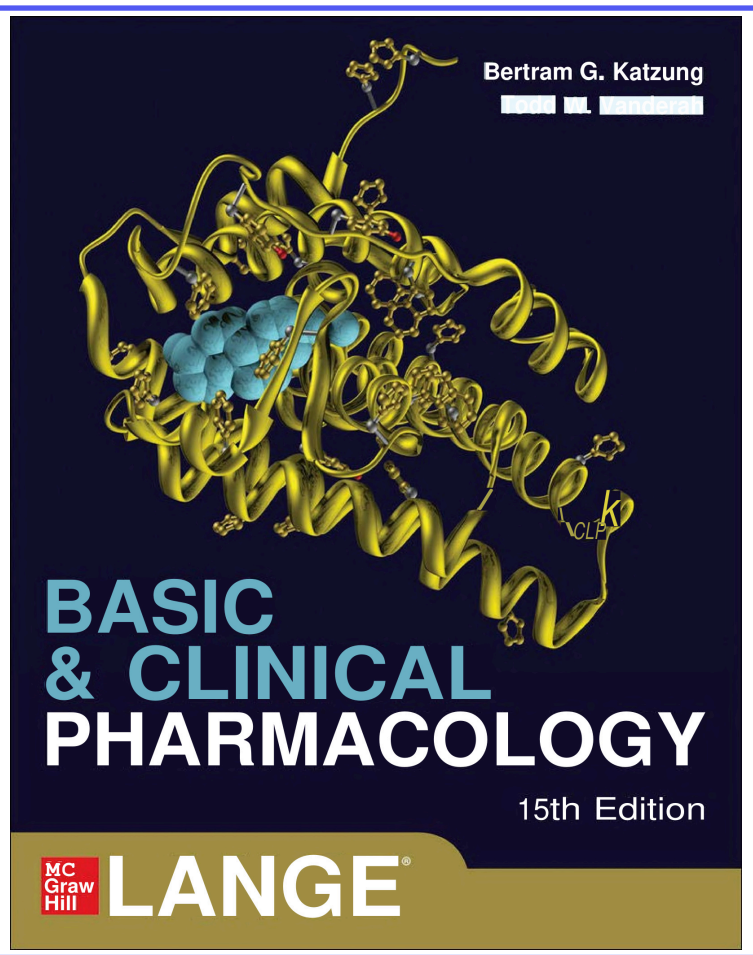


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he body (discussed under Permeation, in following text). Therefore, very large drugs (usually proteins) must often be administered directly into t partment where they have their effect. In the case of alteplase, a clot-dissolving enzyme, the drug is administered directly into the vascular partment by intravenous or intra-arterial infusion.

g Reactivity & Drug-Receptor Bonds

gs interact with receptors by means of chemical forces or bonds. These are of three major types: **covalent, electrostatic,** and **hydrophobic.** alent bonds are very strong and in many cases not reversible under biologic conditions. Thus, the covalent bond formed between the acetyl gro cetylsalicylic acid (aspirin) and cyclooxygenase, its enzyme target in platelets, is not readily broken. The platelet aggregation–blocking effect of irin lasts long after free acetylsalicylic acid has disappeared from the bloodstream (about 15 minutes) and is reversed only by the synthesis of ne yme in new platelets, a process that takes several days. Other examples of highly reactive, covalent bond-forming drugs include the DNA-alkylati nts used in cancer chemotherapy to disrupt cell division in the tumor.

ctrostatic bonding is much more common than covalent bonding in drug-receptor interactions. Electrostatic bonds vary from relatively strong ages between permanently charged ionic molecules to weaker hydrogen bonds and very weak induced dipole interactions such as van der Waal ces and similar phenomena. Electrostatic bonds are weaker than covalent bonds.

rophobic bonds are usually quite weak and are probably important in the interactions of highly lipid-soluble drugs with the lipids of cell mbranes and perhaps in the interaction of drugs with the internal walls of receptor “pockets.”

specific nature of a particular drug-receptor bond is of less practical importance than the fact that drugs that bind through weak bonds to their eptors are generally more selective than drugs that bind by means of very strong bonds. This is because weak bonds require a very precise fit of t g to its receptor if an interaction is to occur. Only a few receptor types are likely to provide such a precise fit for a particular drug structure. Thus, wished to design a highly selective drug for a particular receptor, we would avoid highly reactive molecules that form covalent bonds and instead ose a molecule that forms weaker bonds.

w substances that are almost completely inert in the chemical sense nevertheless have significant pharmacologic effects. For example, xenon, an ert” gas, has anesthetic effects at elevated pressures.

g Shape

shape of a drug molecule must be such as to permit binding to its target site via the bonds just described. Optimally, the drug’s shape is plementary to that of the target site (usually a receptor) in the same way that a key is complementary to a lock. Furthermore, the phenomenon o **rality (stereoisomerism)** is so common in biology that more than half of all useful drugs are chiral molecules; that is, they can exist as ntiomeric pairs. Drugs with two asymmetric centers have four diastereomers, eg, ephedrine, a sympathomimetic drug. In most cases, one of thes ntiomers is much more potent than its mirror image enantiomer, reflecting a better fit to the receptor molecule. If one imagines the receptor site like a glove into which the drug molecule must fit to bring about its effect, it is clear why a “left-oriented” drug is more effective in binding to a left d receptor than its “right-oriented” enantiomer.

more active enantiomer at one type of receptor site may not be more active at another receptor type, eg, a type that may be responsible for som er effect. For example, carvedilol, a drug that interacts with adrenoceptors, has a single chiral center and thus two enantiomers (Table 1–2). One se enantiomers, the (*S*)(–) isomer, is a potent β-receptor blocker. The (*R*)(+) isomer is 100-fold weaker at the β receptor. However, the isomers ar roximately equipotent as α-receptor blockers. Ketamine, a chiral molecule with two isomers, was introduced as an anesthetic. When administer n anesthetic, the racemic mixture is administered intravenously. In contrast, the (*S*) enantiomer has recently been approved for use in nasal spra m as a rapid-acting antidepressant.

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ABLE 1–2

issociation constants (K_d) of the enantiomers and racemate of carvedilol.

Form of Carvedilol	α Receptors (K_d, nmol/L[1])	β Receptors (K_d, nmol/L)
(*R*)(+) enantiomer	14	45
(*S*)(−) enantiomer	16	0.4
(*R,S*)(±) enantiomers	11	0.9

The K_d is the concentration for 50% saturation of the receptors and is inversely proportionate to the affinity of the drug for the receptors.

ata from Ruffolo RR Jr, Gellai M, Hieble JP, et al: The Pharmacology of carvedilol, Eur J Clin Pharmacol 1990;38S2:S82-88.

ally, because enzymes are usually stereoselective, one drug enantiomer is often more susceptible than the other to drug-metabolizing enzymes. sult, the duration of action of one enantiomer may be quite different from that of the other. Similarly, drug transporters may be stereoselective.

fortunately, most studies of clinical efficacy and drug elimination in humans have been carried out with racemic mixtures of drugs rather than wit separate enantiomers. At present, less than half of the chiral drugs used clinically are marketed as the active isomer—the rest are available only emic mixtures. As a result, a majority of patients receive drug doses of which 50% is less active or inactive. A few drugs are currently available in b racemic and the pure, active isomer forms. However, proof that administration of the pure, active enantiomer decreases adverse effects relative se produced by racemic formulations has not been established.

tional Drug Design

ional design of drugs implies the ability to predict the appropriate molecular structure of a drug on the basis of information about its biologic eptor. Until recently, no receptor was known in sufficient detail to permit such drug design. Instead, drugs were developed through random testi hemicals or modification of drugs already known to have some effect. However, the characterization of many receptors during the past three ades has changed this picture. A few drugs now in use were developed through molecular design based on knowledge of the three-dimensional cture of the receptor site. Computer programs are now available that can iteratively optimize drug structures to fit known receptors. As more omes known about receptor structure, rational drug design will become more common.

ceptor Nomenclature

spectacular success of newer, more efficient ways to identify and characterize receptors (see Chapter 2) has resulted in a variety of differing, an etimes confusing, systems for naming them. This in turn has led to a number of suggestions regarding more rational methods of naming eptors. The interested reader is referred for details to the efforts of the International Union of Pharmacology (IUPHAR) Committee on Receptor menclature and Drug Classification (reported in various issues of *Pharmacological Reviews* and elsewhere) and to Alexander SP et al: The Concis ide to PHARMACOLOGY 2017/18: Overview. *Br J Pharmacol* 2017;174:S1. The chapters in this book mainly use these sources for naming receptors

UG-BODY INTERACTIONS

interactions between a drug and the body are conveniently divided into two classes. The actions of the drug on the body are termed **armacodynamic** processes (Figure 1–1); the principles of pharmacodynamics are presented in greater detail in Chapter 2. These properties ermine the group in which the drug is classified, and they play the major role in deciding whether that group is appropriate therapy for a particul ptom or disease. The actions of the body on the drug are called **pharmacokinetic** processes and are described in Chapters 3 and 4. rmacokinetic processes govern the absorption, distribution, and elimination of drugs and are of great practical importance in the choice and inistration of a particular drug for a particular patient, eg, a patient with heart failure who also has impaired renal function. The following agraphs provide a brief introduction to pharmacodynamics and pharmacokinetics.

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armacodynamic Principles

st drugs must bind to a receptor to bring about an effect. However, at the cellular level, drug binding is only the first in a sequence of possible ste

- Drug (D) + receptor-effector (R) → drug-receptor-effector complex → effect
- D + R → drug-receptor complex → effector molecule → effect
- D + R → D-R complex → activation of coupling molecule → effector molecule → effect
- Inhibition of metabolism of endogenous activator → increased activator action on an effector molecule → increased effect

te that the final change in function is accomplished by an **effector** mechanism. The effector may be part of the receptor molecule or may be a arate molecule. A very large number of receptors communicate with their effectors through coupling molecules, as described in Chapter 2.

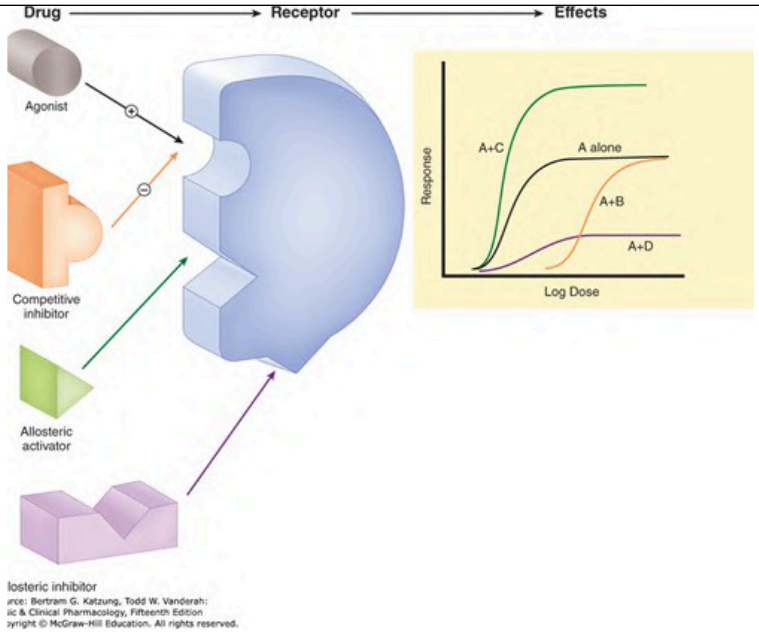
ypes of Drug-Receptor Interactions

onist drugs bind to and *activate* the receptor in some fashion, which directly or indirectly brings about the effect (Figure 1–2A). Receptor activati olves a change in conformation in the cases that have been studied at the molecular structure level. Some receptors incorporate effector machin he same molecule, so that drug binding brings about the effect directly, eg, opening of an ion channel or activation of enzyme activity. Other eptors are linked through one or more intervening coupling molecules to a separate effector molecule. The major types of drug-receptor-effecto pling systems are discussed in Chapter 2. **Pharmacologic antagonist** drugs, by binding to a receptor, compete with and prevent binding by ot lecules. For example, acetylcholine receptor blockers such as atropine are antagonists because they prevent access of acetylcholine and similar nist drugs to the acetylcholine receptor site and they stabilize the receptor in its inactive state (or some state other than the acetylcholine-activat te). These agents reduce the effects of acetylcholine and similar molecules in the body (Figure 1–2B), but their action can be overcome by increasi dosage of agonist. Some antagonists bind very tightly to the receptor site in an irreversible or pseudoirreversible fashion and cannot be displace increasing the agonist concentration. Drugs that bind to the same receptor molecule but do not prevent binding of the agonist are said to act **osterically** and may enhance (Figure 1–2C) or inhibit (Figure 1–2D) the action of the agonist molecule. Allosteric inhibition is not usually overco increasing the dose of agonist.

RE 1–2

gs may interact with receptors in several ways. The effects resulting from these interactions are diagrammed in the dose-response curves at the t. Drugs that alter the agonist (**A**) response may activate the agonist binding site, compete with the agonist (competitive inhibitors, **B**), or act at arate (allosteric) sites, increasing (**C**) or decreasing (**D**) the response to the agonist. Allosteric activators (**C**) may increase the efficacy of the agoni ts binding affinity. The curve shown reflects an increase in efficacy; an increase in affinity would result in a leftward shift of the curve.

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gonists That Inhibit Their Binding Molecules

e drugs mimic agonist drugs by inhibiting the molecules responsible for terminating the action of an endogenous agonist. For example, tylcholinesterase *inhibitors*, by slowing the destruction of endogenous acetylcholine, cause cholinomimetic effects that closely resemble the ions of cholinoceptor *agonist* molecules even though cholinesterase inhibitors do not bind or only incidentally bind to cholinoceptors (see Chapt Because they amplify the effects of physiologically released endogenous agonist ligands, their effects are sometimes more selective and less toxi n those of exogenous agonists.

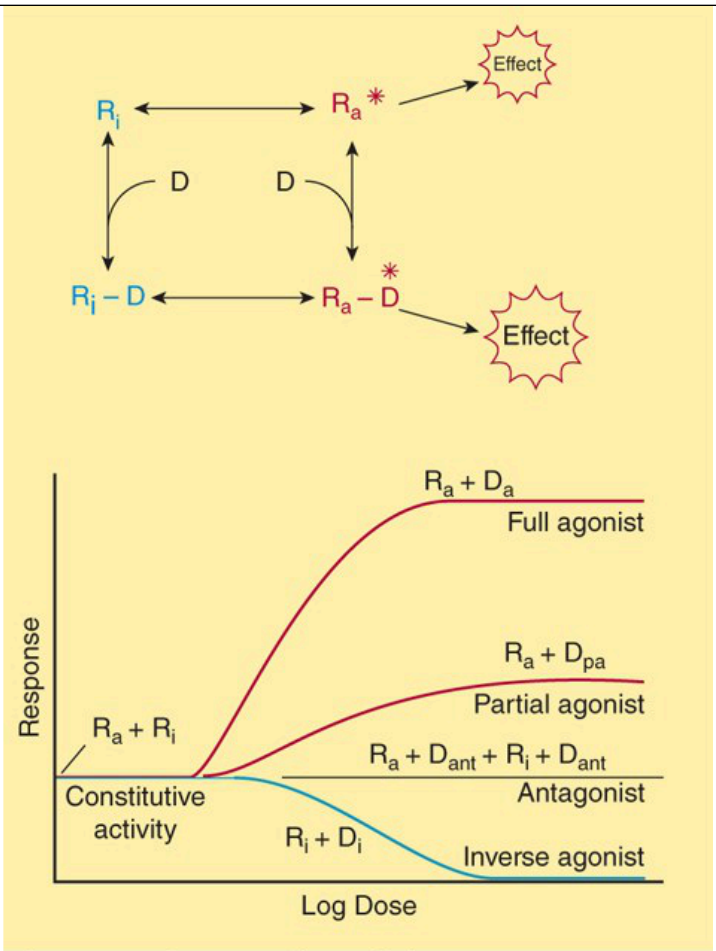
gonists, Partial Agonists, and Inverse Agonists

ure 1–3 describes a useful model of drug-receptor interactions. As indicated, the receptor is postulated to exist partially in the inactive, functional form (R_i) and partially in the activated form (R_a). Thermodynamic considerations indicate that even in the absence of any agonist, so he receptor pool must exist in the R_a form some of the time and may produce the same physiologic effect as agonist-induced activity. This effect, urring in the absence of agonist, is termed **constitutive** or **basal activity.** Agonists have a much higher affinity for the R_a configuration and bilize it, so that a large percentage of the total pool resides in the R_a–D fraction and a large effect is produced. The recognition of constitutive acti y depend on the receptor density, the concentration of coupling molecules (if a coupled system), and the number of effectors in the system.

RE 1–3

odel of drug-receptor interaction. The hypothetical receptor is able to assume two conformations. In the R_i conformation, it is inactive and duces no effect, even when combined with a drug molecule. In the R_a conformation, the receptor can activate downstream mechanisms that duce a small observable effect, even in the absence of drug (constitutive activity). In the absence of drugs, the two isoforms are in equilibrium, an R_i form is favored. Conventional full agonist drugs have a much higher affinity for the R_a conformation, and mass action thus favors the formatio he R_a–D complex with a much larger observed effect. Partial agonists have an intermediate affinity for both R_i and R_a forms. Conventional agonists, according to this hypothesis, have equal affinity for both receptor forms and maintain the same level of constitutive activity. Inverse nists, on the other hand, have a much higher affinity for the R_i form, reduce constitutive activity, and may produce a contrasting physiologic resu

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ny agonist drugs, when administered at concentrations sufficient to saturate the receptor pool, can activate their receptor-effector systems to th ximum extent of which the system is capable; that is, they cause a shift of almost all of the receptor pool to the R_a–D pool. Such drugs are termed **l agonists.** Other drugs, called **partial agonists,** bind to the same receptors and activate them in the same way but do not evoke as great a ponse, no matter how high the concentration. In the model in Figure 1–3, partial agonists do not stabilize the R_a configuration as fully as full nists, so that a significant fraction of receptors exists in the R_i–D pool. Such drugs are said to have low **intrinsic efficacy.** Because they occupy t e receptor site, partial agonists can also prevent access by full agonists. Thus, pindolol, a β-adrenoceptor partial agonist, may act either as an nist (if no full agonist is present) or as an antagonist (if a full agonist such as epinephrine is present). (See Chapter 2.) Intrinsic efficacy is ependent of affinity (as usually measured) for the receptor.

he same model, conventional antagonist action can be explained as fixing the fractions of drug-bound R_i and R_a in the same relative amounts as i absence of any drug. In this situation, no change in activity will be observed, so the drug will appear to be without effect. However, the presence antagonist at the receptor site will block access of agonists to the receptor and prevent the usual agonist effect. Such blocking action can be ter **utral antagonism.**

at will happen if a drug has a much stronger affinity for the R_i than for the R_a state and stabilizes a large fraction in the R_i–D pool? In this scenario g will reduce any constitutive activity, thus resulting in effects that are the opposite of the effects produced by conventional agonists at that eptor. Such drugs are termed **inverse agonists** (Figure 1–3). One of the best documented examples of such a system is the γ-aminobutyric acid BA_A) receptor-effector (a chloride channel) in the nervous system. This receptor is activated by the endogenous transmitter GABA and causes ibition of postsynaptic cells. Conventional exogenous agonists such as benzodiazepines also facilitate the receptor-effector system and cause BA-like inhibition with sedation as the therapeutic result. This sedation can be reversed by conventional neutral antagonists such as flumazenil.

erse agonists of this receptor system cause anxiety and agitation, the inverse of sedation (see Chapter 22). Similar inverse agonists have been fou β adrenoceptors, histamine H_1 and H_2 receptors, and several other receptor systems.

uration of Drug Action

mination of drug action can result from several processes. In some cases, the effect lasts only as long as the drug occupies the receptor, and sociation of drug from the receptor automatically terminates the effect. In many cases, however, the action may persist after the drug has sociated because, for example, some coupling molecule is still present in activated form. In the case of drugs that bind covalently to the receptor , the effect may persist until the drug-receptor complex is destroyed and new receptors or enzymes are synthesized, as described previously for irin. In addition, many receptor-effector systems incorporate desensitization mechanisms for preventing excessive activation when agonist lecules continue to be present for long periods. (See Chapter 2 for additional details.)

eceptors and Inert Binding Sites

function as a receptor, an endogenous molecule must first be **selective** in choosing ligands (drug molecules) to bind; and second, it must **chang function** upon binding in such a way that the function of the biologic system (cell, tissue, etc) is altered. The selectivity characteristic is required id constant activation of the receptor by promiscuous binding of many different ligands. The ability to change function is clearly necessary if the nd is to cause a pharmacologic effect. The body contains a vast array of molecules that are capable of binding drugs, however, and not all of thes ogenous molecules are regulatory molecules. Binding of a drug to a nonregulatory molecule such as plasma albumin will result in no detectable nge in the function of the biologic system, so this endogenous molecule can be called an **inert binding site.** Such binding is not completely hout significance, however, because it affects the distribution of drug within the body and determines the amount of free drug in the circulation. h of these factors are of pharmacokinetic importance (see also Chapter 3).

armacokinetic Principles

ractical therapeutics, a drug should be able to reach its intended site of action after administration by some convenient route. In many cases, the ive drug molecule is sufficiently lipid-soluble and stable to be given as such. In some cases, however, an inactive precursor chemical that is readil orbed and distributed must be administered and then converted to the active drug by biologic processes—inside the body. Such a precursor mical is called a **prodrug.**

nly a few situations is it possible to apply a drug directly to its target tissue, eg, by topical application of an anti-inflammatory agent to inflamed s ucous membrane. Most often, a drug is administered into one body compartment, eg, the gut, and must move to its site of action in another partment, eg, the brain in the case of an antiseizure medication. This requires that the drug be **absorbed** into the blood from its site of inistration and **distributed** to its site of action, **permeating** through the various barriers that separate these compartments. For a drug given lly to produce an effect in the central nervous system, these barriers include the tissues that make up the wall of the intestine, the walls of the illaries that perfuse the gut, and the blood-brain barrier, the walls of the capillaries that perfuse the brain. Finally, after bringing about its effect, g should be **eliminated** at a reasonable rate by metabolic inactivation, by excretion from the body, or by a combination of these processes.

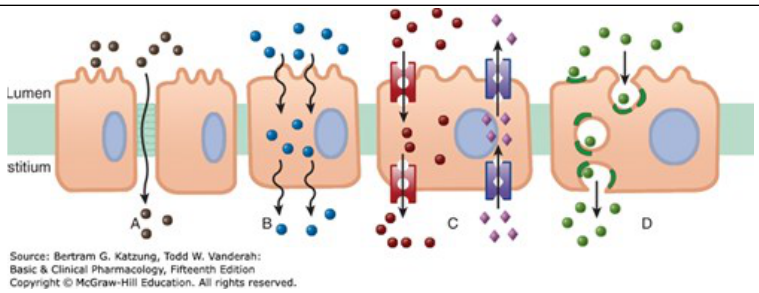
ermeation

g permeation proceeds by several mechanisms. Passive diffusion in an aqueous or lipid medium is common, but active processes play a role in t vement of many drugs, especially those whose molecules are too large to diffuse readily (Figure 1–4). Drug **vehicles** can be very important in ilitating transport and permeation, eg, by encapsulating the active agent in liposomes and in regulating release, as in slow release preparations. wer methods of facilitating transport of drugs by coupling them to **nanoparticles** are under investigation.

RE 1–4

chanisms of drug permeation. Drugs may diffuse passively through aqueous channels in the intercellular junctions (eg, tight junctions, **A**), or ough lipid cell membranes (**B**). Drugs with the appropriate characteristics may be transported by carriers into or out of cells (**C**). Very impermeant gs may also bind to cell surface receptors (dark binding sites), be engulfed by the cell membrane (endocytosis), and then be released inside the c xpelled via the membrane-limited vesicles out of the cell into the extracellular space (exocytosis, **D**).

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queous diffusion

eous diffusion occurs within the larger aqueous compartments of the body (interstitial space, cytosol, etc) and across epithelial membrane tight ctions and the endothelial lining of blood vessels through aqueous pores that—in some tissues—permit the passage of molecules as large as MW 000–30,000.* See Figure 1–4A.

eous diffusion of drug molecules is usually driven by the concentration gradient of the permeating drug, a downhill movement described by Fic (see below). Drug molecules that are bound to large plasma proteins (eg, albumin) do not permeate most vascular aqueous pores. If the drug is rged, its flux is also influenced by electrical fields (eg, the membrane potential and—in parts of the nephron—the transtubular potential).

e capillaries of the brain, the testes, and some other tissues are characterized by the absence of pores that permit aqueous diffusion. They may a tain high concentrations of drug export pumps (MDR pump molecules; see text). These tissues are therefore protected or "sanctuary" sites from ny circulating drugs.

ipid diffusion

id diffusion is the most important limiting factor for drug permeation because of the large number of lipid barriers that separate the compartme he body. Because these lipid barriers separate aqueous compartments, the **lipid:aqueous partition coefficient** of a drug determines how dily the molecule moves between aqueous and lipid media. In the case of weak acids and weak bases (which gain or lose electrical charge-bearin tons, depending on the pH), the ability to move from aqueous to lipid or vice versa varies with the pH of the medium, because charged molecules ract water molecules. The ratio of lipid-soluble form to water-soluble form for a weak acid or weak base is expressed by the Henderson-Hasselbal ation (described in the following text). See Figure 1–4B.

pecial carriers

cial carrier molecules exist for many substances that are important for cell function and too large or too insoluble in lipid to diffuse passively ough membranes, eg, peptides, amino acids, and glucose. These carriers bring about movement by active transport or facilitated diffusion and, ike passive diffusion, are selective, saturable, and inhibitable. Because many drugs are or resemble such naturally occurring peptides, amino aci ugars, they can use these carriers to cross membranes. See Figure 1–4C.

ny cells also contain less selective membrane carriers that are specialized for expelling foreign molecules. One large family of such transporters ds adenosine triphosphate (ATP) and is called the ABC (ATP-binding cassette) family. This family includes the **P-glycoprotein** or **multidrug istance type 1 (MDR1) transporter** found in the brain, testes, and other tissues, and in some drug-resistant neoplastic cells (Table 1–3). Simil nsport molecules from the ABC family, the **multidrug resistance-associated protein (MRP)** transporters, play important roles in the excretio ome drugs or their metabolites into urine and bile and in the resistance of some tumors to chemotherapeutic drugs. Genomic variation in the ression of these transporters has a profound effect on sensitivity to these drugs (see Chapter 5). Several other transporter families have been ntified that do not bind ATP but use ion gradients to drive transport. Some of these (the solute carrier [SLC] family) are particularly important in t ake of neurotransmitters across nerve-ending membranes. The latter carriers are discussed in more detail in Chapter 6.

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ABLE 1–3

ome transport molecules important in pharmacology.

Transporter	Physiologic Function	Pharmacologic Significance
NET	Norepinephrine reuptake from synapse	Target of cocaine and some tricyclic antidepressants
SERT	Serotonin reuptake from synapse	Target of selective serotonin reuptake inhibitors and some tricyclic antidepressants
VMAT	Transport of dopamine and norepinephrine into adrenergic vesicles in nerve endings	Target of reserpine and tetrabenazine
MDR1	Transport of many xenobiotics out of cells	Increased expression confers resistance to certain anticancer drugs; inhibition increases blood levels of digoxin
MRP1	Leukotriene secretion	Confers resistance to certain anticancer and antifungal drugs

DR1, multidrug resistance protein-1; MRP1, multidrug resistance-associated protein-1; NET, norepinephrine transporter; SERT, serotonin reuptake transporter; MAT, vesicular monoamine transporter.

ndocytosis and exocytosis

w substances are so large or impermeant that they can enter cells only by endocytosis, the process by which the substance is bound at a cell-face receptor, engulfed by the cell membrane, and carried into the cell by pinching off of the newly formed vesicle inside the membrane. The stance can then be released into the cytosol by breakdown of the vesicle membrane (Figure 1–4D). This process is responsible for the transport min B_{12}, complexed with a binding protein (intrinsic factor) across the wall of the gut into the blood. Similarly, iron is transported into hemoglobi thesizing red blood cell precursors in association with the protein transferrin. Specific receptors for the binding proteins must be present for thi cess to work.

reverse process (exocytosis) is responsible for the secretion of many substances from cells. For example, many neurotransmitter substances ar red in membrane-bound vesicles in nerve endings to protect them from metabolic destruction in the cytoplasm. Appropriate activation of the ner ing causes fusion of the storage vesicle with the cell membrane and expulsion of its contents into the extracellular space (see Chapter 6).

ick's Law of Diffusion

passive flux of molecules down a concentration gradient is given by Fick's law:

$$\text{x (moles per unit time)} = (C_1 - C_2) \times \frac{\text{Area} \times \text{Permeability coefficient}}{\text{Thickness}}$$

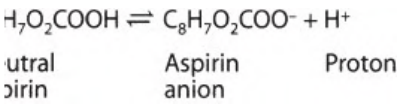
ere C_1 is the higher concentration, C_2 is the lower concentration, area is the cross-sectional area of the diffusion path, permeability coefficient is a asure of the mobility of the drug molecules in the medium of the diffusion path, and thickness is the length of the diffusion path. In the case of lip usion, the lipid:aqueous partition coefficient is a major determinant of mobility of the drug because it determines how readily the drug enters th d membrane from the aqueous medium.

onization of Weak Acids and Weak Bases; the Henderson-Hasselbalch Equation

electrostatic charge of an ionized molecule attracts water dipoles and results in a polar, relatively water-soluble and lipid-insoluble complex.

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ause lipid diffusion depends on relatively high lipid solubility, ionization of drugs may markedly reduce their ability to permeate membranes. A v e percentage of the drugs in use are weak acids or weak bases; Table 1–4 lists some examples. For drugs, a weak acid is best defined as a neutral lecule that can reversibly dissociate into an anion (a negatively charged molecule) and a proton (a hydrogen ion). For example, aspirin dissociate ollows:



ABLE 1–4

onization constants of some common drugs.

Drug	pK_a[1]	Drug	pK_a[1]	Drug	pK_a[1]
Weak acids		**Weak bases**		**Weak bases (cont'd)**	
Acetaminophen	9.5	Albuterol (salbutamol)	9.3	Isoproterenol	8.6
Acetazolamide	7.2	Allopurinol	9.4, 12.3[2]	Lidocaine	7.9
Ampicillin	2.5	Alprenolol	9.6	Metaraminol	8.6
Aspirin	3.5	Amiloride	8.7	Methadone	8.4
Chlorothiazide	6.8, 9.4[2]	Amiodarone	6.6	Methamphetamine	10.0
Chlorpropamide	5.0	Amphetamine	9.8	Methyldopa	10.6
Ciprofloxacin	6.1, 8.7[2]	Atropine	9.7	Metoprolol	9.8
Cromolyn	2.0	Bupivacaine	8.1	Morphine	7.9
Ethacrynic acid	2.5	Chlordiazepoxide	4.6	Nicotine	7.9, 3.1[2]
Furosemide	3.9	Chloroquine	10.8, 8.4	Norepinephrine	8.6
Ibuprofen	4.4, 5.2[2]	Chlorpheniramine	9.2	Pentazocine	7.9
Levodopa	2.3	Chlorpromazine	9.3	Phenylephrine	9.8
Methotrexate	4.8	Clonidine	8.3	Physostigmine	7.9, 1.8[2]
Methyldopa	2.2, 9.2[2]	Cocaine	8.5	Pilocarpine	6.9, 1.4[2]
Penicillamine	1.8	Codeine	8.2	Pindolol	8.6
Pentobarbital	8.1	Cyclizine	8.2	Procainamide	9.2
Phenobarbital	7.4	Desipramine	10.2	Procaine	9.0
Phenytoin	8.3	Diazepam	3.0	Promethazine	9.1

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