BOX 2–2

DRUG TRANSPORT PATHWAYS AND MECHANISMS

Pathways

There are three main pathways of drug movement across cell membranes. The most common pathway is *direct penetration* of the membrane by lipid-soluble drugs, which are able to dissolve in the lipid layer of the cell membrane. Most systemic drugs are formulated to be lipid soluble so they can move through cell membranes, even oral tablets and capsules that must be sufficiently water soluble to dissolve in the aqueous fluids of the stomach and small intestine.

A second pathway involves passage through *protein channels* that go all the way through the cell membrane. Only a few drugs are able to use this pathway because most drug molecules are too large to pass through the small channels. Small ions (eg, sodium and potassium) use this pathway, but their movement is regulated by specific channels with a gating mechanism. The gate is a flap of protein that opens for a few milliseconds to allow ion movement across the cell membrane, then closes (ie, blocks the channel opening) to prevent additional ion movement. On sodium channels, the gates are located on the outside of the cell membrane; when the gates open, sodium ions (Na^+) move from extracellular fluid into the cell. On potassium channels, the gates are located on the inside of the cell membrane; when the gates open, potassium ions (K^+) move from the cell into extracellular fluid.

The stimulus for opening and closing the gates may be voltage gating or chemical (also called ligand) gating. With voltage gating, the electrical potential across the cell membrane determines whether the gate is open or closed. With chemical gating, a chemical substance (a ligand) binds with the protein forming the channel and changes the shape of the protein to open or close the gate. Chemical gating (eg, by neurotransmitters such as acetylcholine) is very important in the transmission of signals from one nerve cell to another and from nerve cells to muscle cells to cause muscle contraction.

The third pathway involves *carrier proteins* that transport molecules from one side of the cell membrane to the other. All of the carrier proteins are selective in the substances they transport; a drug's structure determines which carrier will transport it. These transport systems are an important means of moving drug molecules through the body. They are used, for example, to carry oral drugs from the intestine to the bloodstream, to carry hormones to their sites of action inside body cells, and to carry drug molecules from the blood into renal tubules.

Mechanisms

Once absorbed into the body, drugs are transported to and from target cells by such mechanisms as passive diffusion, facilitated diffusion, and active transport.

Passive diffusion, the most common mechanism, involves movement of a drug from an area of higher concentration to one of lower concentration. For example, after oral administration, the initial concentration of a drug is higher in the gastrointestinal tract than in the blood. This promotes movement of the drug into the bloodstream. When the drug is circulated, the concentration is higher in the blood than in body cells, so that the drug moves (from capillaries) into the fluids surrounding the cells or into the cells themselves. Passive diffusion continues until a state of equilibrium is reached between the amount of drug in the tissues and the amount in the blood.

Facilitated diffusion is a similar process, except that drug molecules combine with a carrier substance, such as an enzyme or other protein.

In *active transport*, drug molecules are moved from an area of lower concentration to one of higher concentration. This process requires a carrier substance and the release of cellular energy.

then excreted. Some active drugs yield metabolites that are also active and that continue to exert their effects on body cells until they are metabolized further or excreted. Other drugs (called prodrugs) are initially inactive and exert no pharmacologic effects until they are metabolized.

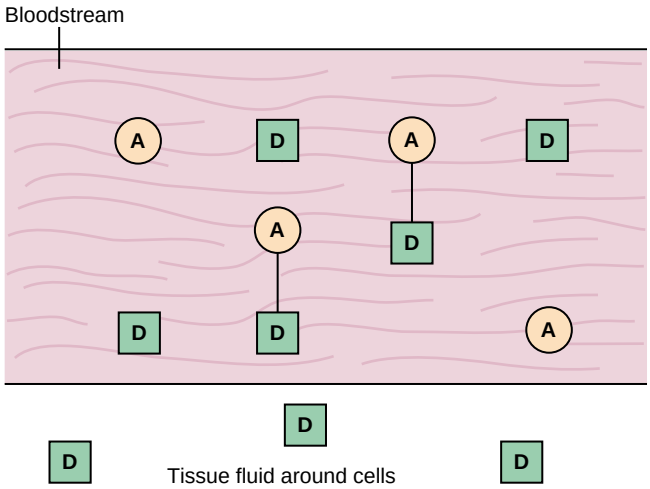

Figure 2–4 Plasma proteins, mainly albumin (A), act as carriers for drug molecules (D). Bound drug (A–D) stays in bloodstream and is pharmacologically inactive. Free drug (D) can leave the bloodstream and act on body cells.

Most drugs are lipid soluble, a characteristic that aids their movement across cell membranes. However, the kidneys, which are the primary excretory organs, can excrete only water-soluble substances. Therefore, one function of metabolism is to convert fat-soluble drugs into water-soluble metabolites. Hepatic drug metabolism or clearance is a major mechanism for terminating drug action and eliminating drug molecules from the body.

Most drugs are metabolized by enzymes in the liver (called the cytochrome P450 [CYP] or the microsomal enzyme system); red blood cells, plasma, kidneys, lungs, and GI mucosa also contain drug-metabolizing enzymes. The cytochrome P450 system consists of 12 groups or families, nine of which metabolize endogenous substances and three of which metabolize drugs. The three groups that metabolize drugs are labeled CYP1, CYP2 and CYP3. Of the many drugs metabolized by the liver, the CYP3 group of enzymes is thought to metabolize about 50%, the CYP2 group about 45%, and the CYP1 group about 5%. Individual members of the groups, each of which metabolizes specific drugs, are further categorized. For example, many drugs are metabolized by CYP2D6, CYP2C9, or CYP3A4 enzymes.

These enzymes, located within hepatocytes, are complex proteins with binding sites for drug molecules (and endogenous substances). They catalyze the chemical reactions of oxidation, reduction, hydrolysis, and conjugation with endogenous sub-