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Lippincott® Illustrated Reviews: Pharmacology

Eighth Edition

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1936–2017

Co-creator and series editor of the *Lippincott Illustrated Reviews* series, in collaboration with Pamela C. Champe, PhD (1945–2008).

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Contents

UNIT I
Principles of Drug Therapy

1

Pharmacokinetics

Venkata Yellepeddi

I. Overview

Pharmacokinetics refers to what the body does to a drug, whereas pharmacodynamics (see Chapter 2) describes what the drug does to the body. Four pharmacokinetic properties determine the onset, intensity, and duration of drug action (Figure 1.1):

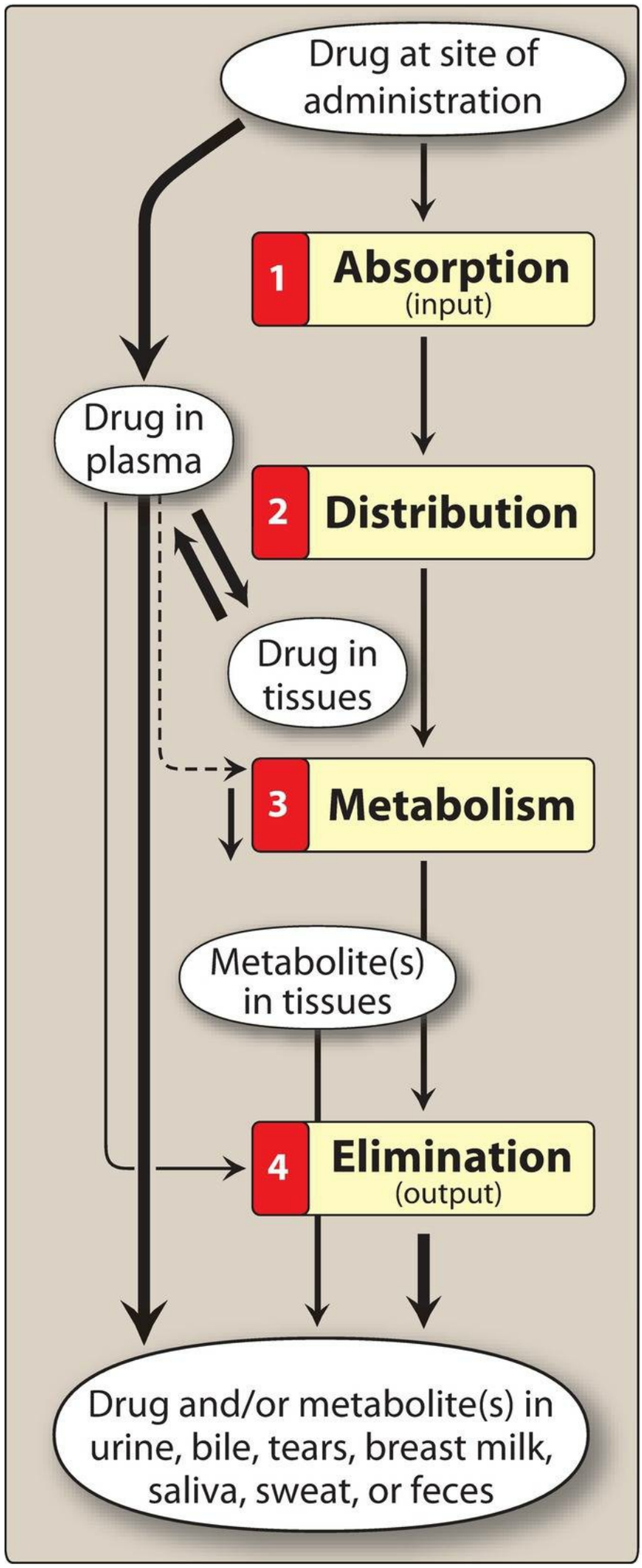


Figure 1.1 Schematic representation of drug absorption, distribution, metabolism, and elimination.

- **Absorption:** First, absorption from the site of administration permits entry of the drug (either directly or indirectly) into plasma.
- **Distribution:** Second, the drug may reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids.
- **Metabolism:** Third, the drug may be biotransformed through metabolism by the liver or other tissues.
- **Elimination:** Finally, the drug and its metabolites are eliminated from the body in urine, bile, or feces.

Using knowledge of pharmacokinetic parameters, clinicians can design optimal drug regimens, including the route of administration, dose, frequency, and duration of treatment.

II. Routes of Drug Administration

The route of administration is determined by properties of the drug (for example, water or lipid solubility, ionization) and by the therapeutic objectives (for example, the need for a rapid onset, the need for long-term treatment, or restriction of delivery to a local site). Major routes of drug administration include enteral, parenteral, and topical, among others (Figure 1.2).

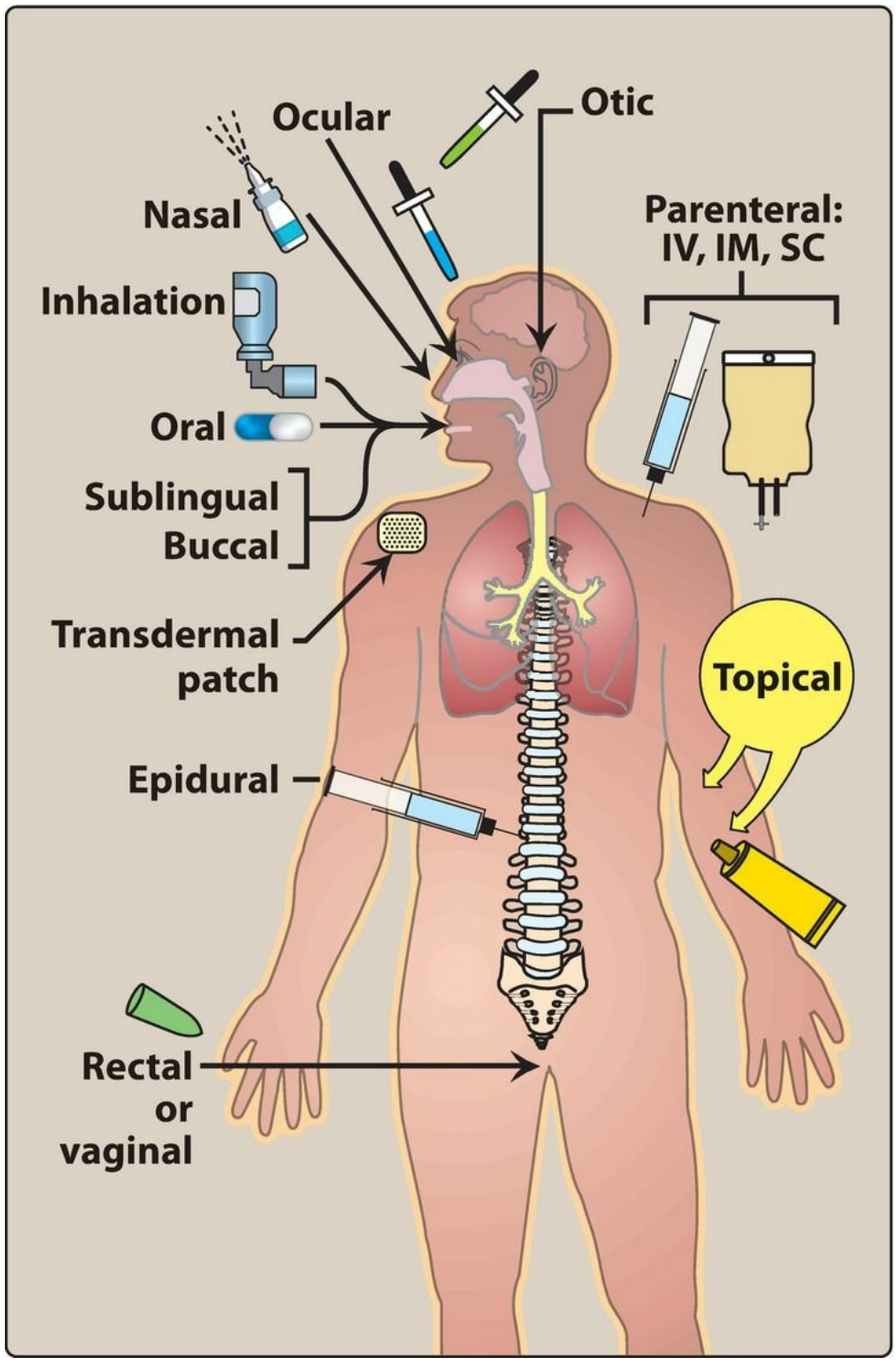


Figure 1.2 Commonly used routes of drug administration. IV = intravenous; IM = intramuscular; SC = subcutaneous.

A. Enteral

Enteral administration (administering a drug by mouth) is the most common, convenient, and economical method of drug administration. The drug may be swallowed, allowing oral delivery, or it may be placed under the tongue (sublingual) or between the gums and cheek (buccal), facilitating direct absorption into the bloodstream.

1. Oral

Oral administration provides many advantages. Oral drugs are easily self-administered, and toxicities and/or overdose of oral drugs may be overcome with antidotes, such as activated charcoal. However, the pathways involved in oral drug absorption are the most complicated, and the low gastric pH inactivates some drugs. A wide range of oral preparations is available including enteric-coated and extended-release preparations.

a. Enteric-coated preparations

An enteric coating is a chemical envelope that protects the drug from stomach acid, delivering it instead to the less acidic intestine, where the coating dissolves and releases the drug. Enteric coating is useful for certain drugs (for example, *omeprazole*) that are acid labile, and for drugs that are irritating to the stomach, such as *aspirin*.

b. Extended-release preparations

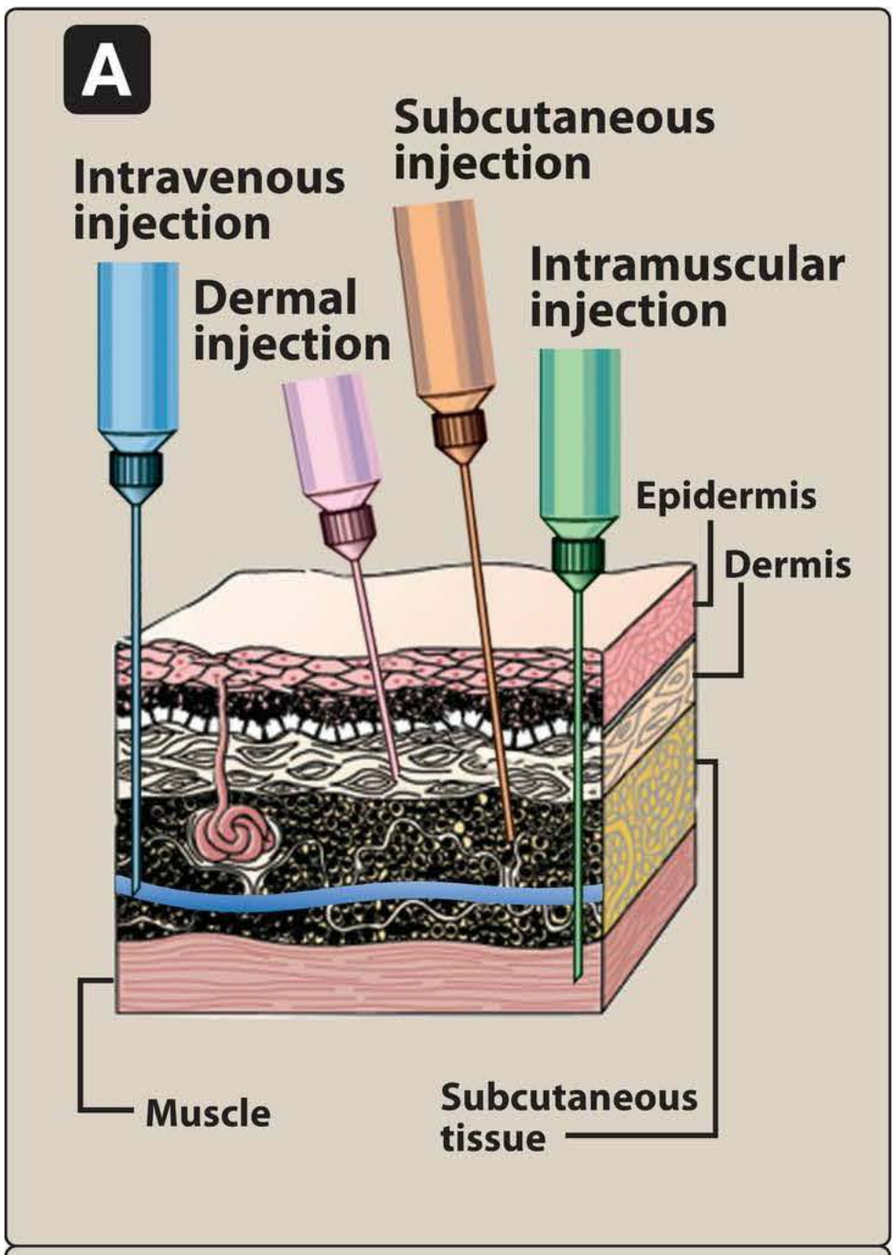
Extended-release (abbreviated ER, XR, XL, SR, etc.) medications have special coatings or ingredients that control drug release, thereby allowing for slower absorption and prolonged duration of action. ER formulations can be dosed less frequently and may improve patient compliance. In addition, ER formulations may maintain concentrations within the therapeutic range over a longer duration, as opposed to immediate-release dosage forms, which may result in larger peaks and troughs in plasma concentration. ER formulations are advantageous for drugs with short half-lives. For example, the half-life of oral *morphine* is 2 to 4 hours, and it must be administered six times daily to provide continuous pain relief. However, only two doses are needed when extended-release tablets are used.

2. Sublingual/buccal

The sublingual route involves placement of drug under the tongue. The buccal route involves placement of drug between the cheek and gum. Both the sublingual and buccal routes of absorption have several advantages, including ease of administration, rapid absorption, bypass of the harsh gastrointestinal (GI) environment, and avoidance of first-pass metabolism (see discussion of first-pass metabolism below).

B. Parenteral

The parenteral route introduces drugs directly into the systemic circulation. Parenteral administration is used for drugs that are poorly absorbed from the GI tract (for example, *heparin*) or unstable in the GI tract (for example, *insulin*). Parenteral administration is also used for patients unable to take oral medications (unconscious patients) and in circumstances that require a rapid onset of action. Parenteral administration provides the most control over the dose of drug delivered to the body. However, this route of administration is irreversible and may cause pain, fear, local tissue damage, and infections. The four major parenteral routes are intravascular (intravenous or intra-arterial), intramuscular, subcutaneous, and intradermal (Figure 1.3).


A
Intravenous injection
Subcutaneous injection
Dermal injection
Intramuscular injection
Epidermis
Dermis
Muscle
Subcutaneous tissue

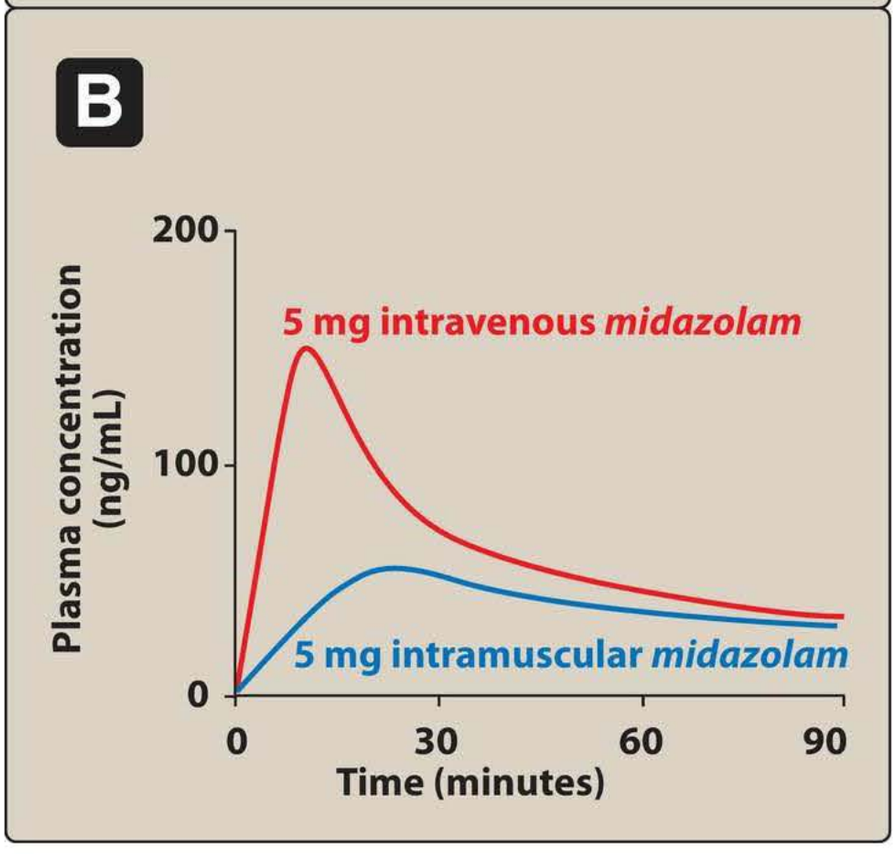

B
200
100
0
Plasma concentration (ng/mL)
5 mg intravenous midazolam
5 mg intramuscular midazolam
0
30
60
90
Time (minutes)

Figure 1.3 A. Schematic representation of subcutaneous and intramuscular injection. **B.** Plasma concentrations of *midazolam* after intravenous and intramuscular injection.

1. Intravenous (IV)

IV injection is the most common parenteral route. It is useful for drugs that are not absorbed orally, such as the neuromuscular blocker *rocuronium*. IV delivery permits a rapid effect and a maximum degree of control over the amount of drug delivered. When injected as a bolus, the full amount of drug is delivered to the systemic circulation almost immediately. If administered as an IV infusion, the drug is infused over a longer period, resulting in lower peak plasma concentrations and an increased duration of circulating drug.

2. Intramuscular (IM)

Drugs administered IM can be in aqueous solutions, which are absorbed rapidly, or in specialized depot preparations, which are absorbed slowly. Depot preparations often consist of a suspension of drug in a nonaqueous vehicle, such as polyethylene glycol. As the vehicle diffuses out of the muscle, drug precipitates at the site of injection. The drug then dissolves slowly, providing a sustained dose over an extended interval.

3. Subcutaneous (SC)

Like IM injection, SC injection provides absorption via simple diffusion and is slower than the IV route. SC injection minimizes the risks of hemolysis or thrombosis associated with IV injection and may provide constant, slow, and sustained effects. This route should not be used with drugs that cause tissue irritation, because severe pain and necrosis may occur.

4. Intradermal (ID)

The intradermal (ID) route involves injection into the dermis, the more vascular layer of skin under the epidermis. Agents for diagnostic determination and desensitization are usually administered by this route.

C. Other

1. Oral inhalation and nasal preparations

Both the oral inhalation and nasal routes of administration provide rapid delivery of drug across the large surface area of mucous membranes of the respiratory tract and pulmonary epithelium. Drug effects are almost as rapid as are those with IV bolus. Drugs that are gases (for example, some anesthetics) and those that can be dispersed in an aerosol are administered via inhalation. This route is effective and convenient for patients with respiratory disorders such as asthma or chronic obstructive pulmonary disease, because drug is delivered directly to the site of action, thereby minimizing systemic side effects. The nasal route involves topical administration of drugs directly into the nose, and it is often used for patients with allergic rhinitis.

2. Intrathecal/intraventricular

The blood–brain barrier typically delays or prevents the absorption of drugs into the central nervous system (CNS). When local, rapid effects are needed, it is necessary to introduce drugs directly into the cerebrospinal fluid.

3. Topical

Topical application is used when a local effect of the drug is desired.

4. Transdermal

This route of administration achieves systemic effects by application of drugs to the skin, usually via a transdermal patch (Figure 1.4). The rate of absorption can vary markedly, depending on the physical characteristics of the skin at the site of application, as well as the lipid solubility of the drug.

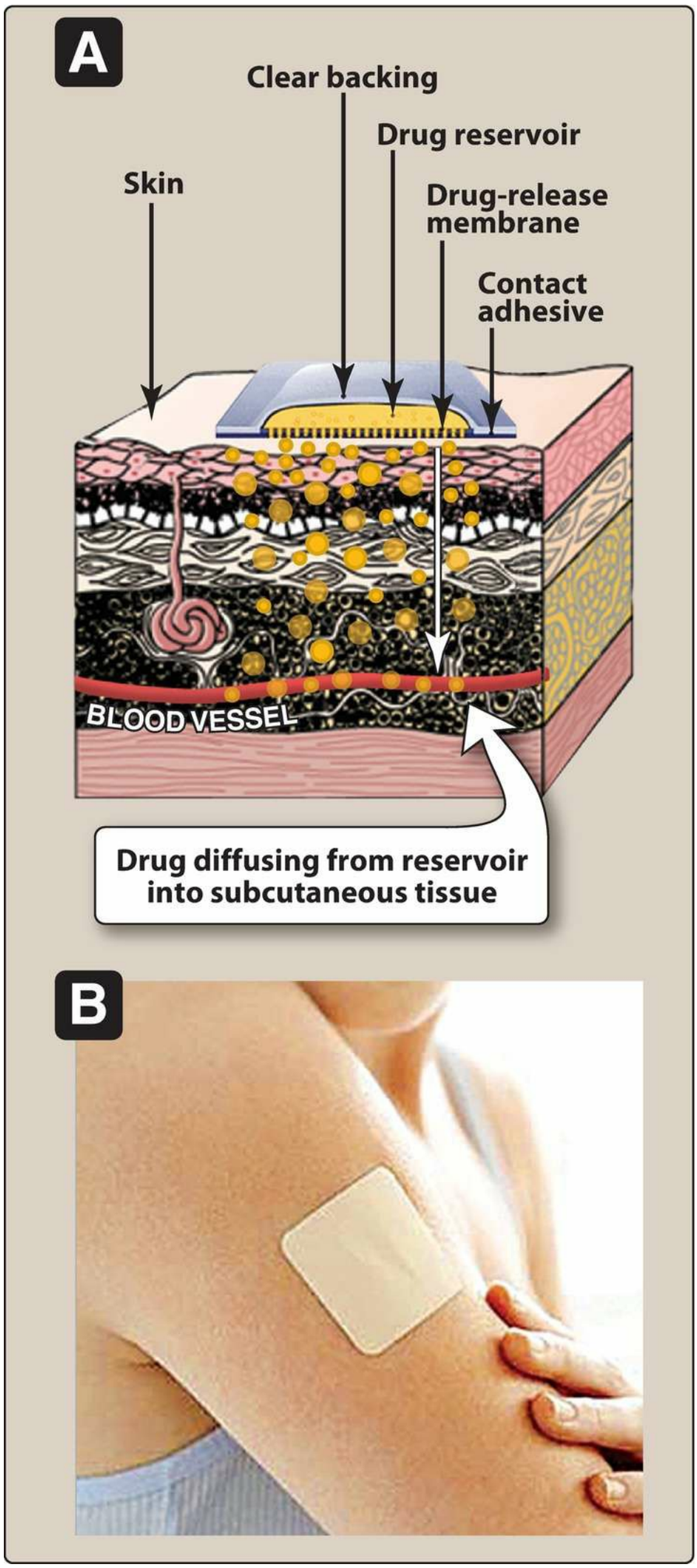


Figure 1.4 A. Schematic representation of a transdermal patch. **B.** Transdermal nicotine patch applied to the arm.

5. Rectal

Because 50% of the drainage of the rectal region bypasses the portal circulation, the biotransformation of drugs by the liver is minimized with rectal administration. The rectal route has the additional advantage of preventing destruction of the drug in the GI environment. This route is also useful if the drug induces vomiting when given orally, if the patient is already vomiting, or if the patient is unconscious. Rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa. Figure 1.5 summarizes characteristics of the common routes of administration, along with example drugs.

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
Oral	• Variable; affected by many factors	• Safest and most common, convenient, and economical route of administration	• Limited absorption of some drugs • Food may affect absorption • Patient compliance is necessary • Drugs may be metabolized before systemic absorption	• *Acetaminophen* tablets • *Amoxicillin* suspension
Sublingual	• Depends on the drug: Few drugs (for example, *nitroglycerin*) have rapid, direct systemic absorption Most drugs erratically or incompletely absorbed	• Bypasses first-pass effect • Bypasses destruction by stomach acid • Drug stability maintained because the pH of saliva relatively neutral • May cause immediate pharmacological effects	• Limited to certain types of drugs • Limited to drugs that can be taken in small doses • May lose part of the drug dose if swallowed	• *Nitroglycerin* • *Buprenorphine*
Intravenous	• Absorption not required	• Can have immediate effects • Ideal if dosed in large volumes • Suitable for irritating substances and complex mixtures • Valuable in emergency situations • Dosage titration permissible • Ideal for high molecular weight proteins and peptide drugs	• Unsuitable for oily substances • Bolus injection may result in adverse effects • Most substances must be slowly injected • Strict aseptic techniques needed	• *Vancomycin* • *Heparin*
Intramuscular	• Depends on drug diluents: Aqueus solution: prompt Depot preparations: slow and sustained	• Suitable if drug volume is moderate • Suitable for oily vehicles and certain irritating substances • Preferable to intravenous if patient must self-administer	• Affects certain lab tests (creatine kinase) • Can be painful • Can cause intramuscular hemorrhage (precluded during anticoagulation therapy)	• *Haloperidol* • *Depot medroxy-progesterone*
Subcutaneous	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable for slow-release drugs • Ideal for some poorly soluble suspensions	• Pain or necrosis if drug is irritating • Unsuitable for drugs administered in large volumes	• *Epinephrine* • *Insulin* • *Heparin*
Inhalation	• Systemic absorption may occur; this is not always desirable	• Absorption is rapid; can have immediate effects • Ideal for gases • Effective for patients with respiratory problems • Dose can be titrated • Localized effect to target lungs; lower doses used compared to that with oral or parenteral administration • Fewer systemic side effects	• Most addictive route (drug can enter the brain quickly) • Patient may have difficulty regulating dose • Some patients may have difficulty using inhalers	• *Albuterol* • *Fluticasone*
Topical	• Variable; affected by skin condition, area of skin, and other factors	• Suitable when local effect of drug is desired • May be used for skin, eye, intra-vaginal, and intranasal products • Minimizes systemic absorption • Easy for patient	• Some systemic absorption can occur • Unsuitable for drugs with high molecular weight or poor lipid solubility	• *Clotrimazole* cream • *Hydrocortisone* cream • *Timolol* eye drops
Transdermal (patch)	• Slow and sustained	• Bypasses the first-pass effect • Convenient and painless • Ideal for drugs that are lipophilic and have poor oral bioavailability • Ideal for drugs that are quickly eliminated from the body	• Some patients are allergic to patches, which can cause irritation • Drug must be highly lipophilic • May cause delayed delivery of drug to pharmacological site of action • Limited to drugs that can be taken in small daily doses	• *Nitroglycerin* • *Nicotine* • *Scopolamine*
Rectal	• Erratic and variable	• Partially bypasses first-pass effect • Bypasses destruction by stomach acid • Ideal if drug causes vomiting • Ideal in patients who are vomiting, or comatose	• Drugs may irritate the rectal mucosa • Not a well-accepted route	• *Bisacodyl* • *Promethazine*

Figure 1.5 The absorption pattern, advantages, and disadvantages of the most common routes of administration.

III. Absorption of Drugs

Absorption is the transfer of a drug from the site of administration to the bloodstream. The rate and extent of absorption depend on the environment where the drug is absorbed, chemical characteristics of the drug, and the route of administration (which influences bioavailability). Routes of administration other than intravenous may result in partial absorption and lower bioavailability.

A. Mechanisms of absorption of drugs from the GI tract

Depending on their chemical properties, drugs may be absorbed from the GI tract by passive diffusion, facilitated diffusion, active transport, or endocytosis (Figure 1.6).

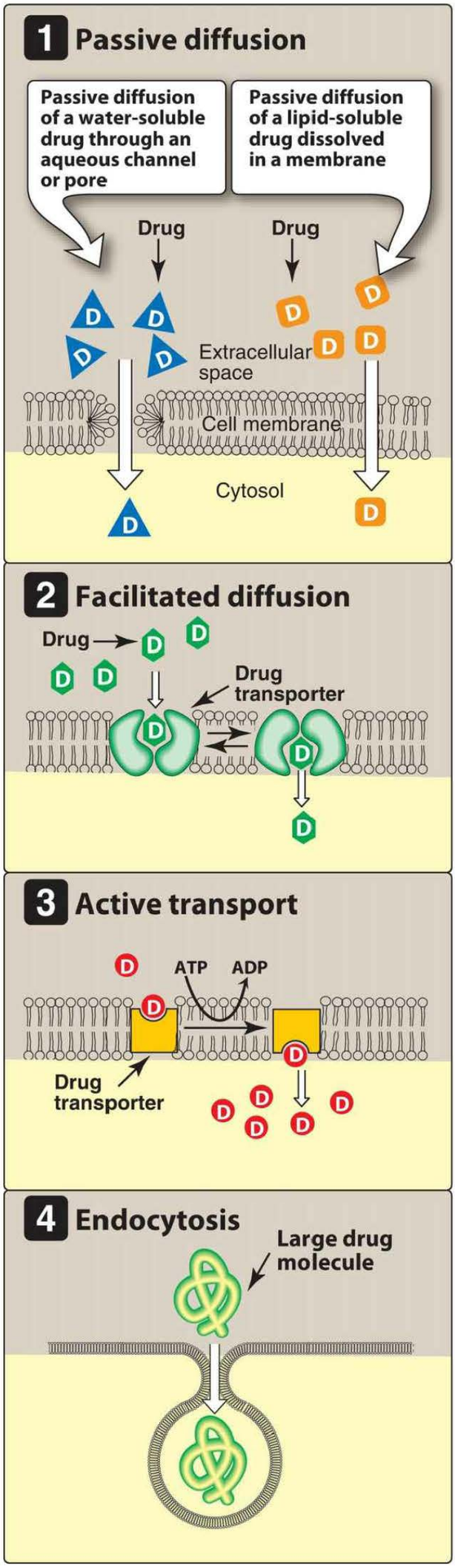

1 Passive diffusion
Passive diffusion of a water-soluble drug through an aqueous channel or pore
Passive diffusion of a lipid-soluble drug dissolved in a membrane
Drug
Drug
Extracellular space
Cell membrane
Cytosol
2 Facilitated diffusion
Drug
Drug transporter
3 Active transport
ATP
ADP
Drug transporter
4 Endocytosis
Large drug molecule

Figure 1.6 Schematic representation of drugs crossing a cell membrane. ATP = adenosine triphosphate; ADP = adenosine diphosphate.

1. Passive diffusion

The driving force for passive diffusion of a drug is the concentration gradient across a membrane separating two body compartments. In other words, the drug moves from an area of high concentration to one of lower concentration. Passive diffusion does not involve a carrier, is not saturable, and shows low structural specificity. The vast majority of drugs are absorbed by this mechanism. Water-soluble drugs penetrate the cell membrane through aqueous channels or pores, whereas lipid-soluble drugs readily move across most biologic membranes due to solubility in the membrane lipid bilayers.

2. Facilitated diffusion

Other agents can enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules. These carrier proteins undergo conformational changes, allowing the passage of drugs or endogenous molecules into the interior of cells. This process is known as facilitated diffusion. It does not require energy, can be saturated, and may be inhibited by compounds that compete for the carrier.

3. Active transport

This mode of drug entry also involves specific carrier proteins that span the membrane. However, active transport is energy dependent, driven by the hydrolysis of adenosine triphosphate (ATP). It is capable of moving drugs against a concentration gradient, from a region of low drug concentration to one of higher concentration. The process is saturable. Active transport systems are selective and may be competitively inhibited by other cotransported substances.

4. Endocytosis and exocytosis

This type of absorption is used to transport drugs of exceptionally large size across the cell membrane. Endocytosis involves engulfment of a drug by the cell membrane and transport into the cell by pinching off the drug-filled vesicle. Exocytosis is the reverse of endocytosis. Many cells use exocytosis to secrete substances out of the cell through a similar process of vesicle formation. Vitamin B_{12} is transported across the gut wall by endocytosis, whereas certain neurotransmitters (for example, norepinephrine) are stored in intracellular vesicles in the nerve terminal and released by exocytosis.

B. Factors influencing absorption

1. Effect of pH on drug absorption

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

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

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

$$BH^+ \qquad B + H^+$$

A drug passes through membranes more readily if it is uncharged (Figure 1.7). Thus, for a weak acid, the uncharged, protonated HA can permeate through membranes, and A^- cannot. For a weak base, the uncharged form B penetrates through the cell membrane, but the protonated form 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 ionization constant, pK_a (Figure 1.8). [Note: The pK_a is a measure of the strength of the interaction of a compound with a proton. The lower the pK_a of a drug, the more acidic it is. Conversely, the higher the pK_a, the more basic is the drug.] Distribution equilibrium is achieved when the permeable form of a drug achieves an equal concentration in all body water spaces.

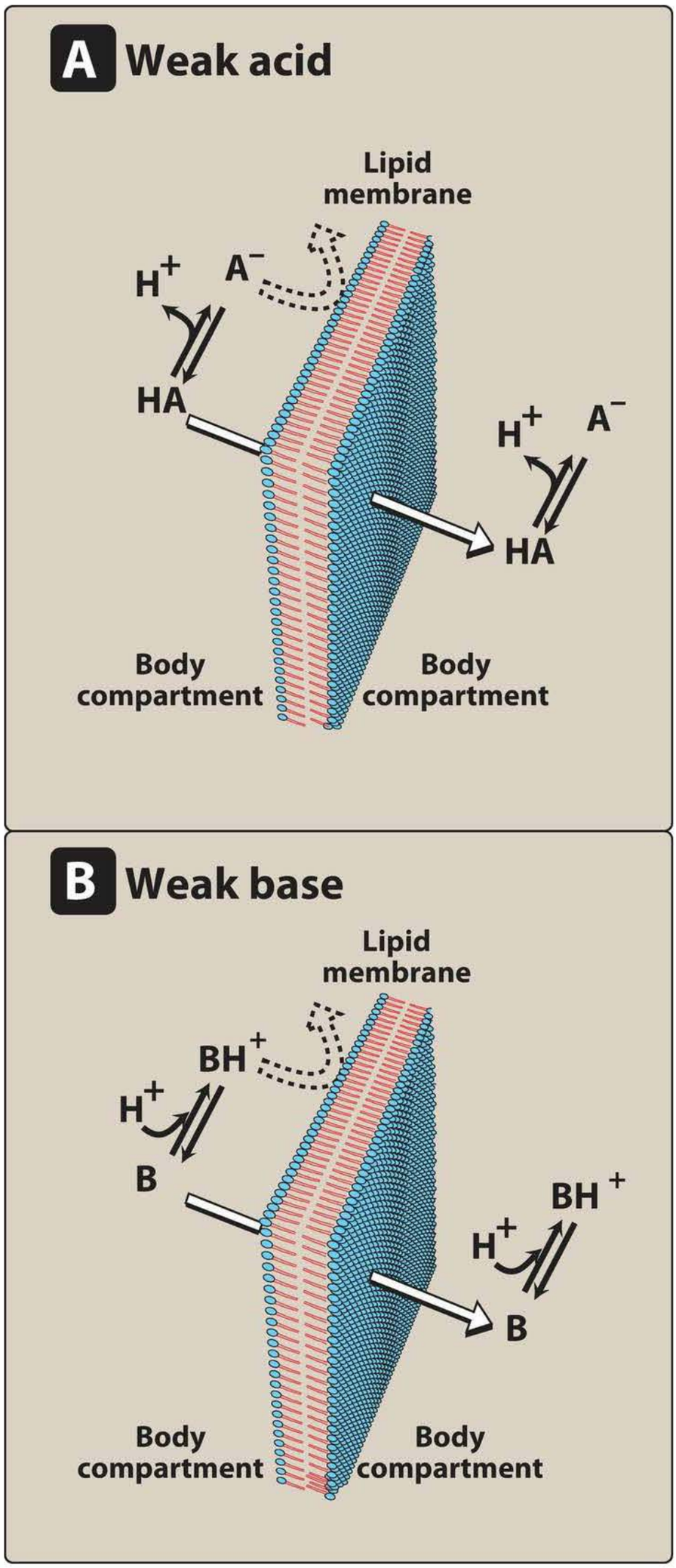

A Weak acid
Lipid membrane
H+
A−
HA
H+
A−
HA
Body compartment
Body compartment
B Weak base
Lipid membrane
BH+
H+
B
BH+
H+
B
Body compartment
Body compartment

Figure 1.7 A. Diffusion of the nonionized form of a weak acid through a lipid membrane. **B.** Diffusion of the nonionized form of a weak base through a lipid membrane.

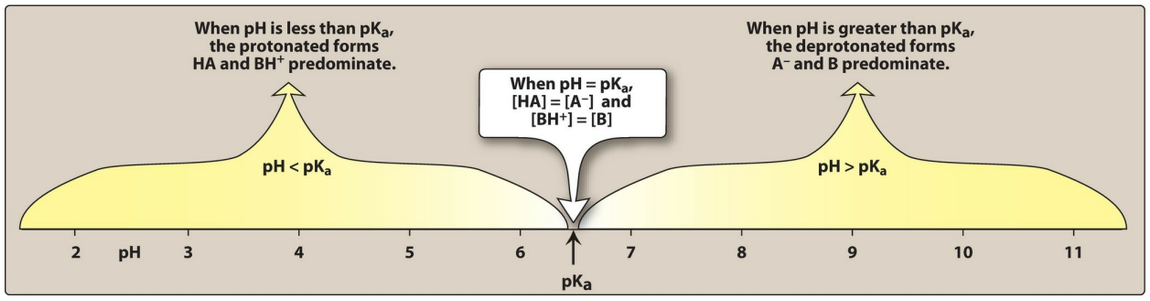


Figure 1.8 The distribution of a drug between its ionized and nonionized forms depends on the ambient pH and pK_a of the drug. For illustrative purposes, the drug has been assigned a pK_a of 6.5.

2. Blood flow to the absorption site

The intestines receive much more blood flow than does the stomach, so absorption from the intestine is favored over the stomach. [Note: Shock severely reduces blood flow to cutaneous tissues, thereby minimizing absorption from SC administration.]

3. Total surface area available for absorption

With a surface rich in brush borders containing microvilli, the intestine has a surface area about 1000-fold that of the stomach, making absorption of the drug across the intestine more efficient.

4. Contact time at the absorption surface

If a drug moves through the GI tract very quickly, as can happen with 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. [Note: 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.]

5. Expression of P-glycoprotein

P-glycoprotein is a transmembrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes (Figure 1.9). It is expressed in tissues throughout the body, including the liver, kidneys, placenta, intestines, and brain capillaries, and is involved in transportation of drugs from tissues to blood. That is, it "pumps" drugs out of cells. Thus, in areas of high expression, P-glycoprotein reduces drug absorption. In addition to transporting many drugs out of cells, it is also associated with multidrug resistance.

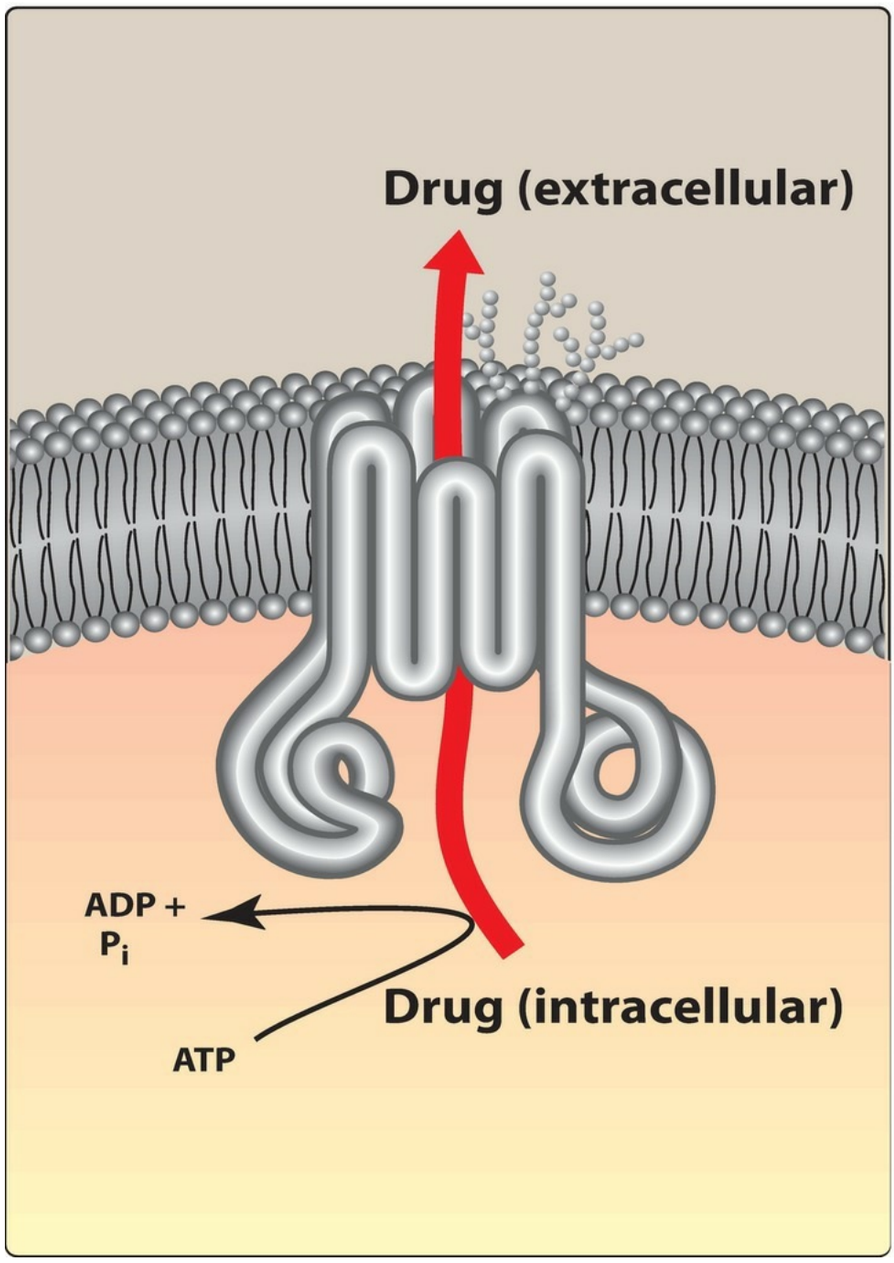


Figure 1.9 The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.

C. Bioavailability

Bioavailability is the rate and extent to which an administered drug reaches the systemic circulation. For example, if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%. Determining bioavailability is important for calculating drug dosages for nonintravenous routes of administration.

1. Determination of bioavailability

Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with levels achieved by IV administration. After IV administration, 100% of the drug rapidly enters the circulation. When the drug is given orally, only part of the administered dose appears in the plasma. By plotting plasma concentrations of the drug versus time, the area under the curve (AUC) can be measured. A schematic depiction of determination of bioavailability is provided in Figure 1.10.

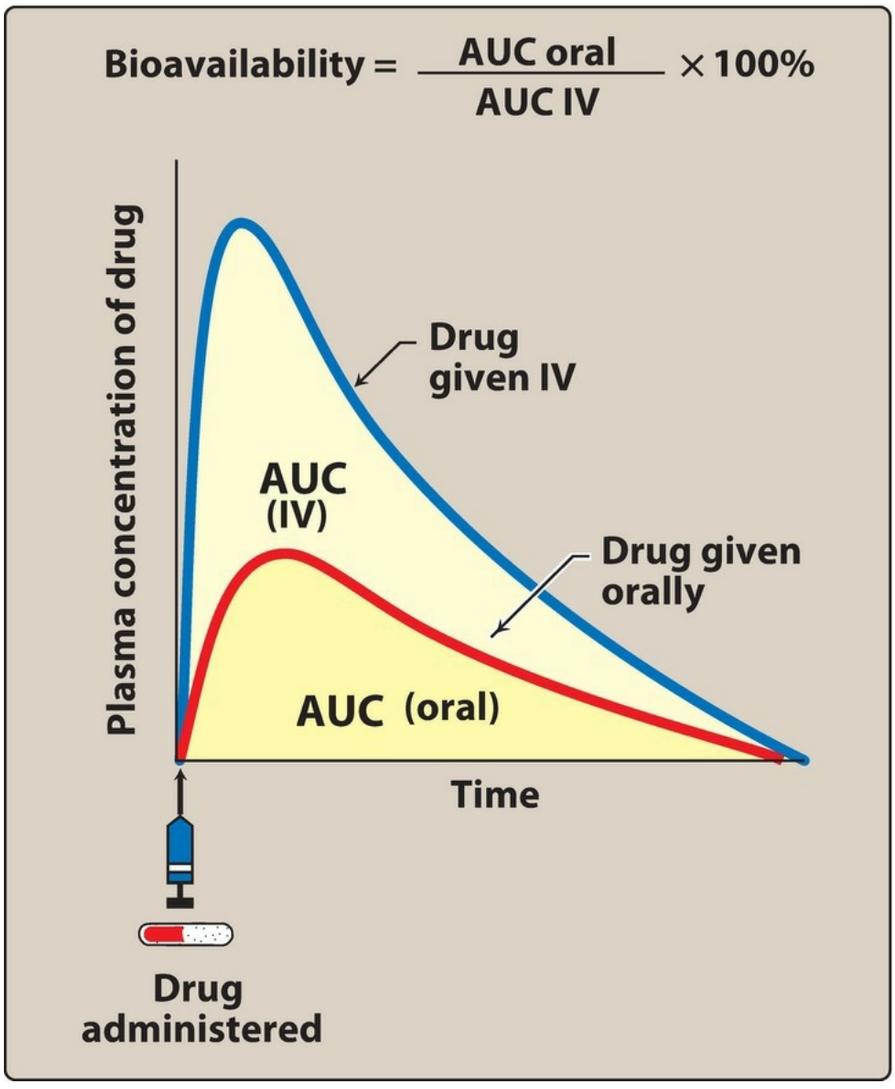


Figure 1.10 Determination of the bioavailability of a drug. AUC = area under curve; IV = intravenous.

2. Factors that influence bioavailability

In contrast to IV administration, which confers 100% bioavailability, orally administered drugs often undergo first-pass metabolism. This biotransformation, in addition to chemical and physical characteristics of the drug, determines the rate and extent to which the agent reaches the systemic circulation.

a. First-pass hepatic metabolism

When a drug is absorbed from the GI tract, it enters the portal circulation before entering the systemic circulation (Figure 1.11). If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the amount of unchanged drug entering the systemic circulation is decreased. This is referred to as first-pass metabolism. [Note: First-pass metabolism by the intestine or liver limits the efficacy of many oral medications. For example, more than 90% of *nitroglycerin* is cleared during first-pass metabolism. Hence, it is primarily administered via the sublingual, transdermal, or intravenous route.] Drugs with high first-pass metabolism should be given in doses sufficient to ensure that enough active drug reaches the desired site of action.

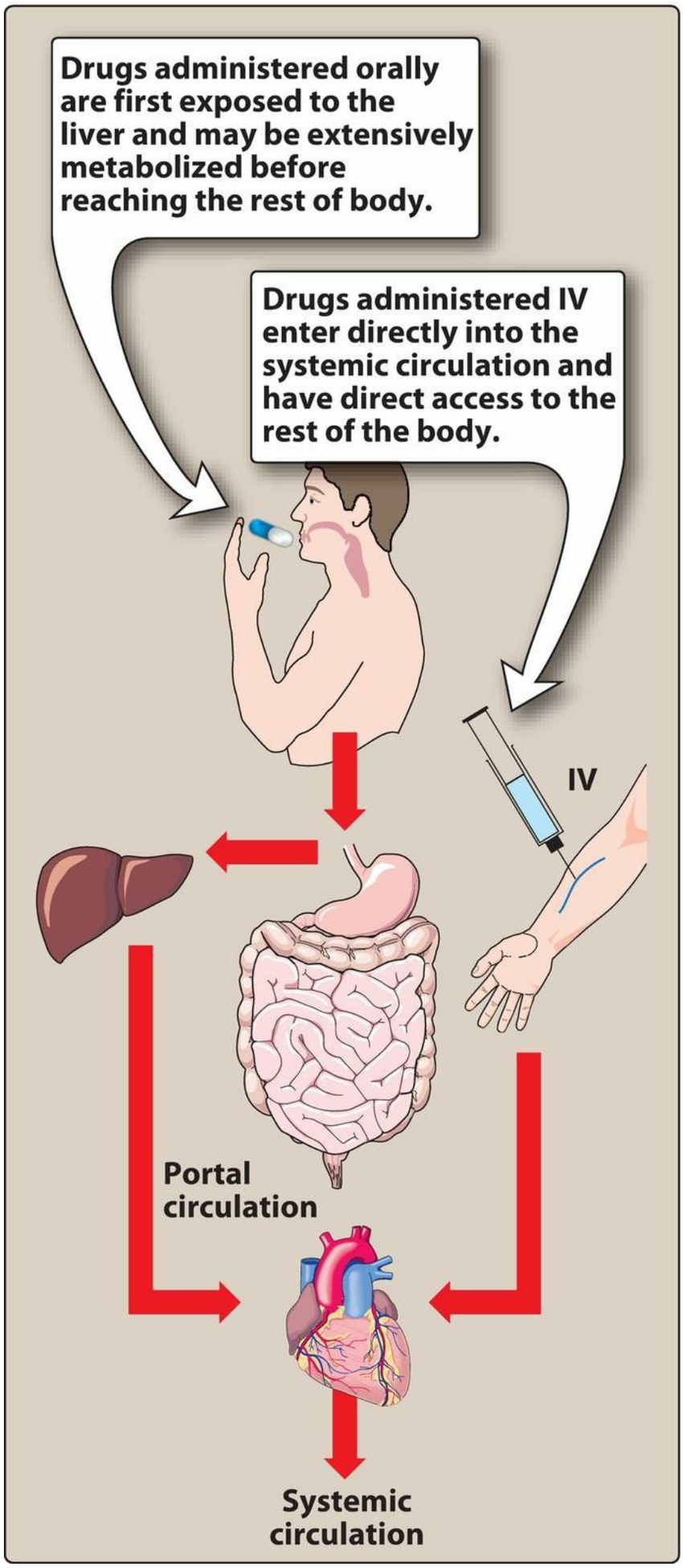


Figure 1.11 First-pass metabolism can occur with orally administered drugs. IV = intravenous.

b. Solubility of the drug

Very hydrophilic drugs are poorly absorbed because of the inability to cross lipid-rich cell membranes. Paradoxically, drugs that are extremely lipophilic are also poorly absorbed, because they are insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells. For a drug to be readily absorbed, it must be largely lipophilic, yet have some solubility in aqueous solutions. This is one reason why many drugs are either weak acids or weak bases.

c. Chemical instability

Some drugs, such as *penicillin G*, are unstable in the pH of gastric contents. Others, such as *insulin*, are destroyed in the GI tract by degradative enzymes.

d. Nature of the drug formulation

Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

D. Bioequivalence and other types of equivalence

Two drug formulations are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations. Two drug formulations are therapeutically equivalent if they are pharmaceutically equivalent (that is, they have the same dosage form, contain the same active ingredient at the same strength, and use the same route of administration) with similar clinical and safety profiles. Thus, therapeutic equivalence requires that drug products are bioequivalent and pharmaceutically equivalent.

IV. Drug Distribution

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the extracellular fluid and tissues. For drugs administered IV, absorption is not a factor, and the initial phase immediately following administration represents the distribution phase, during which the drug rapidly leaves the circulation and enters the tissues (Figure 1.12). The distribution of a drug from the plasma to the interstitium depends on cardiac output and local blood flow, capillary permeability, tissue volume, degree of binding of the drug to plasma and tissue proteins, and relative lipophilicity of the drug.

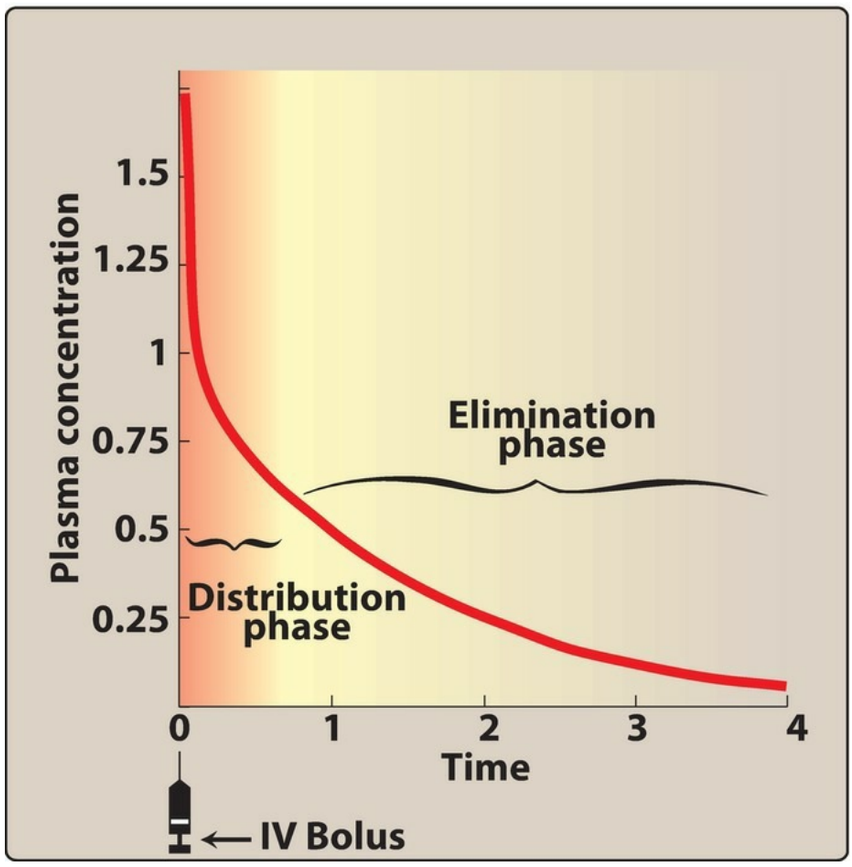


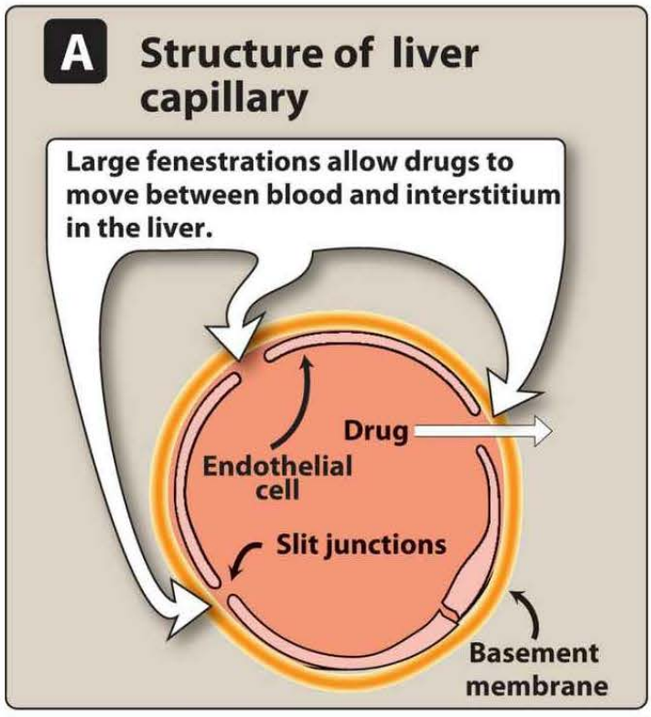
Figure 1.12 Drug concentrations in serum after a single injection of drug. Assume that the drug distributes and is subsequently eliminated.

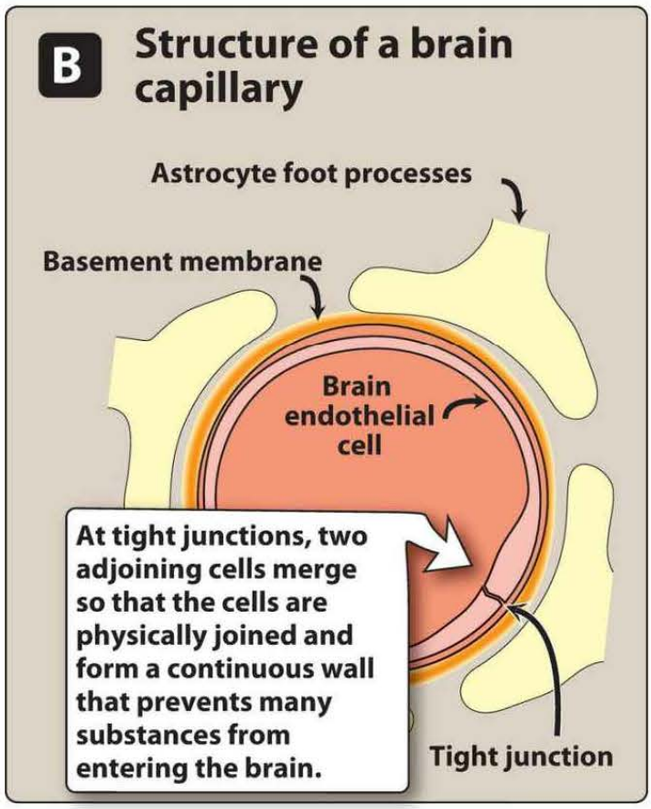
A. Blood flow

The rate of blood flow to the tissue capillaries varies widely. For instance, blood flow to “vessel-rich organs” (brain, liver, and kidney) is greater than that to the skeletal muscles. Adipose tissue, skin, and viscera have still lower rates of blood flow. Variation in blood flow partly explains the short duration of hypnosis produced by an IV bolus of *propofol* (see Chapter 13). High blood flow, together with high lipophilicity of *propofol*, permits rapid distribution into the CNS and produces anesthesia. A subsequent slower distribution to skeletal muscle and adipose tissue lowers the plasma concentration so that the drug diffuses out of the CNS, down the concentration gradient, and consciousness is regained.

B. Capillary permeability

Capillary permeability is determined by capillary structure and by the chemical nature of the drug. Capillary structure varies in terms of the fraction of the basement membrane exposed by slit junctions between endothelial cells. In the liver and spleen, a significant portion of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass (Figure 1.13A). In the brain, the capillary structure is continuous, and there are no slit junctions (Figure 1.13B). To enter the brain, drugs must pass through the endothelial cells of the CNS capillaries or undergo active transport. For example, a specific transporter carries *levodopa* into the brain. Lipid-soluble drugs readily penetrate the CNS because they dissolve in the endothelial cell membrane. By contrast, ionized or polar drugs generally fail to enter the CNS because they cannot pass through the endothelial cells that have no slit junctions (Figure 1.13C). These closely juxtaposed cells form tight junctions that constitute the blood–brain barrier.


A
Structure of liver capillary
Large fenestrations allow drugs to move between blood and interstitium in the liver.
Drug
Endothelial cell
Slit junctions
Basement membrane


B
Structure of a brain capillary
Astrocyte foot processes
Basement membrane
Brain endothelial cell
At tight junctions, two adjoining cells merge so that the cells are physically joined and form a continuous wall that prevents many substances from entering the brain.
Tight junction

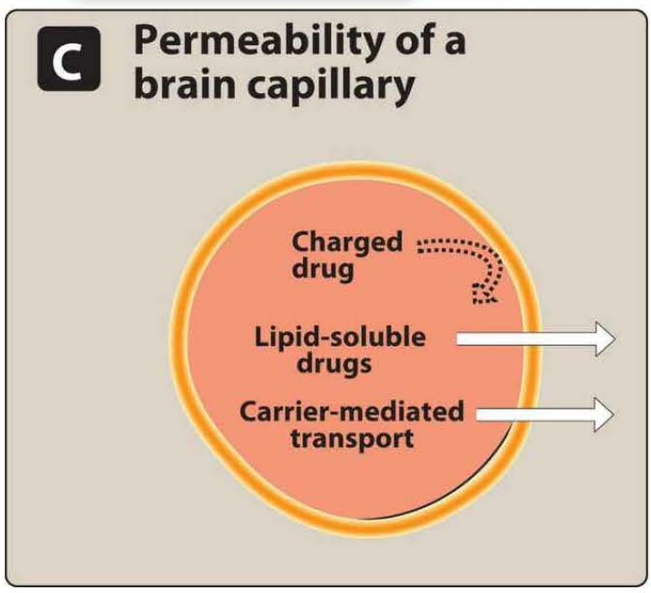

C
Permeability of a brain capillary
Charged drug
Lipid-soluble drugs
Carrier-mediated transport

Figure 1.13 Cross section of liver and brain capillaries.

C. Binding of drugs to plasma proteins and tissues

1. Binding to plasma proteins

Reversible binding to plasma proteins sequesters drugs in a nondiffusible form and slows transfer out of the vascular compartment. Albumin is the major drug-binding protein, and it may act as a drug reservoir. As the concentration of free drug decreases due to elimination, the bound drug dissociates from albumin. This maintains the free-drug concentration as a constant fraction of the total drug in the plasma.

2. Binding to tissue proteins

Many drugs accumulate in tissues, leading to higher concentrations in tissues than in interstitial fluid and blood. Drugs may accumulate because of binding to lipids, proteins, or nucleic acids. Drugs may also undergo active transport into tissues. Tissue reservoirs may serve as a major source of the drug and prolong its actions or cause local drug toxicity. (For example, acrolein, the metabolite of *cyclophosphamide*, can cause hemorrhagic cystitis because it accumulates in the bladder.)

D. Lipophilicity

The chemical nature of a drug strongly influences its ability to cross cell membranes. Lipophilic drugs readily move across most biologic membranes. These drugs dissolve in the lipid membranes and penetrate the entire cell surface. The major factor influencing the distribution of lipophilic drugs is blood flow to the area. By contrast, hydrophilic drugs do not readily penetrate cell membranes and must pass through slit junctions.

E. Volume of distribution

The apparent volume of distribution, V_d, is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (C_0).

$$V_d = \frac{\text{Amount of drug in the body}}{C_0}$$

Although V_d has no physiologic or physical basis, it can be useful to compare the distribution of a drug with the volumes of the water compartments in the body.

1. Distribution into the water compartments in the body

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

a. Plasma compartment

If a drug has a high molecular weight or is extensively protein bound, it is too large to pass through the slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment. As a result, it has a low V_d that approximates the plasma volume, or about 4 L in a 70-kg individual. *Heparin* (see Chapter 21) shows this type of distribution.

b. Extracellular fluid

If a drug has a low molecular weight but is hydrophilic, it can pass through the endothelial slit junctions of the capillaries into the interstitial fluid. However, hydrophilic drugs cannot move across the lipid membranes of cells to enter the intracellular fluid. Therefore, these drugs distribute into a volume that is the sum of the plasma volume and the interstitial fluid, which together constitute the extracellular fluid (about 20% of body weight or 14 L in a 70-kg individual). Aminoglycoside antibiotics (see Chapter 30) show this type of distribution.

Total body water

If a drug has a low molecular weight and has enough lipophilicity, it can move into the interstitium through the slit junctions and pass through the cell membranes into the intracellular fluid. These drugs distribute into a volume of about 60% of body weight or about 42 L in a 70-kg individual. *Ethanol* exhibits this apparent V_d. [Note: In general, a larger V_d indicates greater distribution into tissues; a smaller V_d suggests confinement to plasma or extracellular fluid.]

2. Determination of V_d

The fact that drug clearance is usually a first-order process allows calculation of V_d. First order means that a constant fraction of the drug is eliminated per unit of time. This process can be most easily analyzed by plotting the log of the plasma drug concentration (C_p) versus time (Figure 1.14). The concentration of drug in the plasma can be extrapolated back to time zero (the time of IV bolus) on the Y axis to determine C_0, which is the concentration of drug that would have been achieved if the distribution phase had occurred instantly. This allows calculation of V_d as

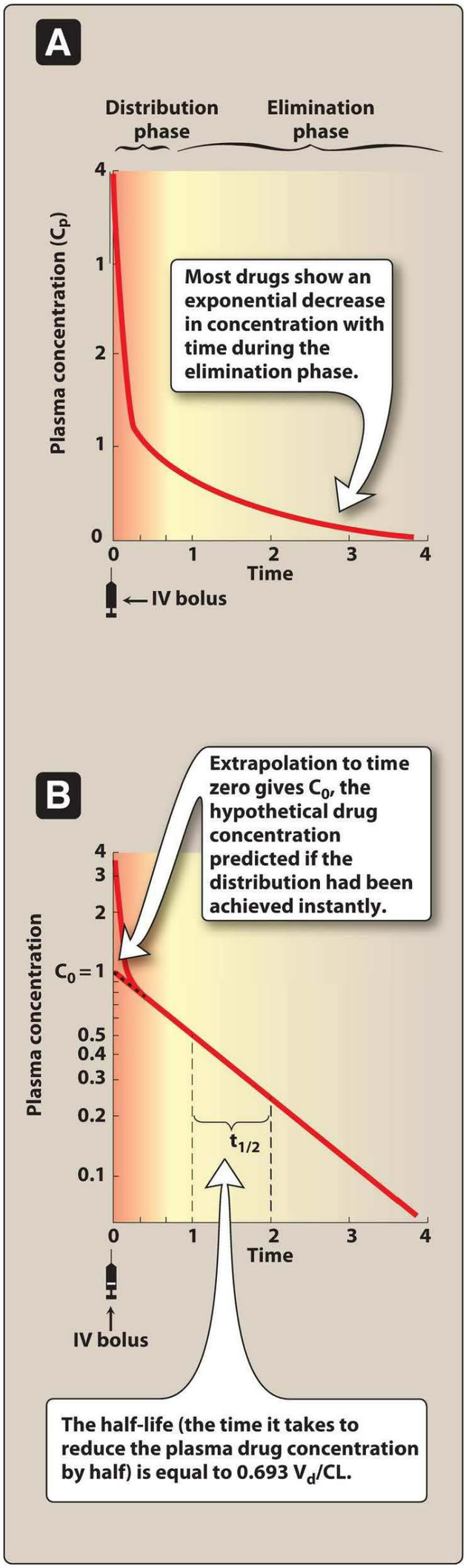

A
Distribution phase
Elimination phase
Plasma concentration (C_p)
4
1
2
1
0
Most drugs show an exponential decrease in concentration with time during the elimination phase.
0
1
2
3
4
Time
← IV bolus
B
Extrapolation to time zero gives C_0, the hypothetical drug concentration predicted if the distribution had been achieved instantly.
Plasma concentration
4
3
2
$C_0 = 1$
0.5
0.4
0.3
0.2
0.1
$t_{1/2}$
0
1
2
3
4
Time
IV bolus
The half-life (the time it takes to reduce the plasma drug concentration by half) is equal to 0.693 V_d/CL.

Figure 1.14 Drug concentrations in plasma after a single injection of drug at time = 0. **A.** Concentration data are plotted on a linear scale. **B.** Concentration data are plotted on a log scale.

$$V_d = \frac{\text{Dose}}{C_0}$$

For example, if 10 mg of drug is injected into a patient and the plasma concentration is extrapolated back to time zero, and C_0 = 1 mg/L (from the graph in Figure 1.14B), then V_d = 10 mg/1 mg/L = 10 L.

3. Effect of V_d on drug half-life

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

V. Drug Clearance Through Metabolism

Once a drug enters the body, the process of elimination begins. The three major routes of elimination are hepatic metabolism, biliary elimination, and urinary excretion. [Note: Elimination is irreversible removal of drug from the body. It involves biotransformation (drug metabolism) and excretion. Excretion is removal of intact drug from the body.] Together, these elimination processes decrease the plasma concentration exponentially. That is, a constant fraction of the drug is eliminated in a given unit of time (Figure 1.14A). Metabolism results in products with increased polarity, which allows the drug to be eliminated. Clearance (CL) estimates the volume of blood from which the drug is cleared per unit of time. Total CL is a composite estimate reflecting all mechanisms of drug elimination and is calculated as follows:

$$CL = 0.693 \times V_d \; / \; t_{1/2}$$

where $t_{1/2}$ is the elimination half-life, V_d is the apparent volume of distribution, and 0.693 is the natural log constant. Drug half-life is often used as a measure of drug CL, because, for many drugs, V_d is a constant.

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, where K_m is Michaelis constant (the substrate concentration at half maximal velocity).

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

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 and elimination is directly proportional to the concentration of free drug, and first-order kinetics is observed (Figure 1.15). This means that a constant fraction of drug is metabolized per unit of time (that is, with each half-life, the concentration decreases by 50%). First-order kinetics is also referred to as linear kinetics.

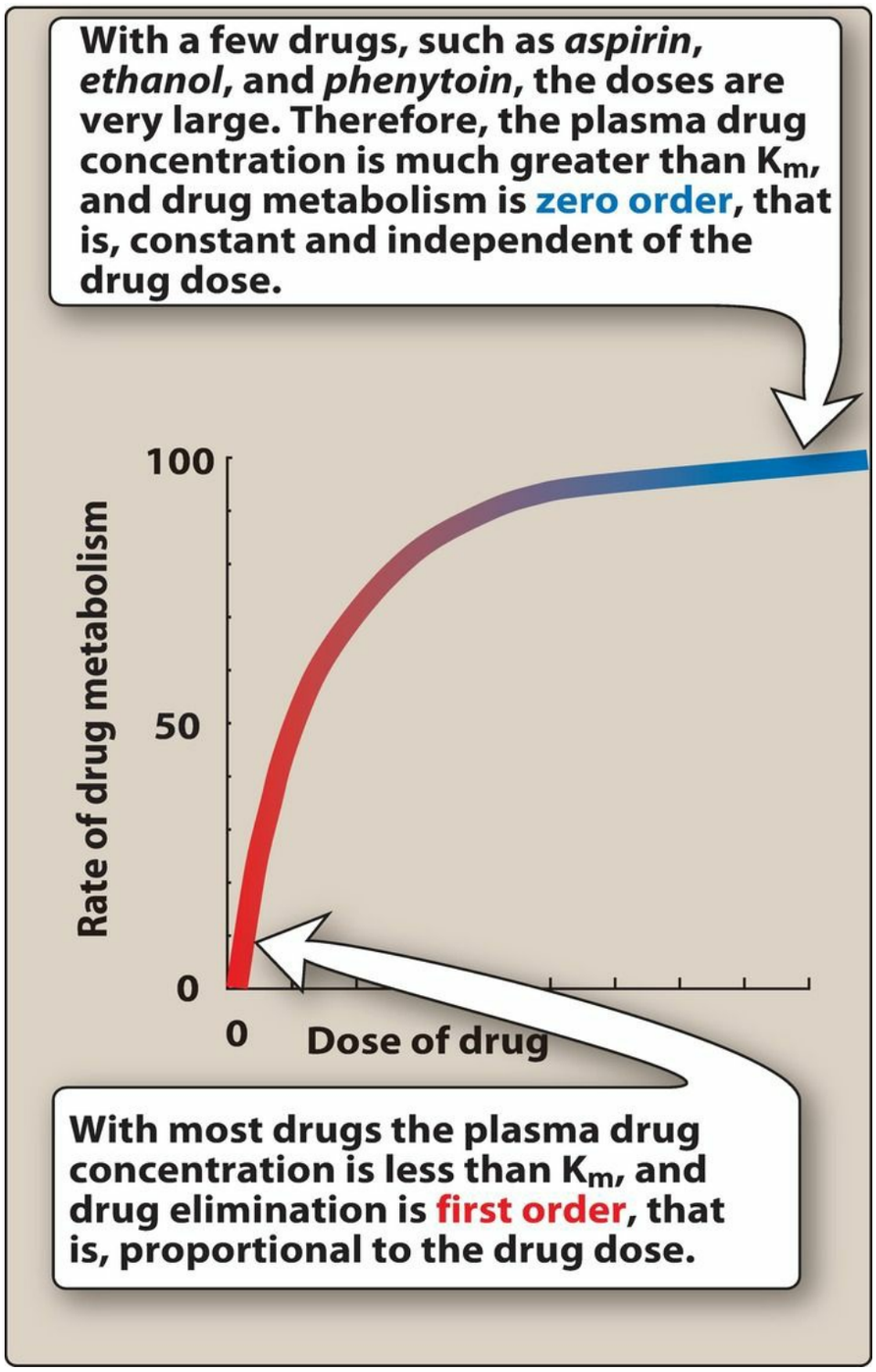


Figure 1.15 Effect of drug dose on the rate of metabolism.

2. Zero-order kinetics

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

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

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 (also called nonlinear kinetics). A constant amount of drug is metabolized per unit of time. The rate of elimination is constant and does not depend on the drug concentration.

B. Reactions of drug metabolism

The kidney cannot efficiently excrete lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents are first metabolized into more polar (hydrophilic) substances in the liver via two general sets of reactions, called phase I and phase II (Figure 1.16).

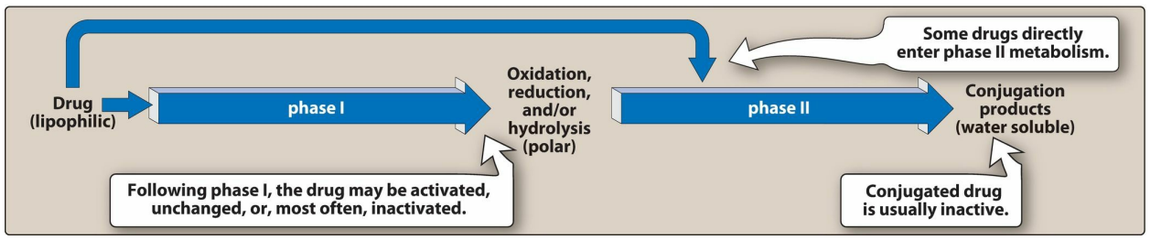


Figure 1.16 The biotransformation of drugs.

1. Phase I

Phase I reactions convert lipophilic drugs into more polar molecules by introducing or unmasking a polar functional group, such as –OH or $–NH_2$. Phase I reactions usually involve reduction, oxidation, or hydrolysis. Phase I metabolism may increase, decrease, or have no effect on pharmacologic activity.

a. Phase I reactions utilizing the P450 system

The phase I reactions most frequently involved in drug metabolism are catalyzed by the cytochrome P450 (CYP) system. The P450 system is important for the metabolism of many endogenous compounds (such as steroids, lipids) and for the biotransformation of exogenous substances (drugs, carcinogens, and environmental pollutants). CYP is a superfamily of heme-containing isozymes located in most cells, but primarily in the liver and GI tract.

[1] Nomenclature

The family name is indicated by the Arabic number that follows CYP, and the capital letter designates the subfamily, for example, CYP3A (Figure 1.17). A second number indicates the specific isozyme, as in CYP3A4.

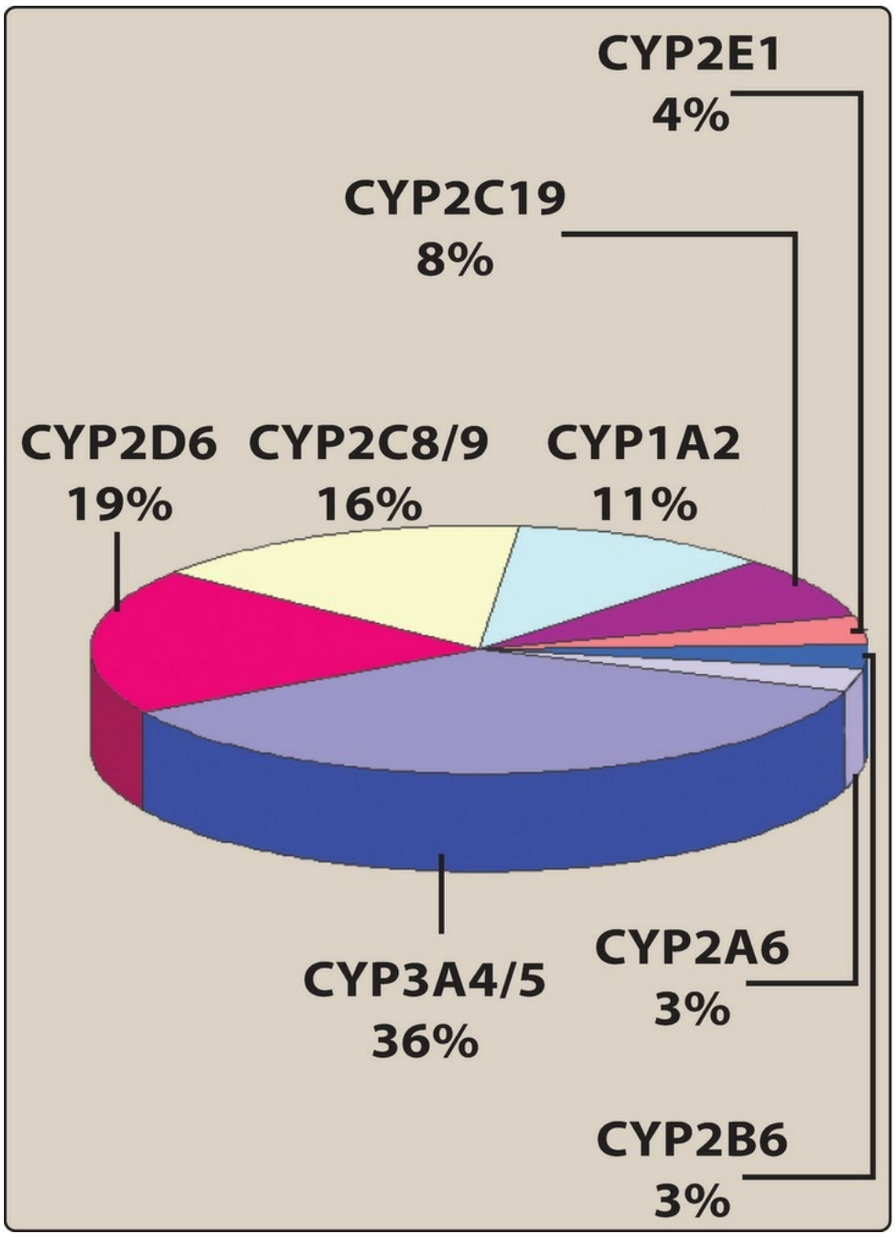


Figure 1.17 Relative contribution of cytochrome P450 (CYP) isoforms to drug biotransformation.

[2] Specificity

Because there are many different genes that encode multiple enzymes, there are many different P450 isoforms. These enzymes have the capacity to modify a large number of structurally diverse substrates. In addition, an individual drug may be a substrate for more than one isozyme. Four isozymes (CYP3A4/5, CYP2D6, CYP2C8/9, and CYP1A2) are responsible for the vast majority of P450-catalyzed reactions (Figure 1.17). Considerable amounts of CYP3A4 are found in intestinal mucosa, accounting for first-pass metabolism of drugs such as *chlorpromazine* and *clonazepam.*

[3] Genetic variability

P450 enzymes exhibit considerable genetic variability among individuals and racial groups. Variations in P450 activity may alter drug efficacy and the risk of adverse events. CYP2D6, in particular, exhibits genetic polymorphism. CYP2D6 mutations result in very low capacities to metabolize substrates. For example, some individuals obtain no benefit from the opioid analgesic *codeine*, because they lack the CYP2D6 enzyme that activates the drug. Similar polymorphisms have been characterized for the CYP2C subfamily of isozymes. For instance, *clopidogrel* carries a warning that patients who are CYP2C19 “poor metabolizers” have a diminished antiplatelet effect when taking this drug and an alternative medication should be considered. *Clopidogrel* is a prodrug, and CYP2C19 activity is required to convert it to the active metabolite.

[4] CYP inducers

The CYP450-dependent enzymes are an important target for pharmacokinetic drug interactions. Certain drugs (for example, *phenobarbital*, *rifampin*, and *carbamazepine*) are capable of inducing CYP isozymes. This results in increased biotransformation of drugs and can lead to significant decreases in plasma concentrations of drugs metabolized by these CYP isozymes, often with concurrent loss of pharmacologic effect. For example, *rifampin*, an antituberculosis drug (see Chapter 32), significantly decreases the plasma concentrations of human

immunodeficiency virus (HIV) protease inhibitors, thereby diminishing the ability to suppress HIV replication. Figure 1.18 lists some of the more important inducers for representative CYP isozymes.

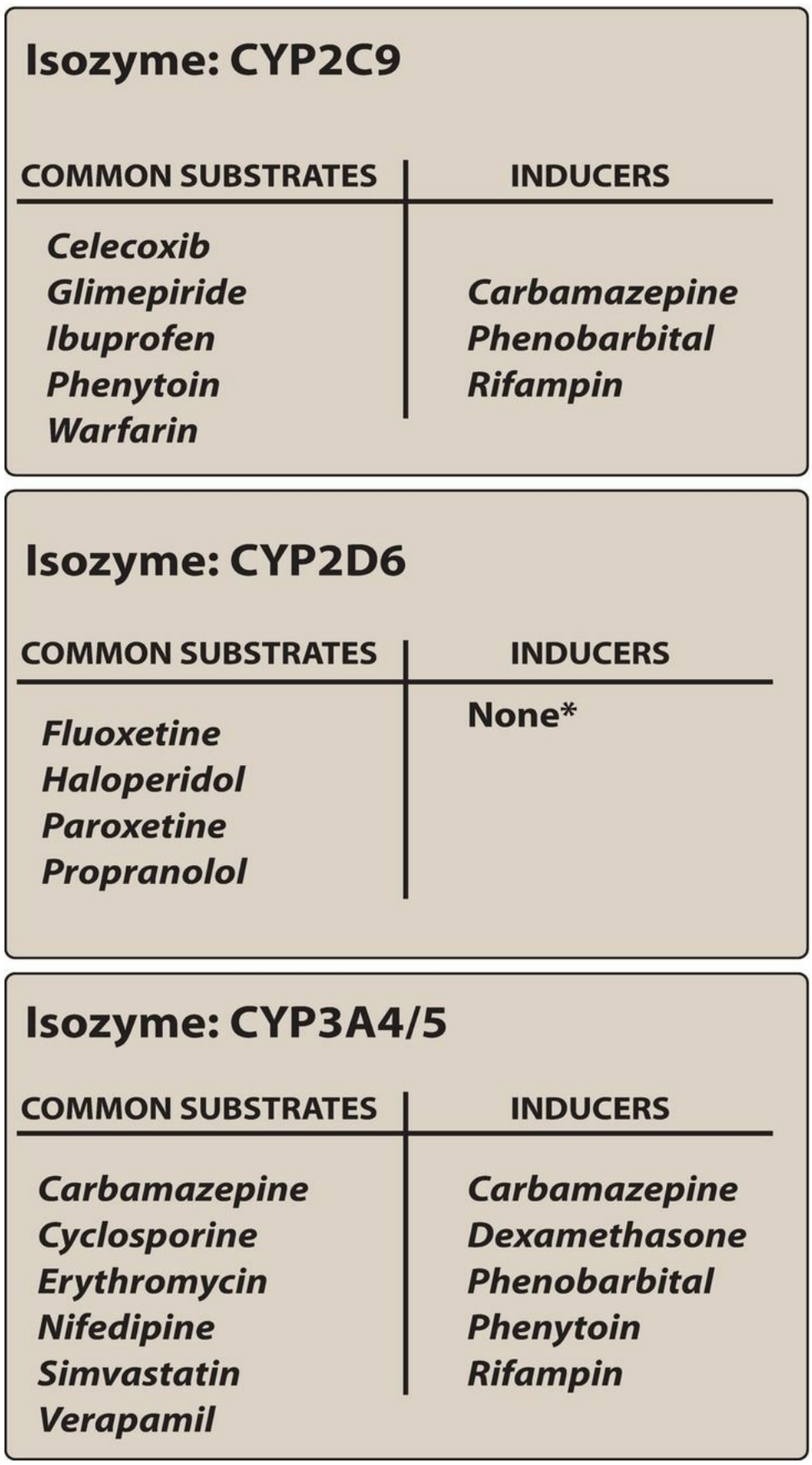


Figure 1.18 Some representative cytochrome P450 isozymes. CYP = cytochrome P. *Unlike most other CYP450 enzymes, CYP2D6 is not very susceptible to enzyme induction.

[5] CYP inhibitors

Inhibition of drug metabolism can lead to significant increases in plasma drug concentration and resultant adverse effects or drug toxicity. The most common form of inhibition is through competition for the same isozyme. Some drugs, however, are capable of inhibiting reactions for which they are not substrates (for example, *ketoconazole*), leading to drug interactions. Numerous drugs inhibit one or more of the CYP-dependent biotransformation pathways of *warfarin*. For example, *omeprazole* is a potent inhibitor of three CYP isozymes involved in *warfarin* metabolism.

When taken with *omeprazole*, plasma concentrations of *warfarin* increase, which leads to greater anticoagulant effect and increased risk of bleeding. [Note: The more important CYP inhibitors are *erythromycin*, *ketoconazole*, and *ritonavir*, because they each inhibit several CYP isozymes.]

b. Phase I reactions not involving the P450 system

These include amine oxidation (for example, oxidation of catecholamines or histamine), alcohol dehydrogenation (for example, *ethanol* oxidation), esterases (for example, metabolism of *aspirin* in the liver), and hydrolysis (for example, of *procaine*).

2. Phase II

This phase consists of conjugation reactions. If the metabolite from phase I is sufficiently polar, it can be excreted by the kidneys. However, many phase I metabolites are still too lipophilic to be excreted. 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 often therapeutically inactive. A notable exception is *morphine-6-glucuronide*, which is more potent than *morphine*. Glucuronidation is the most common and the most important conjugation reaction. [Note: Drugs already possessing an –OH, $–NH_2$, or –COOH group may enter phase II directly and become conjugated without prior phase I metabolism (Figure 1.16).] The highly polar drug conjugates are then excreted by the kidney or in bile.

VI. Drug Clearance by the Kidney

Drugs must be sufficiently polar to be eliminated from the body. Removal of drugs from the body occurs via a number of routes; the most important is elimination through the kidney into the urine. Patients with renal dysfunction may be unable to excrete drugs and are at risk for drug accumulation and adverse effects.

A. Renal elimination of a drug

A drug passes through several processes in the kidney before elimination: glomerular filtration, active tubular secretion, and passive tubular reabsorption.

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 the Bowman space as part of the glomerular filtrate (Figure 1.19). The glomerular filtration rate (GFR) is normally about 120 mL/min/1.73m^2 but may diminish significantly in renal disease. Lipid solubility and pH do not influence the passage of drugs into the glomerular filtrate. However, variations in GFR and protein binding of drugs do affect this process.

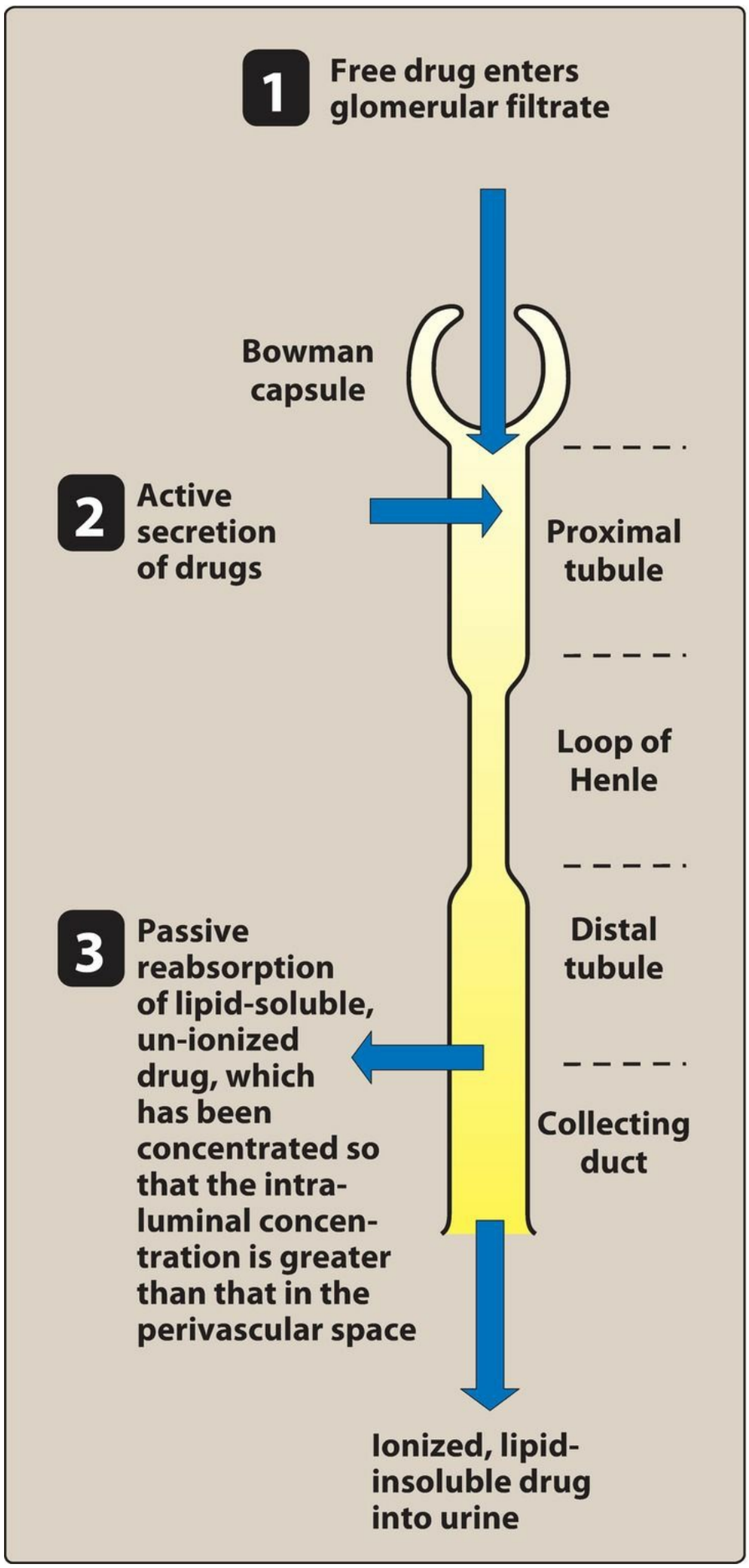


Figure 1.19 Drug elimination by the kidney.

2. Proximal tubular secretion

Drugs that were not transferred into the glomerular filtrate leave the glomeruli through efferent arterioles, which divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule. Secretion primarily occurs in the proximal tubules by two energy-requiring active transport systems: one for anions (for example, deprotonated

forms of weak acids) and one for cations (for example, protonated forms of weak bases). Each of these transport systems shows low specificity and can transport many compounds. Thus, competition between drugs for these carriers can occur within each transport system. [Note: Premature infants and neonates have an incompletely developed tubular secretory mechanism and, thus, may retain certain drugs in the blood.]

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 (Figure 1.20). Manipulating the urine pH to increase the fraction of ionized drug in the lumen may be done to minimize the amount of back diffusion and increase the clearance of an undesirable drug. Generally, weak acids can be eliminated by alkalinization of the urine, whereas elimination of weak bases may be increased by acidification of the urine. This process is called “ion trapping.” For example, a patient presenting with *phenobarbital* (weak acid) overdose can be given *bicarbonate*, which alkalinizes the urine and keeps the drug ionized, thereby decreasing its reabsorption.

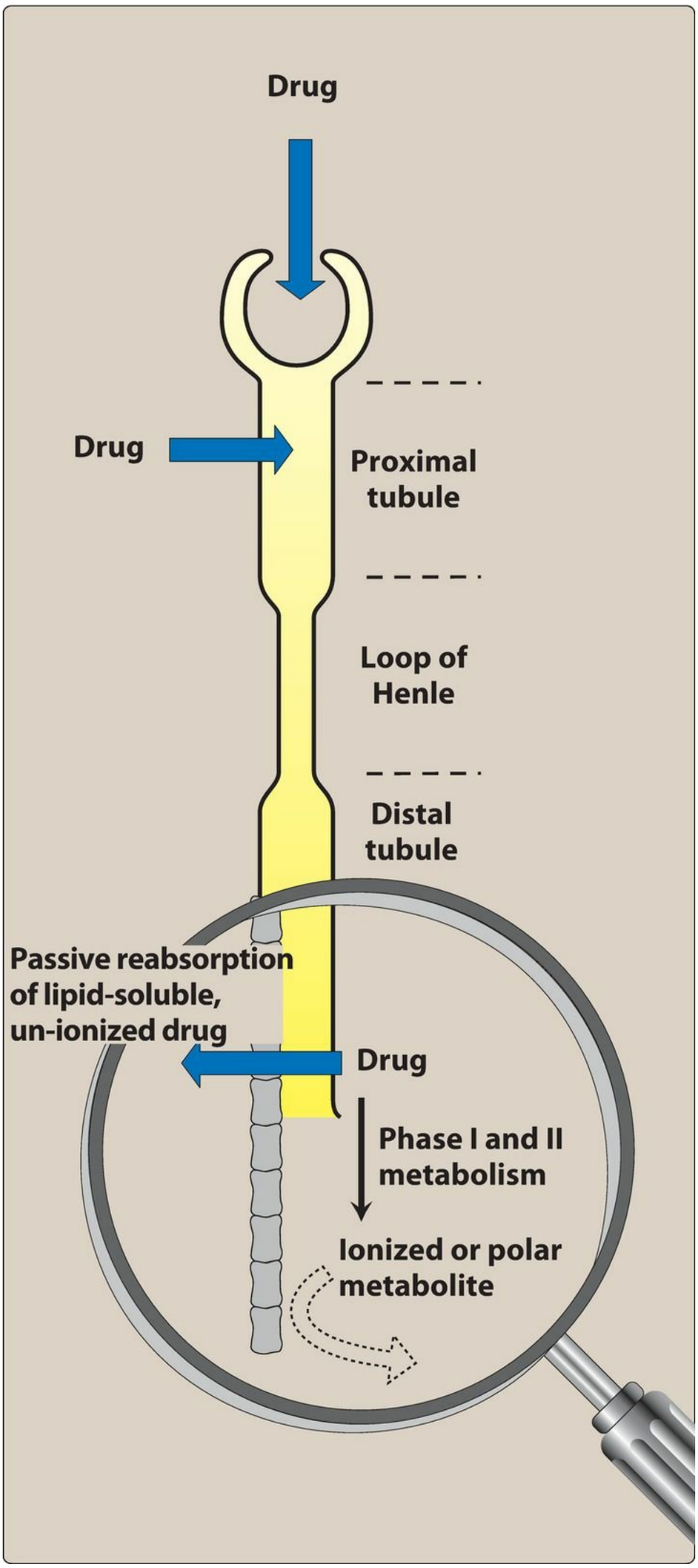


Figure 1.20 Effect of drug metabolism on reabsorption in the distal tubule.

VII. Excretion by Other Routes

Drug excretion may also occur via the intestines, bile, lungs, and breast milk, among others. Drugs that are not absorbed after oral administration or drugs that are secreted directly into the intestines or into bile are excreted in the feces. The lungs are primarily involved in the elimination of anesthetic gases (for example, *desflurane*). Elimination of drugs in breast milk may expose the breast-feeding infant to medications and/or metabolites being taken by the mother and is a potential source of undesirable side effects to the infant. Excretion of most drugs into sweat, saliva, tears, hair, and skin occurs only to a small extent. Total body clearance and drug half-life are important measures of drug clearance that are used to optimize drug therapy and minimize toxicity.

A. Total body clearance

The total body (systemic) clearance, CL_{total}, is the sum of all clearances from the drug-metabolizing and drug-eliminating organs. The kidney is often the major organ of excretion. The liver also contributes to drug clearance through metabolism and/or excretion into the bile. Total clearance is calculated using the following equation:

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

where $CL_{hepatic} + CL_{renal}$ are typically the most important.

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

When a patient has an abnormality that alters the half-life of a drug, adjustment in dosage is required. Patients who may have an increase in drug half-life include those with 1) diminished renal or hepatic blood flow, for example, in cardiogenic shock, heart failure, or hemorrhage; 2) decreased ability to extract drug from plasma, for example, in renal disease; and 3) decreased metabolism, for example, when a concomitant drug inhibits metabolism or in hepatic insufficiency, as with cirrhosis. These patients may require a decrease in dosage or less frequent dosing intervals. In contrast, the half-life of a drug may be decreased by increased hepatic blood flow, decreased protein binding, or increased metabolism. This may necessitate higher doses or more frequent dosing intervals.

VIII. Design and Optimization of Dosage Regimen

To initiate drug therapy, the clinician must select the appropriate route of administration, dosage, and dosing interval. Selection of a regimen depends on various patient and drug factors, including how rapidly therapeutic levels of a drug must be achieved. Therapy may consist of a single dose of a drug, for example, a sleep-inducing agent, such as *zolpidem*. More commonly, drugs are continually administered, either as an IV infusion or in IV or oral fixed-dose/fixed-time interval regimens (for example, “one tablet every 4 hours”). Continuous or repeated administration results in accumulation of the drug until a steady state occurs. Steady-state concentration is reached when the rate of drug elimination is equal to the rate of drug administration, such that plasma and tissue levels remain relatively constant.

A. Continuous infusion regimens

With continuous IV infusion, the rate of drug entry into the body is constant. Most drugs exhibit first-order elimination, that is, a constant fraction of the drug is cleared per unit of time. Therefore, the rate of drug elimination increases proportionately as the plasma concentration increases.

1. Plasma concentration of a drug following continuous IV infusion

Following initiation of a continuous IV infusion, the plasma concentration of a drug rises until a steady state (rate of drug elimination equals rate of drug administration) is reached, at which point the plasma concentration of the drug remains constant.

a. Influence of infusion rate on steady-state concentration

The steady-state plasma concentration (C_{ss}) is directly proportional to the infusion rate. For example, if the infusion rate is doubled, the C_{ss} is doubled (Figure 1.21). Furthermore, the C_{ss} is inversely proportional to the clearance of the drug. Thus, any factor that decreases clearance, such as liver or kidney disease, increases the C_{ss} of an infused drug (assuming V_d remains constant). Factors that increase clearance, such as increased metabolism, decrease the C_{ss}.

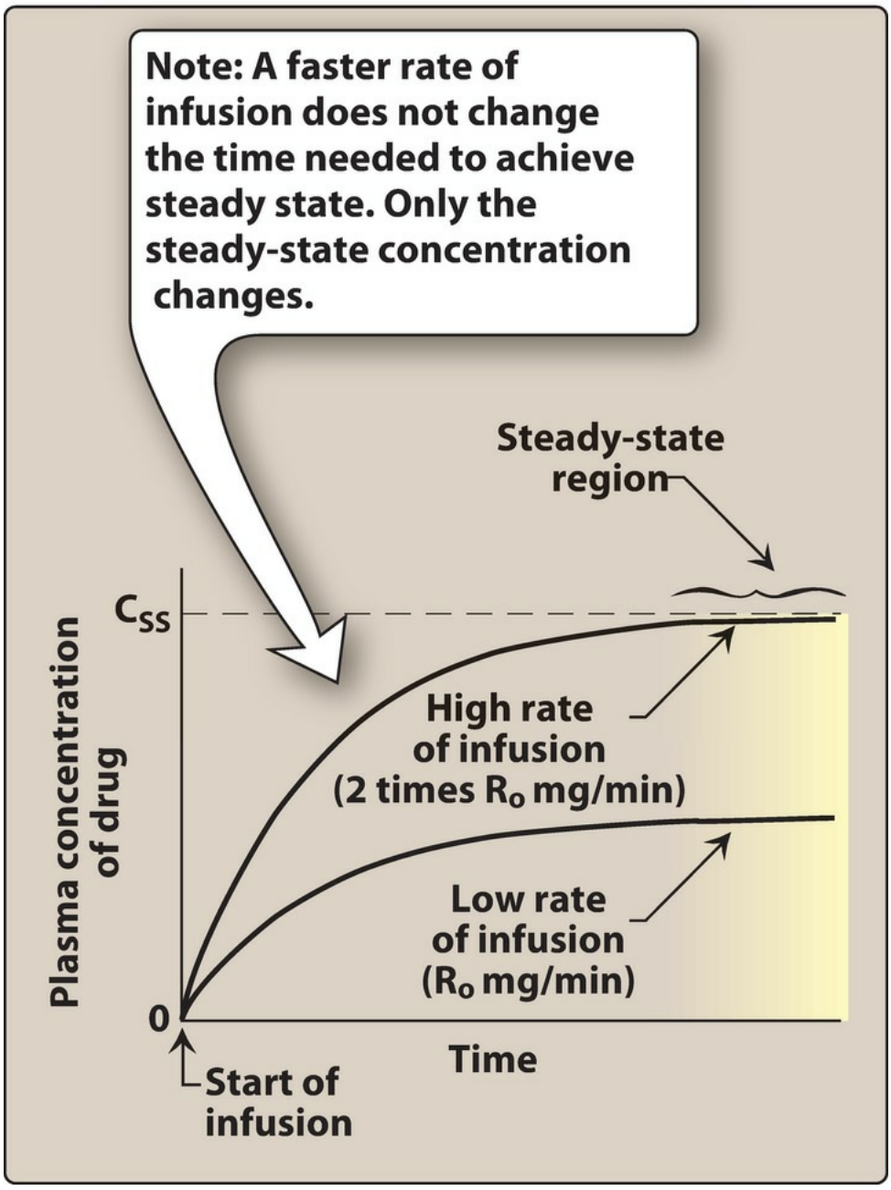


Figure 1.21 Effect of infusion rate on the steady-state concentration of drug in the plasma. R_o = rate of drug infusion; C_{ss} = steady-state concentration.

b. Time to reach steady-state drug concentration

The concentration of a drug rises from zero at the start of the infusion to its ultimate steady-state level, C_{ss} (Figure 1.21). The rate constant for attainment of steady state is the rate constant for total body elimination of the drug. Thus, 50% of C_{ss} of a drug is observed after the time elapsed, since the infusion, t, is equal to $t_{1/2}$, where $t_{1/2}$ (or half-

life) is the time required for the drug concentration to change by 50%. After another half-life, the drug concentration approaches 75% of C_{ss} (Figure 1.22). The drug concentration is 87.5% of C_{ss} at 3 half-lives and 90% at 3.3 half-lives. Thus, a drug reaches steady state in about 4 to 5 half-lives.

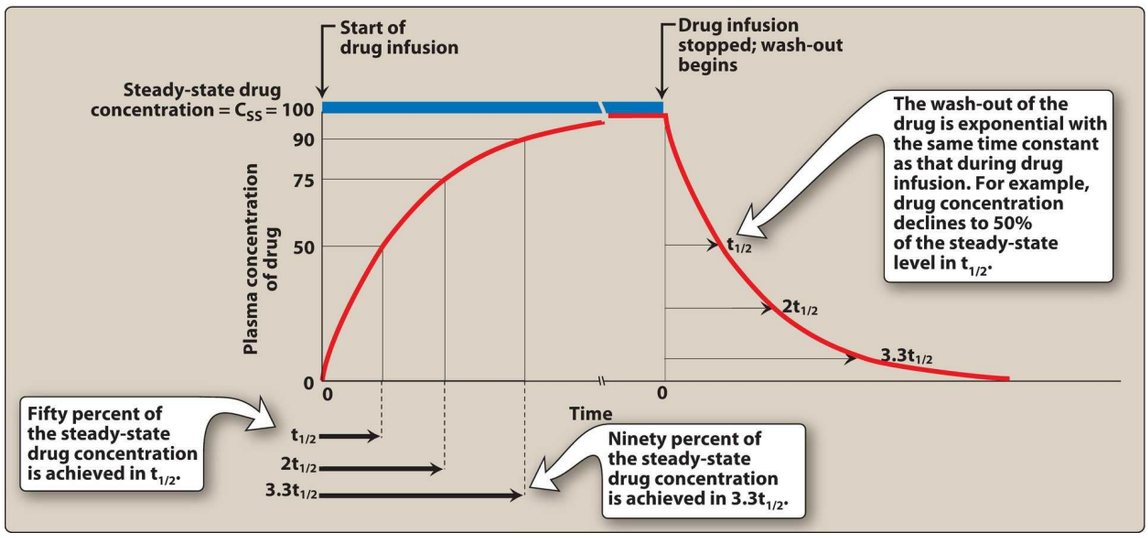


Figure 1.22 Rate of attainment of steady-state concentration of a drug in the plasma after intravenous infusion.

The sole determinant of the rate that a drug achieves steady state is the half-life ($t_{1/2}$) of the drug, and this rate is influenced only by factors that affect half-life. The rate of approach to steady state is not affected by the rate of infusion. When the infusion is stopped, the plasma concentration of a drug declines (washes out) to zero with the same time course observed in approaching steady state (Figure 1.22).

B. Fixed-dose/fixed-time regimens

Administration of a drug by fixed doses rather than by continuous infusion is often more convenient. However, fixed doses of IV or oral medications given at fixed intervals result in time-dependent fluctuations in the circulating level of drug, which contrasts with the smooth ascent of drug concentration with continuous infusion.

1. Multiple IV injections

When a drug is given repeatedly at regular intervals, the plasma concentration increases until a steady state is reached (Figure 1.23). Because most drugs are given at intervals shorter than 5 half-lives and are eliminated exponentially with time, some drug from the first dose remains in the body when the second dose is administered, some from the second dose remains when the third dose is given, and so forth. Therefore, the drug accumulates until, within the dosing interval, the rate of drug elimination equals the rate of drug administration and a steady state is achieved.

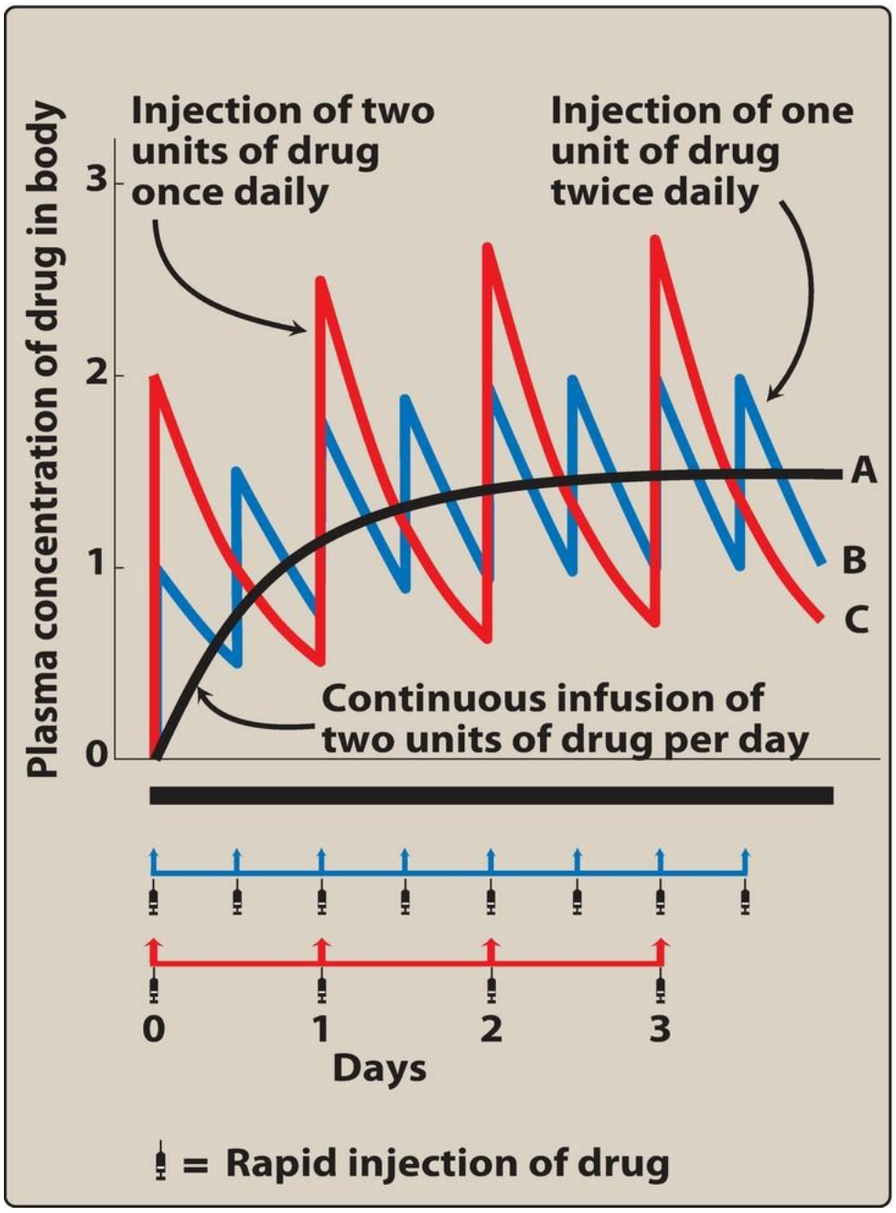


Figure 1.23 Predicted plasma concentrations of a drug given by infusion **(A)**, twice-daily injection **(B)**, or once-daily injection **(C)**. Model assumes rapid mixing in a single body compartment and a half-life of 12 hours.

a. Effect of dosing frequency

With repeated administration at regular intervals, the plasma concentration of a drug oscillates about a mean. Using smaller doses at shorter intervals reduces the amplitude of fluctuations in drug concentration. However, the dosing frequency changes neither the magnitude of C_{ss} nor the rate of achieving C_{ss}.

b. Example of achievement of steady state using different dosage regimens

Curve B of Figure 1.23 shows the amount of drug in the body when 1 unit of a drug is administered IV and repeated

at a dosing 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 given. The minimal amount of drug remaining during the dosing interval progressively 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 of administration. That is, the “rate in” equals the “rate out.” As in the case for IV infusion, 90% of the steady-state value is achieved in 3.3 half-lives.

2. Multiple oral administrations

Most drugs administered on an outpatient basis are oral medications taken at a specific dose one, two, or more times daily. In contrast to IV injection, orally administered drugs may be absorbed slowly, and the plasma concentration of the drug is influenced by both the rate of absorption and the rate of elimination (Figure 1.24).

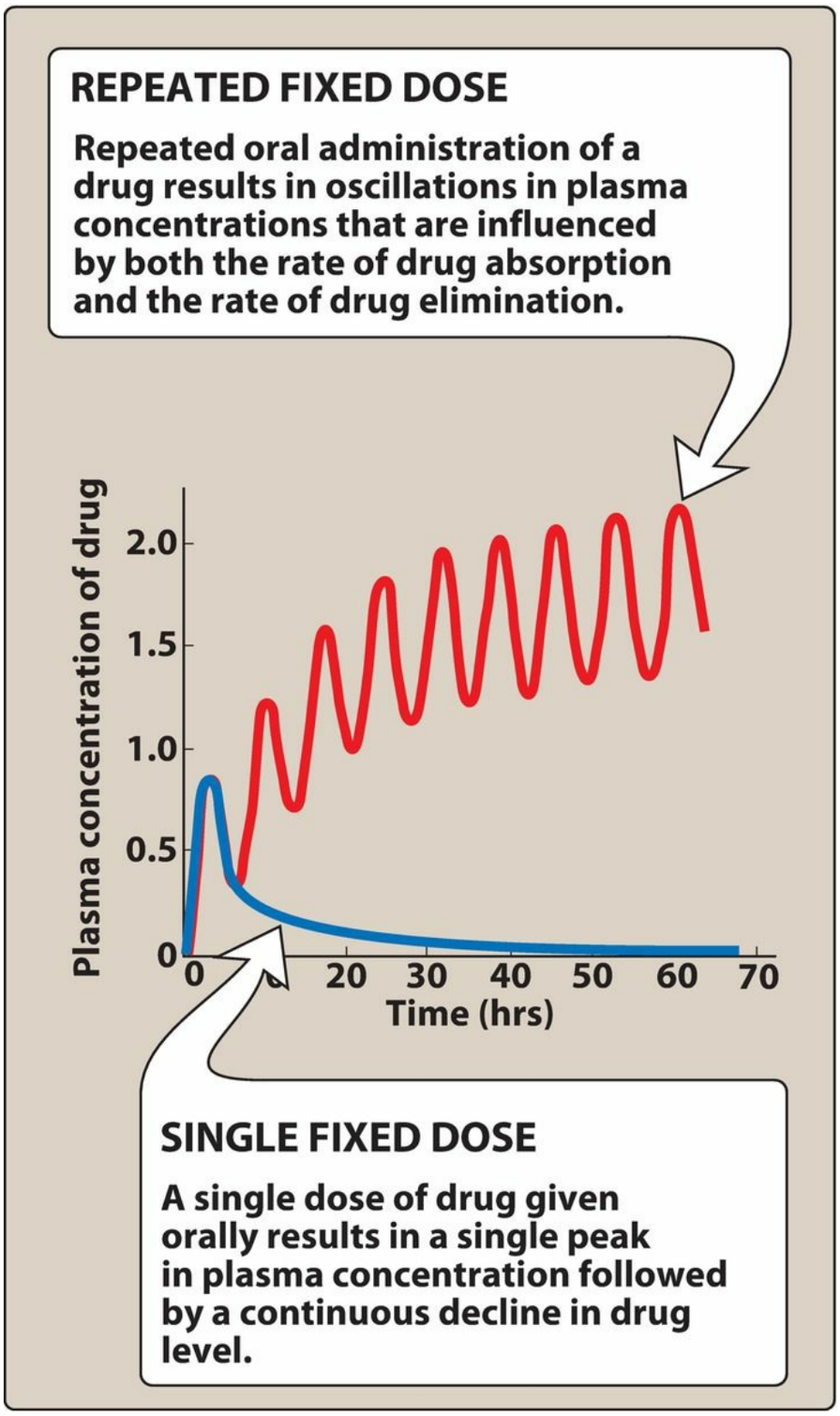


Figure 1.24 Predicted plasma concentrations of a drug given by repeated oral administrations.

C. Optimization of dose

The goal of drug therapy is to achieve and maintain concentrations within a therapeutic response window while minimizing toxicity and/or adverse effects. With careful titration, most drugs can achieve this goal. If the therapeutic window (see Chapter 2) of the drug is small (for example, *digoxin* or *lithium*), extra caution should be taken in selecting a dosage regimen, and drug levels should be monitored to ensure attainment of the therapeutic range. Drug regimens are administered as a maintenance dose and may require a loading dose if rapid effects are warranted.

1. Maintenance dose

Drugs are generally administered to maintain a C_{ss} within the therapeutic window. It takes 4 to 5 half-lives for a drug to achieve C_{ss}. To achieve a given concentration, the rate of administration and the rate of elimination of the drug are important. The dosing rate can be determined by knowing the target concentration in plasma (Cp), clearance (CL) of the drug from the systemic circulation, and the fraction (F) absorbed (bioavailability):

$$\text{Dosing rate} = \frac{(\text{Target } C_{\text{plasma}})\,(CL)}{F}$$

2. Loading dose

Sometimes rapid obtainment of desired plasma levels is needed (for example, in serious infections or arrhythmias). Therefore, a “loading dose” of drug is administered to achieve the desired plasma level rapidly, followed by a maintenance dose to maintain the steady state (Figure 1.25). In general, the loading dose can be calculated as

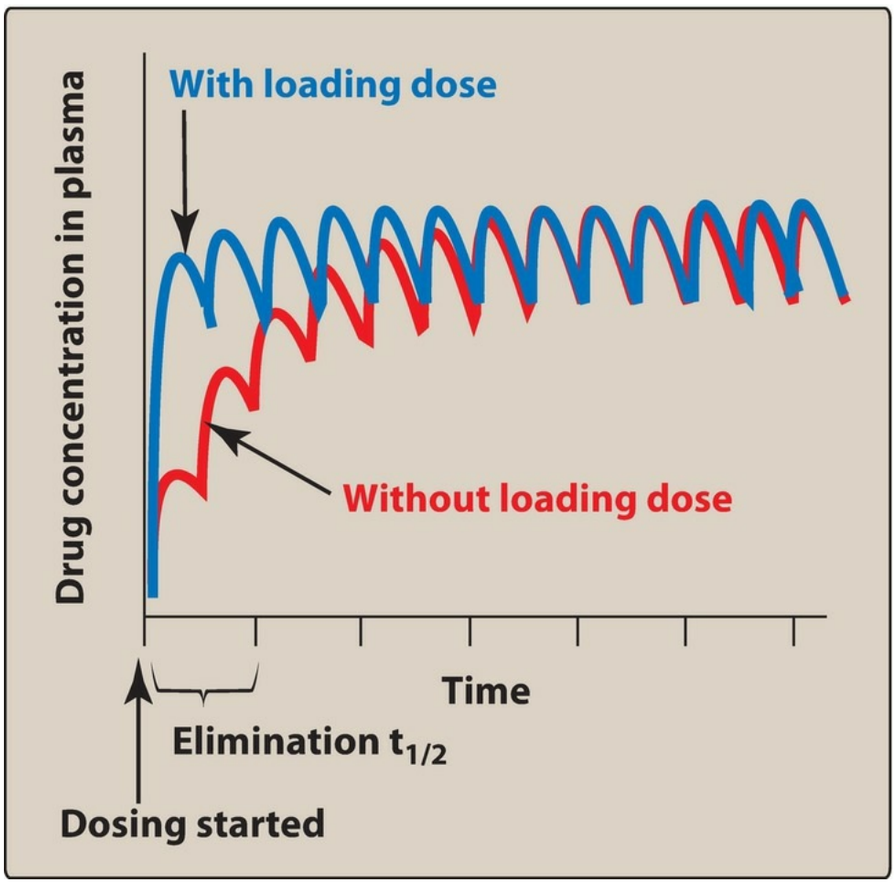


Figure 1.25 Accumulation of drug administered orally without a loading dose and with a single oral loading dose administered at t = 0.

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

Disadvantages of loading doses include increased risk of drug toxicity and a longer time for the plasma concentration to fall if excess levels occur.

3. Dose adjustment

The amount of a drug administered for a given condition is estimated based on an “average patient.” This approach overlooks interpatient variability in pharmacokinetic parameters such as clearance and V_d, which are quite significant in some cases. Knowledge of pharmacokinetic principles is useful in adjusting dosages to optimize

therapy for a given patient. Monitoring drug therapy and correlating it with clinical benefits provides another tool to individualize therapy.

For drugs with a defined therapeutic range, drug concentrations are measured, and the dosage and frequency are adjusted to obtain the desired levels. When determining a dosage adjustment, V_d can be used to calculate the amount of drug needed to achieve a desired plasma concentration. For example, assume a heart failure patient is not well controlled due to inadequate plasma levels of *digoxin*. Suppose the concentration of *digoxin* in the plasma is C_1 and the desired target concentration is C_2, a higher concentration. The following calculation can be used to determine how much additional *digoxin* should be administered to bring the level from C_1 to C_2.

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

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

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

Figure 1.26 shows the time course of drug concentration when treatment is started or dosing is changed.

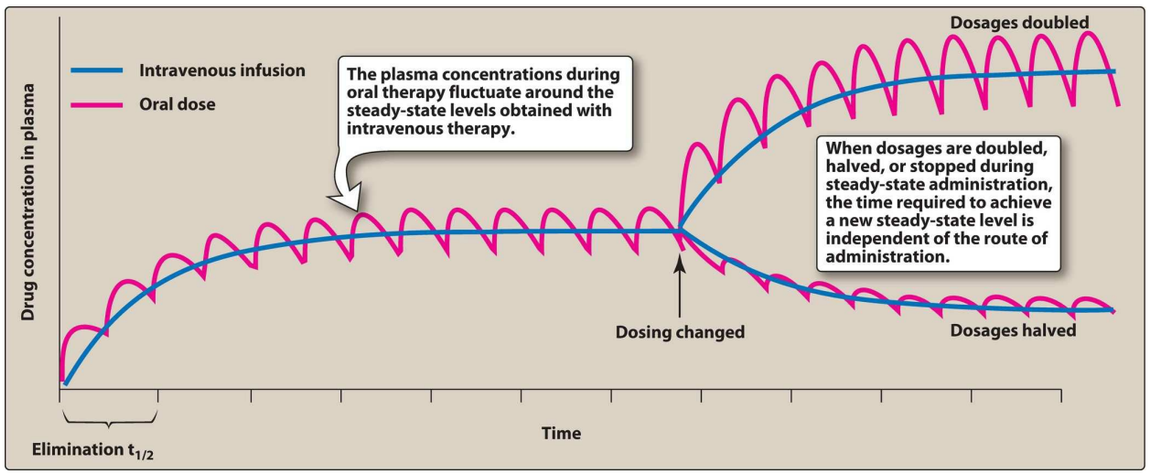


Figure 1.26 Accumulation of drug following sustained administration and following changes in dosing. Oral dosing was at intervals of 50% of $t_{1/2}$.

Study Questions

Choose the ONE best answer.

1.1 An 18-year-old female patient is brought to the emergency department due to drug overdose. Which of the following routes of administration is the most desirable for administering the antidote for the drug overdose?

A. Intramuscular
B. Intravenous
C. Oral
D. Subcutaneous
E. Transdermal

Correct answer = B. The intravenous route of administration is the most desirable because it results in achievement of therapeutic plasma levels of the antidote rapidly.

1.2 Drug A is a weakly basic drug with a pK_a of 7.8. If administered orally, at which of the following sites of absorption will the drug be able to readily pass through the membrane?

A. Mouth (pH approximately 7.0)
B. Stomach (pH of 2.5)
C. Duodenum (pH approximately 6.1)
D. Jejunum (pH approximately 8.0)
E. Ileum (pH approximately 7.0)

Correct answer = D. Because Drug A is a weakly basic drug (pK_a = 7.8), it will be predominantly in the nonionized form in the jejunum (pH of 8.0). For weak bases, the nonionized form will permeate through the cell membrane readily.

1.3 KR2250 is an investigational cholesterol-lowering agent. KR2250 has a high molecular weight and is extensively bound to albumin. KR2250 will have a(n) _____ apparent volume of distribution (V_d).

A. High
B. Low
C. Extremely high
D. Normal

Correct answer = B. Because of its high molecular weight and high protein binding, KR2250 will be effectively trapped within the plasma (vascular) compartment and will have a low apparent volume of distribution.

1.4 A 40-year-old male patient (70 kg) was recently diagnosed with infection involving methicillin-resistant *S. aureus*. He received 2000 mg of vancomycin as an IV loading dose. The peak plasma concentration of vancomycin was 28.5 mg/L. The apparent volume of distribution is:

A. 1 L/kg
B. 7 L/kg
C. 10 L/kg
D. 14 L/kg
E. 70 L/kg

Correct answer = A. V_d = dose/C = 2000 mg/28.5 mg/L = 70.1 L. Because the patient is 70 kg, the apparent volume of distribution in L/kg will be approximately 1 L/kg (70.1 L/70 kg).

1.5 A 55-year-old woman is brought to the emergency department because of seizures. She has a history of renal disease and currently undergoes dialysis. She receives an intravenous infusion of antiseizure Drug X. Which of the following is likely to be observed with use of Drug X in this patient?

	Half-life	Dosage
A.	↑	↑
B.	↓	↓
C.	↑	↔
D.	↑	↓
E.	↔	↔

Correct answer = D. Because the patient has a renal disorder, she may not be able to excrete the drug effectively. Therefore, the half-life of Drug X will be prolonged. As the half-life is prolonged, the dosage must be reduced so the patient will not have serious toxic effects of Drug X.

1.6 A 68-year-old woman is brought to the emergency department for treatment of a myocardial infarction. She is currently taking clopidogrel (antiplatelet agent) and aspirin daily, as well as omeprazole (potent CYP inhibitor) for heartburn. Which of the following is the most likely contributor to her myocardial infarction today?

A. Reduced antiplatelet activity of clopidogrel due to aspirin
B. Reduced antiplatelet activity of clopidogrel due to omeprazole
C. Hypersensitivity reaction due to clopidogrel
D. Increased antiplatelet activity of clopidogrel due to omeprazole
E. Increased antiplatelet activity of clopidogrel due to aspirin

Correct answer = B. Clopidogrel is a prodrug and requires CYP2C19 activity for conversion to an active metabolite. Because omeprazole is a potent CYP inhibitor, clopidogrel is not converted to the active metabolite, and therefore the antiplatelet activity is reduced, potentially contributing to myocardial infarction.

1.7 Which of the following reactions represents Phase II of drug metabolism?

A. Amidation
B. Hydrolysis
C. Oxidation
D. Reduction
E. Sulfation

Correct answer = E. Phase II metabolic reactions involve conjugation reactions to make phase I metabolites more polar. Sulfation and glucuronidation are the most common phase II conjugation reactions.

1.8 A pharmacokinetic study of a new antihypertensive drug is being conducted in healthy human volunteers. The half-life of the drug after administration by continuous intravenous infusion is 12 hours. Which of the following best approximates the time for the drug to reach steady state?

A. 24 hours
B. 48 hours
C. 72 hours
D. 120 hours
E. 240 hours

Correct answer = B. A drug will reach steady state in about 4 to 5 half-lives. Therefore, for this drug with a half-life of 12 hours, the approximate time to reach steady state will be 48 hours.

1.9 A 64-year-old female patient (60 kg) is treated with experimental Drug A for type 2 diabetes. Drug A is available as tablets with an oral bioavailability of 90%. If the V_d is 2 L/kg and the desired steady-state plasma concentration is 3.0 mg/L, which of the following is the most appropriate oral loading dose of Drug A?

A. 6 mg
B. 6.66 mg
C. 108 mg
D. 360 mg
E. 400 mg

Correct answer = E. For oral dosing, loading dose = [(V_d) × (desired steady-state plasma concentration)/F]. The V_d in this case is corrected to the patient's weight is 120 L. The F value is 0.9 (because bioavailability is 90%, that is, 90/100 = 0.9). Thus, loading dose = (120 L × 3.0 mg/L)/0.9 = 400 mg.

1.10 A 74-year-old man was admitted to the hospital for treatment of heart failure. He received 160 mcg of digoxin intravenously, and the plasma digoxin level was 0.4 ng/mL. If the desired plasma concentration of digoxin for optimal therapeutic activity in heart failure is 1.2 ng/mL, and the patient has an estimated V_d of 400 L, calculate the additional dose of digoxin needed for this patient to achieve the desired plasma concentration.

A. 128 mcg
B. 160 mcg
C. 320 mcg
D. 480 mcg
E. 640 mcg

Correct answer = C. The additional dosage of digoxin needed to achieve the desired plasma concentration can be calculated using the equation V_d ($C_2 - C_1$). C_1 is the current plasma concentration (0.4 ng/mL) and C_2 is the desired plasma concentration (1.2 ng/mL). Therefore, the additional dosage of digoxin is [400 L × (1.2 – 0.4) ng/mL)] = 320 mcg.

2

Drug–Receptor Interactions and Pharmacodynamics

Joanna Peris

I. Overview

Pharmacodynamics describes the actions of a drug on the body. Most drugs exert effects, both beneficial and harmful, by interacting with specialized target macromolecules called receptors, which are present on or in the cell. The drug–receptor complex initiates alterations in biochemical and/or molecular activity of a cell by a process called signal transduction (Figure 2.1).

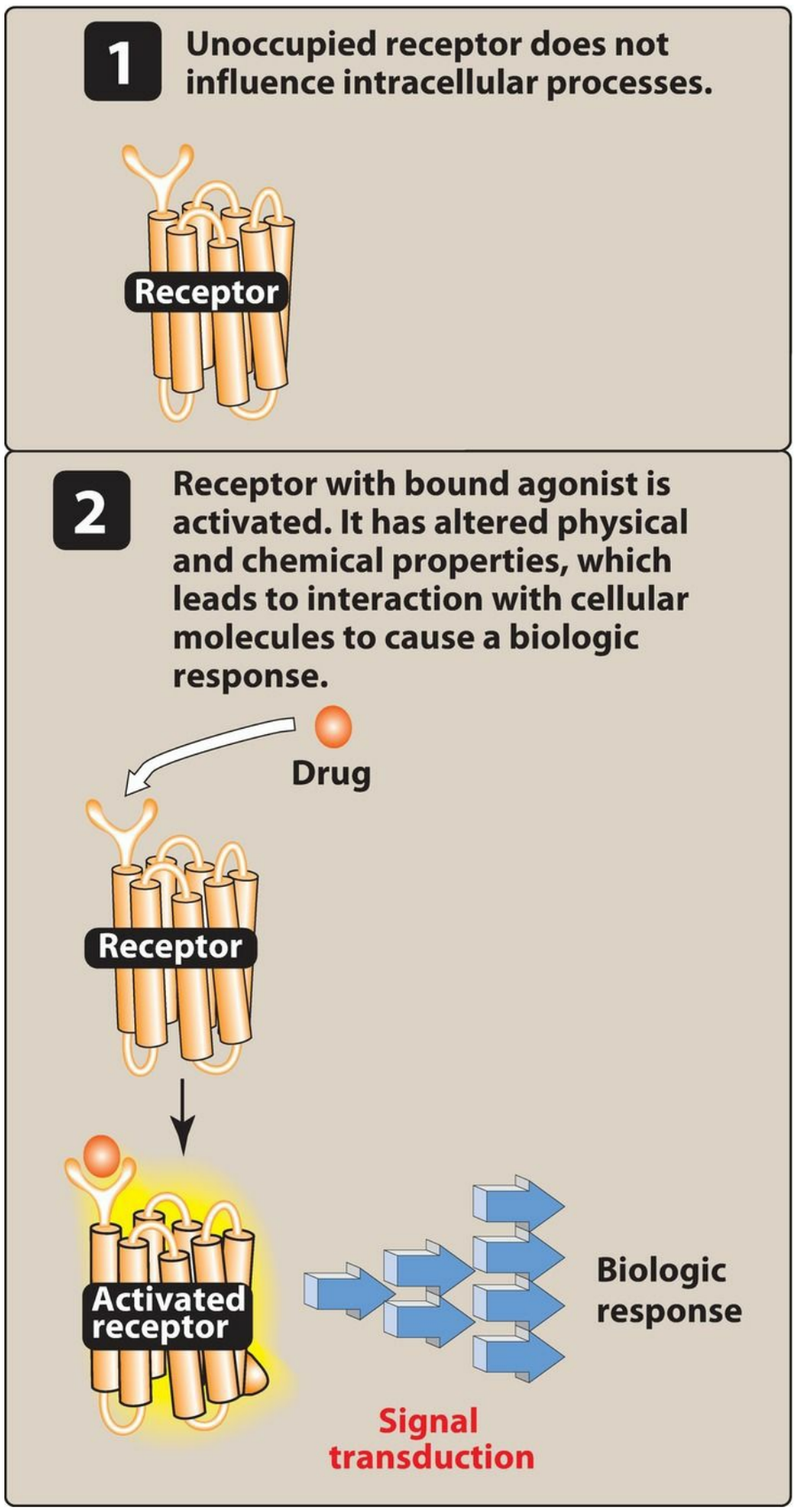


Figure 2.1 The recognition of a drug by a receptor triggers a biologic response.

II. Signal Transduction

Drugs act as signals, and receptors act as signal detectors. A drug is termed an “agonist” if it binds to a site on a receptor protein and activates it to initiate a series of reactions that ultimately result in a specific intracellular response. “Second messenger” or effector molecules are part of the cascade of events that translates agonist binding into a cellular response.

A. The drug–receptor complex

Cells have many different types of receptors, each of which is specific for a particular agonist and produces a unique response. Cardiac cell membranes, for example, contain β-adrenergic receptors that bind and respond to epinephrine or norepinephrine. Cardiac cells also contain muscarinic receptors that bind and respond to acetylcholine. These two receptor populations dynamically interact to control the heart's vital functions.

The magnitude of the cellular response is proportional to the number of drug–receptor complexes. This concept is conceptually similar to the formation of complexes between enzyme and substrate and shares many common features, such as specificity of the receptor for a given agonist. Although much of this chapter centers on the interaction of drugs with specific receptors, it is important to know that not all drugs exert effects by interacting with a receptor. Antacids, for instance, chemically neutralize excess gastric acid, thereby reducing stomach upset.

B. Receptor states

Receptors exist in at least two states, inactive (R) and active (R*), that are in reversible equilibrium with one another, usually favoring the inactive state. Binding of agonists causes the equilibrium to shift from R to R* to produce a biologic effect. Antagonists are drugs that bind to the receptor but do not increase the fraction of R*, instead stabilizing the fraction of R. Some drugs (partial agonists) shift the equilibrium from R to R*, but the fraction of R* is less than that caused by an agonist. The magnitude of biological effect is directly related to the fraction of R*. In summary, agonists, antagonists, and partial agonists are examples of molecules or ligands that bind to the activation site on the receptor and can affect the fraction of R*.

C. Major receptor families

A receptor is defined as any biologic molecule to which a drug binds and produces a measurable response. Thus, enzymes, nucleic acids, and structural proteins can act as receptors for drugs or endogenous agonists. However, the richest sources of receptors are membrane-bound proteins that transduce extracellular signals into intracellular responses. These receptors may be divided into four families: 1) ligand-gated ion channels, 2) G protein–coupled receptors, 3) enzyme-linked receptors, and 4) intracellular receptors (Figure 2.2). Generally, hydrophilic ligands interact with receptors that are found on the cell surface (Figure 2.2A, B, C). In contrast, hydrophobic ligands enter cells through the lipid bilayers of the cell membrane to interact with receptors found inside cells (Figure 2.2D).

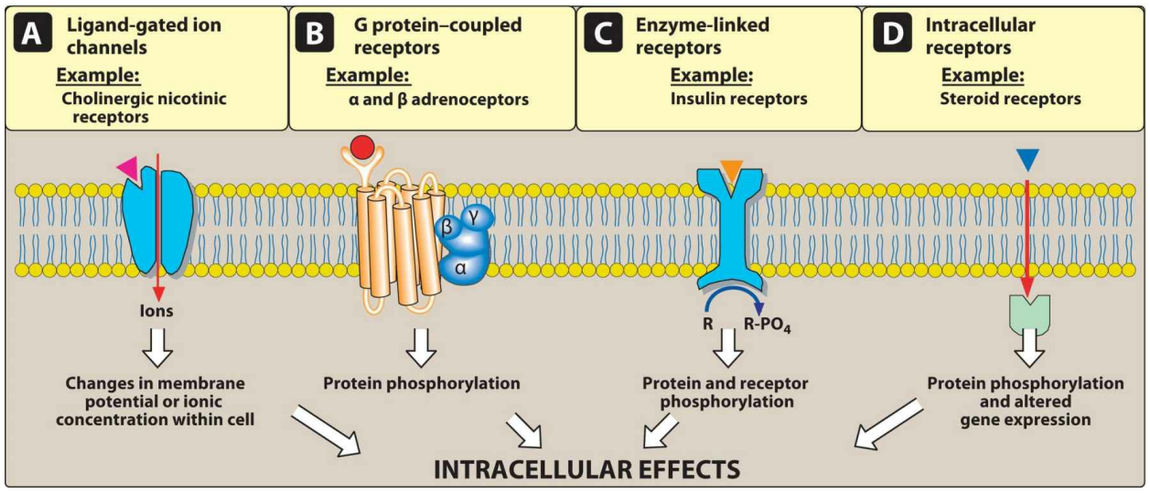


Figure 2.2 Transmembrane signaling mechanisms. **A.** Ligand binds to the extracellular domain of a ligand-gated channel. **B.** Ligand binds to a domain of a transmembrane receptor, which is coupled to a G protein. **C.** Ligand binds to the extracellular domain of a receptor that activates a kinase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

1. Transmembrane ligand-gated ion channels

The extracellular portion of ligand-gated ion channels contains the drug-binding site. This site regulates the opening of the pore through which ions can flow across cell membranes (Figure 2.2A). The channel is usually closed until the receptor is activated by an agonist, which opens the channel for a few milliseconds. Depending on the ion conducted through these channels, these receptors mediate diverse functions, including neurotransmission and muscle contraction. For example, stimulation of the nicotinic receptor by acetylcholine opens a channel that allows sodium influx and potassium outflux across the cell membranes of neurons or muscle cells. This change in ionic concentrations across the membrane generates an action potential in a neuron and contraction in skeletal and cardiac muscle. On the other hand, agonist stimulation of the A subtype of the γ-aminobutyric acid (GABA) receptor increases chloride influx, resulting in hyperpolarization of neurons and less chance of generating an action potential. Drug-binding sites are also found on many voltage-gated ion channels where they can regulate channel function. For example, local anesthetics bind to the voltage-gated sodium channel, inhibiting sodium influx and decreasing neuronal conduction.

2. Transmembrane G protein–coupled receptors

The extracellular portion of this receptor contains the ligand-binding site, and the intracellular portion interacts (when activated) with a G protein. There are many kinds of G proteins (for example, G_s, G_i, and G_q), but all types are composed of three protein subunits. The α subunit binds guanosine triphosphate (GTP), and the β and γ subunits anchor the G protein in the cell membrane (Figure 2.3). Binding of an agonist to the receptor increases GTP binding to the α subunit, causing dissociation of the α-GTP complex from the βγ complex. The α and βγ subunits are then free to interact with specific cellular effectors, usually an enzyme or an ion channel, that cause further actions within the cell. These responses usually last several seconds to minutes. Often, the activated effectors produce “second messenger” molecules that further activate other effectors in the cell, causing a signal cascade effect.

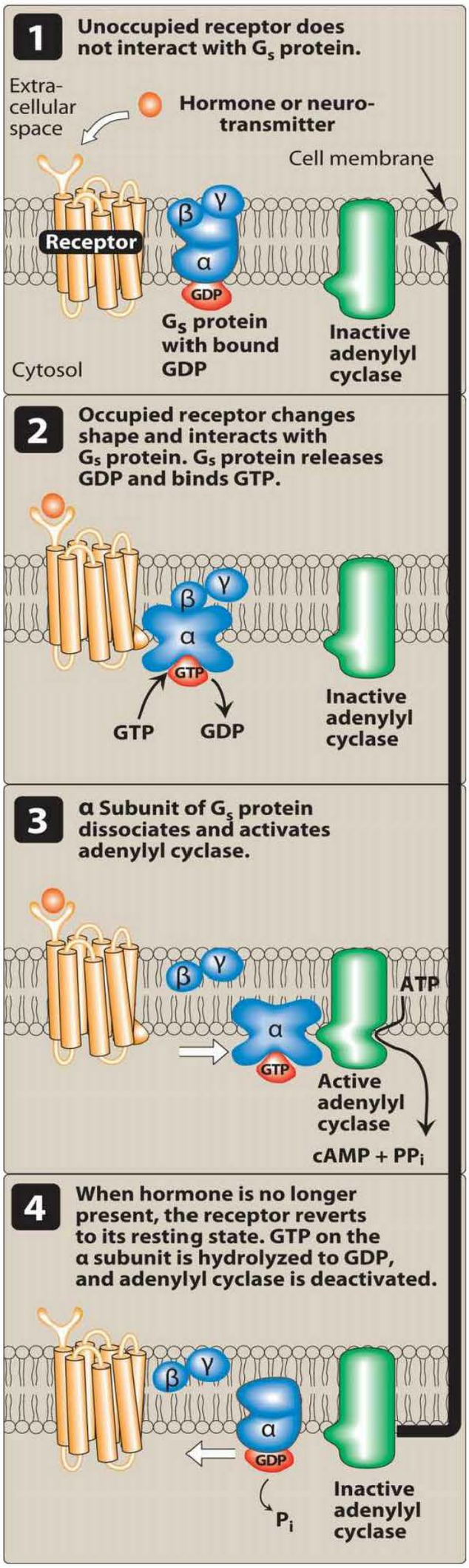

1
Unoccupied receptor does not interact with G_s protein.
Extra-cellular space
Hormone or neuro-transmitter
Cell membrane
Receptor
β
γ
α
GDP
G_S protein with bound GDP
Inactive adenylyl cyclase
Cytosol
2
Occupied receptor changes shape and interacts with G_s protein. G_s protein releases GDP and binds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

Figure 2.3 The recognition of chemical signals by G protein–coupled membrane receptors affects the activity of adenylyl cyclase. PP_i = inorganic pyrophosphate.

A common effector, activated by G_s and inhibited by G_i, is adenylyl cyclase, which produces the second messenger cyclic adenosine monophosphate (cAMP). The effector phospholipase C, when activated by G_q, generates two second messengers: inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). DAG and cAMP activate specific protein kinases within the cell, leading to a myriad of physiological effects. IP_3 increases intracellular calcium concentration, which in turn activates other protein kinases.

3. Enzyme-linked receptors

This family of receptors undergoes conformational changes when activated by a ligand, resulting in increased intracellular enzyme activity (Figure 2.4). This response lasts for minutes to hours. The most common enzyme-linked receptors (for example, growth factors and insulin) possess tyrosine kinase activity. When activated, the receptor phosphorylates tyrosine residues on itself and other specific proteins (Figure 2.4). Phosphorylation can substantially modify the structure of the target protein, thereby acting as a molecular switch. For example, the phosphorylated insulin receptor in turn phosphorylates other proteins that now become active. Thus, enzyme-linked receptors often cause a signal cascade effect like that caused by G protein–coupled receptors.

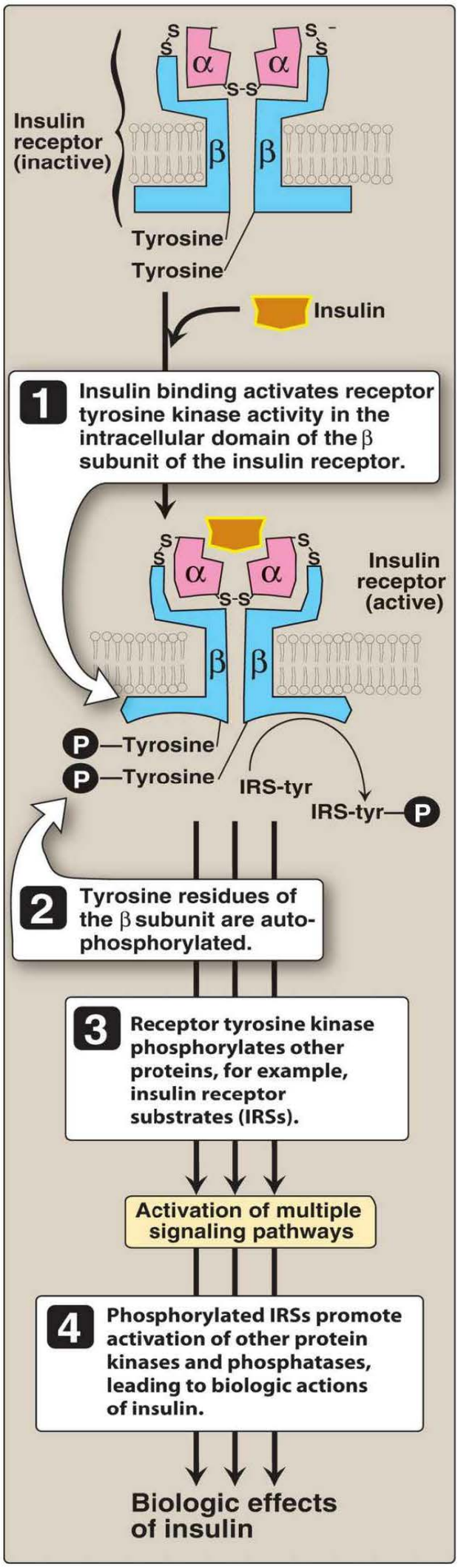
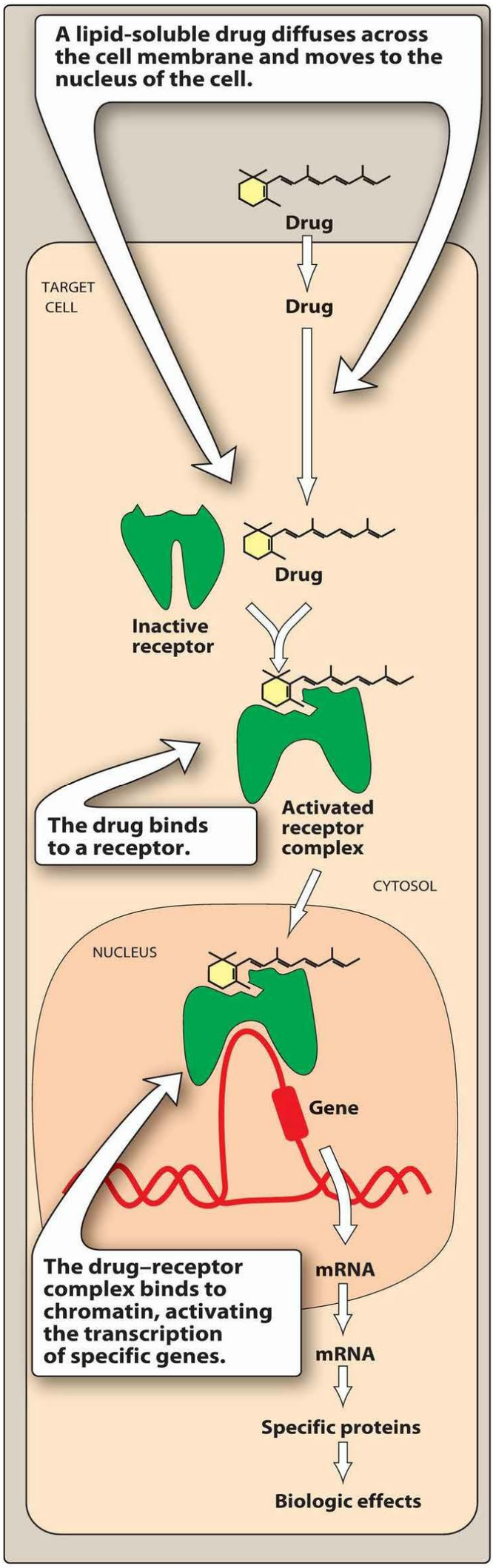

Insulin receptor (inactive)
α
α
S-S
β
β
Tyrosine
Tyrosine
Insulin
1
Insulin binding activates receptor tyrosine kinase activity in the intracellular domain of the β subunit of the insulin receptor.
Insulin receptor (active)
P—Tyrosine
P—Tyrosine
IRS-tyr
IRS-tyr—P
2
Tyrosine residues of the β subunit are auto-phosphorylated.
3
Receptor tyrosine kinase phosphorylates other proteins, for example, insulin receptor substrates (IRSs).
Activation of multiple signaling pathways
4
Phosphorylated IRSs promote activation of other protein kinases and phosphatases, leading to biologic actions of insulin.
Biologic effects of insulin

Figure 2.4 Insulin receptor.

4. Intracellular receptors

The fourth family of receptors differs considerably from the other three in that the receptor is entirely intracellular, and, therefore, the ligand (for example, steroid hormones) must have sufficient lipid solubility to diffuse into the cell to interact with the receptor (Figure 2.5). The primary targets of activated intracellular receptors are transcription factors in the cell nucleus that regulate gene expression. The activation or inactivation of transcription factors alters the transcription of DNA into RNA and subsequently translation of RNA into proteins. The effect of drugs or endogenous ligands that activate intracellular receptors takes hours to days to occur. Other targets of intracellular ligands are structural proteins, enzymes, RNA, and ribosomes. For example, tubulin is the target of antineoplastic agents such as *paclitaxel* (see Chapter 35), the enzyme dihydrofolate reductase is the target of antimicrobials such as *trimethoprim* (see Chapter 31), and the 50S subunit of the bacterial ribosome is the target of macrolide antibiotics such as *erythromycin* (see Chapter 30).


A lipid-soluble drug diffuses across the cell membrane and moves to the nucleus of the cell.
Drug
TARGET CELL
Drug
Drug
Inactive receptor
The drug binds to a receptor.
Activated receptor complex
CYTOSOL
NUCLEUS
Gene
The drug–receptor complex binds to chromatin, activating the transcription of specific genes.
mRNA
mRNA
Specific proteins
Biologic effects