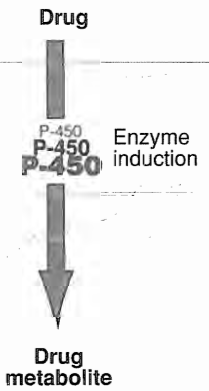



**Figure 1.16**
Schematic representation of drug-induced elevation of hepatic cytochrome P-450.

c. **Phase I reactions not involving the P-450 system:** These include amine oxidation (for example, oxidation of catecholamines or histamine, alcohol dehydrogenation (for example, ethanol oxidation), and hydrolysis (for example, of procainamide).

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 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. 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* (see p. 321). [Note: Drugs already possessing an –OH, –HN2, or –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.

3. **Reversal of order of the Phases:** Not all drugs undergo Phase I and II reactions in that order. For example, *isoniazid* (see p. 332) is first acetylated (a Phase II reaction) and then hydrolyzed to isonicotinic acid (a Phase I reaction).

## 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 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.

Correct answer = D. Both exercise and strong emotions prompt sympathetic output, which slows gastric emptying. In the stomach a weak base is primarily in the protonated, charged form, which does not readily cross the epithelial cells of the stomach. Atropine is a parasympathetic blocker and slows gastric emptying. This delays the rate of drug absorption. A large $V_d$ indicates that most of the drug is outside the plasma space and dialysis would not be effective. A small $V_d$ indicates extensive binding to plasma proteins.

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 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.

Correct answer = C. The direct proportionality between concentration and rate is the definition of first-order. The half-life of a drug is a constant. For first-order reactions, the fraction of the drug eliminated is constant, not the amount. A rate limiting reaction operating at $V_m$ would show zero-order kinetics. First order kinetics show a linear plot of log [drug concentration] versus time.

1.3 All of the following statements are true EXCEPT:

A. Aspirin ($pK_a$ = 3.5) is 90% in its lipid-soluble, protonated form at pH = 2.5.
B. The basic drug promethazine ($pK_a$ = 9.1) is more ionized at pH = 7.4 than at pH = 2.
C. Absorption of a weakly basic drug is likely to occur faster from the intestine than from the stomach.
D. Acidification of the urine accelerates the secretion of a weak base, $pK_a$ = 8.
E. Uncharged molecules more readily cross cell membranes than charged molecules.

Correct choice = B. As the pH of the solution becomes less than the $pK_a$, the ratio $[BH^+]/[B]$ increases; thus $[BH^+]$ is greater at pH = 2. At one pH unit on the acid side of $pK_a$, the $[HA]/[A^-]$ = 10, or 90% is in form HA, the protonated form of aspirin. Weak bases are more charged in the acidic gastric juice and are not readily absorbed. The drug which is a weak base is more ionized in acidified urine and less able to be reabsorbed. Uncharged molecules have a greater solubility in the lipid bilayer of membranes, and thus more readily cross membranes.

1.4 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.

Correct answer = **A.** Drug A is largely bound to albumin and only a small fraction is free. Most of drug A is sequestered on albumin and is inert in terms of exerting pharmacologic actions. If drug B is administered, it displaces drug A from albumin, leading to rapid increase in the concentration of free drug A in plasma, because almost 100% is now free. Drug A moves out of the plasma into the interstitial water and the tissues. The $V_d$ of drug A increases, providing less drug to the organ of excretion, and prolonging the overall lifetime of the drug. Since drug B is already in 100-fold excess of its albumin-binding capacity, dislodging some of drug B from albumin does not significantly affect its serum concentration.

1.5 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 the newborn.
E. involves cytochrome P-450.

Correct answer = **B.** The addition of glucuronic acid prevents recognition of the drug by its receptor. Glucuronic acid is charged, and the drug conjugate has increased water solubility. Conjugation is a Phase II reaction. Neonates are deficient in the conjugating enzymes. Cytochrome P-450 is involved in Phase I reactions.

1.6 Drugs showing zero-order kinetics of elimination

A. are more common that 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 time.

Correct answer = D. Drugs with zero-order kinetics of elimination show a linear relationship between drug concentration and time. In most clinical situations the concentration of a drug is much less than the Michaelis-Menten constant ($K_m$). A decrease in drug concentration is linear with time. The half-life of the drug increases with dose. A constant amount of drug is eliminated per unit time.

1.7 A drug, given as a 100 mg single dose, results in a peak plasma concentration of 20 µg/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.

Correct answer = D. $V_d$ = D/C, where D = total amount of drug in the body and C = plasma concentration of drug. Thus $V_d$ = 100mg/20 µg/ml = 100 mg/20 mg/L = 5 L.


[1]See p. 52 in **Biochemistry** (2nd ed.) for a discussion of effect of substrate levels on reaction velocity.

[2]See p. 6 in **Biochemistry** (2nd ed.) for a discussion of acid-base chemistry.

[3]See p. 8 in **Biochemistry** (2nd ed.) for a discussion of Henderson-Hasselbalch equation.

[4]See p. 52 in **Biochemistry** (2nd ed.) for a discussion of Michaelis-Menten kinetics.

# Pharmacokinetics and Drug Receptors

# 2

## I. OVERVIEW

Pharmacokinetics is defined as 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 (the two most common of these routes being intravenous infusion and oral fixed-dose, fixed-time interval regimens—for example, "one tablet every four hours"). The interactions of the processes described in Chapter 1 determine the pharmacokinetic 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.]

## II. KINETICS OF INTRAVENOUS INFUSION

With continuous intravenous 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 time. Therefore, the rate of drug exit from the body increases proportionately as the plasma concentration increases and at every point in time is proportional to the plasma concentration of the drug.

### A. Steady-state drug levels in blood

Following the initiation of an intravenous 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 $CL_t$ is total body clearance (see p 24), and C is 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

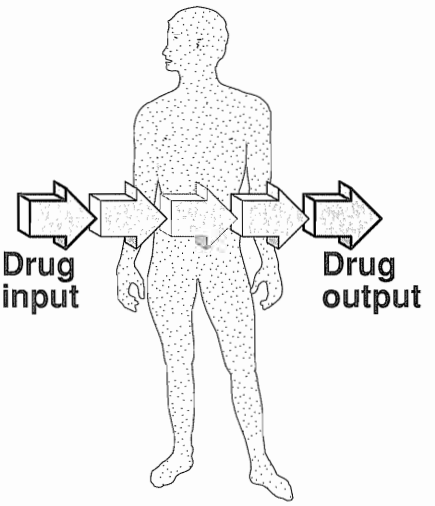



**Figure 2.1**
At steady state, input (rate of infusion) equals output (rate of elimination).

*Lippincott's Illustrated Reviews: Pharmacology, Second Edition.*
by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997.

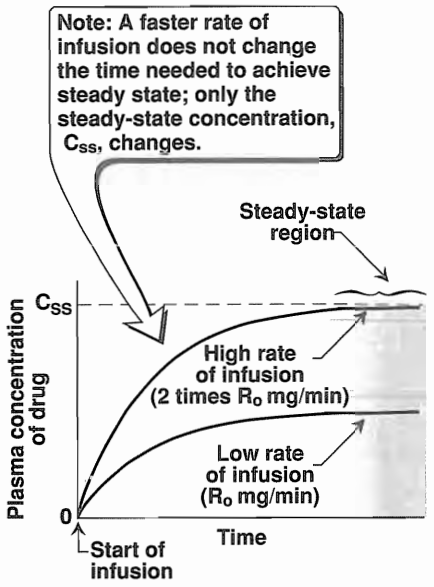



**Figure 2.2**
Effect of infusion rate on the steady-state concentration of drug in plasma. ($R_o$ = rate of infusion of drug.)

plateau, or steady state? Second, what length of time is required to reach the steady-state drug concentration?

### B. Influence of the rate of drug infusion on the steady-state

A steady-state plasma concentration of drug occurs when the rate of drug elimination is equal to the rate of administration (Figure 2.1), as described by the equation:

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

where $C_{ss}$ = the steady state concentration of drug

$R_o$ = the infusion rate (for example, mg/min)

$k_e$ = first-order rate constant for drug elimination from the total body

$V_d$ = volume of distribution

$CL_t$ = total body clearance (see p. 24)

Since $k_e$, $CL_t$, and $V_d$ are constant for most drugs showing linear 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 2.2). 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).

### C. 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 2.3). The fractional rate of approach to a steady state is achieved by a first-order process.

1. **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, 50% of the final steady-state concentration of drug is observed after 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 50%. Waiting another half-life allows the drug concentration to approach 75% of $C_{ss}$ (see Figure 2.3). The drug concentration is 90% 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 4 half-lives.

2. **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 2.2).

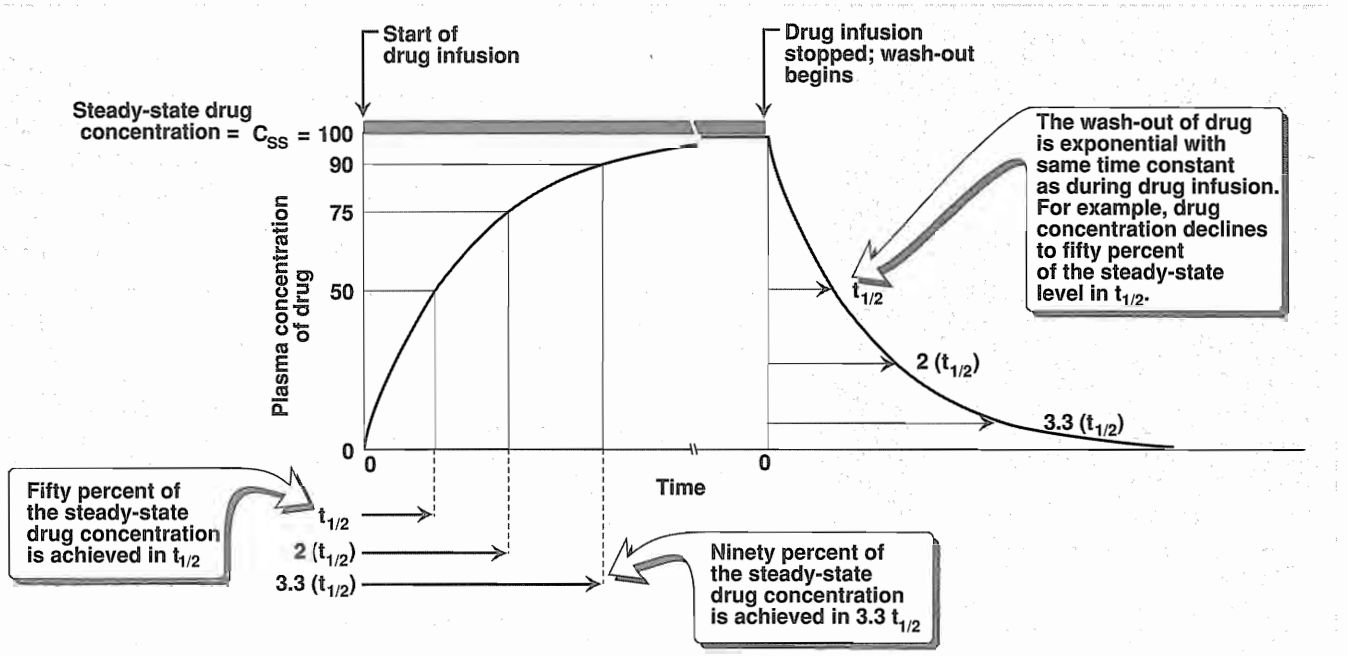



**Figure 2.3**
Rate of attainment of steady-state concentration of drug in plasma.

3. **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 2.3).

4. **Loading dose:** A delay in achieving the desired plasma levels of drug may be clinically unacceptable. Therefore, a "loading dose" 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:

Loading dose = ($V_d$) (desired steady-state plasma concentration)

## III. 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.

### A. Single intravenous injection

For simplicity, assume the injected drug rapidly distributes into a single compartment. Since the rate of elimination is usually first order in regard to drug concentration, the circulating level of drug decreases exponentially with time (Figure 2.4). [Note: The $t_{1/2}$ does not depend on the dose of drug administered.]

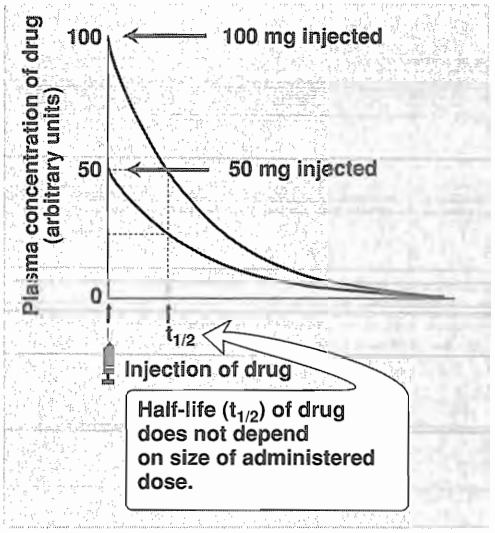



**Figure 2.4**
Effect of dose of single intravenous injection of drug on plasma levels.

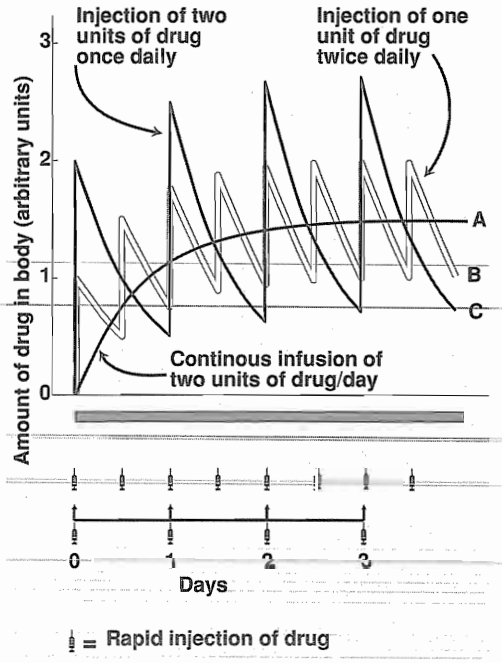



**Figure 2.5**
Predicted plasma concentrations of a drug given by infusion (A), twice daily injection (B), or once daily injection (C). Model assumes rapid mixing in a single body compartment and a $t_{1/2}$ of 12 hours.

### B. Multiple intravenous injections

When a drug is given repeatedly at regular intervals, the plasma concentration increases until a steady state is reached (Figure 2.5). Because most drugs are given at intervals shorter than 5 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 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 elevated plasma concentration) exactly balances the rate of drug administration, that is, a steady state is achieved.

1. **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.

2. **Example of achievement of steady state using different dosage regimens:** The curve B of Figure 2.5 shows the amount of drug in the body when one gram of drug is administered intravenously 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 administered, that is, the "rate in" equals the "rate out." As in the case for intravenous infusion (see p. 18), 90% of the steady-state value is achieved in 3.3 times $t_{1/2}$.

### C. Orally administered drugs

Most drugs that are administered on an outpatient basis are taken orally on a fixed-dose fixed-time interval regimen, for example, a specific dose, taken one, two or three times daily. In contrast to intravenous 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 2.6).

## IV. DOSE-RESPONSE QUANTITATION

### A. Drug receptors

A drug receptor is a specialized target macromolecule, present on the cell surface or intracellularly, that binds a drug and mediates its pharmacologic actions. Drugs may interact with enzymes (for example, inhibition of dihydrofolate reductase by *trimethoprim,* p. 294),

nucleic acids (for example, blockade of transcription by *dactinomycin,* p. 384) or membrane receptors (for example, alteration of membrane permeability by acetylcholine). In each case, the formation of the drug-receptor complex leads to a biologic response, and the magnitude of the response is proportional to the number of drug-receptor complexes:

$$\text{Drug} + \text{Receptor} \rightarrow \text{Drug-receptor complex} \rightarrow \text{Effect}$$

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. However, the receptor not only has the ability to recognize a ligand (drug), but can also couple or transduce this binding into a response by causing a conformational change or a biochemical effect. [Note: For most drugs, the nature of the target molecule is unknown. The actions of a few drugs are not mediated by specific receptors, but depend on nonspecific chemical or physical interactions. For example, anesthetic gases (see p. 112) are thought to alter the structure of the membrane.]

### B. Graded dose-response curve

An agonist is defined as an agent that can bind to a receptor and elicit a response. The magnitude of the drug effect depends on its concentration at the receptor site, which in turn is determined by the dose of drug administered and by factors characteristic of the drug, such as rate of absorption, distribution, and metabolism. The effect of a drug is most easily analyzed by plotting the magnitude of the response versus the log of the drug dose, thus obtaining a graded dose-response curve (Figure 2.7).

1. **Efficacy:** Efficacy is the maximal response produced by a drug. It depends on the number of drug-receptor complexes formed and the efficiency with which the activated receptor produces a cellular action (see Figure 2.7). Efficacy is analogous to maximal velocity for an enzyme catalyzed reaction[2]. [Note: A compound may bind to the receptor and not elicit a response. It is thus said to have zero efficacy, and may act as an antagonist.]

2. **Potency:** Potency, also termed effective dose concentration, is a measure of how much drug is required to elicit a given response. The lower the dose required for a given response, the more potent the drug. Potency is most often expressed as the dose of drug that gives 50% of the maximal response, $ED_{50}$ (see Figure 2.7). A drug with a low $ED_{50}$ is more potent than a drug with a larger $ED_{50}$. The affinity ($K_d$) of the receptor for a drug is an important factor in determining the potency. However, efficacy is more important than potency since it focuses on the effectiveness of the drug. (For example, a more potent drug may not reach its receptor in sufficient concentrations due to some pathologic condition.)

3. **Slope of the dose-response curve:** The slope of the midportion of the dose-response curve varies from drug to drug. A steep slope indicates that a small increase in drug dosage produces a large change in response.

[1,2]See p. 26 for Infolink references to other books in this series.

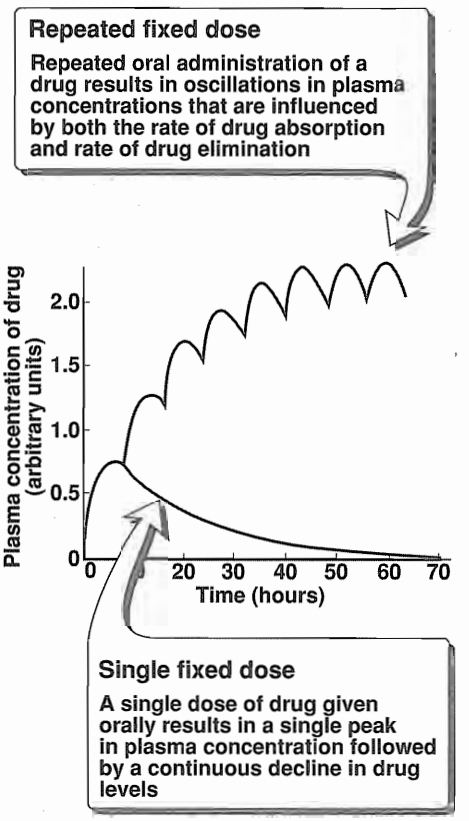



**Figure 2.6**
Predicted plasma concentrations of a drug given by repeated oral administrations.

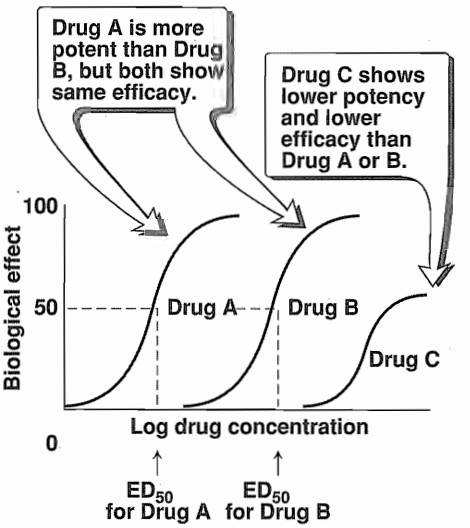



**Figure 2.7**
Typical dose response curve for drugs showing differences in potency and efficacy. $ED_{50}$ = drug dose that shows 50% of maximal response.

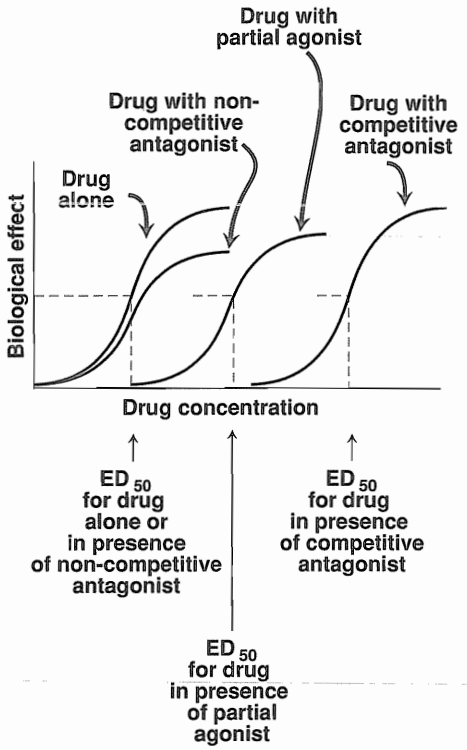



**Figure 2.8**
Effects of drug antagonists.

### C. Reversible antagonists

1. **Competitive:** These agents interact with receptors at the same site as the agonist and, thus, compete for binding of the agonist (Figure 2.8). A competitive antagonist shifts the dose-response curve to the right, causing the drug to behave as if it were less potent. This behavior is analogous to a competitive inhibitor for an enzyme-catalyzed reaction.[3]

2. **Noncompetitive:** These agents either prevent the binding of the agonist or prevent the agonist from activating the receptor. A noncompetitive antagonist decreases the maximal response and is analogous to a noncompetitive inhibitor for an enzyme-catalyzed reaction.[4]

3. **Partial agonist:** Partial agonists block the agonist binding site but cause less response than a full agonist. A partial agonist may have an affinity for the receptor that is increased, decreased, or equivalent to that of an agonist.

## V. 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.

Therapeutic index = toxic dose/effective dose

The therapeutic index is thus a measure of the drug's safety, since a large value indicates that there is a wide margin between doses that are effective and doses that are toxic.

### A. Determination of therapeutic index

The therapeutic index is determined by measuring the frequency of desired response and toxic response at various doses of drug. For example, Figure 2.9 shows the response to *warfarin* (see p. 199), an oral anticoagulant with a narrow therapeutic index, and *penicillin* (see p. 297), 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 2.9A). 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 while 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, since the effective and toxic concentrations are similar.

[4]See p. 26 for Infolink references to other books in this series.

Agents with a low therapeutic index, that is, drugs in which dose is critically important, are those drugs in which bioinequivalence is likely to result in a therapeutic consequence (see p. 7).

2. **Penicillin (example of a drug with a large therapeutic index):** For drugs with a large therapeutic index, such as *penicillin* (see Figure 2.9B), 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, the bioavailability does not critically alter the therapeutic effects.

## VI. DRUG ELIMINATION

Removal of a drug from the body may occur 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 will remove small molecules such as drugs.

### A. Renal elimination of a drug

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 2.10). The glomerular filtration rate (GFR = 125 ml/min) is normally about 20% of the renal plasma flow (RPF = 600 ml/min). Lipid solubility and pH do not influence the passage of drugs into the glomerular filtrate.

2. **Proximal tubular secretion:** Drug that was not transferred into the glomerular filtrate leaves 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 systems, one for anions (for example, deprotonated forms of weak acids) and one for cations (protonated forms of weak bases). Each of these transport systems shows a low specificity and can transport many compounds; thus, competition between drugs for the carriers can occur within each transport system (for example, see *probenecid*, p. 417). [Note: Premature infants and neonates have incompletely developed tubular secretory mechanism and thus may retain certain drugs.]

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. For example, a patient presenting with a *phenobarbital* overdose can be given bicarbonate, which alkalinizes the urine and keeps the drug ionized, thereby decreasing its reabsorption.

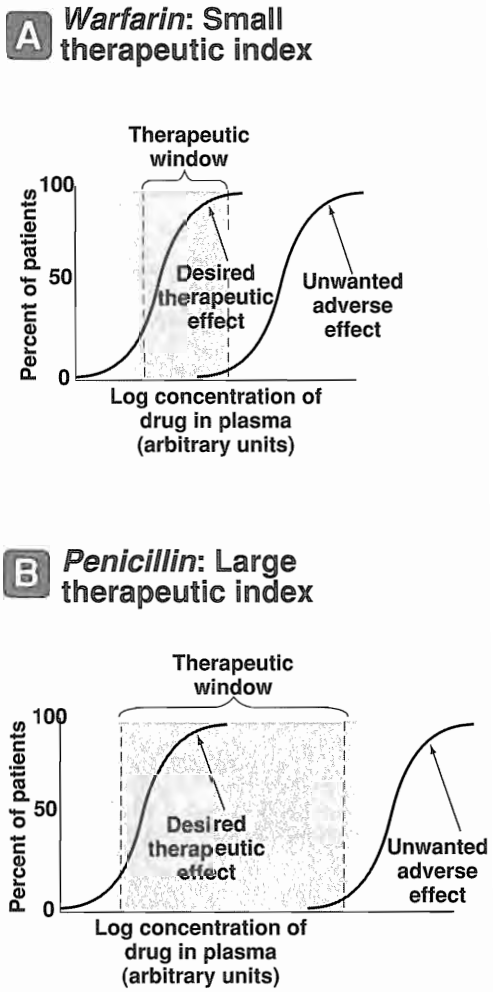



**Figure 2.9**
Cumulative percent of patients responding to plasma levels of drug.

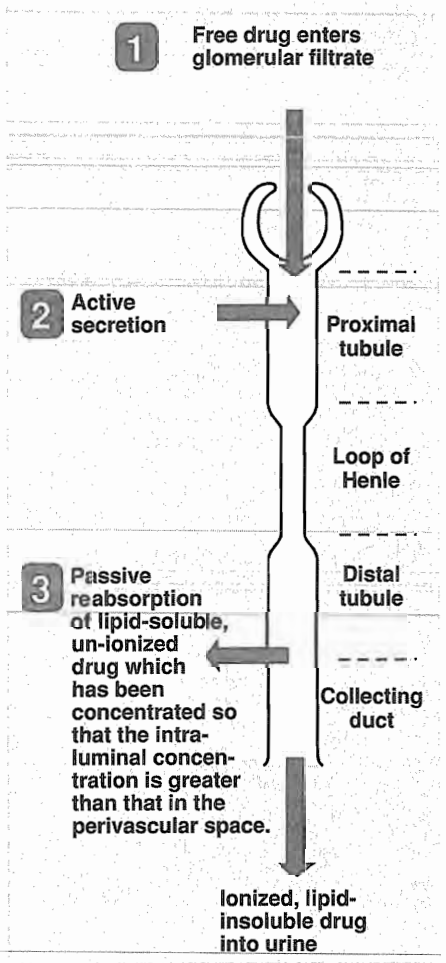



**Figure 2.10**
Drug elimination by the kidney.

If the drug is a weak base, acidification of the urine with $NH_4Cl$ leads to protonation of the drug and an increase in its clearance. This process is called "ion trapping."

4. **Role of drug metabolism:** Most drugs are lipid soluble and diffuse out of the kidney's tubular lumen when the drug concentration in the filtrate becomes greater than that in the perivascular space. In order to minimize this reabsorption, drugs are modified by the body to be more polar using two types of reactions: Phase I reactions (see p. 13) that involve either the addition of hydroxyl groups or the removal of blocking groups from hydroxyl, carboxyl or amino groups, or Phase II reactions (see p. 14) 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 2.11).

## 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 time, for example, as ml/min. Clearance equals the amount of renal plasma flow multiplied by the extraction ratio, and since 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:**

$$\underset{\text{mg/min}}{\text{Excretion rate}} = \underset{\text{ml/min}}{(\text{clearance})} \quad \underset{\text{mg/ml}}{(\text{plasma concentration})}$$

The elimination of a drug usually follows first order kinetics, and the concentration of drug in plasma drops exponentially with time. This may be used to determine the half-life of the drug (the time during which the concentration of the drug decreases from C to $\frac{1}{2}$C).

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

## C. Total body clearance

The total body (systemic) clearance ($CL_{total}$) 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. However, total clearance can be derived from the steady state equation (see p. 18):

$$CL_{total} = k_e V_d$$

### D. Volume of distribution and the half-life of a drug

The half-life of a drug is inversely related to its clearance and directly proportional to its volume of distribution.

$$t_{1/2} = 0.693\ V_d/CL_{total}$$

This equation shows that as the volume of distribution increases, the half-life of a drug becomes longer. The larger the volume of distribution, the more drug is outside the plasma compartment and is unavailable for excretion by the kidney or metabolism by the liver.

### E. Clinical situations resulting in increased 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 longer half-life. The half-life of a drug is increased by:

1. diminished renal plasma flow, for example, in cardiogenic shock, heart failure, or hemorrhage.
2. addition of a second drug that displaces the first from albumin and, hence, increases the volume of distribution of the drug.
3. decreased extraction ratio, for example, as seen in renal disease.
4. decreased metabolism, for example, when another drug inhibits its biotransformation, or hepatic insufficiency as with cirrhosis.

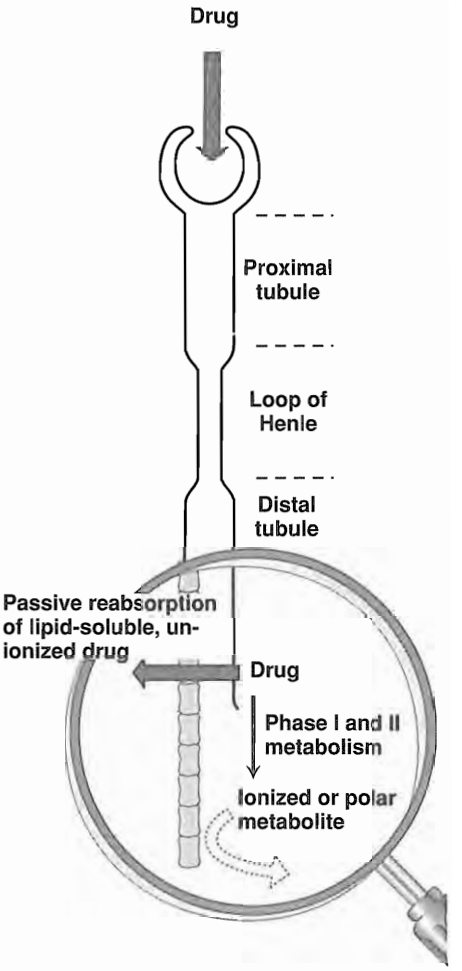



**Figure 2.11**
Effect of drug metabolism on reabsorption in the distal tubule.

## Study Questions

Choose the ONE best answer.

2.1 A drug with a half-life of 12 hours is administered by continuous intravenous infusion. How long will it take for the drug to reach 90% of its final steady-state level?

A. 18 hours.
B. 24 hours.
C. 30 hours.
D. 40 hours.
E. 90 hours.

Correct answer = D. One approaches 90% of the final steady-state in 3.3 times $t_{1/2}$ = 3.3 • 12 ~ 40 hours.

2.2 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 infusion rate, 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.

Correct answer = A. The steady-state concentration of a drug is directly proportional to the infusion rate. Increasing the loading dose provides a transient increase in drug level, but the steady-state level remains unchanged. Doubling both the rate of infusion and concentration of the infused drug leads to a 4-fold increase in the steady-state drug concentration. Tripling or quadrupling the rate of infusion leads to either a 3-fold or 4-fold increase in the steady-state drug concentration.

2.3 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 $ED_{50}$.
E. Variation in response to a drug among different individuals is most likely to occur with a drug showing a large therapeutic index.

Correct answer = D. In the presence of a competitive antagonist, a higher concentration of drug is required to elicit a given response. Efficacy and potency can vary independently, and the maximal response obtained is often more important than the amount of drug needed to achieve it. For example, in Choice A, no information is provided about the efficacy of drug A, so all one can say is that drug A is more potent than drug B. Variability between patients in the pharmacokinetics of a drug is most important clinically when the effective and toxic doses are not very different, as is the case with a drug that shows a small therapeutic index.

2.4 Which of the following most closely describes the clearance rate of a drug that is infused at a rate of 4 mg/min and produces a steady-state concentration of 6 mg/L in the plasma?

A. 67 ml/min.
B. 132 ml/min.
C. 300 ml/min.
D. 667 ml min.
E. 1,200 ml/min.

Correct answer = D. Clearance is the volume of plasma from which all drug is removed in a given time (in this case per minute). At steady state, the excretion rate = infusion rate = 4 mg/min. Thus, clearance (ml/min) = excretion rate (mg/ml)/plasma concentration (mg/ml) = (4 mg/ml)/(0.006 mg/ml) = 667 ml/min.

2.5 The antimicrobial drug, tetracycline, is found to be therapeutically effective when 250 mg of drug are present in the body. The $t_{1/2}$ of tetracycline is 8 hours. What is the correct rate of infusion?

A. 7 mg/hr.
B. 12 mg/hr.
C. 22 mg/hr.
D. 37 mg/hr.
E. 45 mg/hr.

Correct answer = C. The correct rate of infusion is $R=K_dV_dC$, where $K_d = 0.69/t_{1/2} = 0.69/8$ hours = 0.086 $hr^{-1}$; therefore, the instantaneous rate of loss of the tetracycline is 8.6 % per hr of whatever amount of drug is present in the body. ($V_dC$ = the total amount of drug in the body.) When 250 mg of tetracycline are present in the body, the rate of drug loss is 250 mg x 8.6 %/hour = 250 x 0.086 $hr^{-1}$ = 21.5 mg/hr.


[1]See p. 48 in **Biochemistry** (2nd ed.) for a discussion of the interaction of enzyme with substrate.

[2]See p. 53 in **Biochemistry** (2nd ed.) for a discussion of maximal velocity for an enzyme catalyzed reaction.

[3]See p. 54-56 in **Biochemistry** (2nd ed.) for a discussion of competitive and noncompetitive inhibition of an enzyme catalyzed reaction.

UNIT II:
Drugs Affecting the Autonomic Nervous System

# The Autonomic Nervous System

# 3

## I. OVERVIEW

The autonomic nervous system, along with the endocrine system, coordinates the regulation and integration of body 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, where specific effects are caused due to the release of a neuromediator substance. 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 describes the role of neurotransmitters in the communication between extracellular events and chemical changes within the cell.

## 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 cord, that is, any nerves that enter or leave the CNS (Figure 3.1). The peripheral nervous system can be further divided into the efferent division, whose neurons carry signals away from the brain and spinal cord to the peripheral tissues, and the afferent division, whose neurons bring information from the periphery to the CNS.

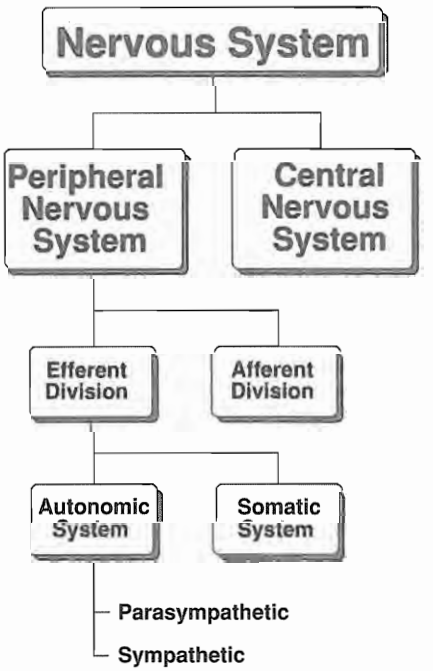



**Figure 3.1**
Organization of the nervous system.

*Lippincott's Illustrated Reviews: Pharmacology, Second Edition.*
by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997.

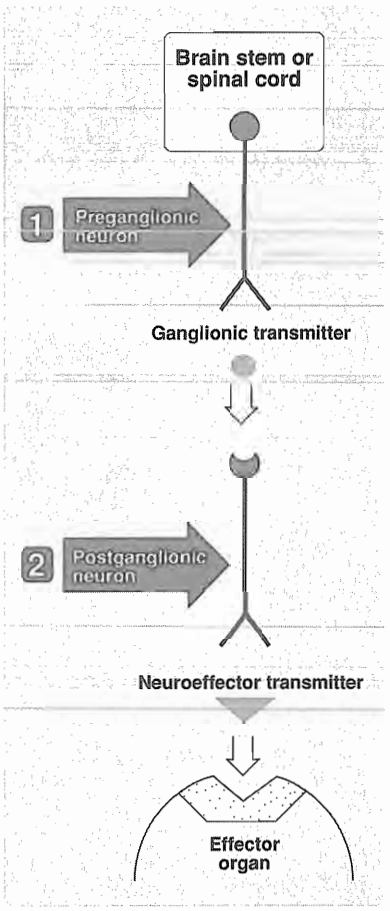



**Figure 3.2**
Efferent neurons of the autonomic nervous system.

## A. Functional divisions within the nervous system

The efferent portion of the peripheral nervous system can be further divided into two major functional subdivisions, the somatic and autonomic systems (see Figure 3.1). The somatic efferents are involved in voluntarily controlled functions such as contraction of the skeletal muscles in locomotion. The autonomic system functions involuntarily to regulate the everyday needs and requirements of the body without the conscious participation of the mind. It is composed primarily of visceral motor (efferent) neurons that innervate smooth muscle of the viscera, cardiac muscle, vasculature and the exocrine glands.

## B. Anatomy 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 brain stem 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 the 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 (Figure 3.2).

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 (see Figure 3.1). The preganglionic neurons of the sympathetic system come from thoracic and lumbar regions of the spinal cord and synapse in two cord-like chains of ganglia that run in parallel on each side of the spinal cord. Axons of the postganglionic neuron extend from these ganglia to the glands and viscera. [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 neurotransmitters, 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 cranial and sacral areas of the spinal cord and synapse in ganglia near or on the effector organs. In both the sympathetic and parasympathetic systems, postganglionic fibers extend from the ganglia to effector organs.

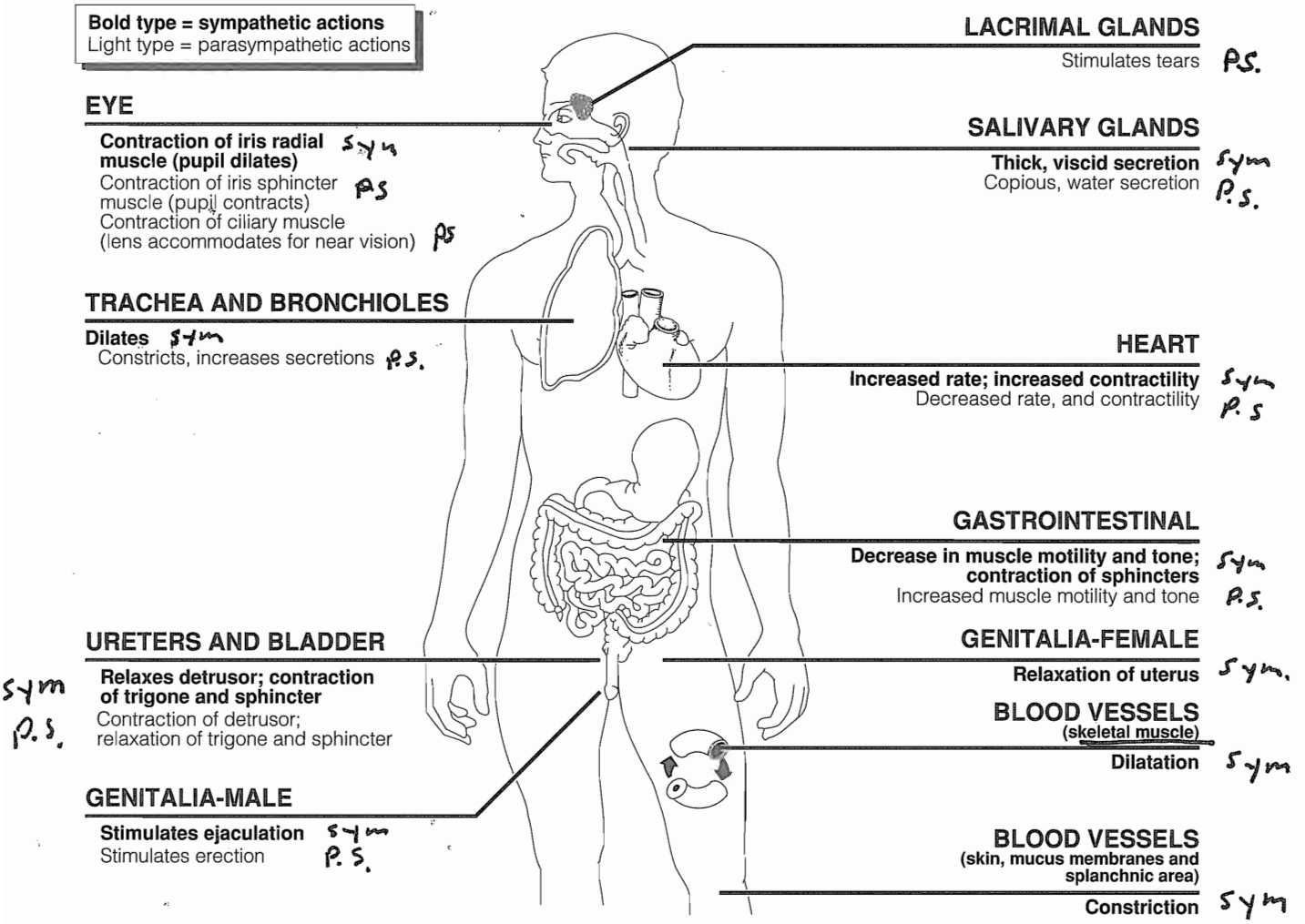



**Figure 3.3**
Action of sympathetic **(bold type)** and parasympathetic (light type) nervous systems on effector organs.

### C. Functions of the sympathetic system

Though 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 heart while diverting flow from the skin and internal organs. Sympathetic stimulation also results in dilation of the pupils and the bronchioles (Figure 3.3).

2. **Fight or flight response:** The changes experienced by the body during emergencies have been referred to as the "fight or flight" 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 blood stream and promote responses in effector organs that contain adrenergic receptors (see Figure 6.6, p. 60). The sympathetic nervous system tends to function as a unit and often discharges as a complete system, 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.

**D. Functions of the parasympathetic system:**

The parasympathetic division maintains essential bodily functions, such as digestive processes and elimination of wastes, and is required for life (see Figure 3.3). It usually acts to oppose or balance the actions of the sympathetic division and is generally dominant over the sympathetic system in "rest and digest" situations (see Figure 3.4). The parasympathetic system is not a functional entity as such and 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.

**E. Role of the CNS in autonomic control of viscera**

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 feed-back is provided by streams of afferent impulses, arising in the viscera and other autonomically innervated structures, that travel to integrating centers in the CNS—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).

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.

**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, the heart has vagal parasympathetic innervation that slows rate of contraction, and sympathetic innervation that speeds contraction. Despite this dual innervation, one system usually predominates in controlling the activity of a given organ. For example, in the heart, the vagus is the predominant controlling factor for rate.

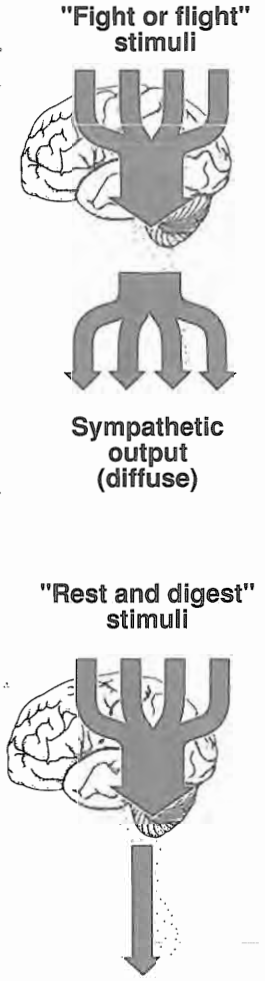



**Figure 3.4**
Sympathetic and parasympathetic actions are elicited by different stimuli.

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.

### A. Local mediators

Most cells in the body secrete chemicals that act locally, that is, they act on cells in their immediate environment. These chemical signals are rapidly destroyed or removed; thus, they do not enter the blood and are not distributed throughout the body. Histamine (see p. 420) and prostaglandins (see p. 419) are examples of local mediators.

### B. Hormones

Specialized endocrine cells secrete hormones into the blood stream, where they travel throughout the body exerting effects on broadly distributed target cells in the body. (Hormones are described in Chapters 25-27.)

### C. Neurotransmitters

Each neuron is a distinct anatomic unit, and no structural continuity exists between most neurons. Communication between nerve cells—and between nerve cells and effector organs—occurs through the release of specific chemical signals, called neurotransmitters, from the nerve terminals. This release depends on processes that are triggered by $Ca^{++}$ uptake and regulated by phosphorylation of synaptic proteins. The neurotransmitters rapidly diffuse across the synaptic cleft or gap (synapse) between nerve endings and combine with specific receptors on the postsynaptic (target) cell (see pp. 37 and 57).

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 shows a binding specificity and is coupled to processes that eventually evoke a response. Most receptors are proteins. They need not be located in the membrane.]

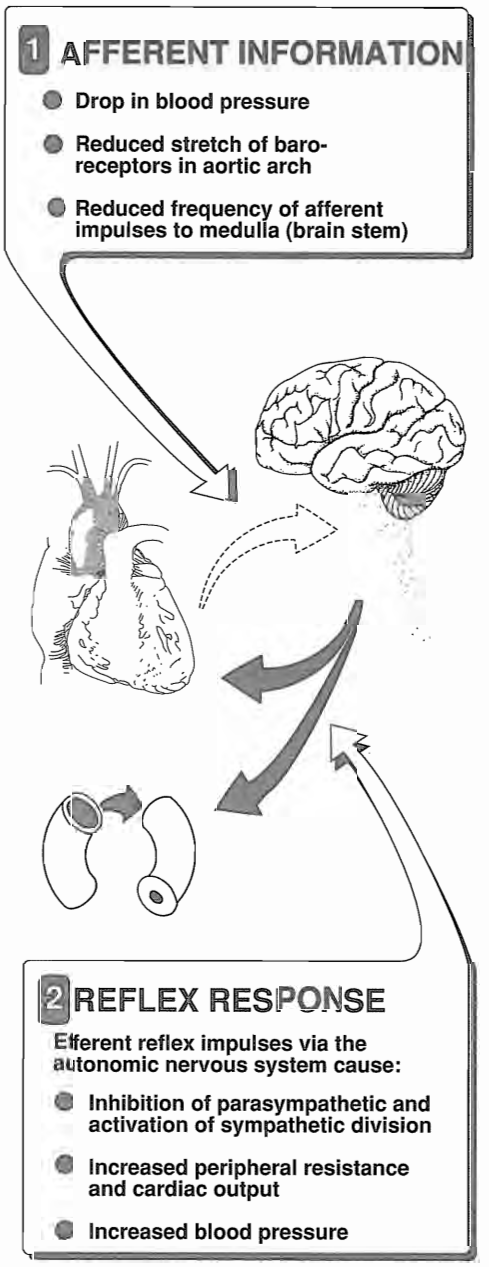



**Figure 3.5**
Baroreceptor reflex arc responds to a decrease in blood pressure.

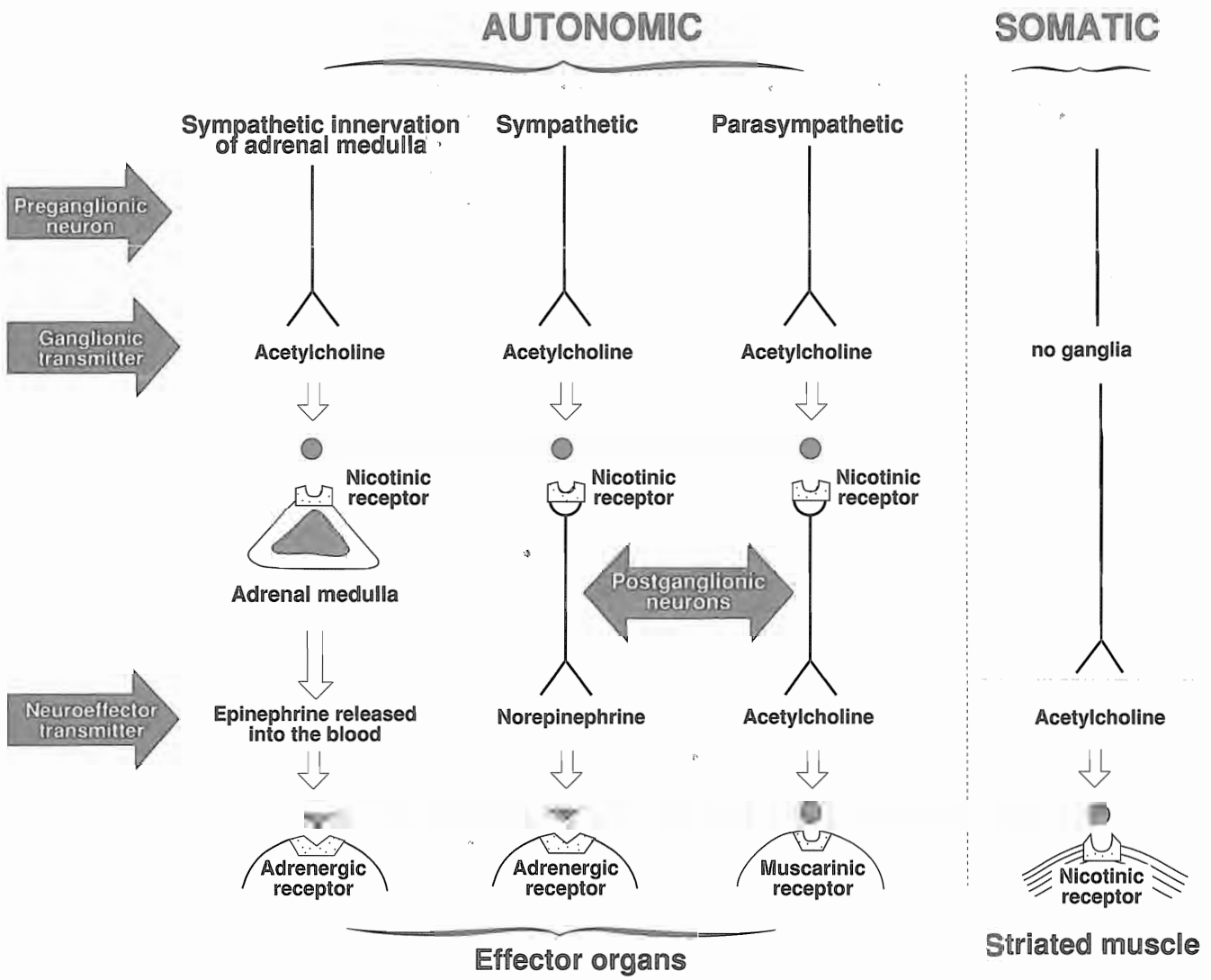



**Figure 3.6**
Summary of the neurotransmitters released and the types of receptors found within the autonomic and somatic nervous systems. [Note: This schematic diagram does not show that the parasympathetic ganglia are close to or on the surface of the effector organs and that the postganglionic fibers are usually shorter than the preganglionic fibers.]

**2. Types of neurotransmitters:** Although over 50 chemical signal molecules in the nervous system have tentatively been identified, 6 signal compounds—norepinephrine (and the closely related epinephrine), acetylcholine, dopamine, serotonin, histamine, and γ-aminobutyric acid—are most commonly involved in the actions of therapeutically useful drugs. Each of these chemical signals binds to a specific family of receptors. Cholinergic and adrenergic neurotransmitters are the primary chemical signals in the autonomic nervous system, whereas a wide variety of neurotransmitters function in the CNS.

**a. Acetylcholine:** The autonomic nerve fibers can be classified into two groups based on the chemical nature of the neurotransmitter released. If transmission is mediated by acetylcholine, the neuron is termed **cholinergic**. Acetylcholine mediates the transmission of nerve impulses across autonomic ganglia in both the sympathetic and parasympathetic nervous systems (Figure 3.6). It is the neurotransmitter at the adrenal medulla. Transmission from the autonomic postganglionic nerves to the effector organs in the parasympathetic system 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.

**b. Norepinephrine and epinephrine:** If norepinephrine or epinephrine is the transmitter, the fiber is called **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 on Figure 3.6.]

## IV. SECOND 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.

### A. Actions of membrane receptors

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). The effect of neurotransmitters on these chemically gated ion channels is discussed on p. 82.

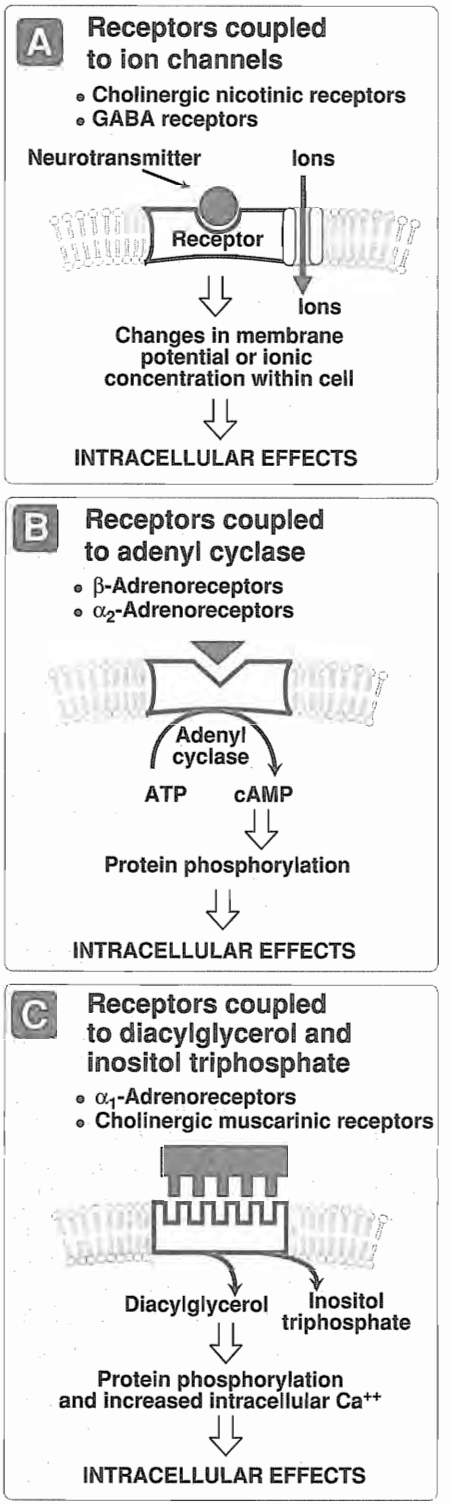



**Figure 3.7**
Three mechanisms whereby binding of a neurotransmitter leads to a cellular effect.

### B. Regulation involving second messenger molecules

Some 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" molecules—so named because they intervene between the original message (the neurotransmitter or hormone) and the ultimate effect on the cell—are part of the cascade of events that translates neurotransmitter binding into a cellular response. The two most widely recognized second messengers are the adenylyl cyclase system and the calcium/phosphatidylinositol system (Figure 3.7B and C).

## Study Questions

Choose the ONE best answer

3.1. All of the following statements concerning the autonomic nervous system are true EXCEPT for which one?

A. The autonomic nervous system is composed entirely of efferent neurons.
B. The sympathetic division is activated in response to stressful situations.
C. The parasympathetic division originates from cell bodies in the central nervous system.
D. The control of blood pressure is mainly a sympathetic activity, with essentially no participation of the parasympathetic system.
E. The parasympathetic nervous system is not required for life.

Correct choice = E. The parasympathetic nervous system is essential for life. Visceral motor (efferent) neurons innervate smooth muscle of the viscera, cardiac muscle, and the exocrine glands. The afferent neurons of the autonomic nervous system are important in the reflex regulation, 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. Conditions such as trauma, fear, hypoglycemia, cold, or exercise activate the sympathetic neurons. Both sympathetic and parasympathetic neurons emerge from the brain stem or spinal cord. Blood pressure is regulated largely by sympathetic control of vascular tone.

3.2. 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.

Correct answer = C. The parasympathetic system maintains essential bodily functions, such as vision, movement of food, and urination. It uses acetylcholine, not norepinephrine, as a neurotransmitter, and discharges as discrete fibers that are activated separately. The postganglionic fibers of the parasympathetic system are short compared to the sympathetic division. The adrenal medulla is under control of the sympathetic system.

3.3. 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.

Correct answer = C.

# Cholinergic Agonists

# 4

## I. OVERVIEW

Drugs affecting the autonomic nervous system are divided into two subgroups 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 group—the adrenergic drugs (discussed in Chapters 6 and 7)—act on receptors that are stimulated by norepinephrine or epinephrine. Both the cholinergic and adrenergic drugs act either by stimulating or blocking neurons of the autonomic nervous system. Figure 4.1 summarizes the cholinergic agonists discussed in this chapter.

## 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). Cholinergic neurons innervate voluntary muscles of the somatic system and are also found in the CNS.

### A. Neurotransmission at cholinergic neurons

Neurotransmission in cholinergic neurons involves six steps. The first four, synthesis, storage, release and binding of the acetylcholine to a receptor, 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 extracellular fluid into the cytoplasm of the cholinergic neuron by a carrier system that cotransports sodium and can be inhibited by the drug *hemicholinium*. Choline acetyltransferase (CAT) catalyzes the reaction of choline with acetyl CoA to form acetylcholine in the cytosol.

2. **Storage of acetylcholine in vesicles:** The acetylcholine is packaged into vesicles by an active transport process coupled to the efflux of protons. The mature vesicle not only contains acetylcholine but also adenosine triphosphate and proteoglycan. The function of the latter substances in the nerve terminal is unknown.

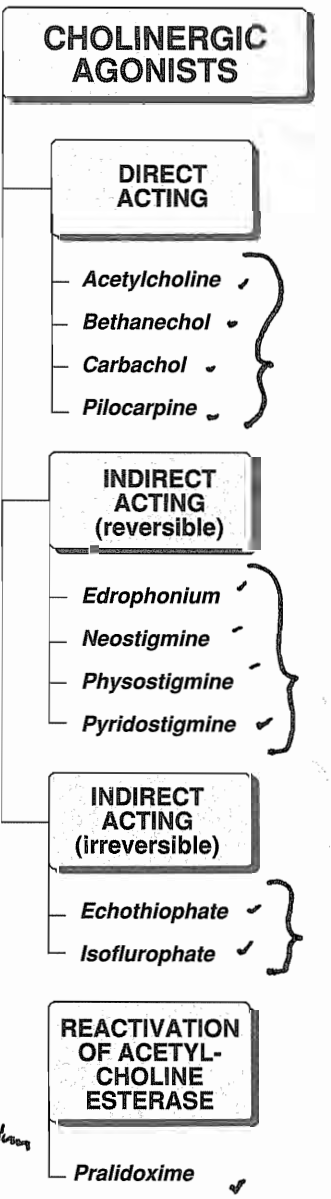



**Figure 4.1**
Summary of cholinergic agonists.

*Lippincott's Illustrated Reviews: Pharmacology, Second Edition.*
by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997.

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 in 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 acetylcholine into the synapse. This release is blocked by botulinum toxin. By contrast, black widow spider venom causes all of the cellular acetylcholine stored in synaptic vesicles to spill into the synaptic gap.

4. **Binding to receptor:** Acetylcholine released from the synaptic vesicles diffuses across the synaptic space and binds to either postsynaptic receptors on the target cell or to presynaptic receptors in the membrane of the neuron that released the acetylcholine.

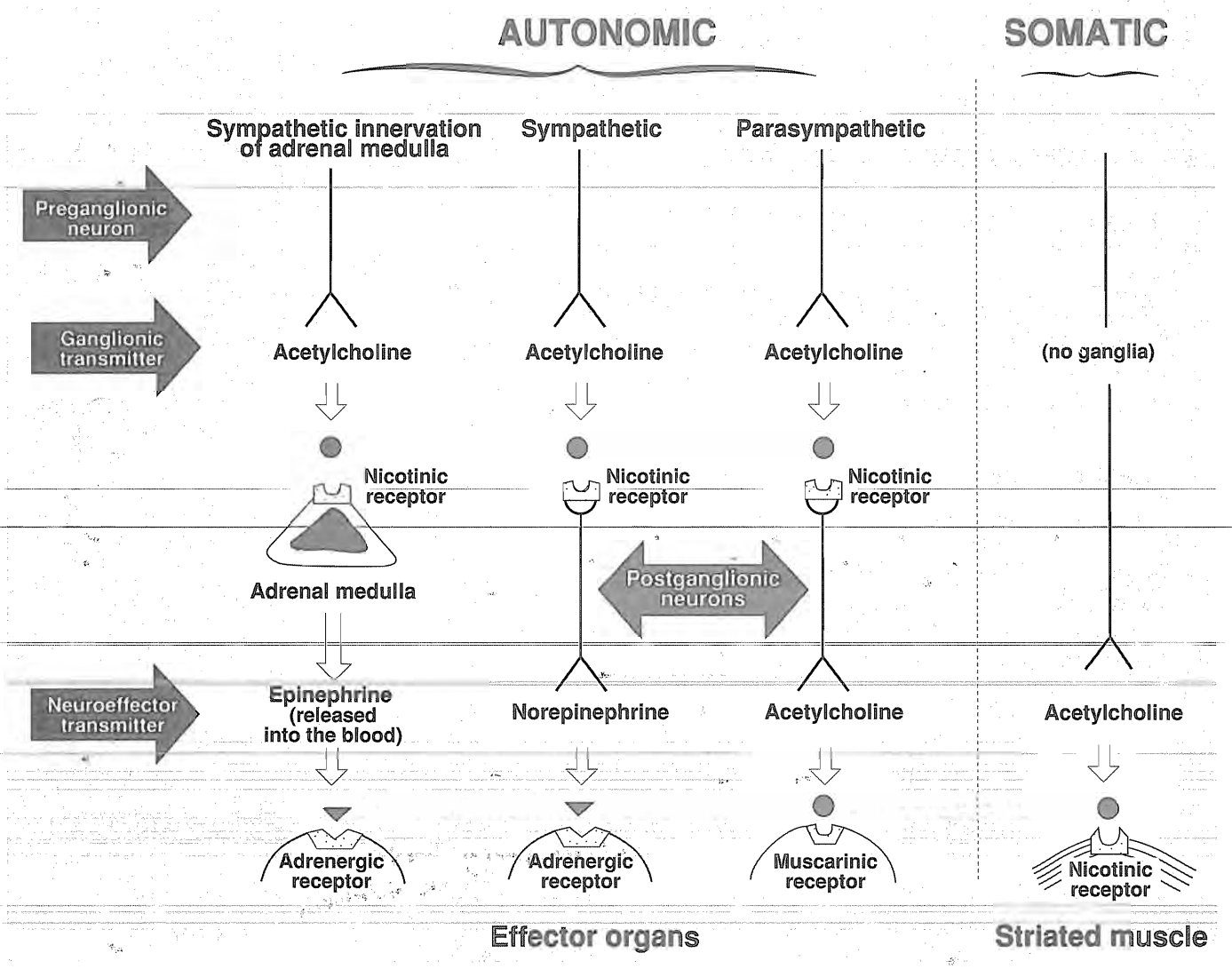



**Figure 4.2**
Sites of actions of cholinergic agonists in the autonomic and somatic nervous systems.

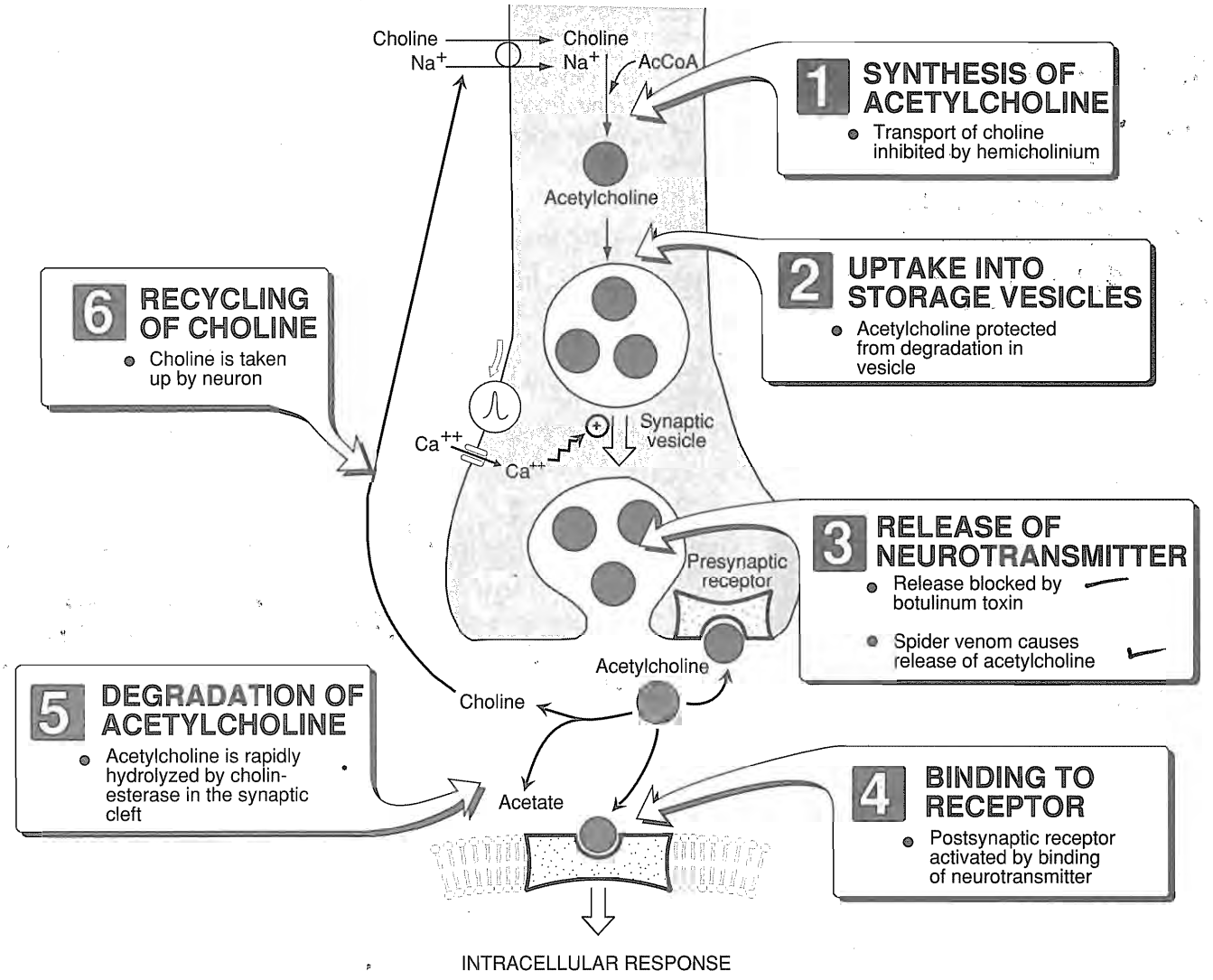



**Figure 4.3**
Synthesis and release of acetylcholine from the cholinergic neuron.

Binding to the receptor leads to a biological 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. 33 and below).

5. **Degradation of acetylcholine:** The signal at the postjunctional effector site is rapidly terminated. This occurs in the synaptic cleft where acetylcholinesterase cleaves acetylcholine to choline and acetate (see Figure 4.3).

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 and 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).

### 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 4.4). Using binding studies and specific inhibitors, several subclasses of muscarinic receptors have been pharmacologically distinguished as $M_1$, $M_2$, $M_3$, $M_4$, and $M_5$.

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 heart, smooth muscle, brain and exocrine glands (see Figure 4.2). 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 exocrine glands and smooth muscle. [Note: Drugs with muscarinic actions preferentially stimulate muscarinic receptors on these tissues, but at high concentration may show some activity at nicotinic receptors (see Figure 4.4).]

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, which in turn activates phospholipase C. This leads to the hydrolysis of phoshatidylinositol-(4,5)-bisphosphate ($PIP_2$) to yield diacylglycerol (DAG) and inositol (1,4,5)-trisphosphate ($IP_3$), which cause an increase in intracellular $Ca^{++}$. This cation can then interact to stimulate or inhibit enzymes, or cause hyperpolarization, secretion or contraction.[1] In contrast, activation of the $M_2$ subtype on the cardiac muscle stimulates a G protein that inhibits adenylyl cyclase and increases $K^+$ conductance, 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, selectively inhibits $M_1$ 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. Therefore, *pirenzepine* may be useful in the treatment of gastric and duodenal ulcers (see p. 239). [Note: At the present time there are no clinically important agents that interact with the $M_4$ and $M_5$ receptors.]

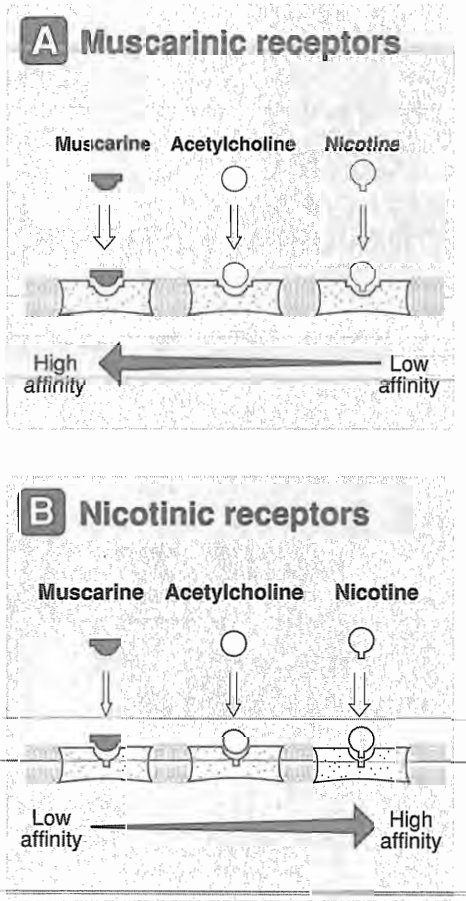



**Figure 4.4**
Types of cholinergic receptors.

[1] See p. 44 for Infolink references to other books in this series.

4. **Nicotinic receptors:** These receptors, in addition to binding acetylcholine, also recognize nicotine but show only a weak affinity for muscarine (see Figure 4.4). Nicotine initially stimulates and then blocks the receptor. Nicotinic receptors are located in the CNS, adrenal medulla, autonomic ganglia, and the neuromuscular junction (see Figure 4.2). Drugs with nicotinic action stimulate the nicotinic receptors located on these tissues. 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* (see p. 50).

## IV. DIRECT-ACTING CHOLINERGIC AGONISTS

Cholinergic agonists mimic the effects of acetylcholine by binding directly to cholinoceptors. These agents are synthetic esters of choline, such as *carbachol* and *bethanechol*, or naturally occurring alkaloids, such as *pilocarpine* (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.

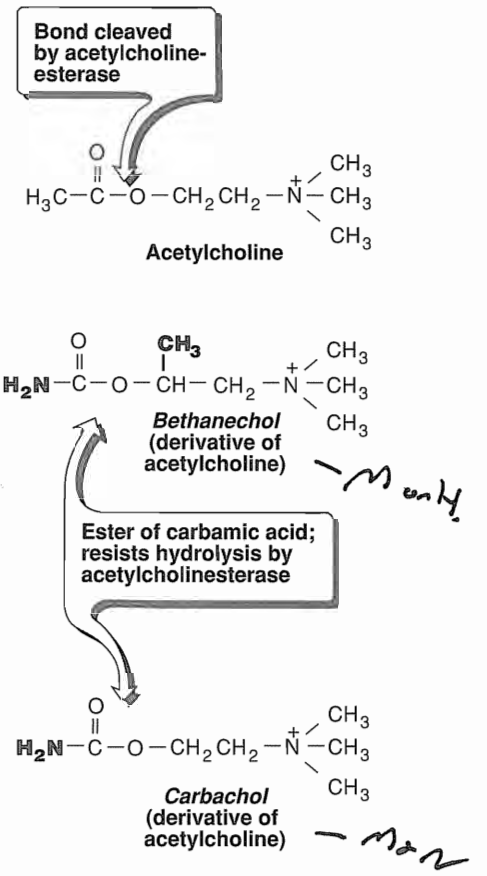



**Figure 4.5**
Comparison of the structures of some cholinergic agonists.

### A. Acetylcholine

Acetylcholine [a se teel KOE leen] is a quarternary ammonium compound that cannot penetrate membranes. Although it is the neurotransmitter of parasympathetic and cholinergic nerves, it is therapeutically of no importance because of its multiplicity of actions and its rapid inactivation by acetylcholinesterase. 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 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.]

2. **Decrease in blood pressure:** Injection of acetylcholine causes vasodilation and the lowering of blood pressure. Although no innervation of the vasculature by the parasympathetic system exists, there are cholinergic receptors on the blood vessels that respond by causing vasodilation. The vasodilation is due to an acetylcholine-induced rise in intracellular $Ca^{++}$—caused by the phosphatidylinositol system—that results in the formation of nitric oxide (NO) from arginine in endothelial cells.[2] [Note: NO is also known as endothelium-derived relaxing factor (EDRF).] (See p. 176 for more detail on nitric oxide.) In the absence of adminis-

[2]See p. 44 for Infolink references to other books in this series.

tered cholinergic agents, the vascular receptors have no known function, since acetylcholine is never released into the blood in any significant quantities. *Atropine* (see p. 45) 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 stimulated. In the genitourinary tract, the tone of the detrusor urinae muscle is increased. 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).

## B. Bethanechol

*Bethanechol* [be THAN e kole] is structurally related to acetylcholine; the acetate is replaced by carbamate and the choline is methylated (see Figure 4.5). Hence, it is not hydrolyzed by acetylcholinesterase, although it is inactivated through hydrolysis by other esterases. It has little or no nicotinic actions 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, and it also stimulates the detrusor muscles of the bladder while 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.

3. **Adverse effects:** *Bethanechol* causes the actions 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. 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 one hour.

1. **Actions:** *Carbachol* has profound effects on both the cardiovascular system and the gastrointestinal system because of its ganglion-stimulating activity and 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.

2. **Therapeutic uses:** Because of its high potency and relatively long duration of action, *carbachol* is rarely used therapeutically, except in the eye as a miotic agent to cause contraction of the pupil and a decrease in intraocular pressure.

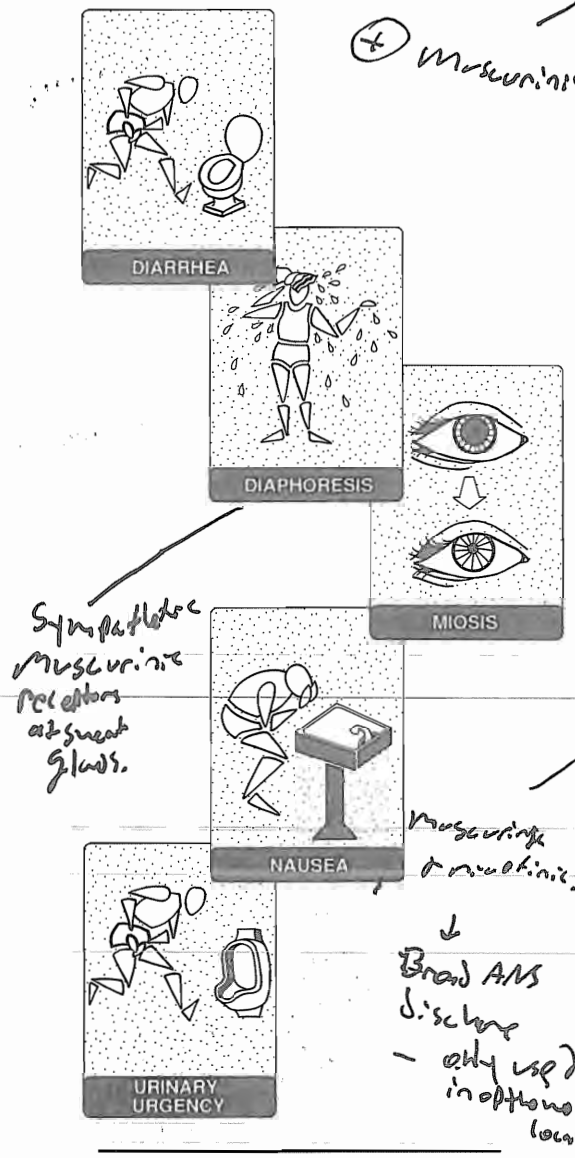



**Figure 4.6**
Some adverse effects observed with cholinergic drugs.

3. **Adverse effects:** At doses used ophthalmologically, there are little to no side effects.

### 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. *Pilocarpine* exhibits muscarinic activity and is primarily used in ophthalmology.

1. **Actions:** Applied topically to the cornea, *pilocarpine* produces a rapid miosis and contraction of the ciliary muscle. The eye undergoes a spasm of accommodation, and 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. 45).] *Pilocarpine* is one of the most potent stimulators of secretions such as sweat, tears, and saliva, but it is not used for this purpose.

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 1 day and can be repeated. Cholinesterase inhibitors, such as *isoflurophate* and *echothiophate*, have longer durations of action. [Note: Carbonic anhydrase inhibitors, such as *acetazolamide* (see p. 226), *epinephrine* (see p. 61), and the β adrenergic blocker, *timolol* (see p. 76), are effective in treating glaucoma chronically but are not used for the emergency lowering of intraocular pressure.]

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

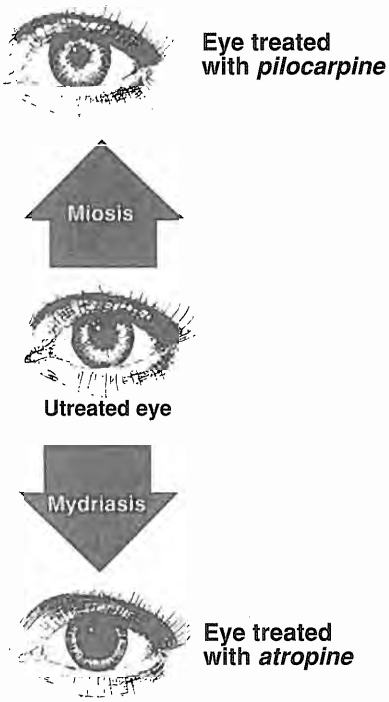



**Figure 4.7**
Actions of *pilocarpine* and *atropine* on the iris and ciliary muscle of the eye.

## V. ANTICHOLINESTERASES (REVERSIBLE)

Acetylcholinesterase is an enzyme that specifically cleaves acetylcholine to acetate and choline. It is located both pre-and post-synaptically 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 the neuromuscular junction and the brain.

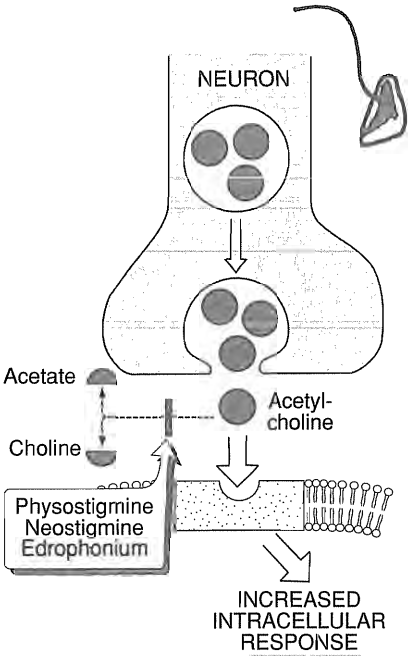



**Figure 4.8**
Mechanisms of action of indirect (reversible) cholinergic agonists.

## A. Physostigmine

*Physostigmine* [fi zoe STIG meen] is an alkaloid (a nitrogenous compound found in plants) and a tertiary amine. It is a substrate for acetylcholinesterase, and forms a relatively stable enzyme-substrate intermediate that reversibly inactivates acetylcholinesterase. The result is potentiation of cholinergic activity throughout the body.

1. **Actions:** *Physostigmine* has a wide range of actions because it stimulates not only muscarinic and nicotinic sites of the autonomic nervous system but also the nicotinic receptors of the neuromuscular junction. Its duration of action is about 2–4 hours. *Physostigmine* can enter and stimulate the CNS.

2. **Therapeutic uses**: The drug increases intestinal and bladder motility, which serve as its therapeutic action in atony of either organ. Placed topically in the eye, it produces miosis and spasm of accommodation and 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* (see p. 45), *phenothiazines* (see p. 127), and tricyclic antidepressants (see p. 119).

3. **Adverse effects:** The effects of *physostigmine* on the CNS may lead to convulsions when high doses are used. Bradycardia 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 reversibly inhibits acetylcholinesterase as does *physostigmine*. Unlike *physostigmine*, *neostigmine* is more polar and therefore 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 2–4 hours. It is used to stimulate the bladder and GI tract, and is also used as an antidote for *tubocurarine* and other competitive neuromuscular blocking agents (see p. 50). *Neostigmine* has found use in symptomatic treatment of myasthenia gravis, an autoimmune disease caused by antibodies to the nicotinic receptor that bind to the acetylcholine receptors of neuromuscular junctions. This causes their degradation, and thus makes fewer receptors available for interaction with the neurotransmitter. Adverse effects of *neostigmine* include the actions of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm.

## C. Pyridostigmine:

*Pyridostigmine* [peer id doe STIG meen] is another cholinesterase inhibitor that is used in the chronic management of myasthenia gravis. Its duration of action (3–6 hours) is longer than that of *neostigmine* (2–4 hours).

### D. Edrophonium

The actions of *edrophonium* [ed roe FOE nee um] are similar to those of *neostigmine*, except that it is more rapidly absorbed and has a short duration of action (10–20 minutes). *Edrophonium* is a quarternary 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 since excess drug may provoke a cholinergic crisis. *Atropine* is the antidote.

## VI. 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.

### A. Isoflurophate

1. **Mechanism of action:** *Isoflurophate* [eye soe FLURE oh fate] (diisopropylfluorophosphate, DFP) is an organophosphate that covalently binds to a serine-OH at the active site of acetylcholinesterase (Figure 4.9). 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 isopropyl groups (Figure 4.9). 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. Newer nerve agents, available to the military, age in minutes or seconds. DFP ages in 6–8 hours.

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

3. **Therapeutic uses:** An ophthalmic ointment of the drug is used topically in the eye for the chronic treatment of open-angle glaucoma. The effects may last for up to one week after a single administration. [Note: *Echothiophate* [ek oe THI oh fate] is a newer drug that covalently bonds to acetylcholinesterase. Its use is the same as *isoflurophate*.]

4. **Reactivation of acetylcholinesterase:** *Pralidoxime* (PAM) is a synthetic pyridinium compound that can reactivate inhibited acetylcholinesterase. The presence of a charged group allows it to approach an anionic site on the enzyme where it essentially displaces the organophosphate and regenerates the enzyme. If given before aging of the alkylated enzyme occurs, it can reverse the effects of *isoflurophate* except for those in the CNS. With the newer nerve agents, which produce aging of the enzyme complex within seconds, *pralidoxime* is less effective.

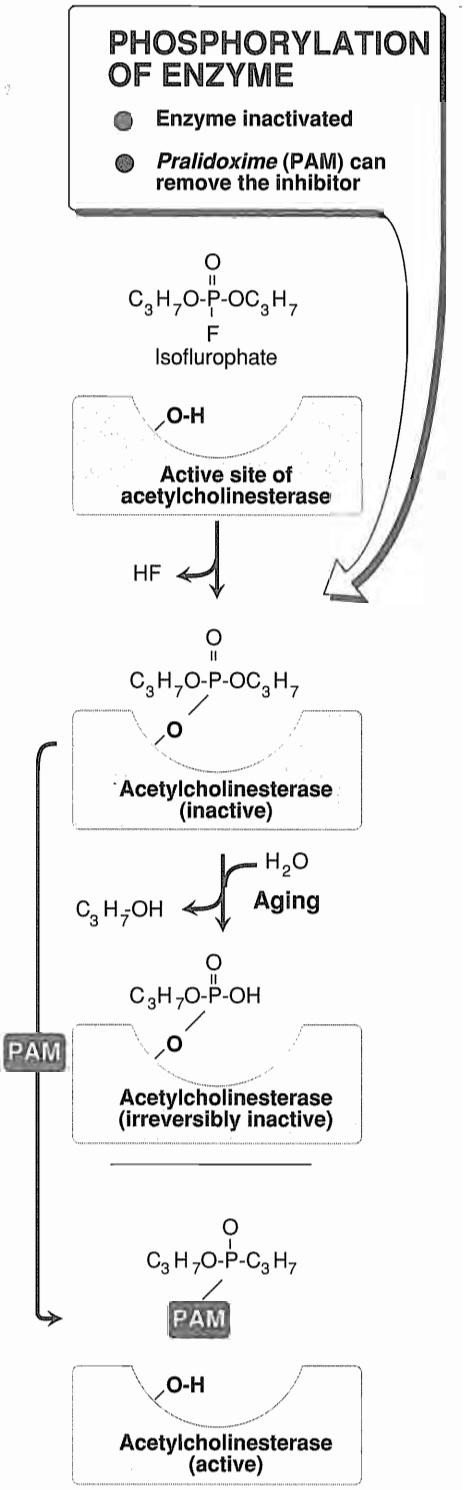



**Figure 4.9**
Covalent modification of acetylcholinesterase by isoflurophate; also shown is the reactivation of the enzyme with *pralidoxime*.

Choose the ONE best answer

4.1. Which of the following is NOT an expected symptom of poisoning with isoflurophate?

A. Paralysis of skeletal muscle
B. Increased bronchial secretions
C. Miosis
D. Tachycardia
E. Convulsions

Correct answer = D. Bradycardia (rather than tachycardia) and decreased cardiac output result from increased parasympathetic stimulation. Since isoflurophate inhibits acetylcholinesterase and increases the concentration of acetylcholine at the synapse, it mimics (parasympathetic) stimulation.

4.2. Which of the following INCORRECTLY matches a cholinergic agonist with a pharmacologic action?

A. Bethanechol: stimulates atonic bladder.
B. Carbachol: induces release of epinephrine from the adrenal medulla.
C. Acetylcholine: decreases heart rate and cardiac output.
D. Pilocarpine: reduces intraocular pressure.
E. Physostigmine: decreases intestinal motility.

Correct answer = E. Physostigmine potentiates cholinergic activity throughout the body and therefore it increases intestinal and bladder motility.

4.3. Pilocarpine:

A. is used to lower intraocular pressure in glaucoma.
B. is cleaved by acetylcholinesterase.
C. selectively binds to nicotinic receptors.
D. inhibits secretions such as sweat, tears, and saliva.
E. cannot enter the brain.

Correct answer = A. Pilocarpine is used in glaucoma where it is the treatment of choice for the acute attack. It is not cleaved by acetylcholinesterase. It binds mainly to muscarinic receptors, and can enter the brain. Pilocarpine is a potent stimulator of secretions.

4.4 Neostigmine:

A. is contraindicated in glaucoma.
B. has a shorter duration of action than edrophonium.
C. decreases the acetylcholine concentration at the neuromuscular junction.
D. may result in bowel hypermotility, salivation, and sweating.
E. exacerbates tubocurarine poisoning.

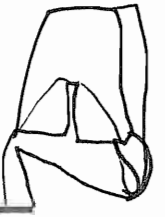
Correct answer = D. Neostigmine stimulates muscarinic receptors. It has a longer duration of action than edrophonium, lasting for 2–4 hours, compared to 10–20 minutes for the latter drug. Neostigmine increases the acetylcholine concentration at the neuromuscular junction, making this drug useful in treating myasthenia gravis. It can also be used to lower intraocular pressure, but pilocarpine is more effective.


[1]See p. 83 in **Biochemistry** (2nd ed.) for a discussion of $Ca^{++}$ as a regulatory signal.

[2]See p. 85 in **Biochemistry** (2nd ed.) for a discussion of nitric oxide as a regulatory signal.

# Cholinergic Antagonists

# 5



## I. OVERVIEW

The cholinergic antagonists (also called cholinergic blockers or anticholinergic drugs) bind to cholinoceptors but do not trigger the usual receptor-mediated intracellular effects. The most useful of these agents selectively block the 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. A third family of compounds, the neuromuscular blocking agents, interfere with transmission of efferent impulses to skeletal muscles. Figure 5.1 summarizes the cholinergic antagonists discussed in this chapter.

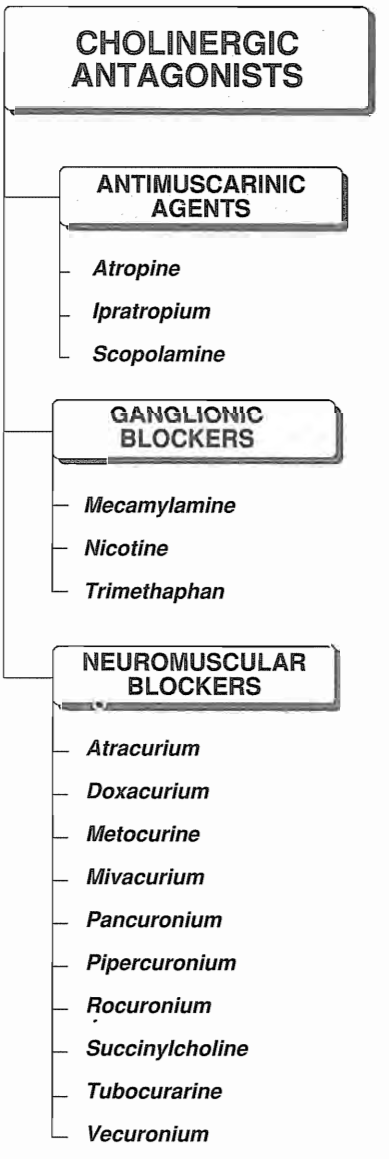



**Figure 5.1**
Summary of cho

## II. ANTIMUSCARINIC AGENTS

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 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.

### A. Atropine

*Atropine* [A troh peen], a belladonna alkaloid, has a high affinity for muscarinic receptors, where it binds competitively, preventing acetylcholine from binding to that site (Figure 5.3). *Atropine* is both a central and peripheral muscarinic blocker. 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 mydriasis (dilation of the pupil; see Figure 4.6), unresponsiveness to light and cycloplegia (inability to focus for near vision). In patients with glaucoma, intraocular pressure may rise dangerously.

*Lippincott's Illustrated Reviews: P*
by Mary J. Mycek, Richard A. H
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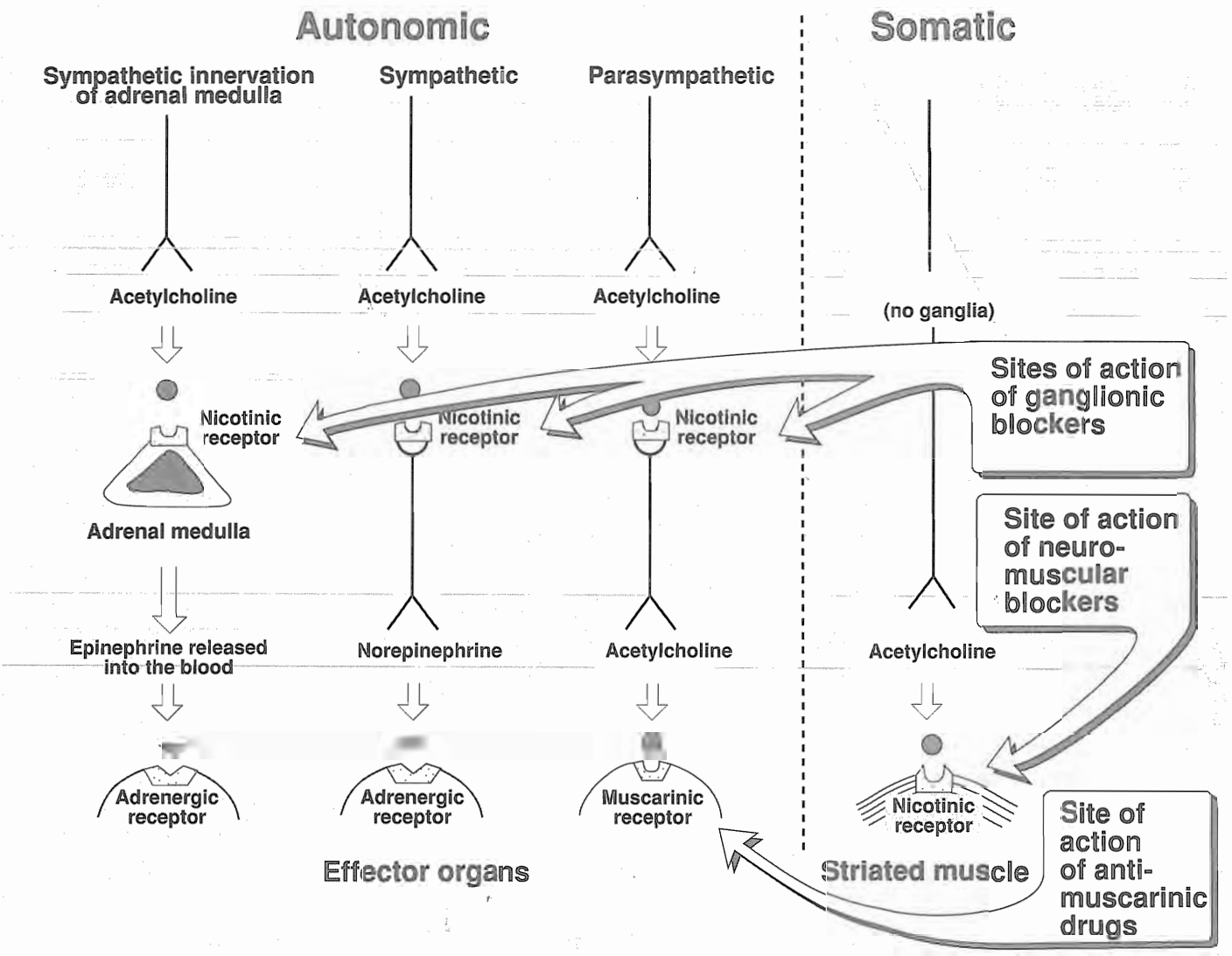
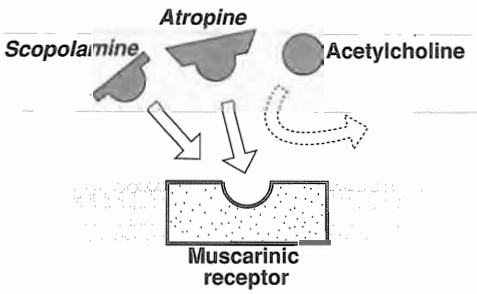



**Figure 5.2**
Sites of actions of cholinergic antagonists.

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of *atropine* and
ith acetylcholine
receptor.

**b. Gastrointestinal (GI):** *Atropine* can be used as an antispasmodic to reduce activity of the GI tract. *Atropine* and *scopolamine* (which is discussed in the next section) 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. 239), 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 α-adrenergic agonists may be more effective with fewer side effects.

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, newer data indicate that the effect results from blockade of the $M_1$ receptors on the inhibitory presynaptic neurons, thus permitting increased acetylcholine release. With higher doses of *atropine*, the cardiac receptors on the SA node are blocked, and the cardiac rate increases modestly (tachycardia). 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 to produce a drying effect on the oral mucous membranes (xerostomia). The salivary glands are exquisitely sensitive to *atropine*. Sweat and lacrimal glands are also affected. Inhibition of secretions by the former can cause elevated body temperature.

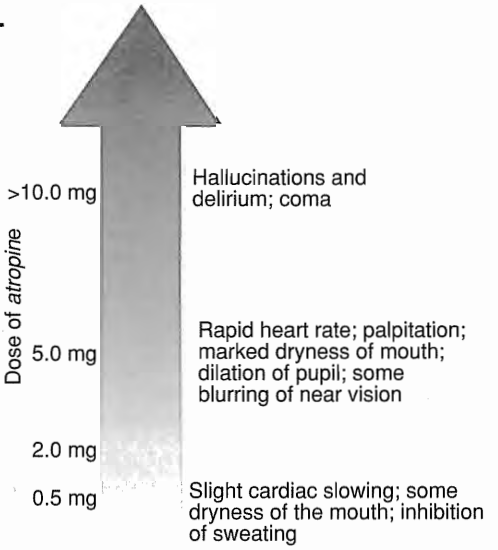



**Figure 5.4**
Dose-dependent effects of *atropine*.

2. **Therapeutic uses:**

a. **Ophthalmic:** In the eye, topical *atropine* exerts both mydriatic and cycloplegic effects and permits the measurement of refractive errors without interference by the accommodative capacity of the eye. [Note: *Phenylephrine* (see p. 66), or similar α-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.] *Atropine* may induce an attack in individuals with narrow angle glaucoma.

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

c. **As antidote for cholinergic agonists:** *Atropine* is used for the treatment of overdoses of organophosphate (contained in certain insecticides) and some types of mushroom poisoning (certain mushrooms contain cholinergic substances). Its ability to enter the central nervous system (CNS) is of particular importance. *Atropine* blocks the effects of excess acetylcholine that results from inhibition of acetylcholinesterase by drugs such as *physostigmine* (see p. 42).

d. **Antisecretory agent:** 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 is 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, "sandy eyes", tachycardia, and constipation. Effects on the CNS include restlessness, confusion, halluci-

nations, and delirium, which may progress to depression, collapse of the circulatory and respiratory systems and death. In older individuals, the use of *atropine* to induce mydriasis and cycloplegia is considered too risky since it may exacerbate an attack of glaucoma in someone with a latent condition.

### B. Scopolamine

*Scopolamine* [skoe POL a meen], another belladonna alkaloid, produces peripheral effects similar to those of *atropine*. However, *scopolamine* has greater action on the CNS and a longer duration of action in comparison to those of *atropine*. It has some special actions indicated below.

1. **Actions:** *Scopolamine* is one of the most effective anti-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 can instead produce excitement.

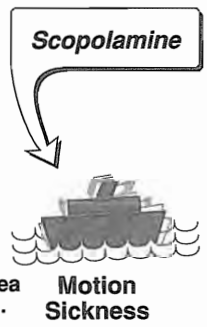



**Figure 5.5**
*Scopolamine* is an effective anti-motion sickness agent.

2. **Therapeutic uses:** Though similar to *atropine*, its therapeutic use is limited to prevention of motion sickness (for which *scopolamine* is particularly effective) and blocking of short-term memory. [Note: As with all such drugs used for this condition, it is much more effective prophylactically than for treating motion sickness after it occurs. The amnesic action of *scopolamine* is sometimes made use of 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* (see Figure 22.5, p. 220), is useful in treating asthma and chronic obstructive pulmonary disease in patients unable to take adrenergic agonists. *Ipratropium* is also used in the management of chronic obstructive pulmonary disease (see p. 222). Important characteristics of the muscarinic antagonists are summarized in Figure 5.6.

## III. GANGLIONIC BLOCKERS

Ganglionic blockers specifically act on the nicotinic receptors, probably by blocking the ion channels of the autonomic ganglia (see Figure 5.2). These drugs show no selectivity toward the parasympathetic or sympathetic ganglia and are not effective as neuromuscular antagonists (see p. 50). Thus, these drugs block the entire output of the autonomic nervous system at the nicotinic receptor. The responses observed are complex and unpredictable, making it impossible to achieve selective actions. Therefore, ganglionic blockade is rarely used therapeutically today. However, they often serve as tools in experimental pharmacology.

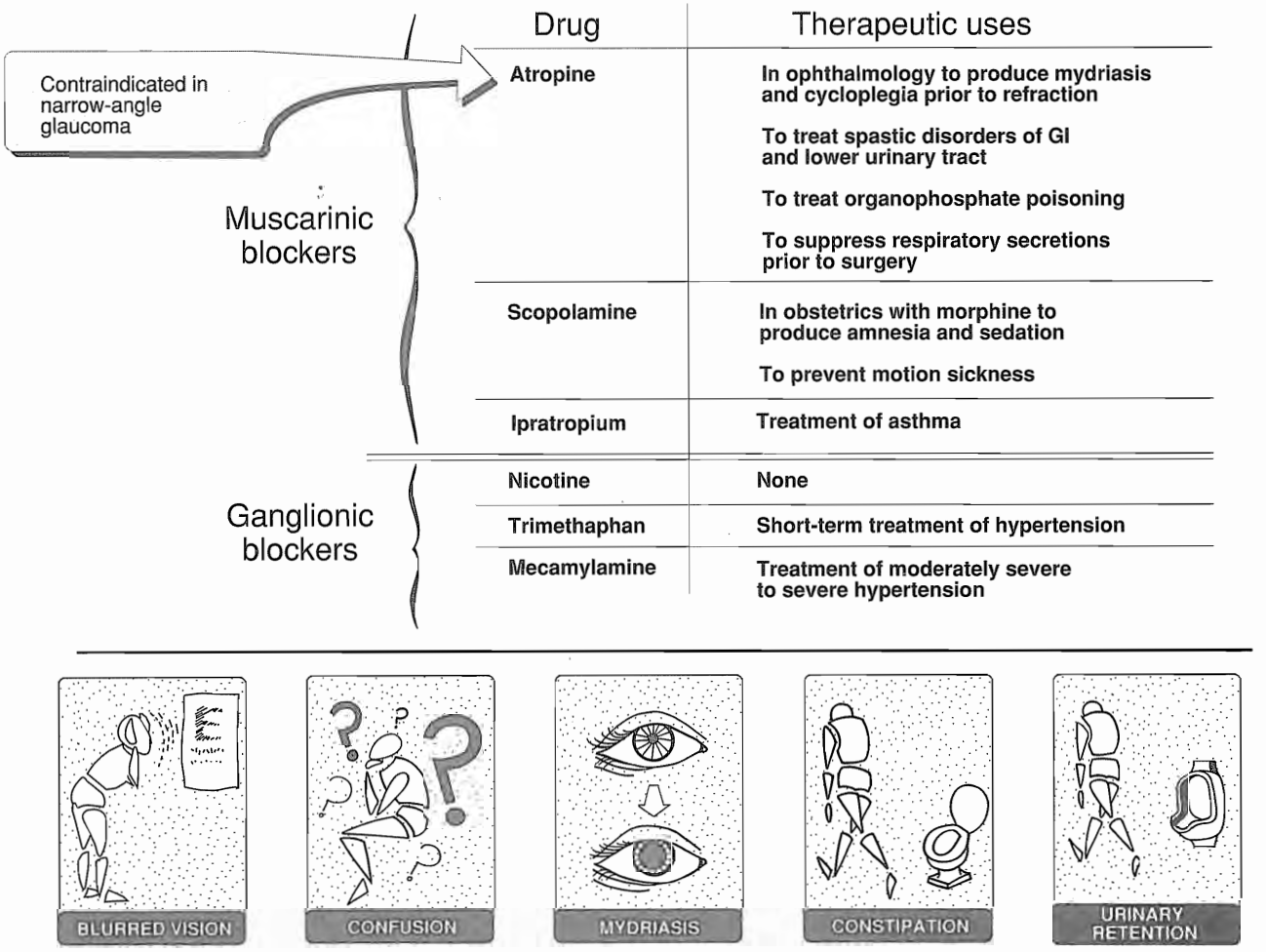



**Figure 5.6**
Summary of cholinergic antagonists.

### A. Nicotine

A component of cigarette smoke, *nicotine* [NIC o teen] has many undesirable actions. Depending on the dose, *nicotine* depolarizes ganglia, resulting first in stimulation of and followed by paralysis of all ganglia. The stimulatory effects are complex, including an increase in 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. 100 for a full discussion of *nicotine*.

### B. Trimethaphan

*Trimethaphan* [trye METH a fan] is a short-acting, competitive nicotinic ganglionic blocker that must be given by intravenous infusion. Today, the drug is used for the emergency lowering of blood pressure, for example, in hypertension caused by pulmonary edema or dissecting aortic aneurysm when other agents cannot be used.

### C. Mecamylamine

*Mecamylamine* [mek a MILL a meen] produces a competitive nicotinic block 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 *trimethaphan*.

## IV. NEUROMUSCULAR BLOCKING DRUGS

This section presents drugs that 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 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 to produce complete muscle relaxation, without having to employ higher anesthetic doses to achieve comparable muscular relaxation. A second group of muscle relaxants, the central muscle relaxants, are used to control spastic muscle tone. These drugs include *diazepam* (which binds at GABA receptors, see p. 90), *dantrolene* (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 central nervous system).

### A. Nondepolarizing (competitive) blockers

The first drug that was found 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. The neuromuscular blocking agents have significantly increased the safety of anesthesia, since less anesthetic is required to produce muscle relaxation.

#### 1. Mechanism of action

**a. At low doses:** Nondepolarizing neuromuscular blocking drugs combine with the nicotinic receptor and prevent the binding of acetylcholine (Figure 5.7). These drugs thus prevent depolarization of the muscle cell membrane and inhibit muscular contraction. Because these agents compete with acetylcholine at the receptor, they are called competitive blockers. Their action can be overcome by increasing the concentration of acetylcholine in the synaptic gap, for example, by administration of cholinesterase inhibitors such as *neostigmine* (see p. 42) or *edrophonium* (see p. 43). Anesthesiologists often employ this strategy to shorten the duration of the neuromuscular blockade.

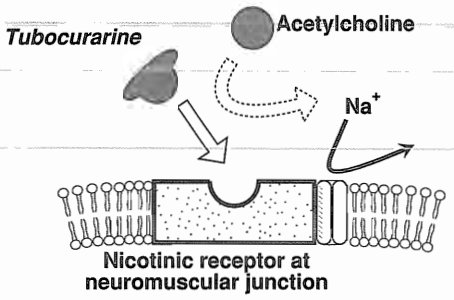



**Figure 5.7**
Mechanism of action of competitive neuromuscular blocking drugs.

**b. At high doses:** Nondepolarizing blockers block the ion channels of the end-plate. This leads to further weakening of neuromuscular transmission and 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.

3. **Therapeutic uses:** These blockers are used therapeutically as adjuvant drugs in anesthesia during surgery to relax skeletal muscle.

4. **Pharmacokinetics:** All neuromuscular blocking agents are injected intravenously since their uptake via oral absorption is minimal. 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. For example, *tubocurarine, pancuronium, mivacurium, metocurine*, and *doxacurium* are excreted in the urine unchanged. *Atracurium* is degraded spontaneously in the plasma and by ester hydrolysis. 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 onset and duration of action of the neuromuscular blocking drugs are shown in Figure 5.8.

5. **Adverse effects:** The effects of the neuromuscular blocking drugs are shown in Figure 5.8.

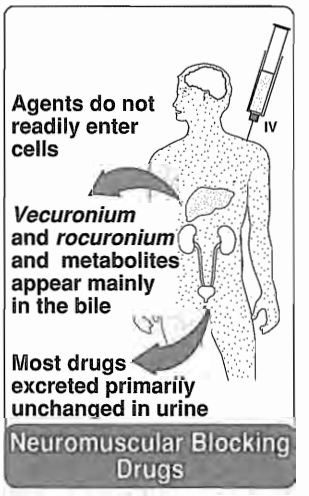
6. **Drug Interactions .**

   a. **Cholinesterase inhibitors:** Drugs such as *neostigmine, physostigmine*, and *edrophonium* (see p. 42) 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.

   b. **Halogenated hydrocarbon anesthetics:** Drugs such as *halothane* (see p. 113) act to enhance neuromuscular blockade by exerting a stabilizing action at the neuromuscular junction.

   c. **Aminoglycoside antibiotics:** Drugs like *gentamicin or tobramycin* (see p. 315) 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.



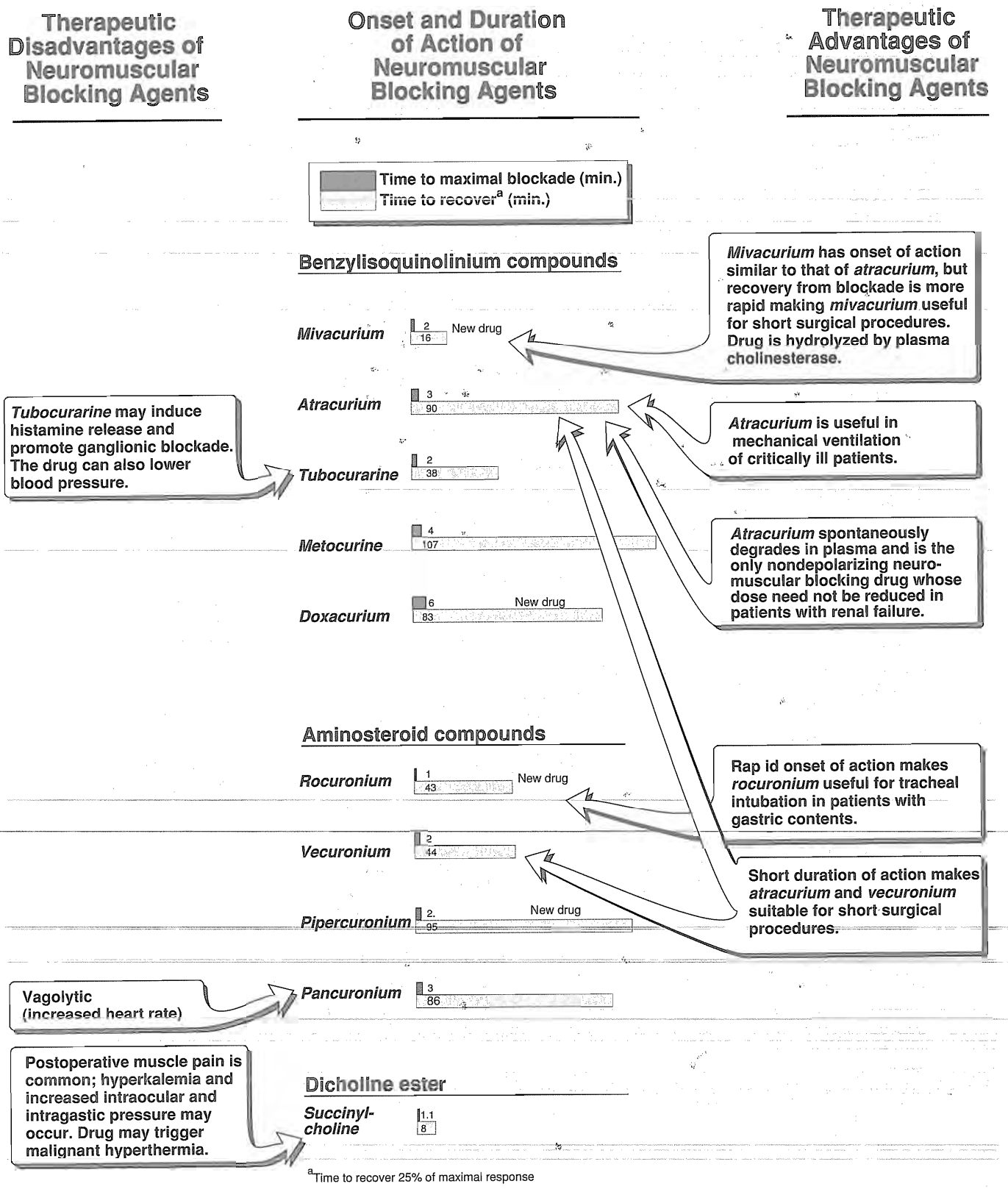



**Figure 5.8**
Onset and duration of action of neuromuscular blocking drugs (center column); summary of therapeutic considerations. [Note: "New drug" indicates drug approved after 1992.]

## 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 5.9). 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 long time, and providing a constant stimulation of the receptor. 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). The continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses. With time, the 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.

2. **Actions:** The sequence of paralysis may be slightly different, but as is seen 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 in high doses, although it does have weak histamine-releasing action. Normally, the duration of action of *succinylcholine* is extremely short, since this drug is rapidly broken down by plasma cholinesterase.

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 rapid hydrolysis by plasma cholinesterase. It is therefore usually given by continuous infusion.

5. **Adverse effects:**

   a. **Hyperthermia:** When *halothane* (see p. 113) is used as an anesthetic, administration of *succinylcholine* has occasionally caused malignant hyperthermia (with muscular rigidity and hyperpyrexia) in genetically susceptible people (Figure 5.8). This is treated by rapidly cooling the patient and by administration of *dantrolene*, which blocks release of $Ca^{++}$ from the sarcoplasmic reticulum of muscle cells, thus reducing heat production and relaxing muscle tone.

   b. **Apnea:** A genetically related deficiency of plasma cholinesterase or presence of an atypical form of the enzyme can lead to apnea due to paralysis of the diaphragm.

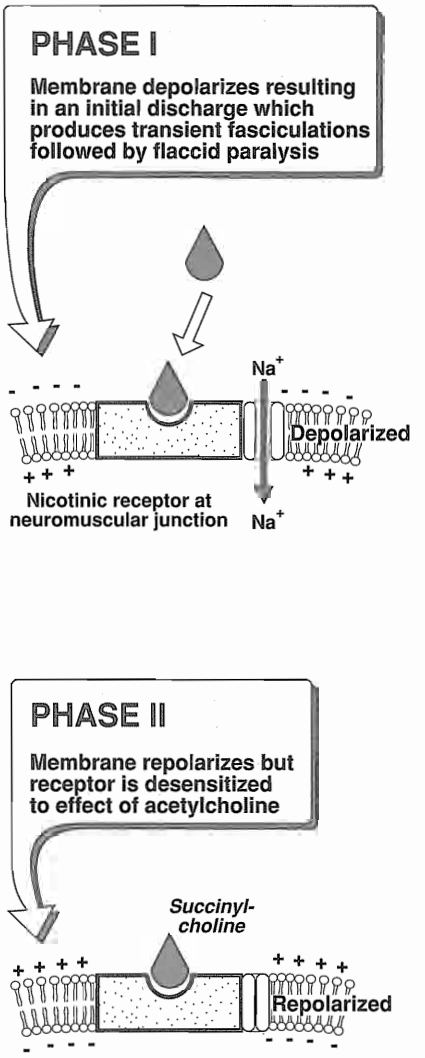



**Figure 5.9**
Mechanism of action of depolarizing neuromuscular blocking drugs.

Questions 5.1 to 5.6

For each description (below) select the most appropriate drug (A to I).

5.1 Depolarizes neuromuscular end-plate

5.2 Reverses the effects of nondepolarizing blockers, such as tubocurarine

5.3 May cause the release of histamine

5.4 Acts at peripheral and central muscarinic cholinergic receptors

5.5 Used as adjunctive therapy in treating asthma

5.6 Degraded spontaneously in the plasma

A. Succinylcholine
B. Neostigmine
C. Tubocurarine
D. Scopolamine.
E. Carbachol
F. Atracurium
G. Atropine
H. Ipratropium

Correct answers
5.1 A: Succinylcholine
5.2 B: Neostigmine
5.3 C: Tubocurarine
5.4 D: Scopolamine
5.5 H: Ipratropium
5.6 I: Atricurium

Choose the ONE best answer.

5.7. Which ONE of the following drugs most closely resembles atropine in its pharmacologic actions?

A. Scopolamine
B. Trimethaphan
C. Physostigmine
D. Acetylcholine
E. Carbachol

The correct answer = A. Scopolamine has effects similar to those of atropine. Trimethaphan is a ganglionic blocker affecting nicotinic receptors; atropine affects primarily muscarinic receptors. Physostigmine, an anticholinesterase drug, is the antidote for an excess of atropine. Atropine blocks the effects of acetylcholine and direct-acting agonists, such as carbachol.

5.8. Which ONE of the following drugs does NOT produce miosis (marked constriction of the pupil)?

A. Carbachol
B. Isoflurophate
C. Atropine
D. Pilocarpine
E. Neostigmine

Correct answer = C. On the eye, atropine blocks all cholinergic activity resulting in mydriasis (dilation of the pupil). Carbachol (a direct acting cholinergic agonist), isoflurophate (an indirect-acting cholinergic agonist), pilocarpine (a direct-acting cholinergic agonist), and neostigmine (an indirect-acting cholinergic agonist) all mimic the effect of parasympathetic stimulation and produce miosis.

5.9. Which ONE of the following drugs would be useful in the long-term treatment of myasthenia gravis?

A. Edrophonium
B. Atropine
C. Neostigmine
D. Scopolamine
E. Bethanechol

Correct answer = C. Neostigmine provides symptomatic treatment of myasthenia gravis by inhibiting acetylcholinesterase and thereby increasing acetylcholine. In contrast, edrophonium, an indirect cholinergic agonist, is useful in the diagnosis of myasthenia gravis, but its duration of action is too short for effective long-term treatment. Atropine and scopolamine block the action of acetylcholine on the cholinergic receptors of the neuromuscular junction. Bethanechol is not effective at the neuromuscular junction.

5.10 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

The correct answer = D. The patient is exhibiting signs of cholinergic stimulation. Since he is a farmer, insecticide poisoning is a likely diagnosis. Thus either intravenous or intramuscular doses of atropine are indicated to antagonize the muscarinic symptoms. Physostigmine and edrophonium are cholinesterase inhibitors and would exacerbate the problem. Norepinephrine would not be effective in combatting the cholinergic stimulation. Trimethaphan being a ganglionic blocker would also worsen the condition.