Unit IV: Pharmacodynamics:

Mechanism of drug action

Pharmacodynamics is the study of the biochemical and physiologic effects of drugs and their mechanisms of action on the body or on microorganisms and other parasites within or on the body. It considers both **drug action**, which refers to the initial consequence of a drug-receptor interaction, and **drug effect**, which refers to the subsequent effects. The drug action of digoxin, for example, is inhibition of membrane Na^+/K^+-ATPase; the drug effect is augmentation of cardiac contractility. In this example, the clinical response might comprise improved exercise tolerance.

Not all drugs exert their pharmacologic actions via receptor-mediated mechanisms. The action of some drugs—including inhalation anesthetic agents, osmotic diuretics, purgatives, antiseptics, antacids, chelating agents, and urinary acidifying and alkalinizing agents—is attributed to their chemical action or physicochemical properties. Certain cancer and antiviral chemotherapeutic agents, which are analogues of pyrimidine and purine bases, elicit their effects when they are incorporated into nucleic acids and serve as substrates for DNA or RNA synthesis. The effect of most drugs, however, results from their interactions with receptors. These interactions and the resulting conformational changes in the receptor initiate biochemical and physiologic changes that characterize the drug's response.

❖ Drug concentration and effects

Drug therapy is intended to result in a particular pharmacologic response of desired intensity and duration while avoiding adverse drug reactions. The relationship between the administered dose and the clinical response has been investigated for some drugs using a pharmacokinetic/pharmacodynamic

(PK/PD) modeling approach, which is generally based on the plasma concentration-response relationship. For other drugs, a simpler relationship between the concentration and effect in an idealized in vitro system is modeled mathematically to conceptualize receptor occupancy and drug response. The model assumes that the drug interacts reversibly with its receptor and produces an effect proportional to the number of receptors occupied, up to a maximal effect when all receptors are occupied. The reaction scheme for the model is:

$$\text{Drug (D)} + \text{Receptor (R)} \underset{k_1}{\overset{k_2}{\leftrightarrow}} \text{DR} \rightarrow \text{Effect}$$

in which k_2 and k_1 are rate constants.

The relationship between effect and the concentration of free drug for the model is given by the Hill equation, which can be written as:

$$E = \frac{E_{max} \times C_n}{EC_{50} + C_n}$$

in which E is the effect observed at concentration C, E_{max} is the maximal response that can be produced by the drug (efficacy), EC_{50} is the concentration of drug that produces 50% of maximal effect (potency), and the Hill coefficient n is the slope of the $\log_{10}$ concentration-effect relationship (sensitivity).

The above equation describes a rectangular hyperbola when response (y-axis) is plotted against concentration (x-axis). However, dose- or concentration-response data is generally plotted as drug effect (y-axis) against $\log_{10}$ dose or concentration (x-axis). The transformation yields a sigmoidal curve that allows the potency of different drugs to be readily compared. In addition, the effect of drugs used at therapeutic concentrations commonly falls on the portion of the sigmoidal curve that is approximately linear, ie, between 20% and 80% of maximal effect. This makes for easier interpretation of the plotted data.

❖ Agonists and antagonists

An **agonist** is a drug that binds to receptors and thereby alters (stabilizes) the proportion of receptors in the active conformation, resulting in a biologic response. A full agonist results in a maximal response by occupying all or a fraction of receptors. A partial agonist results in less than a maximal response even when the drug occupies all of the receptors.

There are four types of drug antagonism. **Chemical antagonism** involves chemical interaction between a drug and either a chemical or another drug leading to a reduced or nil response. **Physiologic antagonism** occurs when two drugs acting on different receptors and pathways exert opposing actions on the same physiologic system. **Pharmacokinetic antagonism** is the result of one drug suppressing the effect of a second drug by reducing its absorption, altering its distribution, or increasing its rate of elimination. **Pharmacologic antagonism** occurs when the antagonist inhibits the effect of a full or partial agonist by acting on the same pathway but not necessarily on the same receptor.

Pharmacologic antagonists comprise three subcategories. A **reversible competitive antagonist** results in inhibition that can be overcome by increasing the concentration of agonist. The presence of a reversible competitive antagonist causes a parallel rightward shift of the log concentration-effect curve of the agonist without altering E_{max} or EC_{50}. An **irreversible competitive antagonist** also involves competition between agonist and antagonist for the same receptors, but stronger binding forces prevent the effect of the antagonist being fully reversed, even at high agonist concentrations. The presence of an irreversible competitive antagonist causes a rightward shift of the log concentration-effect curve of the agonist that generally displays decreased slope and reduced maximum effect.

A **noncompetitive antagonist** inhibits agonist activity by blocking one of the sequential reactions between receptor activation and the pharmacologic response. Noncompetitive antagonism is generally reversible but can be irreversible. Noncompetitive antagonists and irreversible competitive antagonists cause similar perturbations in the log concentration-effect curve of agonists. Isolated tissue experiments are used to distinguish the two subcategories, because noncompetitive antagonists are generally reversible.

Agonists, but not antagonists, elicit an effect even when they bind to the same site on the same receptor. An explanation is provided by both structural and functional studies, which indicate that receptors exist in at least two conformations, active and inactive, and these are in equilibrium. Because agonists have a higher affinity for the receptor's active conformation, agonists drive the equilibrium to the active state, thereby activating the receptor. Conversely, antagonists have a higher affinity for the receptor's inactive conformation and push the equilibrium to the inactive state, producing no effect.

The concept of **spare receptors** explains a maximum response being achieved when only a fraction of the total number of receptors is occupied. For example, an action potential and maximal twitch of muscle fibers is elicited when 0.13% of the total number of receptors at a skeletal neuromuscular junction is simultaneously activated. From a functional perspective, spare receptors are significant, because they increase both the sensitivity and speed of a tissue's responsiveness to a ligand.

❖ Structure-activity relationships

Structure-activity relationships are exploited in drug design, because small changes in chemical structure can produce profound changes in potency. For example, the substitution of a proton by a methyl group accounts

for codeine being ~1,000 times less potent than morphine in its action on opioid receptors.

❖ Signal transduction and drug action

Most receptors are proteins. The best characterized of these are regulatory proteins, enzymes, transport proteins, and structural proteins. Nucleic acids are also important drug receptors, particularly for cancer chemotherapeutic agents. The receptors for several neurotransmitters modulate the opening and closing of ion channels through ligand gating or voltage gating. The nicotinic acetylcholine receptor is an example of a ligand-gated receptor; it allows Na^+ to flow down its concentration gradient into cells, resulting in depolarization. Most clinically useful neuromuscular blocking drugs compete with acetylcholine for the receptor but do not initiate ion-channel opening. Other ligand-gated ion channels include the CNS receptors for the excitatory amino acids (glutamate and aspartate), the inhibitory amino acids (γ-aminobutyric acid [GABA] and glycine), and certain serotonin (5-HT3) receptors. The sodium channel receptor is an example of a voltage-gated receptor; these are present in the membranes of excitable nerve, cardiac, and skeletal muscle cells. In the resting state, the Na^+/K^+-ATPase pump in these cells maintains an intracellular Na^+ concentration much lower than that in the extracellular environment. Membrane depolarization causes channel opening and a transient influx of Na^+ ions, followed by inactivation and return to the resting state. The action of local anesthetics is due to their direct interaction with voltage-gated Na^+ channels.

Many transmembrane receptors are linked to guanosine triphosphate binding proteins, which activate second messenger systems. Two important second messenger systems are cyclic adenosine monophosphate (cAMP) and the phosphoinositides. In cAMP second messenger systems, binding of the ligand

to the receptor increases or decreases adenylyl cyclase activity, which in turn regulates the formation of cAMP from adenosine triphosphate. The activation of protein kinase A by cAMP results in the phosphorylation of proteins and a physiologic effect. From a therapeutic standpoint, drug binding to β-adrenergic, histamine H_2, or dopamine D_1 receptors activates adenylyl cyclase, whereas binding to muscarinic M_2, α_2-adrenergic, dopamine D_2, opiate μ and δ, adenosine A_1, or GABA type B receptors inhibits adenylyl cyclase. In phosphoinositide second messenger systems, membrane phosphatidylinositol 4,5-biphosphate is hydrolyzed to 1,4,5-trisphosphate (IP3) and 1,2-diacylglycerol (DAG) by activation of phospholipase C. Both IP3 and DAG activate kinases, and in the case of IP3, this involves the mobilization of calcium from intracellular stores. The action of numerous drugs is due to their interaction with receptors that rely on these second messengers, which include α_1-adrenergic, muscarinic M_1 or M_2, serotonin 5-HT2, and thyrotropin-releasing hormone receptors.

Protein tyrosine kinase receptors are generally transmembrane enzymes that phosphorylate proteins exclusively on tyrosine residues, rather than on serine or threonine residues. They include endocrine hormone receptors for insulin and receptors for several growth hormones.

Intracellular receptors mediate the action of hormones such as glucocorticoids, estrogen, and thyroid hormone and related drugs. The hormones, which regulate gene expression in the nucleus, are lipophilic and freely diffuse through the cell membrane to reach the receptor. Glucocorticoid receptors reside predominantly in the cytoplasm in an inactive form until they bind to the glucocorticoid steroid ligand. This results in receptor activation and translocation to the nucleus, where the receptor interacts with specific DNA

sequences. Unlike glucocorticoid receptors, the receptors for estrogen and thyroid hormone reside in the nucleus.

Intracellular receptors are also important in mediating the action of antimicrobial drugs, including the penicillins, sulfonamides, trimethoprim, aminoglycosides, phenicols, macrolides, and fluoroquinolones. The mechanisms of action include inhibition of bacterial protein synthesis, inhibition of cell wall synthesis, inhibition of enzymatic activity, alteration of cell membrane permeability, and blockade of specific biochemical pathways.

Receptor-mediated mechanisms of action of several classes of anthelmintics are well understood. For example, the benzimidazoles and pro-benzimidazoles bind to nematode tubulin, preventing its polymerization during microtubular assembly and thus disrupting cell division. Depletion of ATP as the result of salicylanilides uncoupling oxidative phosphorylation and the inhibition of enzymes in the glycolytic pathway by benzene sulfonamides are other examples. Several classes of anthelmintics interfere with neurotransmission in parasites. A case in point is macrocyclic lactones, which potentiate inhibitory neurotransmission via GABA and glutamate-gated chlorine channels.