CHAPTER 2

Pharmacodynamics

REHABILITATION FOCUS

It is estimated that medications are involved in up to 80% of all treatments and impact every aspect of a patient's life. As a result, physical therapists must recognize that drugs may alter a patient's clinical presentation, which at times may require that physical therapy interventions be modified. Knowledge of drug classes and their mechanisms of actions is key to understanding patients' responses to medications. The beneficial clinical effects of drugs occur within specific concentration ranges. These ranges are unique to the different pharmacologic classes of drugs and, for some drugs, unique to the specific individual. Concentrations *below* the effective range provide no therapeutic benefit, while concentrations *above* the range almost always result in adverse drug reactions (ADRs). As discussed in the Chapter 3, the goal of dosing regimens is to utilize knowledge of the therapeutic range for each drug to determine the frequency and dose for a specific person.

Both the therapeutic and toxic effects of the majority of drugs result from interactions with their specific molecular targets—receptors. A drug molecule is an exogenous ligand that interacts with a receptor and initiates a chain of biochemical and physiologic events leading to the drug's observed effects. Pharmacodynamics is the branch of pharmacology concerned with the interaction between drug and receptor and the subsequent results.

A drug's mechanism of action is based on whether it mimics or inhibits an endogenous ligand or has some other unrecognized effect(s). A drug may directly compete with an endogenous ligand for a specific receptor or modulate the affinity (binding strength) of the receptor for the endogenous ligand. Some drugs may permanently inactivate the receptor to which they bind or stimulate additional cellular homeostatic mechanisms, which can result in a clinical effect lasting after the drug itself is no longer present in the body.

Key principles underlying the receptor concept form the basis of understanding the actions and clinical uses of drugs. These principles also have important practical consequences for drug development. First, receptors largely determine the quantitative relationship between dose or concentration of a drug and its pharmacologic effects. The receptor's affinity for binding a drug determines the concentration of drug required to form a significant number of drug-receptor complexes. In addition, the total number of receptors may limit the maximal effect a drug may produce. Second, receptors are responsible for the *selectivity* of drug action. The molecular size, shape, and electrical charge of a drug determine whether it will bind to a particular receptor among the vast array of chemically different binding sites available within the body. Accordingly, changes in a drug's chemical structure can dramatically alter its affinity for different classes of receptors, with resulting alterations in therapeutic and toxic effects. Finally, receptor activation (by agonists) or receptor blockade (by antagonists) are the primary factors responsible for many clinical effects of drugs. Knowledge of whether a drug is an agonist, antagonist, or partial agonist makes it possible to understand the actions of a drug, an individual's physiologic responses to a drug, a drug's potential ADRs, as well as interactions with many other drugs.

DRUG-RECEPTOR BONDS

Receptors are specific molecules that drugs interact with to produce changes in cellular function, and ultimately to produce functional changes in the whole person. Most receptors are proteins. A few receptors are macromolecules such as DNA. Enzymes that are affected by drugs are also considered receptors.

In order to respond to *specific* chemical stimuli, receptors must be selective in their ligand-binding characteristics. The receptor site presents a unique three-dimensional configuration upon which the drug can bind. The complementary configuration of the drug is in part what creates the affinity of the drug for the receptor site (**Figure 2-1**). Drugs that bind to a limited group of receptor types may be classified as selective, whereas drugs that bind to a larger number of receptor types may be considered nonselective.

Drugs interact with receptors by means of chemical bonds. The three major types of bonds are covalent, electrostatic, and hydrophobic. Covalent bonds are strong and in many cases not reversible under biologic conditions. Electrostatic bonds are weaker, more common, and often reversible. Hydrophobic bonds are the weakest, and probably most important in the interactions of lipid-soluble drugs, and within hydrophobic "pockets" of receptors.

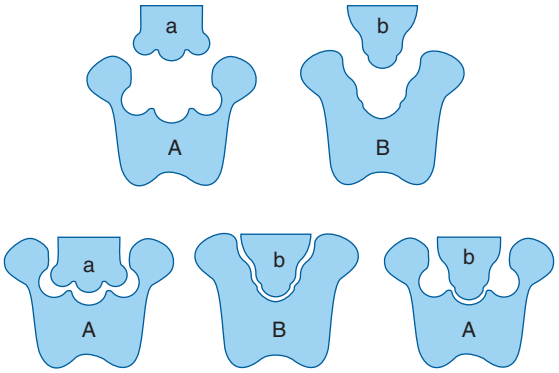

FIGURE 2-1 Model of specificity of a drug for the receptor. The structure of drug "a" allows binding only to receptor "A." In contrast, the structure of drug "b" allows binding to either receptor "A" or "B." Drug "a" would be considered selective to receptor "A," while drug "b" would be considered nonselective.

DOSE-RESPONSE CURVES

Graded Dose-Response Relationships

In order to initiate a sequence of cellular events that ultimately results in physiologic and clinical responses, a drug or an endogenous ligand (eg, hormone or neurotransmitter) must bind to a specific receptor. The response induced by activation of this receptor system can be measured against the concentration (dose) and displayed in a graded dose-response curve (Figure 2-2A). Plotting the data with a logarithmic dose axis usually results in a sigmoid curve, which simplifies the manipulation and interpretation of the dose-response data (Figure 2-2B).

The concentration of a drug required to achieve 50% of the maximal response is called the EC_{50}. For some ligands, the EC_{50} also estimates the drug concentration that binds 50% of available receptors. Thus, the dose-response curve relates the binding of the drug to the receptor (ie, the affinity of the drug for the receptor). A drug's efficacy is its ability to produce a measurable response, which is primarily determined by the nature of the drug and its receptor and associated effector system. The minimal effective dose is the concentration below which a drug produces no clinical benefit. At higher concentrations, the maximal efficacy of the drug (maximal effect; E_{max}) will be reached and no additional beneficial clinical response is observed.

Quantal Dose-Response Relationships

When the minimum dose required to produce an intended magnitude of response is evaluated for a *population*, a quantal dose-response relationship may be determined. When the fraction of the population that responds at each dose is plotted against the log of the dose administered, a cumulative quantal dose-response curve is obtained (Figure 2-3). From this curve, several clinically important doses can be determined. These include the median effective dose (ED_{50}) and the median toxic dose (TD_{50}). In preclinical animal studies, the median lethal dose (LD_{50}) is also calculated. Two key safety characteristics may also be determined: the therapeutic index and the therapeutic window. The therapeutic index is calculated by dividing the TD_{50} (or LD_{50}) by the ED_{50}. A very safe drug might be expected to have a very large toxic dose and a much smaller effective dose; thus, a safe drug would have a relatively high therapeutic index. Unfortunately, varying slopes for the dose-response plots sometimes make the therapeutic index a poor measure of safety. An alternative and potentially more clinically useful safety index is the therapeutic window. The therapeutic window is the dosage range between the minimum effective dose and the minimum toxic dose.

Potency

Potency is defined as the amount of drug needed to produce a given effect. Potency can be determined from either graded dose-response curves or quantal dose-response curves; however, the obtained values are not identical. In graded dose-response curves, potency is characterized by the EC_{50}

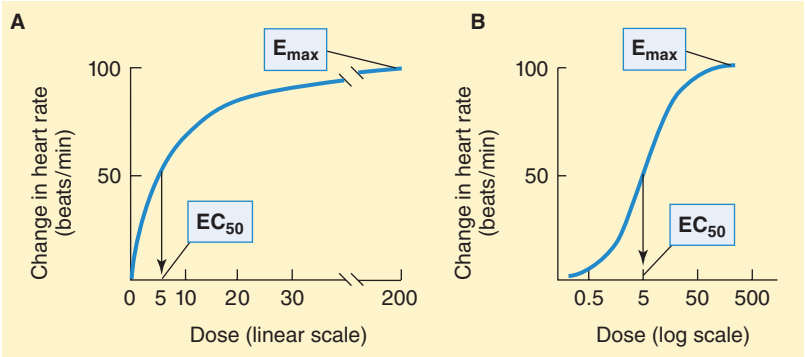

FIGURE 2-2 Graded dose-response graphs in which drug dose or concentration is plotted against a chosen clinical effect (change in heart rate). The EC_{50} is the dose of a drug at which the effect is half-maximal. The E_{max} is the dose of a drug at which the maximal beneficial clinical response is produced. When the dose axis is linear **(A)**, a hyperbolic curve is commonly obtained; when the dose axis is logarithmic **(B)**, a sigmoidal curve is often obtained.

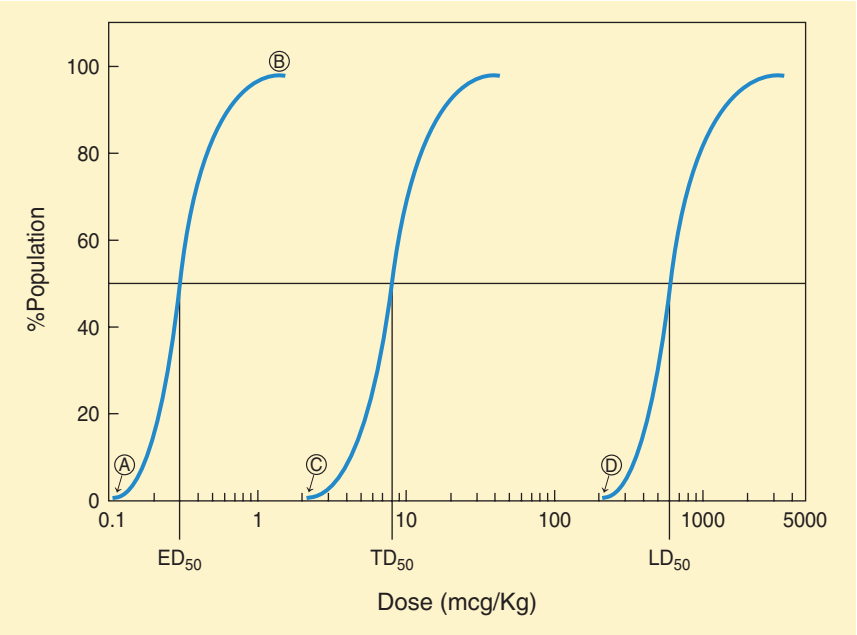

FIGURE 2-3 **Quantal dose-response plot.** The curves are generated from the frequency distribution of doses of a hypothetical drug required to produce a specified effect. The median effective dose (ED_{50}), median toxic dose (TD_{50}), and median lethal dose (LD_{50}) are depicted. A: minimal effective dose (MED; 0.1 mcg/kg). B: maximal effective dose (1.5 mcg/kg). C: minimal toxic dose (MTD; 2.0 mcg/kg). D: minimal lethal dose (200 mcg/kg). The therapeutic index is calculated by dividing the TD_{50} (8 mcg/kg) by the ED_{50} (0.3 mcg/kg) to obtain approximately 27. The therapeutic window is the range between the MED (A) and the MTD (C), which is 0.1-2 mcg/kg.

(Figure 2-2). The smaller the EC_{50}, the greater the potency of the drug. In quantal dose-response curves, the ED_{50}, TD_{50}, and LD_{50} measurements are identified as the potency variables (Figure 2-3).

DRUG-RECEPTOR DYNAMICS

Full Agonists, Partial Agonists, and Inverse Agonists

Figure 2-4 illustrates the modern two-state receptor theory, which considers the receptor to have at least two states: active (R_a) and inactive (R_i). In the absence of ligand, a receptor might be completely inactive or fully active. Alternatively, an equilibrium state might exist with most receptors in the inactive state and some receptors in the activated state ($R_i + R_a$). Many receptor systems exhibit some activity in the *absence* of a ligand, suggesting that some fraction of the receptor population is always in the activated state. This type of activity in the absence of ligand is called constitutive activity.

A full agonist is a drug (or endogenous ligand such as a neurotransmitter or hormone) that is capable of fully activating the effector system upon binding to the receptor. In the model system illustrated in Figure 2-4, a full agonist drug (D_a) has high affinity for the activated receptor conformation (R_a), and sufficiently high drug concentrations result in all the receptors achieving the activated state ($R_a - D_a$). In contrast, a partial agonist produces less than the full effect, even when it has saturated the receptors (R_a-D_{pa} + R_i-D_{pa}), presumably by combining with both receptor conformations, but favoring the active state. In the presence of a full agonist, a partial agonist actually acts as an inhibitor. In this model, neutral antagonists bind with *equal* affinity to the R_i and R_a states, preventing binding by an agonist and preventing any deviation from the level of constitutive activity. In contrast, inverse agonists have a higher affinity for the inactive R_i state than for R_a and decrease or abolish any constitutive activity ($R_i - D_i$).

Full agonists demonstrate both affinity and maximal efficacy for the receptors that ultimately result in the physiologic response(s). A partial agonist binds to the receptor at the same location as the full agonist. However, the partial agonist achieves a *lower* maximal effect, even with full receptor occupancy (Figure 2-5). By definition, partial agonists have a lower maximal efficacy than full agonists, and in the presence of full agonists, they may inhibit the full agonists, decreasing their response.

A concept worth emphasizing is the distinction between a drug's potency and its efficacy. Figure 2-5 presents two full agonists (A and B) that produce equal and maximal efficacy. However, agonist B has a lower affinity for the receptor compared to A. As a result of this binding difference, agonist A is described as having a higher potency compared to B because a lower dose of A is needed to achieve the same effect. The partial agonist C demonstrates a lower maximal efficacy than either of the full agonists (A or B), yet has a higher potency than either of the full agonists. Thus, potency and efficacy are not interchangeable. In other words, one drug may have a higher potency and a lower maximal efficacy than another drug that acts at the same receptor.

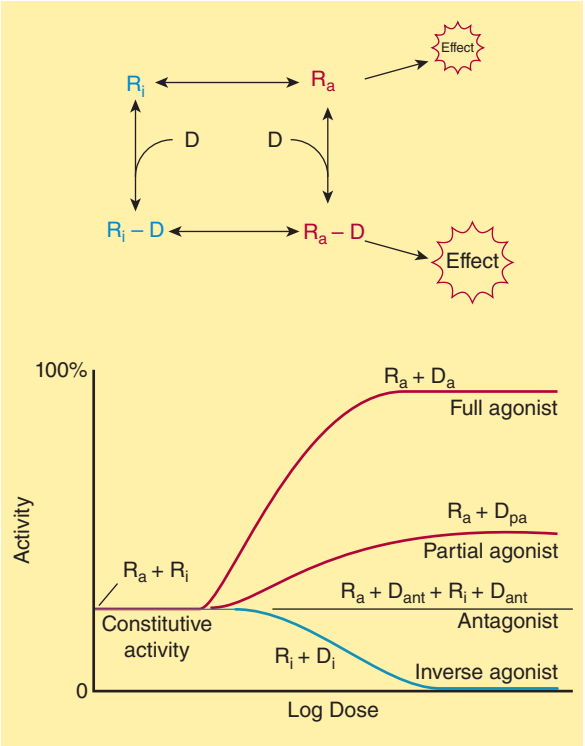

FIGURE 2-4 **Upper panel:** One model of drug-receptor interactions. The receptor is able to assume two conformations: R_i and R_a. In the R_i state, the receptor is inactive and produces no effect, even when combined with a drug (D) molecule. In the R_a state, the receptor activates its effectors and an effect is measured, even in the absence of drug. In the absence of a drug, the equilibrium between R_i and R_a determines the degree of constitutive activity. When D is present and binds with the R_a state of the receptor, the magnitude of the response is greater. **Lower panel:** A full agonist drug (D_a) has a much higher affinity for the R_a than for the R_i receptor conformation, and a maximal effect is produced at sufficiently high drug concentration ($R_a + D_a$). A partial agonist drug (D_{pa}) has somewhat greater affinity for the R_a than for the R_i conformation and produces less effect, even at saturating concentrations ($R_a + D_{pa}$). A neutral antagonist (D_{ant}) binds with equal affinity to both receptor conformations and prevents binding of agonist ($R_a + D_{ant} + R_i + D_{ant}$). An inverse agonist ($D_i$) binds much more avidly to the R_i receptor conformation ($R_i + D_i$), prevents conversion to the R_a state, and reduces constitutive activity.

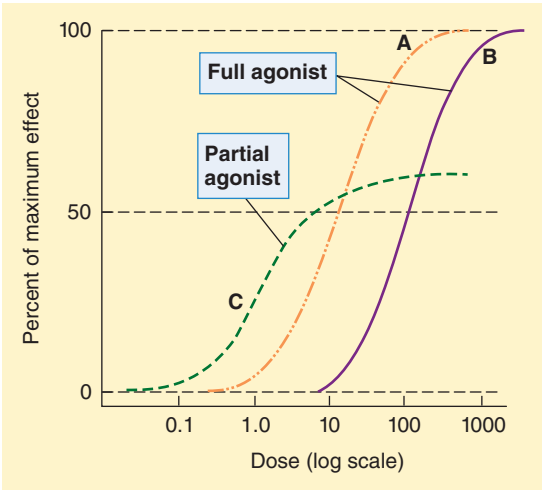

FIGURE 2-5 **Comparison of theoretical log dose-response curves for full agonists (A and B) and a partial agonist (C).** Both full agonists demonstrate the same maximal efficacy. Drug A is more potent than drug B because the EC_{50} for drug A is approximately 10, whereas the EC_{50} for drug B is approximately 100. The partial agonist demonstrates affinity and efficacy at the same receptor site as the full agonists. However, compared to the full agonists, the partial agonist produces a lower maximal effect (ie, less efficacy). The EC_{50} for partial agonist C is approximately 1. A partial agonist may be more potent (as depicted), less potent, or equally potent as the full agonist.

Competitive and Noncompetitive Antagonists

Whereas full agonists demonstrate both affinity and efficacy, antagonists demonstrate affinity, but not efficacy. A competitive antagonist is a drug that binds to, or very close to, the agonist receptor site in a reversible way, but does not activate the effector system for that receptor. Competitive antagonists bind the receptor without shifting the ratio of R_a to R_i (Figure 2-4). If given in high enough concentration, the agonist can effectively displace the competitive antagonist and fully activate the receptors. In the presence of a competitive antagonist, the dose-response curve for an agonist shifts the ED_{50} to higher doses (ie, horizontally to the right on the dose axis), but the same maximal effect (E_{max}) can still be achieved (Figure 2-6A).

In contrast, a noncompetitive antagonist causes a downward shift of the maximum response, with no shift of the curve on the dose axis. Noncompetitive antagonists bind to the agonist receptor site either covalently or with very strong electrostatic and hydrogen bonds. Once bound to the receptor, noncompetitive antagonists release slowly such that their binding may be considered irreversible or nearly irreversible. From a functional viewpoint, this may be considered noncompetitive antagonism because—unlike the situation with a competitive antagonist—the effects of a noncompetitive antagonist cannot be overcome by higher doses of the agonist. The log dose-response curve for noncompetitive antagonists results in a decrease in E_{max} and a minimal rightward shift of the ED_{50} (Figure 2-6B).

Allosteric Regulation

Some drugs bind at a different site on a receptor than that of the endogenous ligand or agonist. If a drug binds to the receptor at a different site and *potentiates* the effects of the ligand or agonist, the drug is known as an allosteric activator. If a drug binds to the receptor at a different site and *inhibits* the effects of the ligand or agonist, the drug is an allosteric inhibitor. The log dose-response curve for an allosteric inhibitor results in a minimal rightward shift of the ED_{50} and a decrease in the E_{max}. Thus, no concentration of agonist can displace the allosteric inhibitor. Figure 2-7 illustrates the effects of allosteric modulators on dose-response relationships. The allosteric activator

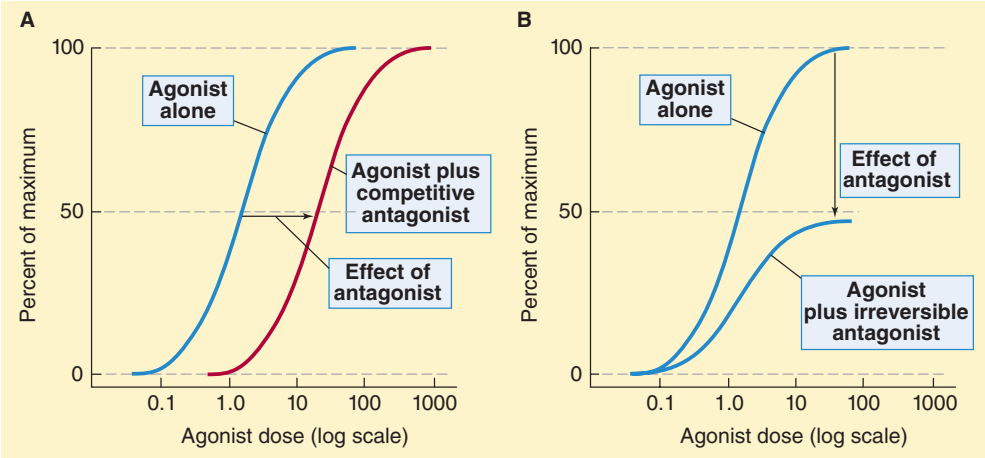

FIGURE 2-6 **Agonist dose-response curves in the presence of competitive and irreversible (noncompetitive) antagonists.** Note the use of a logarithmic scale for drug concentration. **(A)** The effect of a competitive antagonist is illustrated by the shift of the agonist curve to the right, increasing the ED_{50} for the agonist in the presence of the competitive antagonist. There is no decrease in the maximal response for the agonist (E_{max}). **(B)** An irreversible antagonist shifts the agonist curve downward, decreasing the E_{max} of the agonist. There is little to no shift to the right for the ED_{50}.

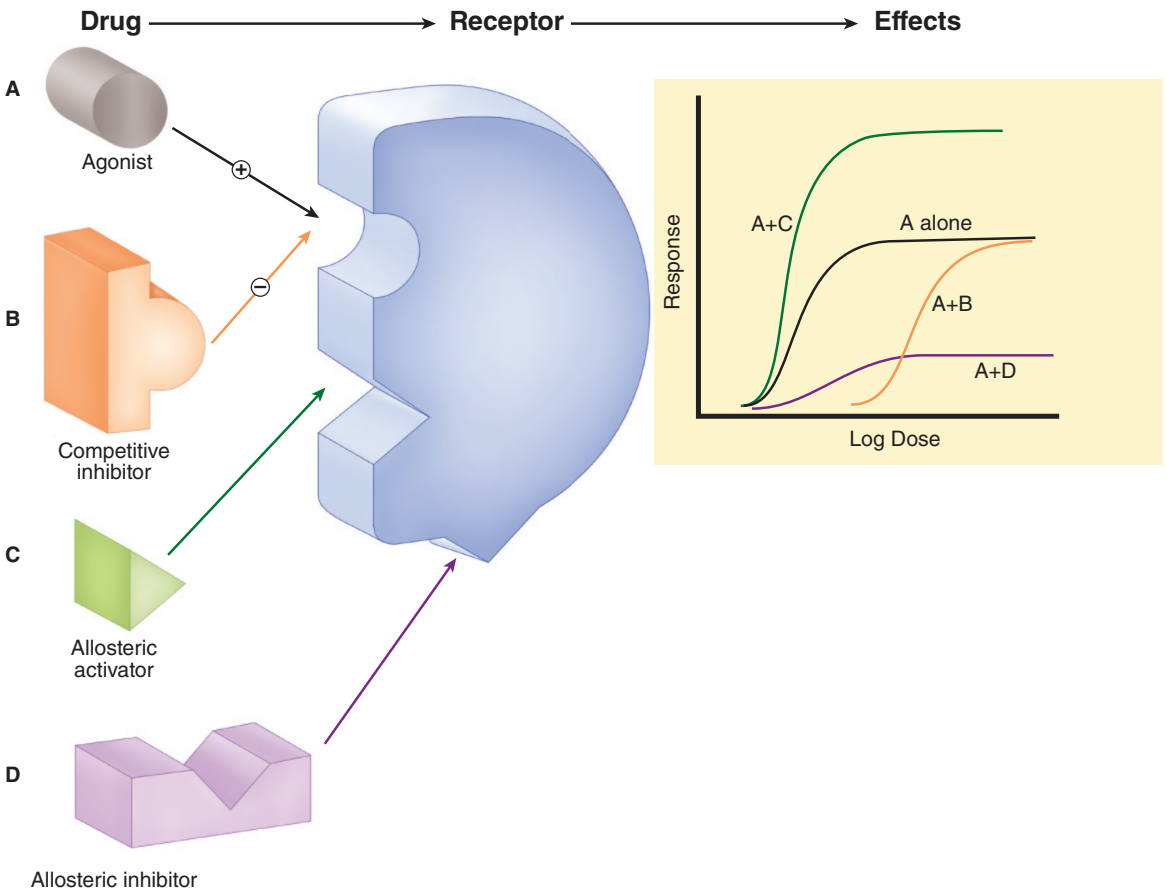

FIGURE 2-7 **Potential mechanisms of drug interaction with a receptor.** Possible effects resulting from these interactions are diagrammed in the dose-response curves. The traditional agonist (drug A)-receptor binding process results in the dose-response curve denoted "A alone." B is an antagonist that competes with the agonist for binding to the same receptor site. The dose-response curve produced by increasing doses of agonist A in the presence of a fixed concentration of competitive antagonist B is indicated by the curve "A + B." Drugs C and D act at different sites on the receptor molecule; they are *allosteric* activators or inhibitors. Allosteric activators and inhibitors can bind reversibly or irreversibly but they do not compete with the agonist for binding to the receptor site.

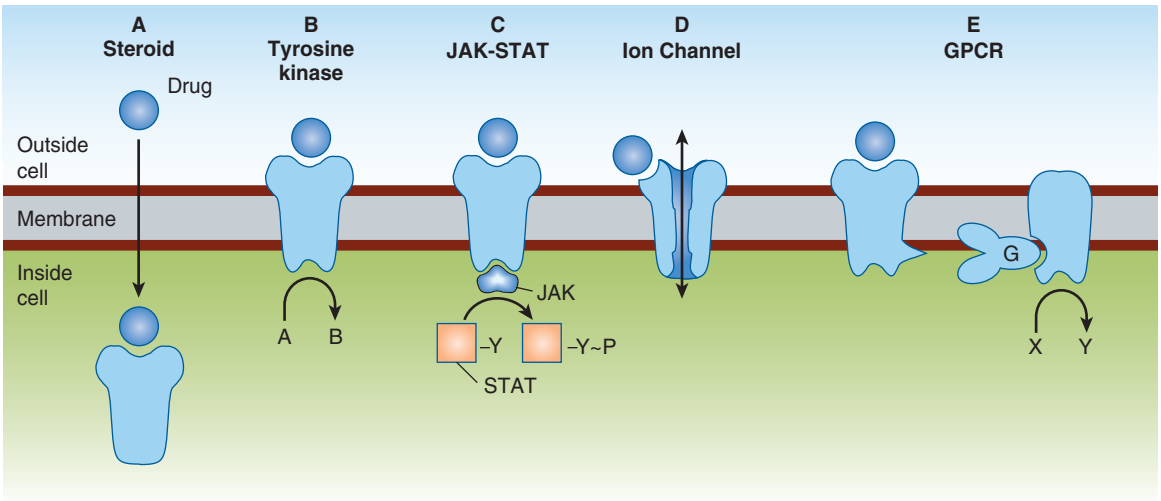

FIGURE 2-8 Signaling mechanisms for drug effects. Five major transmembrane signaling mechanisms: **(A)** transmembrane diffusion of the drug to bind to an intracellular receptor; **(B)** transmembrane enzyme receptors, whose outer domain provides the receptor function and inner domain provides the effector mechanism converting A to B; **(C)** transmembrane receptors that, after activation by an appropriate ligand, activate separate cytoplasmic tyrosine kinase molecules (Janus kinases, JAKs), which phosphorylate signal transducer and activator of transcription (STAT) proteins that regulate transcription (Y, tyrosine; P, phosphate); **(D)** transmembrane channels that are gated open or closed by binding of a drug to the receptor site; **(E)** G protein-coupled receptors (GPCR) that use a coupling protein to activate a separate effector molecule.

increases the response of the agonist (Figure 2-7, A + C), shifting the curve to the left. In contrast, the allosteric inhibitor decreases the agonist maximal response (E_{max}) with minimal rightward shift for the ED_{50} (Figure 2-7, A + D). Note the similarity in the dose-response curves between the allosteric inhibitor (Figure 2-7, A + D) and the irreversible antagonist (Figure 2-6B), even though the mechanisms of action are different. That is, an increase in agonist concentration will not reverse the inhibitory effects of an allosteric inhibitor or of an irreversible antagonist.

Physiologic and Chemical Antagonism

Antagonism is not restricted to an antagonist binding to the same receptor as the agonist. Physiologic antagonism may occur by one drug binding to a receptor that produces an effect opposite to that of a different drug binding at a different receptor. A classic example of physiologic antagonism is a drug that stimulates the parasympathetic nervous system, which antagonizes a drug that activates the sympathetic nervous system. Chemical antagonism is not receptor dependent. In this case, an antagonist interacts with another drug to remove it or prevent it from binding to the target receptor. An example of chemical antagonism is the binding of protamine sulfate to heparin to form a stable complex that is devoid of activity. This chemical antagonism is clinically utilized to rapidly reverse the anticoagulant effects of heparin (Chapter 11).

SIGNALING MECHANISMS

After an agonist binds to the receptor, some effector mechanism produces the cellular change that ultimately accomplishes a biologic effect. The receptor-effector system may be in the intracellular space, extracellular space, or across the plasma membrane. Most drug-receptor interactions involve signaling across the plasma membrane such that the agonist binds to a site on the receptor's extracellular surface, which then activates the effector mechanism inside the cell to initiate a series of intracellular changes.

Figure 2-8 shows five well-characterized mechanisms of transmembrane signaling. Each uses a different strategy to circumvent the barrier posed by the lipid bilayer of the plasma membrane. Each receptor type is made up of distinctive protein families with a specific mechanism to transduce one or many different signals. These protein families include receptors on the cell surface and within the cell, as well as enzymes and other components that generate, amplify, coordinate, and terminate postreceptor signaling within the cell.

Intracellular Receptors

Intracellular receptors bind to lipid-soluble agonists that are able to cross the phospholipid bilayer plasma membrane (Figure 2-8A). A classic example of an agent that activates intracellular receptors is the gas nitric oxide (NO). Whether endogenously released by the endothelial lining of blood vessels or liberated by a drug, NO diffuses across the plasma membrane of the endothelial cells and into smooth muscle cells to stimulate the intracellular enzyme guanylate cyclase, which produces cyclic guanosine monophosphate (cGMP), a second messenger.

Other endogenous agonists that act on intracellular receptors include the steroid hormones derived from cholesterol (adrenocorticosteroids, gonadal hormones, and vitamin D) and thyroid hormones. When these agonists bind to their intracellular receptors, the drug-receptor complex is often

translocated to the nucleus to subsequently stimulate gene transcription. Because this mechanism of action involves regulating gene expression, two therapeutically important consequences should be highlighted. First, these hormones produce their effects after a characteristic lag period of 30 minutes to several hours, the timeframe required for synthesizing new proteins. Thus, therapeutically administered steroid and thyroid hormones cannot be expected to alter a pathologic state within minutes. Second, the physiologic effect from stimulation of these intracellular receptors may persist for hours or days *after* the plasma agonist concentration has been reduced to zero. The persistence of the effect is primarily due to the relatively slow turnover of most enzymes and proteins, which can remain active in cells for hours or days after they have been synthesized. Consequently, this means that the beneficial (or toxic) effects of a gene-activated system will usually decrease slowly following termination of the administered drug that stimulated the process.

Receptors on Transmembrane Proteins

Some transmembrane receptors have intracellular enzymatic activity that is allosterically regulated when an agonist binds to a site on the receptor's extracellular domain (Figure 2-8B and C). These membrane-spanning receptors consist of an extracellular binding domain and a cytoplasmic domain that may have enzymatic activity directly linked to the receptor, or a separate enzyme molecule associated with the cytoplasmic domain. These receptors include those that mediate the first steps in signaling by insulin, various growth factors (interleukin 6, interferon), and trophic hormones. For example, when insulin binds to the extracellular domain, the receptor changes its conformation, bringing together the intracellular kinase domains of two adjacent receptors that become enzymatically active and phosphorylate additional downstream signaling proteins. Activated receptors catalyze phosphorylation of tyrosine residues on different target signaling proteins, thereby allowing a single type of activated receptor to modulate a number of biochemical processes.

Receptors on Transmembrane Ion Channels

Many useful drugs act by mimicking or blocking the actions of endogenous agents that regulate the flow of ions through plasma membrane channels (Figure 2-8D). Receptors for the neurotransmitters acetylcholine, serotonin, gamma-aminobutyric acid, glycine, aspartate, and glutamate transmit their signals across the plasma membrane by increasing transmembrane conductance of the relevant ion (usually sodium, potassium, calcium, or chloride) and thereby altering the membrane potential. The ion channel opened by activation of the receptor-ion channel complex eventually closes, terminating the event. The effect lasts only as long as the drug occupies the receptor, so that dissociation of drug from the receptor automatically terminates the effect.

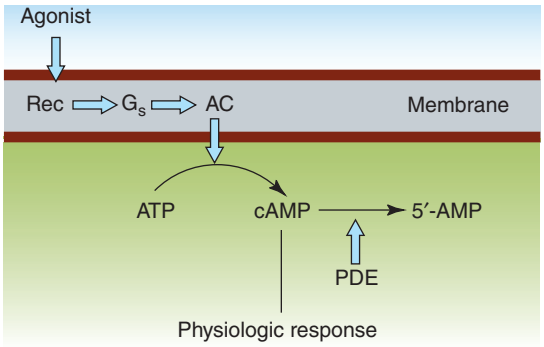

FIGURE 2-9 The cyclic adenosine monophosphate (cAMP) second messenger pathway. Key proteins include hormone receptors (Rec), a stimulatory G protein (G_s), catalytic adenylate cyclase (AC), and phosphodiesterases (PDE) that hydrolyze cAMP. Hydrolysis of cAMP terminates the activity of the second messenger.

G Protein-Coupled Receptors

Many extracellular ligands act by increasing the intracellular concentrations of second messengers such as cyclic adenosine monophosphate (cAMP), calcium ion, or the phosphoinositides (Figure 2-8E). In most cases, the transmembrane signaling system has three separate components. First, the extracellular ligand binds to a specific cell-surface receptor. Next, receptor binding triggers the activation of a G protein located on the cytoplasmic face of the plasma membrane. The activated G protein then changes the activity of an effector element, usually an enzyme or ion channel. This last effector then changes the concentration of the intracellular second messenger.

Termination of drug action in G protein-coupled receptor (GPCR) systems often involves the inactivation of the second messenger (as exemplified by cAMP) by a phosphodiesterase (Figure 2-9). For example, when norepinephrine and epinephrine act on G protein-coupled β-adrenergic receptors in the heart, one effect is increased heart rate. Caffeine, a universally common drug, increases heart rate. One mechanism by which caffeine increases heart rate is by inhibiting the phosphodiesterase that inactivates cAMP. Thus, caffeine does not increase heart rate by directly interacting with the extracellular domain of β-adrenergic receptors, but rather by modulating the activity of the downstream effector system to increase the duration of cAMP's actions.

RECEPTOR REGULATION

The number of receptors present in a biologic system and available for interaction with a drug is not constant. That is, the actual number of receptors available for binding the agonist varies, as does the ability of the receptor to initiate a signal as a result of the agonist binding. The variables responsible for this receptor regulation include repeated short-term or long-term activation of the receptors and other variations in the homeostasis of the cell. Changes can occur over a short duration (minutes) and a longer duration (days). Pharmacologic therapy can cause changes in receptor regulation that may have significant effects.

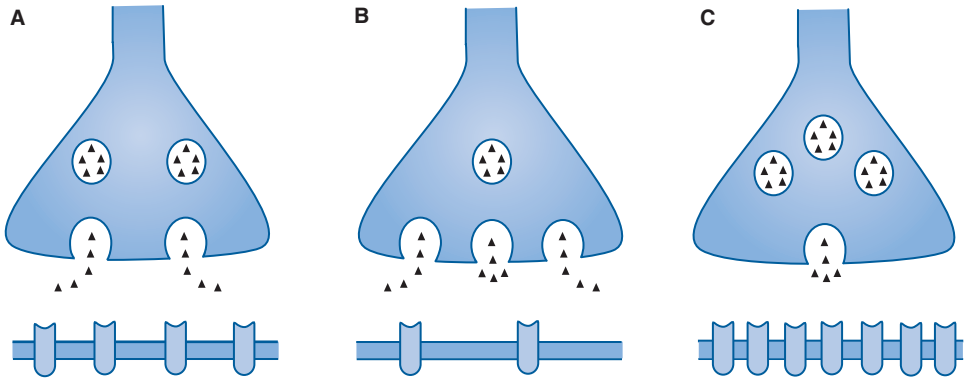

FIGURE 2-10 **A generic synapse with neurotransmitter receptors located on the postsynaptic membrane under three conditions: A**, normal number of receptors; **B**, decreased number of receptors (downregulation); **C**, increased number of receptors (upregulation). Downregulation may result from increased neurotransmitter release from the presynaptic terminal and stimulation of the receptors by an agonist over hours or days. Upregulation may result from chronic blockade of receptors by a competitive antagonist or diminished stimulation of the receptor for a similar period.

Downregulation

Frequent or continuous receptor stimulation often results in short-term diminution of the receptor response, sometimes called tachyphylaxis. Several mechanisms are responsible for this phenomenon. First, an intracellular molecule may block access of a G protein to the activated receptor molecule. Alternatively, receptors may be internalized by endocytosis after repeated stimulation, removing them from the pool of receptors available for stimulation. Finally, repetitive frequent stimulation may result in loss of some essential substrate required for intracellular downstream effects.

Long-term changes in the number of receptors or their responsiveness to stimulation involve different mechanisms (Figure 2-10). Downregulation is a decrease in the number of receptors available for binding by the agonist (Figure 2-10B). Downregulation results from exposure of the receptors to an agonist for periods of hours to days. Downregulation occurs slowly and is usually the result of degradation of receptors exceeding synthesis of new receptors. Both tachyphylaxis and downregulation can result in a decrease in the maximal response when an agonist stimulates the receptors. A likely familiar clinical example of tachyphylaxis is the rebound congestion that occurs after several days of using intranasal decongestants (such as oxymetazoline). This response is thought to be due to downregulation of α-adrenergic receptors and desensitization of the response.

Upregulation

Upregulation is an *increase* in the number of receptors available for binding and stimulation (Figure 2-10C). Prolonged lack of receptor stimulation or chronic blockade of receptors might decrease the rate of receptor degradation; if the rate of receptor synthesis is maintained, the result is a net increase in the total number of receptors available for stimulation. Due to the increase in the total number of receptors available in an upregulated system, stimulation may result in an enhanced maximal response. A clinically relevant example would be the chronic use of β-receptor antagonists, which results in upregulation of β receptors on the heart (Chapter 6).

CHAPTER 2 QUESTIONS

1. Which of the following would bind mainly to the inactive form of the receptor and decrease the constitutive activity of the receptor-mediated system?

   a. Inverse agonist
   b. Full agonist
   c. Partial agonist
   d. Neutral antagonist

2. Four drugs bind to the same receptor. The drug and dose for each drug that produces a 50% maximal response is listed below. Which drug has the greatest potency?

   a. Drug A 5 mcg/kg
   b. Drug B 2 mcg/kg
   c. Drug C 6 mcg/kg
   d. Drug D 3 mcg/kg

3. Which of the following formulas represents the therapeutic index?

   a. TD_{50} divided by the LD_{50}
   b. LD_{50} divided by the TD_{50}
   c. TD_{50} divided by the ED_{50}
   d. ED_{50} divided by the LD_{50}

4. Which of the therapeutic indices below represents the safest drug based on the therapeutic index?

   a. 5
   b. 0
   c. −3
   d. 8

5. Drug A is a full agonist at a receptor. When drug B is added, the maximal response to drug A is decreased, but there is minimal change in the dosage of drug A required to generate a 50% maximal response. Drug B binds at a different site at the same receptor for drug A. Which of the following is drug B?

   a. Allosteric inhibitor
   b. Partial agonist
   c. Competitive antagonist
   d. Irreversible antagonist

6. A drug binds to a receptor, causing the intracellular formation of cyclic adenosine monophosphate (cAMP) by the enzyme adenylate cyclase. This system is which of the following?

   a. Intracellular receptor
   b. G protein-coupled receptor
   c. Tyrosine kinase–mediated receptor
   d. Ligand-gated ion channel receptor

7. Which of the following phenomena is an increase in the number of receptors after long-term blockade by an antagonist?

   a. Tachyphylaxis
   b. Downregulation
   c. Upregulation
   d. Bradyphylaxis

8. Drug A binds to both the active and inactive forms of the receptor, favoring the active form of the receptor. What type of drug is drug A?

   a. Full agonist
   b. Competitive antagonist
   c. Allosteric inhibitor
   d. Partial agonist

9. Drug A stimulated the sympathetic nervous system. Drug B counters the effects of drug A by stimulating the parasympathetic nervous system. Which of the following processes does this represent?

   a. Physiologic antagonism
   b. Chemical antagonism
   c. Competitive antagonism
   d. Allosteric inhibition

10. Drug A binds to a receptor causing an influx of sodium ions into a cell. Which of the following receptor types does this represent?

    a. Intracellular receptor
    b. Ligand-gated ion channel
    c. G protein-coupled receptor
    d. Tyrosine kinase–mediated receptor

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CHAPTER 3

Pharmacokinetics and Pharmacogenomics

REHABILITATION FOCUS

Pharmacokinetics is the branch of pharmacology that is concerned with the effects of the body on both endogenous ligands and drugs. Almost all drugs (except those delivered directly to the target tissue where the proposed receptors are located) are absorbed from the site of administration and transported by the circulation to various tissues before they arrive at the target tissue. At the same time, chemical reactions in the tissues attempt to convert drugs into forms that allow for easier removal from the body. This sequence of actions represents the absorption, distribution, biotransformation, and elimination of drugs.

Chapter 2 defined the effective drug concentration as its concentration at the receptor site. However, the concentration of the drug in the blood is more readily measured. Except for topically applied agents, the effective drug concentration is usually proportional to its concentration in the plasma or whole blood. The plasma concentration is a function of the rate of input of the drug through absorption, distribution to the peripheral tissues (including the target tissue), and elimination from the body. These are all functions of time. If the rate of drug delivery is known, the remaining processes are well described by the pharmacokinetic parameters known as volume of distribution and clearance. Although these parameters are unique for a particular drug in a particular patient, average values in large populations can be used to predict drug concentrations. These parameters allow the calculation of loading and maintenance doses required for dosage regimens.

Dosage regimens depend on the pharmacodynamics (Chapter 2) and pharmacokinetics of the drug (this chapter) as well as an individual's specific comorbidities. While general guidelines for dosing regimens are available, certain comorbidities will affect drug clearance, or the rate at which active drug is removed from the body. Decreased clearance will increase how long the drug stays in the body and thus how long its effects—beneficial and adverse—will last. Renal disease or reduced cardiac output often decrease the clearance of drugs that depend on renal function. Altered clearance by liver disease is less common but can occur, especially if hepatic biotransformation of the drug is reduced. When liver blood flow is reduced, such as in heart failure, clearance for drugs that are extensively cleared from the blood by the liver also decreases. When clearance of a drug is reduced by such conditions, the dose (specific amount of medication taken at one time) and possibly the dosage (frequency of doses over a specific period of time) must be modified appropriately. During an episode of care, physical therapists often become aware of a patient's new or progressive comorbidities as well as potential drug interactions. It is important for therapists to initiate and participate in discussion with other (prescribing) healthcare professionals to determine whether these factors may affect the dosing regimen and the rehabilitation treatment program for the patient. Ongoing interprofessional communication can improve dosing regimens by providing the prescriber a clearer picture of how the medication is altering the patient's clinical presentation. In addition, clear communication between patients and healthcare providers can improve medication adherence and potentially decrease the risk and frequency of adverse drug reactions (ADRs).

PHYSICAL AND CHEMICAL NATURE OF DRUGS

Currently available drugs include inorganic ions, nonpeptide organic molecules, small peptides and proteins, nucleic acids, lipids, and carbohydrates. The majority of drugs have molecular weights between 100 and 1000, though some may be as small as molecular weight (MW) 7 for lithium to over MW 50,000 for thrombolytic enzymes. Drugs are often found in or derived from plants or animals, but many are partially or completely synthetic. Although it is a popular misconception that natural drugs or herbs are safer than synthesized drugs, the safety of a drug is based on its pharmacodynamic and pharmacokinetic properties, *not* its source.

Aqueous and Lipid Solubility

An important property of a drug is its solubility in various components of the body. For simplicity, the body can be considered to have aqueous compartments (extracellular and intracellular environments) and lipid compartments (lipid bilayer of all cell membranes). The aqueous solubility of a drug often depends on the degree of ionization or polarity of the molecule. Water molecules behave as dipoles and are attracted to charged molecules, forming an aqueous shell around them. Conversely, the lipid solubility of a molecule is inversely proportional to its charge.

Many drugs are weak bases or weak acids. For such molecules, the pH of the medium determines the fraction of ionized versus nonionized molecules. If the pKa (acid dissociation constant) of the drug and the pH of the medium are known, the fraction of molecules in the ionized state can be predicted from the Henderson-Hasselbalch equation (Equation [1]):

$$\text{Log (Protonated form/Unprotonated form)} = pK_a - pH \quad (1)$$

In Equation (1), "protonated" means associated with a proton (H^+). This equation applies to both acids and bases. Weak bases are ionized and, therefore, more polar and more water soluble when they are protonated. In contrast, weak acids are not ionized when they are protonated, and so are less water soluble. Equations (2) and (3) summarize these points for weak bases and weak acids:

$$\text{Weak base} \quad \underset{\text{(Protonated)}}{RNH_3^+} \quad \Leftrightarrow \quad \underset{\text{(Unprotonated)}}{RNH_2 + H^+} \quad (2)$$

$$\text{Weak acid} \quad \underset{\text{(Protonated)}}{RCOOH} \quad \Leftrightarrow \quad \underset{\text{(Unprotonated)}}{RCOO^- + H^+} \quad (3)$$

The Henderson-Hasselbalch relationship is clinically important when it is necessary to estimate or alter the partition of drugs between compartments of differing pH. For example, most drugs are freely filtered at the glomeruli, but lipid-soluble drugs can be rapidly reabsorbed from the tubular urine. If a person takes an overdose of a drug that is a weak acid (eg, aspirin), the excretion of this drug is faster in alkaline urine. This is because a drug that is a weak acid dissociates to its charged, polar form in alkaline solution, and this form cannot readily diffuse from the renal tubule back into the blood. Therefore, the drug stays trapped in the tubule and is excreted into the urine. Conversely, excretion of a weak base (eg, pyrimethamine) is faster in acidic urine (**Figure 3-1**).

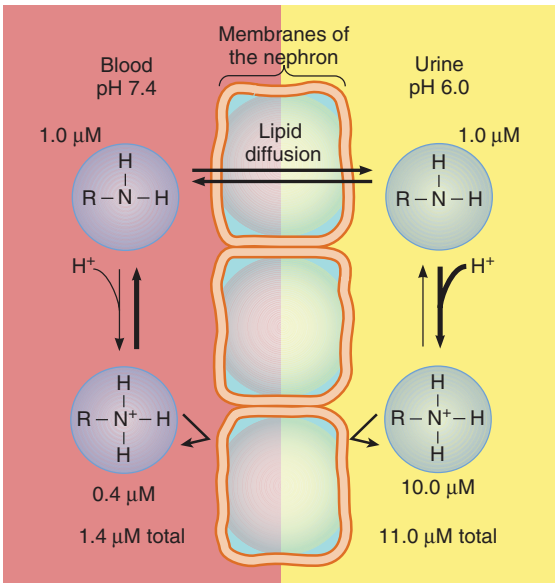

FIGURE 3-1 Henderson-Hasselbalch principle applied to drug excretion in the urine. Because the nonionized form diffuses readily across the lipid barriers of the nephron, this form may reach equal concentrations in the blood and urine; in contrast, the ionized form does not diffuse as readily. Protonation occurs within the blood and the urine according to the Henderson-Hasselbalch equation. Pyrimethamine, a weak base of pKa 7.0, is used in this example. In the blood at pH of 7.4, only 0.4 µmol of the protonated form is present for each 1.0 µmol of the unprotonated form. Thus, the total concentration in the blood is 1.4 µmol/L. In the urine at pH 6.0, 10 µmol of the nondiffusible ionized form will be present for each 1.0 µmol of the unprotonated, diffusible form. Therefore, the total urine concentration (11 µmol/L) may be almost 8 times higher than the blood concentration.

ROUTES OF ADMINISTRATION AND ABSORPTION

When drugs enter the body at sites remote from the target tissue, they require transport by the circulation to the intended site of action. To enter the blood, a drug must be absorbed from its site of administration. Absorption, therefore, describes the entry of the drug into the body. Not all routes of administration result in similar amounts of drug reaching the systemic circulation and the target tissue. In fact, for some drugs and certain routes, the amount absorbed may be only a small fraction of the amount administered. Thus, the rate and efficiency of a drug's absorption differ depending on its route of administration. The two main routes of administration are enteral and parenteral. Enteral routes involve the gastrointestinal (GI) system whereas parenteral routes bypass the GI system. Parenteral routes of drug administration include the vasculature, musculoskeletal, pulmonary, and integumentary systems. **Table 3-1** lists the common routes of drug administration and their general characteristics.

Enteral Administration

Enteral routes of administration include oral, sublingual or buccal, and rectal. Oral administration is defined as swallowing of the drug and absorption from the GI lumen. The majority of drugs currently prescribed are intended for oral delivery because this route offers maximum convenience and is preferred when chronic drug treatment is required. Oral absorption may be slower and less complete compared to some parenteral routes. When a drug is administered orally and absorbed from the stomach and intestine, the drug moves through the hepatic portal vein and through the liver. Enzymes within the liver may transform some percentage of the drug into an inactive form prior to entering the systemic circulation. This effect of the liver on oral administration of a drug is known as the first-pass effect (or, first-pass inactivation or metabolism), and is discussed later in the chapter. The extent of first-pass inactivation varies dramatically, depending on the drug. When first-pass effect is high, considerable fractions of these drugs are lost during absorption and the oral route is not clinically practical. All parenteral routes avoid the first-pass effect.

Sublingual administration involves placing the drug (eg, in form of a tablet, drop, or spray) under the tongue. Buccal