College of pharmacy
3rd year stage, pharmacology lecture.

Drug–Receptor Interactions and Pharmacodynamics.

Most drugs exert their effects, both beneficial and harmful, by interacting with receptors—that is, specialized target macromolecules—present on the cell surface or intracellularly. Receptors bind drugs and initiate events leading to alterations in biochemical and/or biophysical activity of a cell, and consequently, the function of an organ . Drugs may interact with receptors in many different ways. Drugs may bind to**1-** enzymes (for example, inhibition of dihydrofolate reductase by trimethoprim, , **2-**nucleic acids (for example, blockade of transcription by dactinomycin, , or **3-**membrane receptors (for example, alteration of membrane permeability by pilocarpine, .
In each case, the formation of the drug–receptor complex leads to a biologic response. Most receptors are named to indicate the type of drug/chemical that interacts best with it; for example, the receptor for histamine is called a histamine receptor.
Cells may have tens of thousands of receptors for certain ligands (drugs). Cells may also have different types of receptors, each of which is specific for a particular ligand. On the heart, for example, there are β receptors for norepinephrine, and muscarinic receptors for acetylcholine. These receptors dynamically interact to control vital functions of the heart. The magnitude of the response is proportional to the number of drug–receptor complexes:
This concept is closely related to the formation of complexes between enzyme and substrate, or antigen and antibody; these interactions have many common features, perhaps the most noteworthy being specificity of the receptor for a given ligand. However, the receptor not only has the ability to recognize a ligand, but can also couple or transduce this binding into a response by causing a conformational change or a biochemical effect.
It is important to be aware that not all drugs exert their effects by interacting with a receptor; for example, antacids chemically neutralize excess gastric acid, reducing the symptoms of "heartburn."

Chemistry of Receptors and Ligands

Interaction of receptors with ligands involves the formation of chemical bonds, most commonly electrostatic and hydrogen bonds, as well as weak interactions involving van der Waals forces. These bonds are important in determining the selectivity of receptors, because the strength of these non-covalent bonds is related inversely to the distance between the interacting atoms. Therefore, the successful binding of a drug requires an exact fit of the ligand atoms with the complementary receptor atoms. The bonds are usually reversible, except for a handful of drugs (for example, the nonselective α-receptor blocker phenoxybenzamine, and acetylcholinesterase inhibitors in the organophosphate class) that covalently bond to their targets. The size, shape, and charge distribution of the drug molecule determines which of the myriad binding sites in the cells and tissues of the patient can interact with the ligand. The metaphor of the "lock and key" is a useful concept for understanding the interaction of receptors with their ligands. The precise fit required of the ligand echoes the characteristics of the "key," whereas the opening of the "lock" reflects the activation of the receptor. The interaction of the ligand with its receptor thus exhibits a high degree of specificity. The induced-fit model has largely replaced the lock-and-key concept as the preferred model describing the interaction of a receptor and a ligand. In the presence of a ligand, the receptor undergoes a conformational change to bind the ligand. The change in conformation of the receptor caused by binding of the agonist activates the receptor, which leads to the pharmacologic effect. This model suggests that the receptor is flexible, not rigid as implied by the lock-and-key model.

Major Receptor Families

Pharmacology defines a receptor as any biologic molecule to which a drug binds and produces a measurable response. Thus, enzymes and structural proteins can be considered to be pharmacologic receptors. However, the richest sources of therapeutically exploitable pharmacologic receptors are proteins that are responsible for transducing 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 will interact with depends on the nature of the ligand. Hydrophobic ligands interact with receptors that are found on the cell surface (families 1, 2, and 3). In contrast, hydrophobic ligands can enter cells through the lipid bilayers of the cell membrane to interact with receptors found inside cells (family 4).

*Ligand-gated ion channels

The first receptor family comprises ligand-gated ion channels that are responsible for regulation of the flow of ions across cell membranes . The activity of these channels is regulated by the binding of a ligand to the channel. Response to these receptors is very rapid, having durations of a few milliseconds. The nicotinic receptor and the γ-aminobutyric acid (GABA) receptor are important examples of ligand-gated receptors, the functions of which are modified by numerous drugs. Stimulation of the nicotinic receptor by acetylcholine results in sodium influx, generation of an action potential, and activation of contraction in skeletal muscle. Benzodiazepines, on the other hand, enhance the stimulation of the GABA receptor by GABA, resulting in increased chloride influx and hyperpolarization of the respective cell. Although not ligand-gated, ion channels, such as the voltage-gated sodium channel, are important drug receptors for several drug classes, including local anesthetics.

*G protein–coupled receptors

A second family of receptors consists of G protein–coupled receptors. These receptors are comprised of a single peptide that has seven membrane-spanning regions, and these receptors are linked to a G protein (G_s and others) having three subunits, an α subunit that binds guanosine triphosphate (GTP) and a βγ subunit . Binding of the appropriate ligand to the extracellular region of the receptor activates the G protein so that GTP replaces guanosine diphosphate (GDP) on the α subunit. Dissociation of the G protein occurs, and both the α-GTP subunit and the βγ subunit subsequently interact with other cellular effectors, usually an enzyme or ion channel. These effectors then change the concentrations of second messengers that are responsible for further actions within the cell. Stimulation of these receptors results in responses that last several seconds to minutes.

Second messengers: These are essential in conducting and amplifying signals coming from G protein–coupled receptors. A common pathway turned on by G_s, and other types of G proteins, is the activation of adenylyl cyclase by α-GTP subunits, which results in the production of cyclic adenosine monophosphate (cAMP)—a second messenger that regulates protein phosphorylation. G proteins also activate phospholipase C, which is responsible for the generation of two other second messengers, namely inositol-1,4,5-trisphosphate and diacylglycerol. These effectors are responsible for the regulation of intracellular free calcium concentrations, and of other proteins as well. This family of receptors transduces signals derived from odors, light, and numerous neurotransmitters, including norepinephrine, dopamine, serotonin, and acetylcholine.

G protein–coupled receptors also activate guanylyl cyclase, which converts (GTP) to cyclic guanosine monophosphate (cGMP), a fourth second messenger that stimulates cGMP-dependent protein kinase. cGMP signaling is important in only a few cells, for example, intestinal mucosa and vascular smooth muscle, where it causes relaxation of vascular smooth muscle cells. Some drugs such as sildenafil produce vasodilation by interfering with specific phosphodiesterases, the enzymes that metabolically break down cGMP.

***Enzyme-linked receptors**

A third major family of receptors consists of those having cytosolic enzyme activity as an integral component of their structure or function . Binding of a ligand to an extracellular domain activates or inhibits this cytosolic enzyme activity. Duration of responses to stimulation of these receptors is 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) are those that have a tyrosine kinase activity as part of their structure. Typically, upon binding of the ligand to receptor subunits, the receptor undergoes conformational changes, converting from its inactive form to an active kinase form. The activated receptor autophosphorylates, and phosphorylates tyrosine residues on specific proteins. 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 target molecules—insulin-receptor substrate peptides—that subsequently activate other important cellular signals such as IP3 and the mitogen-activated protein kinase system. This cascade of activations results in a multiplication of the initial signal.

*** 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 . This places constraints on the physical and chemical properties of the ligand in that it must have sufficient lipid solubility to be able to move across the target cell membrane. Because these receptor ligands are lipid soluble, they are transported in the body attached to plasma proteins, such as albumin. For example, steroid hormones exert their action on target cells via this receptor mechanism. The activated ligand–receptor complex migrates to the nucleus, where it binds to specific DNA sequences, resulting in the regulation of gene expression. The time course of activation and response of these receptors is much longer than that of the other mechanisms described above. Because gene expression and, therefore, protein synthesis is modified, cellular responses are not observed until considerable time has elapsed (thirty minutes or more), and the duration of the response (hours to days) is much greater than that of other receptor families.

Some Characteristics of Receptors

A. Spare receptors

A characteristic of many receptors, particularly those that respond to hormones, neurotransmitters, and peptides, is their ability to amplify signal duration and intensity. The family of G protein–linked receptors exemplifies many of the possible responses initiated by ligand binding to a receptor. Specifically, two phenomena account for the amplification of the ligand–receptor signal. First, a single ligand–receptor complex can interact with many G proteins, thereby multiplying the original signal many-fold. Second, the activated G proteins persist for a longer duration than the original ligand–receptor complex. The binding of albuterol, for example, may only exist for a few milliseconds, but the subsequent activated G proteins may last for hundreds of milliseconds. Further prolongation and amplification of the initial signal is

mediated by the interaction between G proteins and their respective intracellular targets. Because of this amplification, only a fraction of the total receptors for a specific ligand may need to be occupied to elicit a maximal response from a cell. Systems that exhibit this behavior are said to have spare receptors. Spare receptors are exhibited by insulin receptors, where it has been estimated that 99 percent of the receptors are "spare." This constitutes an immense functional reserve that ensures adequate amounts of glucose enter the cell. On the other end of the scale is the human heart, in which about five to ten percent of the total β-adrenoceptors are spare. An important implication of this observation is that little functional reserve exists in the failing heart; most receptors must be occupied to obtain maximum contractility.

B. Desensitization of receptors

Repeated or continuous administration of an agonist (or an antagonist) may lead to changes in the responsiveness of the receptor. To prevent potential damage to the cell (for example, high concentrations of calcium, initiating cell death), several mechanisms have evolved to protect a cell from excessive stimulation. When repeated administration of a drug results in a diminished effect, the phenomenon is called tachyphylaxis. The receptor becomes desensitized to the action of the drug . In this phenomenon, the receptors are still present on the cell surface but are unresponsive to the ligand. Other types of desensitization occur when receptors are down-regulated. Binding of the agonist results in molecular changes in the membrane-bound receptors, such that the receptor undergoes endocytosis and is sequestered from further agonist interaction. These receptors may be recycled to the cell surface, restoring sensitivity, or alternatively, may be further processed and degraded, decreasing the total number of receptors available. Some receptors, particularly voltage-gated channels, require a finite time (rest period) following stimulation before they can be activated again. During this recovery phase they are said to be "refractory" or "unresponsive."

C. Importance of the receptor concept

It is important that we understand the roles and functions of receptors because most drugs interact with receptors that will determine selective therapeutic and toxic effects of the drug. Moreover, receptors largely determine the quantitative relations between dose of a drug and pharmacologic effect.

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Dose–Response Relationships

An agonist is defined as an agent that can bind to a receptor and elicit a biologic response. The magnitude of the drug effect depends on the drug concentration at the receptor site, which in turn is determined by the dose of drug administered and by factors characteristic of the drug pharmacokinetic profile, such as rate of absorption, distribution, and metabolism.

A. Graded dose–response relations

As the concentration of a drug increases, the magnitude of its pharmacologic effect also increases. The relationship between dose and response is a continuous one, and it can be mathematically described for many systems by application of the law of mass action, assuming the simplest model of drug binding:

$$[\text{Drug}] + [\text{Receptor}] \rightleftarrows [\text{Drug–receptor complex}]$$

The response is a graded effect, meaning that the response is continuous and gradual. This contrasts with a **quantal response**, which describes an all-or-nothing response. A graph of this

relationship is known as a graded dose–response curve. Plotting the magnitude of the response against increasing doses of a drug

Potency: Two important properties of drugs can be determined by graded dose–response curves. The first is ***potency***, a measure of the amount of drug necessary to produce an effect of a given magnitude. For a number of reasons, the concentration producing an effect that is fifty percent of the maximum is used to determine potency; it commonly designated as the EC_{50}. Therapeutic preparations of drugs will reflect the potency. For example, candesartan and irbesartan are angiotensin–receptor blockers that are used alone or in combination to treat hypertension. Candesartan is more potent than irbesartan because the dose range for candesartan is 4 to 32 mg, as compared to a dose range of 75 to 300 mg for irbesartan. An important contributing factor to the dimension of the EC_{50} is the affinity of the drug for the receptor.

Efficacy [intrinsic activity]: The second drug property that can be determined from graded dose–response plots is the efficacy of the drug. This is the ability of a drug to illicit a physiologic response when it interacts with a receptor. Efficacy is dependent on the number of drug–receptor complexes formed and the efficiency of the coupling of receptor activation to cellular responses. Analogous to the maximal velocity for enzyme-catalyzed reactions, the maximal response (E_{max}) or efficacy is more important than drug potency. A drug with greater efficacy is more therapeutically beneficial than one that is more potent. Figure 2.7 shows the response to drugs of differing potency and efficacy.

Drug–receptor binding: The quantitative relationship between drug concentration and receptor occupancy applies the law of mass action to the kinetics of the binding of drug and receptor molecules. By making the assumption that the binding of one drug molecule does not alter the binding of subsequent molecules, we can mathematically express the relationship between the percentage (or fraction) of bound receptors and the drug concentration:

where [D] = the concentration of free drug; [DR] = the concentration of bound drug; [R_t] = the total concentration of receptors, and is equal to the sum of the concentrations of unbound (free) receptors and bound receptors and; K_d = [D][R]/[DR], and is the dissociation constant for the drug from the receptor. The value of K_d can be used to determine the affinity of a drug for its receptor. Affinity describes the strength of the interaction (binding) between a ligand and its receptor. The higher the K_d value, the weaker the interaction and the lower the affinity. The converse occurs when a drug has a low K_d. The binding of the ligand to the receptor is strong, and the affinity is high. Equation (1) defines a curve that has the shape of a rectangular hyperbola (Figure 2.8). As the concentration of free drug increases, the ratio of the concentrations of bound receptors to total receptors approaches unity. Doses are often plotted on a logarithmic scale, because the range from lowest to highest concentrations of doses often spans several orders of magnitude. It is important to note the similarity between these curves and those representing the relationship between dose and effect.

Figure 2.7 Typical dose-response curve for drugs showing differences in potency and efficacy. (EC_{50} = drug dose that shows fifty percent of maximal response.)

- Relationship of binding to effect: The binding of the drug to its receptor initiates events that ultimately lead to a measurable biologic response. The mathematical model that

describes drug concentration and receptor binding can be applied to dose (drug concentration) and response (or effect), providing the following assumptions are met: 1) The magnitude of the response is proportional to the amount of receptors bound or occupied, 2) the E_{max} occurs when all receptors are bound, and 3) binding of the drug to the receptor exhibits no cooperativity. In this case,

where [E] = the effect of the drug at concentration [D] and [E_{max}] = the maximal effect of the drug.

- Agonists: If a drug binds to a receptor and produces a biologic response that mimics the response to the endogenous ligand, it is known as an agonist. For example, phenylephrine is an agonist at α_1-adrenoceptors, because it produces effects that resemble the

action of the endogenous ligand, norepinephrine. Upon binding to α_1-adrenoceptors on the membranes of vascular smooth muscle, phenylephrine mobilizes intracellular Ca^{2+}, causing contraction of the actin and myosin filaments. The shortening of the muscle cells decreases the diameter of the arteriole, causing an increase in resistance to the flow of blood through the vessel. Blood pressure therefore rises to maintain the blood flow. As this brief description illustrates, an agonist may have many effects that can be measured, including actions on intracellular molecules, cells, tissues, and intact organisms. All of these actions are attributable to interaction of the drug molecule with the receptor molecule. In general, a full agonist has a strong affinity for its receptor and good efficacy.

- Antagonists: Antagonists are drugs that decrease the actions of another drug or endogenous ligand. Antagonism may occur in several ways. Many antagonists act on the identical receptor macromolecule as the agonist. Antagonists, however, have no intrinsic activity and, therefore, produce no effect by themselves. Although antagonists have no intrinsic activity, they are able to bind avidly to target receptors because they possess strong affinity. If both the antagonist and the agonist bind to the same site on the receptor, they are said to be "competitive." For example, the antihypertensive drug prazosin competes with the endogenous ligand, norepinephrine, at α_1-adrenoceptors, decreasing vascular smooth muscle tone and reducing blood pressure. Plotting the effect of the competitive antagonist characteristically causes a shift of the agonist dose–response curve to the right. Competitive antagonists have no intrinsic activity. If the antagonist binds to a site other than where the agonist binds, the interaction is "noncompetitive" or "allosteric" (Figure 2.9). [Note: A drug may also act as a chemical antagonist by combining with another drug and rendering it inactive. For example, protamine ionically binds to heparin, rendering it inactive and antagonizing heparin's anticoagulant effect.]
- Functional antagonism: An antagonist may act at a completely separate receptor, initiating effects that are functionally opposite those of the agonist. A classic example is the antagonism by epinephrine to histamine-induced bronchoconstriction. Histamine binds to H_1 histamine receptors on bronchial smooth muscle, causing contraction and narrowing of the bronchial tree. Epinephrine is an agonist at β_2-adrenoceptors on

bronchial smooth muscle, which causes the muscles to actively relax. This functional antagonism is also known as “physiologic antagonism.”

- Partial agonists: Partial agonists have efficacies (intrinsic activities) greater than zero, but less than that of a full agonist. Even if all the receptors are occupied, partial agonists cannot produce an E_{max} of as great a magnitude as that of a full agonist. However, a partial agonist may have an affinity that is greater than, less than, or equivalent to that of a full agonist. A unique feature of these drugs is that, under appropriate conditions, a partial agonist may act as an antagonist of a full agonist. Consider what would happen to the E_{max} of an agonist in the presence of increasing concentrations of a partial agonist (Figure 2.10). As the number of receptors occupied by the partial agonist increases, the E_{max} would decrease until it reached the E_{max} of the partial agonist. This potential of partial agonists to act both agonistically and antagonistically may be therapeutically exploited.

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  For example, aripiprazole, an atypical neuroleptic agent, is a partial agonist at selected dopamine receptors. Dopaminergic pathways that were overactive would tend to be inhibited by the partial agonist, whereas pathways that were underactive may be stimulated. This might explain the ability of aripiprazole to improve many of the symptoms of schizophrenia, with a small risk of causing extrapyramidal adverse effects (see p. 33).

VI. Quantal Dose–Response Relationships

Another important dose–response relationship is that of the influence of the magnitude of the dose on the proportion of a population that responds. These responses are known as quantal responses, because, for any individual, the effect either occurs or it does not. Even graded responses can be considered to be quantal if a predetermined level of the graded response is designated as the point at which a response occurs or not. For example, a quantal dose–response relationship can be determined in a population for the antihypertensive drug atenolol. A positive response is defined as at least a 5 mm Hg fall in diastolic blood pressure. Quantal dose–response curves are useful for determining doses to which most of the population responds.

A. Therapeutic index

The therapeutic index of a drug is the ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population of individuals:

where TD_{50} = the drug dose that produces a toxic effect in half the population and ED_{50} = the drug dose that produces a therapeutic or desired response in half the population. The therapeutic index is a measure of a drug's safety, because a larger value indicates a wide margin between doses that are effective and doses that are toxic.

B. Determination of therapeutic index

The therapeutic index is determined by measuring the frequency of desired response, and toxic response, at various doses of drug. By convention, the doses that produce the therapeutic effect and the toxic effect in fifty percent of the population are employed; these are known as the ED_{50} and TD_{50}, respectively. In humans, the therapeutic index of a drug is determined using drug trials and accumulated clinical experience. These usually reveal a range of effective doses and a different (sometimes overlapping) range of toxic doses. Although some drugs have narrow

therapeutic indices, they are routinely used to treat certain diseases. Several lethal diseases, such as Hodgkin's lymphoma, are treated with narrow therapeutic index drugs; however, treatment of a simple headache, for example, with a narrow therapeutic index drug would be unacceptable. Figure 2.11 shows the responses to warfarin, an oral anti-coagulant with a narrow therapeutic index, and penicillin, an antimicrobial drug with a large therapeutic index.

Warfarin (example of a drug with a small therapeutic index): As the dose of warfarin is increased, a greater fraction of the patients respond (for this drug, the desired response is a two-fold increase in prothrombin time) until eventually, all patients respond (see Figure 2.11A). However, at higher doses of warfarin, a toxic response occurs, namely a high degree of anticoagulation that results in hemorrhage. [Note: that when the therapeutic index is low, it is possible to have a range of concentrations where the effective and toxic responses overlap. That is, some patients hemorrhage, whereas others achieve the desired two-fold prolongation of prothrombin time. Variation in patient response is, therefore, most likely to occur with a drug showing a narrow therapeutic index, because the effective and toxic concentrations are similar. Agents with a low therapeutic index—that is, drugs for which dose is critically important—are those drugs for which bioavailability critically alters the therapeutic effects (see p. 7).

Penicillin (example of a drug with a large therapeutic index): For drugs such as penicillin (see Figure 2.11B), it is safe and common to give doses in excess (often about ten-fold excess) of that which is minimally required to achieve a desired response. In this case, bioavailability does not critically alter the therapeutic effects.