Goodman & Gilman's The Pharmacological Basis of THERAPEUTICS

eleventh edition

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SECTION I

General Principles

CHAPTER 1

PHARMACOKINETICS AND PHARMACODYNAMICS

The Dynamics of Drug Absorption, Distribution, Action, and Elimination

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Numerous factors in addition to a known pharmacological action in a specific tissue at a particular receptor contribute to successful drug therapy. When a drug enters the body, the body begins immediately to work on the drug: absorption, distribution, metabolism (biotransformation), and elimination. These are the processes of *pharmacokinetics*. The drug also acts on the body, an interaction to which the concept of a drug receptor is key, since the receptor is responsible for the selectivity of drug action and for the quantitative relationship between drug and effect. The mechanisms of drug action are the processes of *pharmacodynamics*. The time course of therapeutic drug action in the body can be understood in terms of pharmacokinetics and pharmacodynamics (Figure 1–1).

I. Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination

PHYSICOCHEMICAL FACTORS IN TRANSFER OF DRUGS ACROSS MEMBRANES

The absorption, distribution, metabolism, and excretion of a drug all involve its passage across cell membranes. Mechanisms by which drugs cross membranes and the

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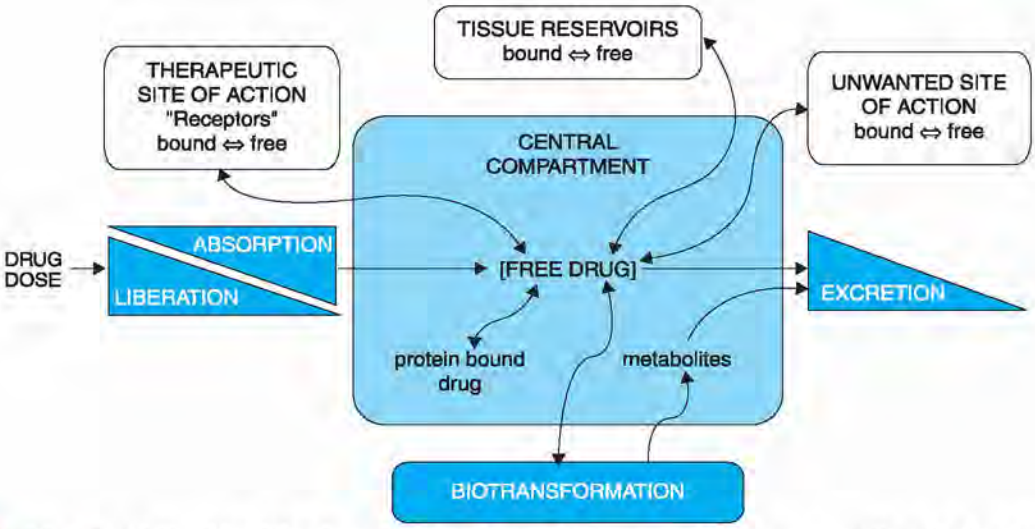

Figure 1–1. The interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its concentration at its sites of action. Possible distribution and binding of metabolites in relation to their potential actions at receptors are not depicted.

physicochemical properties of molecules and membranes that influence this transfer are critical to understanding the disposition of drugs in the human body. The characteristics of a drug that predict its movement and availability at sites of action are its molecular size and shape, degree of ionization, relative lipid solubility of its ionized and nonionized forms, and its binding to serum and tissue proteins.

In most cases, a drug must traverse the plasma membranes of many cells to reach its site of action. Although barriers to drug movement may be a single layer of cells (intestinal epithelium) or several layers of cells and associated extracellular protein (skin), the plasma membrane represents the common barrier to drug distribution.

Cell Membranes. The plasma membrane consists of a bilayer of amphipathic lipids with their hydrocarbon chains oriented inward to the center of the bilayer to form a continuous hydrophobic phase and their hydrophilic heads oriented outward. Individual lipid molecules in the bilayer vary according to the particular membrane and can move laterally and organize themselves with cholesterol (*e.g.*, sphingolipids), endowing the membrane with fluidity, flexibility, organization, high electrical resistance, and relative impermeability to highly polar molecules. Membrane proteins embedded in the bilayer serve as receptors, ion channels, or transporters to transduce electrical or chemical signaling pathways and provide selective targets for drug actions. These proteins may be associated with caveolin and sequestered within caveolae, they may be excluded from caveolae, or they may be organized in signaling domains rich in cholesterol and sphingolipid not containing caveolin.

Cell membranes are relatively permeable to water either by diffusion or by flow resulting from hydrostatic or osmotic differences across the membrane, and bulk flow of water can carry with it drug molecules. However, proteins with drug molecules bound to them are too large and polar for this type of transport to occur; thus, transmembrane movement generally is limited to unbound drug. Paracellular transport through intercellular gaps is sufficiently large that passage across most capillaries is limited by blood flow and not by other factors (*see* below). As described later, this type of transport is an important factor in filtration across glomerular membranes in the kidney. Important exceptions exist in such capillary diffusion, however, because "tight" intercellular junctions are present in specific tissues, and paracellular transport in them is limited. Capillaries of the central nervous system (CNS) and a variety of epithelial tissues have tight junctions (*see* below). Bulk flow of water can carry with it small water-soluble substances, but bulk-flow transport is limited when the molecular mass of the solute exceeds 100 to 200 daltons. Accordingly, most large lipophilic drugs must pass through the cell membrane itself.

Passive Membrane Transport. Drugs cross membranes either by passive processes or by mechanisms involving the active participation of components of the membrane. In passive transport, the drug molecule usually penetrates by diffusion along a concentration gradient by virtue of its solubility in the lipid bilayer. Such transfer is directly proportional to the magnitude of the concentration gradient across the membrane, to the lipid–water partition coefficient of the drug, and to the membrane surface area exposed to the drug. The greater the partition coefficient, the higher is the concentration of drug in the membrane, and the faster is its diffusion. After a steady state is attained, the concentration of the unbound drug is the same on both sides of the membrane if the drug is a nonelectrolyte. For ionic compounds, the steady-state concentrations depend on the electrochemical gradient for the ion and on differences in pH across the membrane, which may influence the state of ionization of the molecule disparately on either side of the membrane.

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