Pharmacology

Lecture 2

Drug distribution:

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and the tissues.

For drugs administered IV, absorption is not a factor, and the initial phase (from immediately after administration through the rapid fall in concentration) represents the distribution phase, during which the drug rapidly leaves the circulation and enters the tissues. The distribution of a drug from the plasma to the interstitium depends on cardiac output and local blood flow, capillary permeability, the tissue volume, the degree of binding of the drug to plasma and tissue proteins, and the relative lipophilicity of the drug.

A. Blood flow

The rate of blood flow to the tissue capillaries varies widely. For instance, blood flow to the "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.

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. In the brain, the capillary structure is continuous, and there are no slit junctions. To enter the brain, drugs must pass through the endothelial cells of the CNS capillaries or be actively transported.

By contrast, lipid-soluble drugs readily penetrate the CNS because they dissolve in the endothelial cell membrane. Ionized or polar drugs generally fail to enter the CNS because they cannot pass through the endothelial cells that have no slit junctions. These closely juxtaposed cells form tight junctions that constitute the blood–brain barrier.

C. Binding of drugs to plasma proteins and tissues

1. Binding to plasma proteins: Reversible binding to plasma proteins sequesters drugs in a non-diffusible form and slows their transfer out of the vascular compartment. Albumin is the major drug-binding protein and may act as a drug reservoir (as the concentration of free drug decreases due to elimination, the bound drug dissociates from the protein). 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 the extracellular fluid and blood. Drugs may accumulate as a result of binding to lipids, proteins, or nucleic acids. Drugs may also be actively transported into tissues. Tissue reservoirs may serve as a major source of the drug and prolong its actions or cause local drug toxicity.

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. In 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.

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. 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

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

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, then V_d = 10 mg/1 mg/L = 10 L.

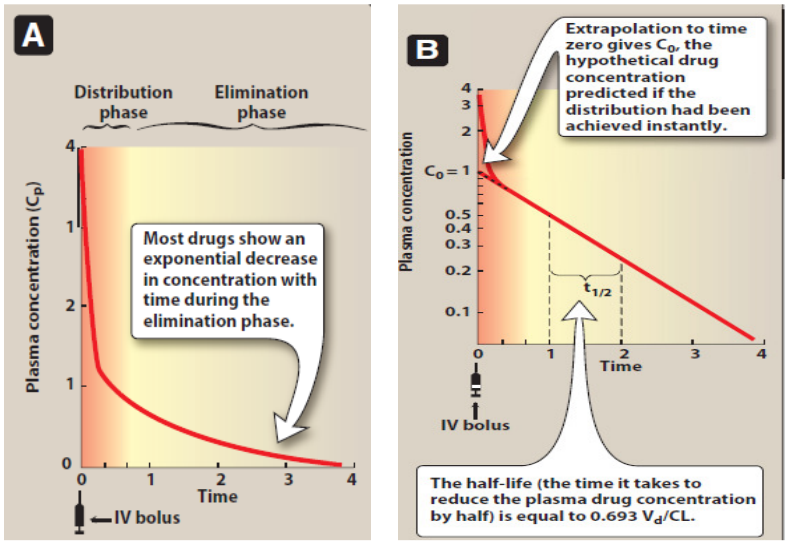

Figure 1: Drug concentrations in plasma after a single injection of drug at time = 0. A. Concentration data are plotted on a linear scale. B. Concentration data are plotted on a log scale.

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 elimination. Together, these elimination processes decrease the plasma concentration exponentially. That is, a constant fraction of the drug present is eliminated in a given unit of time.

Most drugs are eliminated according to first-order kinetics, although some, such as *aspirin* in high doses, are eliminated according to zero-order or nonlinear kinetics. Metabolism leads to production of products with increased polarity, which allows the drug to be eliminated. Clearance (CL) estimates the amount of drug cleared from the body per unit of time.

The kidney cannot efficiently eliminate 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.

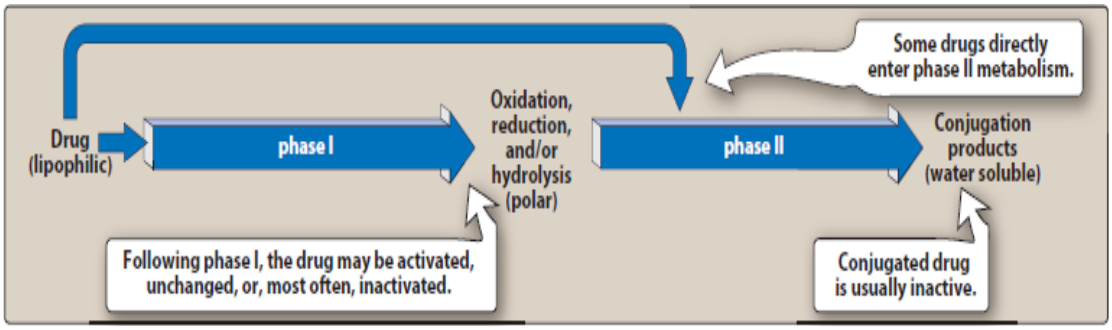

Figure 2: The biotransformation of drugs

Drug clearance through 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 being 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.

Elimination of drugs via the kidneys into urine involves the processes of 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. The glomerular filtration rate (GFR) is normally about 125 mL/min 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.

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.

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.

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. As a general rule, 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.

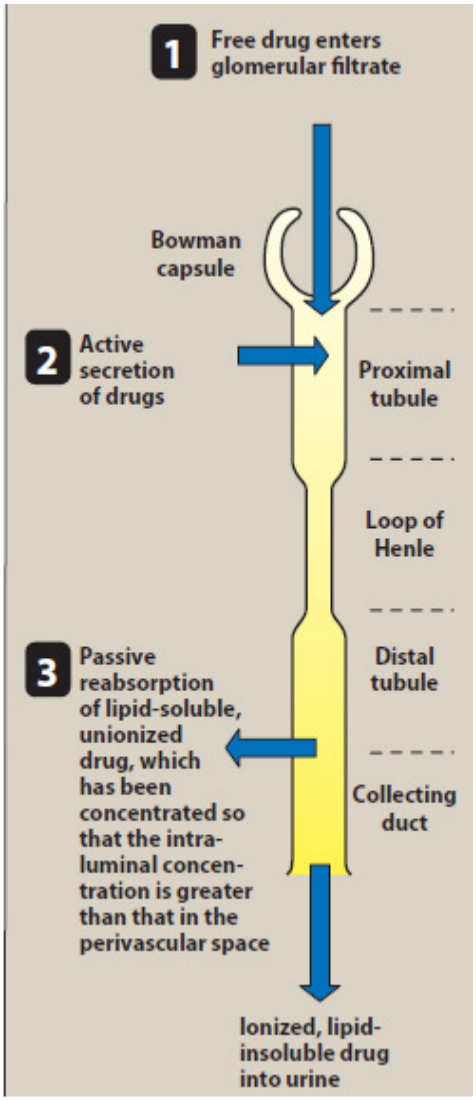

Figure 3: Drug elimination by the kidney

Drug–Receptor Interactions and Pharmacodynamics

Pharmacodynamics describes the actions of a drug on the body and the influence of drug concentrations on the magnitude of the response. Most drugs exert their effects, both beneficial and harmful, by interacting with receptors (that is, specialized target macromolecules) present on the cell surface or within the cell. The drug–receptor complex initiates alterations in biochemical and/or molecular activity of a cell by a process called signal transduction.

Most drug targets (receptors) are protein molecules. Even general anesthetics, which were long thought to produce their effects by an interaction with membrane lipid, now appear to interact mainly with membrane proteins.

All rules need exceptions, and many antimicrobial and antitumor drugs, as well as mutagenic and carcinogenic agents, interact directly with DNA rather than protein.

Types of Receptors:

Pharmacology defines a receptor 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 therapeutically relevant pharmacologic receptors are 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.
4) intracellular receptors .

The type of receptor a ligand interacts with depends on the chemical nature of the ligand. Hydrophilic ligands interact with receptors that are found on the cell surface. In contrast, hydrophobic ligands enter cells through the lipid bilayers of the cell membrane to interact with receptors found inside cells.

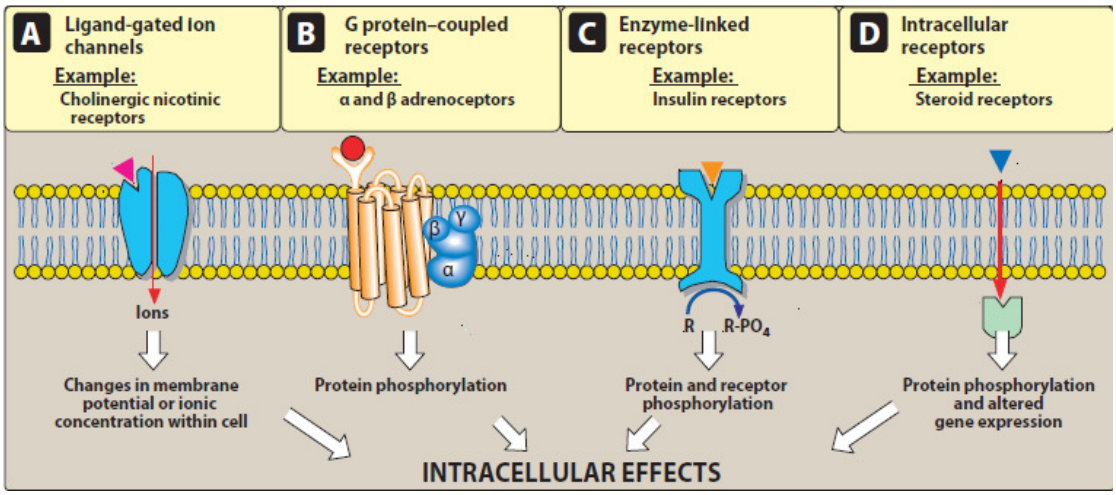

Figure 4: Transmembrane signaling mechanisms.

1. **Transmembrane ligand-gated ion channels:**

The extracellular portion of ligand-gated ion channels usually contains the ligand binding site. This site regulates the shape of the pore through which ions can flow across cell membranes (Figure 4A). The channel is usually closed until the receptor is activated by an agonist, which opens the channel briefly for a few milliseconds. Depending on the ion conducted through these channels, these receptors mediate diverse functions, including neurotransmission, and cardiac or muscle contraction. For example, stimulation of the nicotinic receptor by acetylcholine results in sodium influx and potassium outflux, generating an action potential in a neuron or contraction in skeletal muscle. On the other hand, agonist stimulation of the γ-aminobutyric acid (GABA) receptor increases chloride influx and hyperpolarization of neurons. Voltage-gated ion channels may also possess ligand-binding sites that 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 domain of this receptor contains the ligand-binding area, and the intracellular domain interacts (when activated) with a G protein or effector molecule (Figure 4B). There are many kinds of G proteins (for example, Gs, Gi, and Gq), but they all 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. 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. These two complexes can then interact with other cellular effectors, usually an enzyme, a

protein, or an ion channel, that are responsible for further actions within the cell. These responses usually last several seconds to minutes (Figure 5).

Sometimes, the activated effectors produce second messengers that further activate other effectors in the cell, causing a signal cascade effect.

A common effector, activated by Gs and inhibited by Gi, is adenylyl cyclase, which produces the second messenger cyclic adenosine monophosphate (cAMP). Gq activates phospholipase C, generating two other second messengers: inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). DAG and cAMP activate different protein kinases within the cell, leading to a myriad of physiological effects. IP3 regulates intracellular free calcium concentrations, as well as some protein kinases.

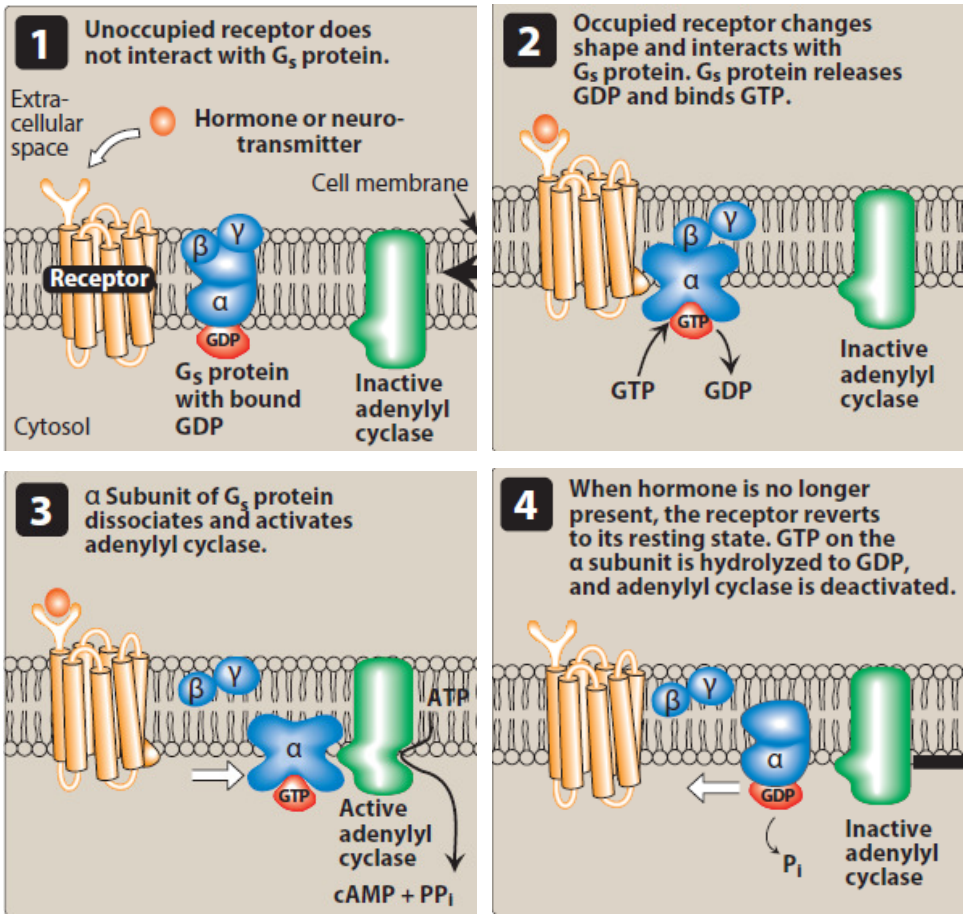

Figure 5: The recognition of chemical signals by G protein–coupled membrane receptors affects the activity of adenylyl cyclase.

3. **Enzyme-linked receptors:**

This family of receptors consists of a protein that may form dimers or multisubunit complexes. When activated, these receptors undergo conformational changes resulting in increased cytosolic enzyme activity, depending on their structure and function (Figure 6). This response lasts on the order of minutes to hours. The most common enzyme-linked receptors (epidermal growth factor, platelet-derived growth factor, atrial natriuretic peptide, insulin, and others) possess tyrosine kinase activity as part of their structure. The activated receptor phosphorylates tyrosine residues on itself and then other specific proteins (Figure 6). Phosphorylation can substantially modify the structure of the target protein, thereby acting as a molecular switch. For example, when the peptide hormone insulin binds to two of its receptor subunits, their intrinsic tyrosine kinase activity causes autophosphorylation of the receptor itself. In turn, the phosphorylated receptor phosphorylates other peptides or proteins that subsequently activate other important cellular signals. This cascade of activations results in a multiplication of the initial signal, much like that with G protein–coupled receptors.

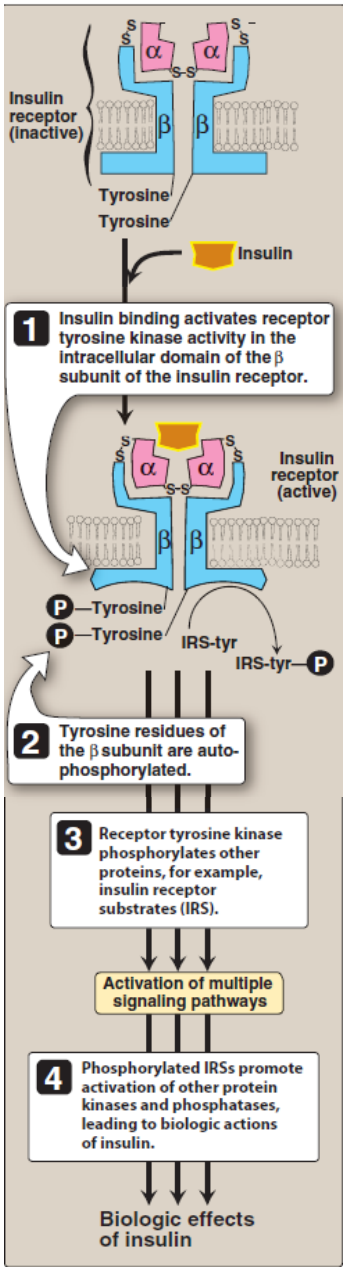

Figure 6: Insulin receptor.

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 must diffuse into the cell to interact with the receptor. In order to move across the target cell membrane, the ligand must have sufficient lipid solubility. The primary targets of these ligand–receptor complexes are transcription factors in the cell nucleus.

Binding of the ligand with its receptor generally activates the receptor via dissociation from a variety of binding proteins. The activated ligand–receptor complex then translocates to the nucleus, where it often dimerizes before binding to transcription factors that regulate gene expression. The activation or inactivation of

these factors causes the transcription of DNA into RNA and translation of RNA into an array of proteins. The time course of activation and response of these receptors is on the order of hours to days. For example, steroid hormones exert their action on target cells via intracellular receptors. Other targets of intracellular ligands are structural proteins, enzymes, RNA, and ribosomes. For example, tubulin is the target of antineoplastic agents such as *paclitaxel*, the enzyme dihydrofolate reductase is the target of antimicrobials such as *trimethoprim*, and the 50S subunit of the bacterial ribosome is the target of macrolide antibiotics such as *erythromycin*.