Chapter 54

Drug Absorption, Distribution, Metabolism, and Excretion

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INTRODUCTION

Drugs differ widely in their pharmacodynamic effects and clinical applications, as well as in penetration, absorption, and usual route of administration. They also differ in their distribution among the body tissues, and in disposition and mode of termination of action. Certain general principles that help explain the differences have both pharmaceutical and therapeutic implications. These principles facilitate an understanding of both the features that are common to a class of drugs and the differences among the members of that class.

To have the desired action, a drug must achieve absorption and transport to the appropriate tissue or organ, penetrate to the responding cell surface or subcellular structure, and elicit a response or alter ongoing processes. The drug may be distributed simultaneously or sequentially to a number of tissues, be bound or stored, be metabolized to inactive or active products, or be excreted. The basic entry, movement, and disposition of drugs and metabolites within the body are summarized in Figure 54-1. Each of the processes or events depicted relates importantly to therapeutic and toxic effects of a drug and to the mode of administration, and drug design must take each into account. The extent to which all the components of absorption, distribution, metabolism (biotransformation), and elimination apply varies enormously with the drug or xenobiotic (the latter being a term widely used to refer to not only drugs but any chemical not part of the normal biochemistry and physiology of the body) and the dose (level of exposure), and to some extent is subject to interindividual variation, the latter often arising from genetic and disease state influences.

Pharmacokinetics is the science that treats the rate and extent of absorption, rates of distribution among body compartments, rate of elimination, and related phenomena. Because of its importance, other chapters in this book are devoted to the subject. This chapter will consider the physiological bases of the processes.

STRUCTURE AND PROPERTIES OF MEMBRANES

In almost all stages of absorption, distribution, metabolism (biotransformation), and elimination, a drug must pass through several to many biological membranes during the processes. Since membranes are traversed in all of these events, a brief description of biological membranes and membrane processes is in order, as well as the relationship of the physicochemical properties of a drug molecule to penetration and transport.

Numerous sophisticated techniques have established the nature of the plasma, mitochondrial, nuclear, and other cell membranes. The description of the plasma membrane that follows is much oversimplified, but it will suffice to provide a background for an understanding of drug penetration into and through membranes. The cell membrane has been characterized as a bimolecular layer of lipid material entrained between two parallel monomolecular layers of protein. However, rather than forming a continuous layer, the protein layer comprises "islands" sporadically scattered over the surfaces. For many proteins, much of the protein is below the surface and within the fatty bilayer. The lipid bilayer can be envisaged as a somewhat orderly, lamellar array of phospholipid molecules associated tail-to-tail, each tail being an alkyl chain or steroid group, and the heads being polar groups. The disorder that does exist is the result of the different degrees of saturation of the fatty acids and the interspersed cholesterol molecules that break up the close packing of the fatty acid tails. Cholesterol maintains the mechanical stability of cell membranes, is a determinant of membrane fluidity, and—with relevance to drug passage across membranes—decreases permeability to water-soluble molecules. Moreover, the lamellar portion is penetrated by large globular proteins with a highly hydrophobic interior (like the lipid layers), and by some fibrous proteins as well.

The plasma membrane is asymmetrical. The lipid composition varies from cell type to cell type and perhaps from site to site on the same membrane. There are, for example, differences between the membrane of the endoplasmic reticulum and the plasma membrane, even though the membranes are co-extensive. The membrane surface facing the cytoplasm is rich in phosphatidylethanolamine and phosphatidylserine, while the surface facing the outside is rich in phosphatidylcholine and sphingomyelin. Oligosaccharide chains linked to lipids (glycolipids), and oligo- and polysaccharide chains attached to proteins (glycoproteins) are confined to non-cytosolic facing surfaces. Sugar moieties attached to the outer proteins are most often attached to the asparagine residue. These sugar moieties are important to both cellular and immunological recognition and adhesion, and they have other functions as well. Where membranes are double, the inner and outer layers differ considerably; the inner and outer membranes of mitochondria have strikingly different compositions and properties.

The cell membrane appears to be perforated by water-filled pores of various sizes, varying from about 4 to 10 Å, most of which are about 7 Å. Probably all major ion (water-filled) channels penetrate the large proteins assemblies that traverse the membrane. Through these pores pass inorganic ions and small organic molecules. Among the common inorganic ions, because sodium ions are more hydrated than potassium and chloride ions, they are larger and do not pass as freely through the pores as do potassium and chloride. Ion (ion plus water) movement can be by diffusion down a chemical concentration gradient. However, movement of ions through the pores can be controlled by counterion transport, or expenditure of intracellular

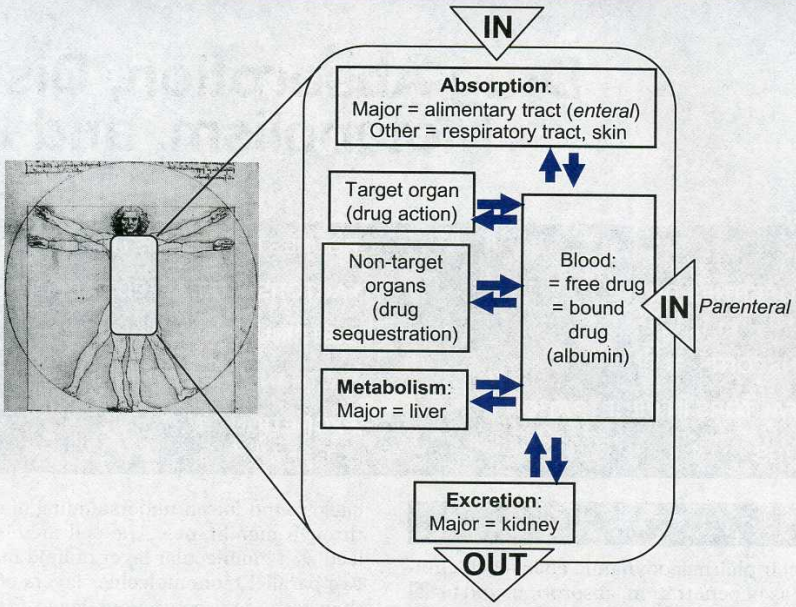

Figure 54-1. Interrelationship of the major components of drug entry, distribution, metabolism, and elimination within the body.

energy—adenosine triphosphate (ATP) hydrolysis—by so-called ABC transporters (see Excretion in this chapter). Vascular endothelium appears to have pores at least as large as 40 Å, but these seem to be interstitial passages rather than transmembrane pores. Lipid molecules small enough to pass through the cell membrane pores may do so, but they have a higher probability of entering into the lipid layer (since pores constitute less than 1 percent of the cell surface upon which the drug molecule impinges); from there these molecules will equilibrate chemically with the interior of the cell. Other proteins may be confined to one or the other surface and not traverse the membrane. Often proteins on the inner surface protein are linked to intracellular structural proteins that contribute to cell shape.

DIFFUSION AND TRANSPORT

Transport is the movement of a drug from one place to another within the body. The drug may diffuse freely in uncombined form with a kinetic energy appropriate to its thermal environment, or it may move in combination with extracellular or cellular constituents, sometimes in connection with energy-yielding processes that allow the molecule or complex to overcome barriers to simple diffusion.

SIMPLE NONIONIC DIFFUSION AND PASSIVE TRANSPORT

Molecules in solution move in a purely random fashion, provided they are not charged and moving in an electrical gradient. Such random movement is called diffusion; if the molecule is uncharged, it is called nonionic diffusion. In a population of drug molecules, the probability that during unit time any drug molecule will move across a boundary is directly proportional to the number of molecules adjoining that boundary and, therefore, to the drug concentration. Except at dilutions so extreme that only a few molecules are present, the actual rate of movement (molecules per unit time) is directly proportional to the probability of movement and, therefore, to the concentration. Once molecules have passed through the boundary to the opposite side, their random motion may cause some to return and others to continue to move farther away from the boundary. The rate of return is likewise proportional to the concentration on the opposite side of the boundary. It follows that, although molecules are moving in both directions, there will be a net movement from the region of higher to that of lower concentration, and the net transfer will be proportional to the concentration differential. If the boundary is a membrane, which has both substance and dimension, the rate of movement is also directly proportional to the permeability and inversely proportional to the thickness. These factors combine into Fick's law of diffusion:

$$dQ/dt = \bar{D}A(C_1 - C_2)/x$$

where Q is the net quantity of drug transferred across the membrane, t is time, C_1 is the concentration on one side and C_2 that on the other, x is the thickness of the membrane, A is the area, and is the diffusion coefficient, related to permeability. Since a biological membrane is heterogeneous, with pores of different sizes and probably with varying thickness and composition, both and x probably vary from place to place. Nevertheless, some mean values can be assumed. It is customary to combine the membrane factors into a single constant, called a permeability constant or coefficient, P, so that $P = / x$, and A in the equation above has unit value. The rate of net transport (diffusion) across the membrane then becomes:

$$dQ/dT = P(C_1 - C_2)$$

As diffusion continues, C_1 approaches C_2, and the net rate, dQ/dt, approaches zero in exponential fashion, characteristic of a first-order process. Equilibrium is defined as that state in which $C_1 = C_2$. The equilibrium is, of course, dynamic, with equal numbers of molecules being transported in each direction during unit time. If water also is moving through the membrane, it may either facilitate the movement of drug or impede it, according to the relative directions of movement of water and drug; this effect of water movement is called solvent drag.

IONIC OR ELECTROCHEMICAL DIFFUSION

If a drug is ionized, the transport properties are modified. The probability of penetrating the membrane is still a function of concentration, but it is also a function of the potential difference or electrical gradient across the membrane. A cationic

drug molecule will be repelled from the positive charge on the outside of the membrane, and only those molecules with a high kinetic energy will pass through the ion barrier. If the cation is polyvalent, it may not penetrate at all.

Once inside the membrane, a cation will be simultaneously attracted to the negative charge on the intracellular surface of the membrane and repelled by the outer surface; it is said to be moving along the electrical gradient. If it is also moving from a higher toward a lower concentration, it is said to be moving along its electrochemical gradient, which is the sum of the influences of the electrical field and the concentration differential across the membrane.

Once inside the cell, cations will tend to be kept inside by the attractive negative charge on the interior of the cell, and the intracellular concentration of drug will increase until—by sheer numbers of accumulated drug particles—the rate of outward diffusion or mass escape equals that of inward transport. At this point electrochemical equilibrium is said to have occurred. At electrochemical equilibrium at body temperature (37°C), ionized drug molecules will be distributed according to the Nernst equation:

$$\pm \log C_0/C_i = ZE/61$$

where C_0 is the molar extracellular and C_i the intracellular concentration, Z is the number of charges per molecule, and E is the membrane potential in millivolts. Log C_0/C_i is positive when the molecule is negatively charged and negative when the molecule is positively charged.

FACILITATED DIFFUSION

Sometimes a substance moves more rapidly through a biological membrane than can be accounted for by the process of simple diffusion. This accelerated movement is termed facilitated diffusion. It is due to the presence of a special molecule within the membrane, called a carrier, with which the transported substance combines. There is considered to be greater permeability to the carrier–drug complex than to the drug alone, so that the transport rate is enhanced. After the complex has traversed the membrane, it dissociates. For the carrier process to be continuous, either the carrier must return to the original side of the membrane to be used again, or it must constantly be produced on one side and eliminated on the other. Many characteristics of facilitated diffusion, formerly attributed to ion carriers, can be explained by ion exchange. Facilitated diffusion only transports a molecule along its electrochemical gradient.

ACTIVE TRANSPORT

Active transport can be defined as energy-dependent movement of a substance through a biological membrane against an electrochemical gradient. It is characterized as follows:

1. The substance is transported from a region of lower to one of higher electrochemical activity.
2. Metabolic poisons (that most often reduce ATP concentrations) interfere with transport.
3. The transport system shows a requirement for specific chemical structures.
4. Closely related chemicals are competitive for the transport system.
5. The transport rate approaches an asymptote (i.e., saturates) as concentration increases.

Characteristics 3, 4, and 5 are in common with those of carrier-mediated facilitated diffusion.

Many drugs are secreted by active transport from the renal tubules into urine, from liver cells into bile or blood, from intestinal cells into the lumen of the gastrointestinal (GI) tract, or from the cerebrospinal fluid into blood, but the role of active transport of drugs in the distribution into most body compartments and tissues has been less extensively documented, although it is now an active area of research. Active transport is often required for the movement of drug metabolites, entities that generally have less lipid solubility than the parent drug, across cell membranes.

PINOCYTOSIS AND EXOCYTOSIS

Many (perhaps all) cells are capable of a type of phagocytosis called pinocytosis. The cell membrane has been observed to invaginate into a sac-like structure containing extracellular materials and then pinch off the sac at the membrane, so that the sac remains as a vesicle or vacuole within the interior of the cell. Because metabolic activity is required and because an extracellular substance can be transported against an electrochemical gradient, pinocytosis shows some of the same characteristics as active transport. However, pinocytosis is relatively slow and inefficient compared with most active transport, except in GI absorption, where for some xenobiotics pinocytosis may be of some importance.

It is not known to what extent pinocytosis contributes to the transport of most drugs, but many macromolecules and even larger particles can be absorbed by the gut. Exocytosis is the reverse of pinocytosis. Granules, vacuoles, or other organelles within the cell move to the cell membrane, fuse with it, and extrude their contents into the interstitial space.

PHYSICOCHEMICAL FACTORS IN PENETRATION

Drugs and other substances may traverse the membrane primarily either through the pores, or by movement into the membrane lipids and subsequent diffusion from the membrane into the cytosol or other fluid on the far side of the membrane. The physicochemical prerequisites differ according to which route is taken. To pass through the pores, the *diameter* of the molecule must be smaller than the pore, but the molecule can be longer than the pore diameter. The probability that a long, thin molecule will be suitably oriented, however, is low unless there is also bulk flow, and therefore transmembrane passage of such molecules is slow.

Water-soluble molecules with low lipid solubility are usually thought to pass through the membrane mainly via the pores. If there is a membrane carrier or active-transport system, a low solubility of the drug in membrane lipids is no impediment to penetration, because the drug–carrier complex is assumed to have an appropriate solubility, and energy from an active-transport system enables the drug to penetrate the energy barrier imposed by the lipids. Actually, the lipids are not an important energy barrier; rather, the barrier is the force of attraction of the solvent water for its dipolar-to-polar solute, so that it is difficult for the solute to leave the water and enter the lipid.

Drugs with a high solubility in the membrane lipids pass easily through the membrane. Even when their dimensions are small enough to permit passage through pores, lipid-soluble drugs primarily pass through the membrane lipids, not only because chemical partition favors the lipid phase but also because, as mentioned previously, the surface area occupied by pores is only a small fraction of the total membrane area.

LIPID SOLUBILITY AND PARTITION COEFFICIENTS

Over a century ago, the importance of lipid solubility in the penetration and absorption of drugs was being investigated. Eventually it was recognized that more important than lipid solubility was the lipid-to-water partition (or distribution) coefficient; in other words, a high lipid solubility does not favor penetration unless the water solubility is low enough so that the drug is not entrained in the aqueous phase. When the water solubility of a substance is so low that a significant concentration in water or extracellular fluid cannot be achieved, absorption may be negligible despite a favorable partition coefficient. Hence, such substances as mineral oil or petrolatum are virtually unabsorbed. The optimal partition coefficient for permeation of the skin appears to be lower than that for the permeation of the cell membrane, perhaps being as low as unity.

DIPOLARITY, POLARITY, AND NONIONIC DIFFUSION

The partition coefficient of a drug depends upon the polarity and the size of the molecule. Drugs with a high dipole moment, even though nonionized, have low lipid solubility and hence penetrate poorly. An example of a highly dipolar substance with a low partition coefficient, which does not penetrate into cells, is sulfisoxazole. Sulfadiazine is somewhat less dipolar, has a chloroform-to-water partition coefficient 10 times that of sulfisoxazole, and readily penetrates cells. Ionization not only greatly diminishes lipid solubility but also may impede passage through charged membranes.

It is often stated that ionized molecules do not penetrate membranes, except for ions of small diameter. This is not necessarily true because of the presence of membrane carriers for some ions that effectively shield or neutralize the charge (formation of ion pairs). The renal tubular transport systems, which transport such obligate ions as tetraethylammonium, probably form ion pairs. Furthermore, if an ionized molecule has a large non-polar moiety such that appreciable lipid solubility is imparted to the molecule despite the charge, the drug may penetrate, though usually at a slow rate. Nevertheless, when a drug is a weak acid or base, the nonionized form, with a favorable partition coefficient, passes through a biological membrane so much more readily than the ionized form that for all practical purposes, only the nonionized form is said to pass through the membrane. This has become known as the principle of nonionic diffusion.

ABSORPTION OF DRUGS

Absorption is the process of movement of a drug from the site of application into the extracellular compartment of the body. Inasmuch as there is a great similarity among the various membranes through which a drug may pass to gain access to the extracellular fluid, it might be expected that the particular site of application (or route) would make little difference to the successful absorption of the drug. Actually it makes a great deal of difference; many factors, other than the structure and composition of the membrane, determine the ease with which a drug is absorbed. These factors are discussed in the following sections, along with an account of the ways that drug formulations can be manipulated to alter the ability of a drug to be absorbed readily.

ROUTES OF ADMINISTRATION

Drugs can be administered by many different routes, including oral, rectal, sublingual or buccal, parenteral, inhalation, and topical. The choice of a route depends upon both convenience and necessity.

ORAL ROUTE

This is obviously the most convenient route for access to the systemic circulation, providing that various factors do not militate against it. Oral administration does not always give rise to plasma concentrations sufficiently high to be effective; some drugs are absorbed unpredictably or erratically; patients occasionally have an absorption malfunction. Drugs cannot be given by mouth to patients who have GI intolerance, are being prepared for anesthesia, or have had GI surgery. Oral administration is also precluded in comatose patients.

In the drug development setting, Lipinski's "Rule of Five" predicts that, in general, an orally active drug has no more than one violation of the following criteria:

- not more than five hydrogen bond donors (oxygen or nitrogen atoms with one or more hydrogen atoms)
- not more than ten (2 × 5) hydrogen bond acceptors (nitrogen or oxygen atoms)
- a molecular mass not greater than (100 × 5) 500 daltons
- an octanol-to-water partition coefficient log *P* not greater than 5.

RECTAL ROUTE

Drugs that are ordinarily administered by the oral route can usually be administered by injection or by the alternative lower enteral route, through the anal portal into the rectum or lower intestine. With regard to the latter, rectal suppositories or retention enemas were formerly used quite frequently, but their popularity has abated somewhat as a result of improvements in parenteral preparations. Nevertheless, they continue to be valid—and sometimes very important—ways of administering a drug, especially in pediatric and geriatric patients, and retention enema may offer a useful substitute for the oral route. However, rectal suppositories may be inadequate when rapid absorption and high plasma levels are required.

SUBLINGUAL OR BUCCAL ROUTE

Even though an adequate plasma concentration may eventually be achievable by the oral route, it may rise much too slowly for use in some situations when a rapid response is desired. In such situations parenteral therapy is usually indicated. However, patients with angina pectoris may get quite prompt relief from an acute attack by the sublingual or buccal administration of nitroglycerin, so that parenteral administration can be avoided. When only small amounts of drugs are required to gain access to the blood, the buccal route may be very satisfactory, providing the physicochemical prerequisites for absorption by this route are present in the drug and dosage form.

PARENTERAL ROUTES

These routes, by definition, include any route other than the oral-GI (enteral) tract, but in common medical usage the term excludes topical administration and includes only various hypodermic routes. Parenteral administration includes the intravenous, intramuscular, and subcutaneous routes. Parenteral routes are an option whenever enteral routes are contraindicated or are inadequate.

The intravenous route may be preferred on occasion, even when a drug may be well absorbed by the oral route. There is no delay imposed by absorption before the administered drug reaches the circulation, and blood levels rise virtually as rapidly as the time necessary to empty the syringe or infusion bottle. Consequently, the intravenous route is the preferred route when an emergency calls for an immediate response.

In addition to the rapid rise in plasma concentration of drug, another advantage of intravenous administration is the greater predictability of the peak plasma concentration, which with some drugs can be calculated with a fair degree of precision. Smaller doses are generally required by the intravenous than by other routes, but this usually affords no advantage, inasmuch as the sterile injectable dosage form costs more than enteric preparations, and the requirements for medical or paramedical supervision of administration also may add to the cost and inconvenience.

Because of the rapidity with which drug enters the circulation, dangerous side effects to the drug may occur that often are not extant by other routes. The principal untoward effect is a depression of cardiovascular function. Consequently, some drugs must be given quite slowly to avoid vasculotoxic concentrations of drug in the plasma. Acute, serious allergic responses are also more likely to occur by the intravenous route than by other routes.

Many drugs are too irritating to be given by the oral, intramuscular, or subcutaneous route, and must of necessity be given intravenously. However, such drugs also may cause damage to the veins (phlebitis) or, if extravasated, cause necrosis around the injection site. Consequently, such irritant drugs may be diluted in isotonic solutions of saline, dextrose, or other media, and given by slow infusion, providing that the slower rate of delivery does not negate the purpose of the administration in emergency situations.

Absorption by the intramuscular route is relatively fast, and this parenteral route may be used when an immediate effect

is not required but a prompt effect is desirable. Intramuscular deposition can also be made of certain repository preparations where rapid absorption is not desired. Absorption from an intramuscular depot is more predictable and uniform than from a subcutaneous site. Irritation around the injection site is a frequent accompaniment of intramuscular injection, depending upon the drug and other ingredients. Because of the dangers of accidental intravenous injection, medical supervision is generally required. Sterilization is necessary.

In subcutaneous administration, the drug is injected into the connective tissue just below the skin. Absorption is slower than by the intramuscular route but nevertheless can be prompt with some drugs. Often, however, absorption by this route may be no faster than by the oral route. Therefore, when a fairly prompt response is desired with some drugs, the subcutaneous route may not offer much advantage over the oral route, unless for some reason the drug cannot be given orally.

The slower rate of absorption by the subcutaneous route is usually the reason for choosing the route, and the drugs given by this route are usually those for which it is desirable to distribute the drug's action over several hours, to avoid either too intense a response, too short a response, or frequent injections. Examples of drugs given by this route are insulin and sodium heparin, neither of which is absorbed orally, and both of which should be absorbed slowly over many hours. In the treatment of asthma, epinephrine is usually given subcutaneously to avoid the dangers of rapid absorption and consequent dangerous cardiovascular effects. Many repository preparations, including tablets or pellets, are given subcutaneously. As with other parenteral routes, irritation may occur. Sterile preparations are also required. However, medical supervision is not always required, and self-administration by this route is customary with certain drugs, such as insulin.

Intradermal injection, in which the drug is injected into the dermis instead of below it, is rarely used, except in certain diagnostic and test procedures, such as screening for allergic or local irritant responses.

Occasionally, even by the intravenous route, it is not possible, practical, or safe to achieve plasma concentrations high enough so that an adequate amount of drug penetrates into special compartments (e.g., the cerebrospinal fluid) or various cavities (e.g., the pleural cavity). The brain is especially difficult to penetrate with water-soluble drugs. The name blood–brain barrier is applied to the impediment to penetration. When drugs do penetrate, the choroid plexus often secretes them back into the blood very rapidly, so that adequate levels of drugs in the cerebrospinal fluid can be difficult to achieve. Consequently, intrathecal or intraventricular administration may be indicated.

Body cavities such as the pleural cavity are normally wetted by a small amount of effusate that is in diffusion equilibrium with the blood and hence is accessible to drugs. However, infections and inflammations may cause the cavity to fill with serofibrinous exudate that is too dense to be in rapid diffusion equilibrium with the blood. Intracavitary administration thus may be required. It is extremely important that sterile, nonirritating preparations be used for intrathecal or intracavitary administration.

INHALATION ROUTE

Inhalation may be employed for delivering gaseous or volatile substances into the systemic circulation, as with most general anesthetics. Absorption is virtually as rapid as the drug can be delivered into the alveoli of the lungs, since the alveolar and vascular epithelial membranes are quite permeable, blood flow is abundant, and there is a very large surface for absorption.

Aerosols of nonvolatile substances can also be administered by inhalation, but the route is used infrequently for delivery into the systemic circulation because of various factors that contribute to blood concentrations that are erratic or difficult to achieve. Whether or not an aerosol reaches and is retained in pulmonary alveoli depends critically upon particle size. Particles larger than 1 micrometer in diameter tend to settle in the bronchioles and bronchi, whereas particles smaller than 0.5 micrometer fail to settle and mainly are exhaled. Aerosols are employed mostly when the purpose of administration is an action of the drug upon the respiratory tract itself. An example of a drug commonly given as an aerosol is isoproterenol, which is employed to relax the bronchioles during an asthma attack.

TOPICAL ROUTE

Although the stratum corneum is not a membrane in the same sense as a cell membrane, it offers a barrier to diffusion, which is of significance in the topical application of drugs. The stratum corneum consists of several layers of dead, keratinized, cutaneous epithelial cells enmeshed in a matrix of keratin fibers and bound together with cementing desmosomes and penetrating tonofibrils of keratin. Varying amounts of lipids and fatty acids from dying cells, sebum, and sweat are contained among the dead squamous cells. Immediately beneath the layer of dead cells and above the viable epidermal epithelial cells is a layer of keratohyaline granules and various water-soluble substances, such as amino acids, purines, monosaccharides, and urea.

Both the upper and lower layers of the stratum corneum are involved in the cutaneous barrier to penetration. The barrier to penetration from the surface is in the upper layers for water-soluble substances and the lower layers for lipid-soluble substances, and the barrier to the outward movement of water is in the lowest layer.

Topical administration is employed to deliver a drug at, or immediately beneath, the point of application. Although occasionally enough drug is absorbed into the systemic circulation to cause systemic effects, absorption is too erratic for the topical route to be used routinely for systemic therapy. However, various transdermal preparations are employed quite successfully for systemic use. A large number of topical medicaments are applied to the skin, although topical drugs are also applied to the eye, nose, throat, ear, vagina, etc.

In humans, percutaneous absorption probably occurs mainly from the surface. Absorption through the hair follicles occurs, but the follicles in humans occupy too small a portion of the total integument to be of primary importance. Absorption through sweat and sebaceous glands generally appears to be minor. When the medicament is rubbed on vigorously, the amount of the preparation that is forced into the hair follicles and glands is increased. Rubbing also forces some material through the stratum corneum without molecular dispersion and diffusion through the barrier. When the skin is diseased or abraded, the cutaneous barrier may be disrupted or defective, so that percutaneous absorption may be increased. Since much of a drug that is absorbed through the epidermis diffuses into the circulation without reaching a high concentration in some portions of the dermis, systemic administration may be preferred in lieu of, or in addition to, topical administration.

FACTORS THAT AFFECT ABSORPTION

In addition to the physicochemical properties of drug molecules and biological membranes, various factors affect the rate of absorption and determine, in part, the choice of route of administration.

CONCENTRATION

It is self-evident that the concentration, or more exactly, the thermodynamic activity, of a drug in a drug preparation will have an important bearing upon the rate of absorption, since the rate of diffusion of a drug away from the site of administration is directly proportional to the concentration. Thus, a 2 percent solution of lidocaine will induce local anesthesia more rapidly than a 0.2 percent solution. However, drugs administered in solid form are not necessarily absorbed at the maximal rate (see, Physical State of Formulation and Dissolution Rate below).

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