Drug–Receptor Interactions and Pharmacodynamics

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Joanna Peris

I. OVERVIEW

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 (Figure 2.1).

II. SIGNAL TRANSDUCTION

Drugs act as signals, and their receptors act as signal detectors. Receptors transduce their recognition of a bound agonist by initiating a series of reactions that ultimately result in a specific intracellular response. [Note: The term "agonist" refers to a naturally occurring small molecule or a drug that binds to a site on a receptor protein and activates it.] "Second messenger" or effector molecules are part of the cascade of events that translates agonist binding into a cellular response.

A. The drug–receptor complex

Cells have many different types of receptors, each of which is specific for a particular agonist and produces a unique response. Cardiac cell membranes, for example, contain β receptors that bind and respond to epinephrine or norepinephrine, as well as muscarinic receptors specific for acetylcholine. These different receptor populations dynamically interact to control the heart's vital functions.

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 agonist. Most receptors are named for the type of agonist that interacts best with it. For example, the receptor for histamine is called a histamine receptor. Although much

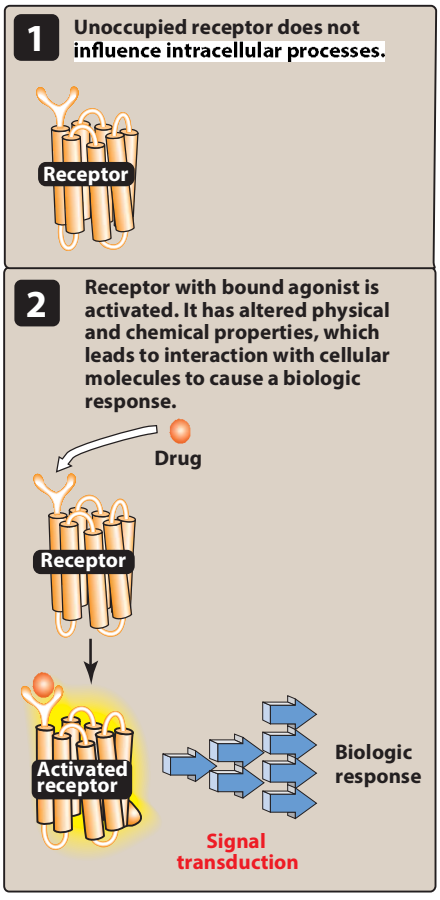

Figure 2.1
The recognition of a drug by a receptor triggers a biologic response.

of this chapter centers on the interaction of drugs with specific receptors, it is important to know that not all drugs exert their effects by interacting with a receptor. Antacids, for instance, chemically neutralize excess gastric acid, thereby reducing the symptoms of "heartburn."

B. Receptor states

Receptors exist in at least two states, inactive (R) and active (R*), that are in reversible equilibrium with one another, usually favoring the inactive state. Binding of agonists causes the equilibrium to shift from R to R* to produce a biologic effect. Antagonists occupy the receptor but do not increase the fraction of R* and may stabilize the receptor in the inactive state. Some drugs (partial agonists) cause similar shifts in equilibrium from R to R*, but the fraction of R* is less than that caused by an agonist (but still more than that caused by an antagonist). The magnitude of biological effect is directly related to the fraction of R*. Agonists, antagonists, and partial agonists are examples of ligands, or molecules that bind to the activation site on the receptor.

C. Major receptor families

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, and 4) intracellular receptors (Figure 2.2). The type of receptor a ligand interacts with

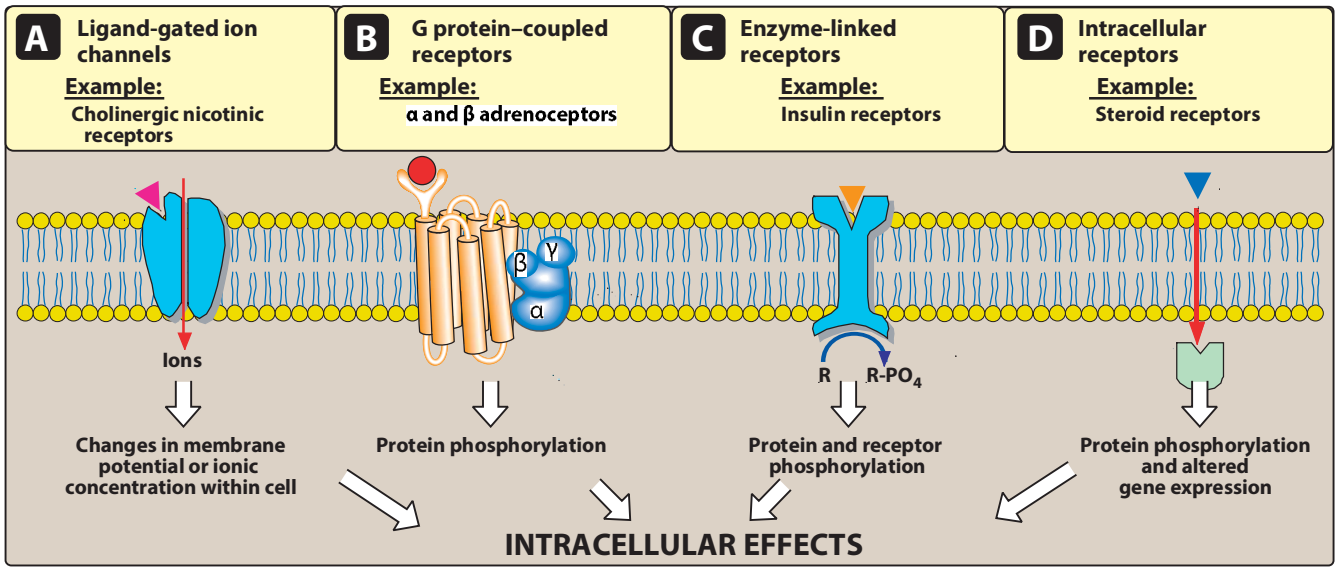

Figure 2.2
Transmembrane signaling mechanisms. **A.** Ligand binds to the extracellular domain of a ligand-gated channel. **B.** Ligand binds to a domain of a transmembrane receptor, which is coupled to a G protein. **C.** Ligand binds to the extracellular domain of a receptor that activates a kinase enzyme. **D.** Lipid-soluble ligand diffuses across the membrane to interact with its intracellular receptor. R = inactive protein.

depends on the chemical nature of the ligand. Hydrophilic ligands interact with receptors that are found on the cell surface (Figures 2.2A, B, C). In contrast, hydrophobic ligands enter cells through the lipid bilayers of the cell membrane to interact with receptors found inside cells (Figure 2.2D).

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 2.2A). 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. There are many kinds of G proteins (for example, G_s, G_i, and G_q), 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 (Figure 2.3). 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. 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 G_s and inhibited by G_i, is adenylyl cyclase, which produces the second messenger cyclic adenosine monophosphate (cAMP). G_q activates phospholipase C, generating two other second messengers: inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). DAG and cAMP activate different protein kinases within the cell, leading to a myriad of physiological effects. IP_3 regulates intracellular free calcium concentrations, as well as some protein kinases.

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

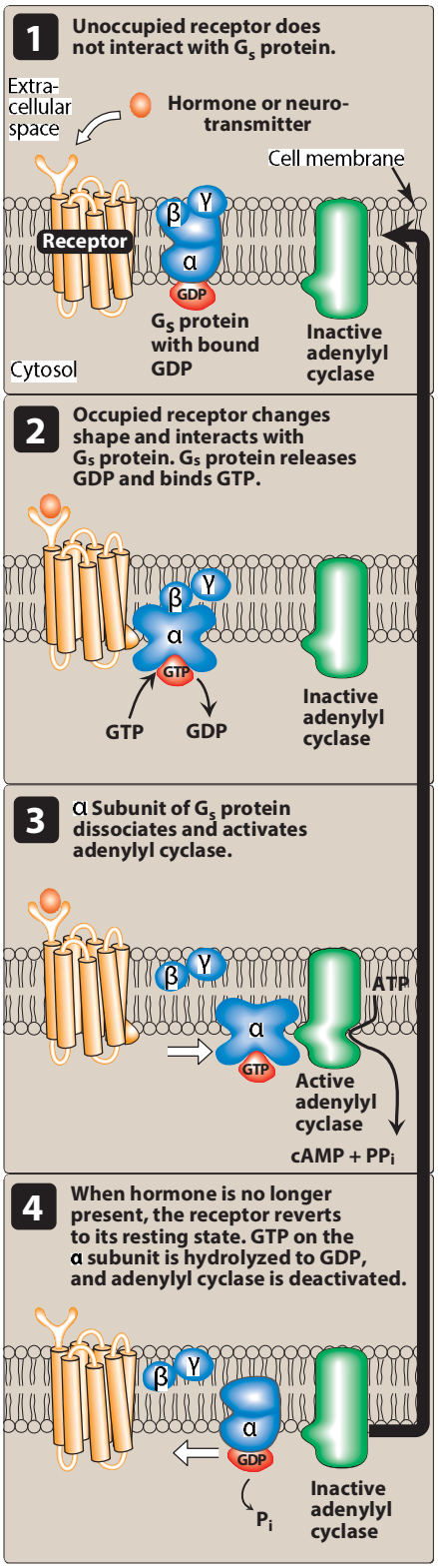

Figure 2.3
The recognition of chemical signals by G protein–coupled membrane receptors affects the activity of adenylyl cyclase. PP_i = inorganic pyrophosphate.

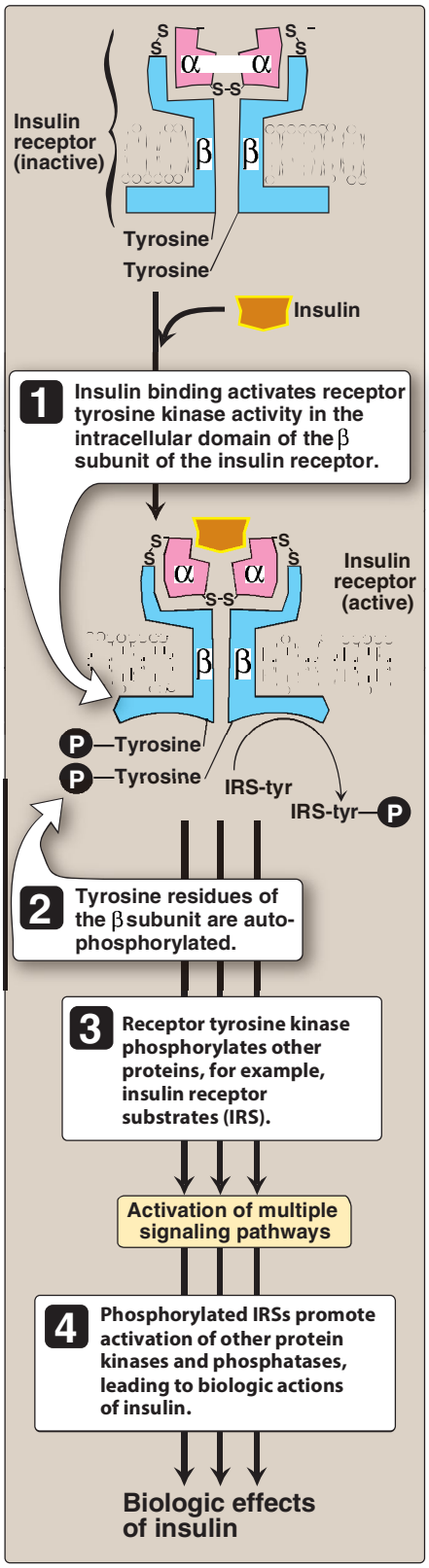

Figure 2.4
Insulin receptor.

their structure and function (Figure 2.4). 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 2.4). 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.

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 (Figure 2.5). 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* (see Chapter 46), the enzyme dihydrofolate reductase is the target of antimicrobials such as *trimethoprim* (see Chapter 40), and the 50S subunit of the bacterial ribosome is the target of macrolide antibiotics such as *erythromycin* (see Chapter 39).

D. Some characteristics of signal transduction

Signal transduction has two important features: 1) the ability to amplify small signals and 2) mechanisms to protect the cell from excessive stimulation.

1. **Signal amplification:** A characteristic of G protein–linked and enzyme-linked receptors is their ability to amplify signal intensity and duration. For example, a single agonist–receptor complex can interact with many G proteins, thereby multiplying the original signal manyfold. Additionally, activated G proteins persist for a longer duration than does the original agonist–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 are 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. Systems that exhibit this behavior are said to have spare receptors. Spare receptors are exhibited by insulin receptors, where it is estimated that 99% of receptors are "spare." This constitutes an immense functional reserve that ensures that adequate amounts of glucose enter the cell. On the other hand, in the human heart, only about 5% to 10% of the total β-adrenoceptors are spare. An important implication of this observation is that little functional reserve exists in the failing heart, because most receptors must be occupied to obtain maximum contractility.

2. **Desensitization and down-regulation 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 a receptor is exposed to repeated administration of an agonist, the receptor becomes desensitized (Figure 2.6) resulting in a diminished effect. This phenomenon, called tachyphylaxis, is due to either phosphorylation or a similar chemical event that renders receptors on the cell surface unresponsive to the ligand. In addition, receptors may be down-regulated such that they are internalized and sequestered within the cell, unavailable for 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 ion channels, require a finite time following stimulation before they can be activated again. During this recovery phase, unresponsive receptors are said to be "refractory." Similarly, repeated exposure of a receptor to an antagonist may result in up-regulation of receptors, in which receptor reserves are inserted into the membrane, increasing the total number of receptors available. Up-regulation of receptors can make the cells more sensitive to agonists and/or more resistant to the effect of the antagonist.

III. DOSE–RESPONSE RELATIONSHIPS

Agonist drugs mimic the action of the original endogenous ligand for the receptor (for example, *isoproterenol* mimics norepinephrine on β_1 receptors of the heart). The magnitude of the drug effect depends on the drug concentration at the receptor site, which, in turn, is determined by both the dose of drug administered and by the drug's pharmacokinetic profile, such as rate of absorption, distribution, metabolism, and elimination.

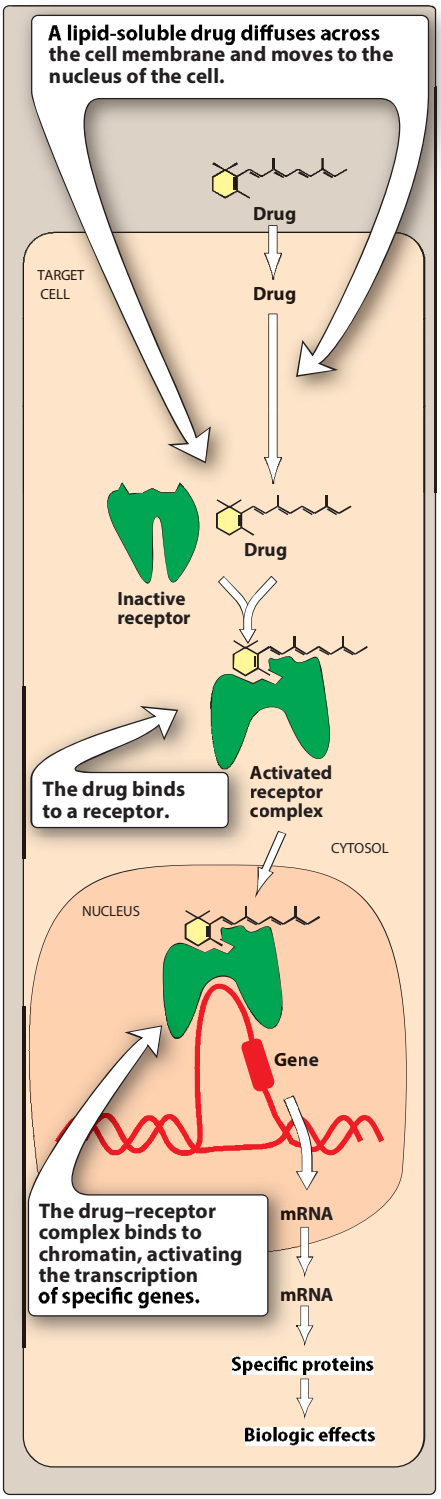

Figure 2.5
Mechanism of intracellular receptors. mRNA = messenger RNA.

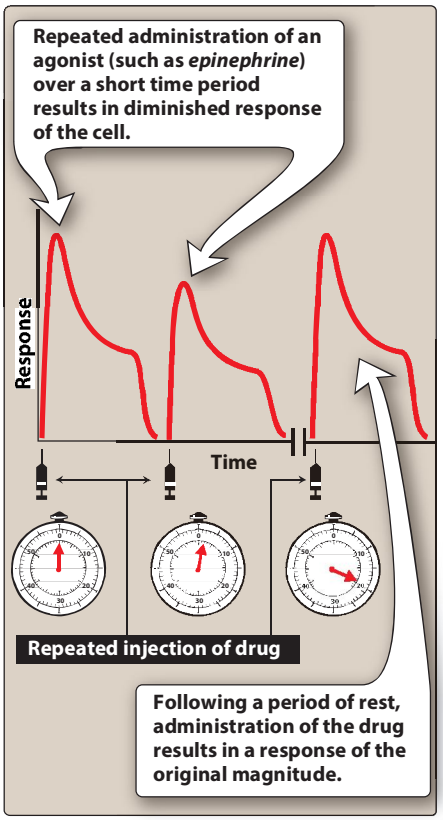

Figure 2.6
Desensitization of receptors.

A. Graded dose–response relations

As the concentration of a drug increases, its pharmacologic effect also gradually increases until all the receptors are occupied (the maximum effect). Plotting the magnitude of response against increasing doses of a drug produces a graded dose–response curve that has the general shape depicted in Figure 2.7A. The curve can be described as a rectangular hyperbola, which is a familiar curve in biology because it can be applied to diverse biological events, such as enzymatic activity, and responses to pharmacologic agents. Two important properties of drugs, potency and efficacy, can be determined by graded dose–response curves.

1. **Potency:** Potency is a measure of the amount of drug necessary to produce an effect of a given magnitude. The concentration of drug producing 50% of the maximum effect (EC_{50}) is usually used to determine potency. In Figure 2.7, the EC_{50} for Drugs A and B indicate that Drug A is more potent than Drug B, because a lesser amount of Drug A is needed when compared to Drug B to obtain 50-percent effect. Therapeutic preparations of drugs reflect their potency. For example, *candesartan* and *irbesartan* are angiotensin receptor blockers that are used to treat hypertension. The therapeutic dose range for *candesartan* is 4 to 32 mg, as compared to 75 to 300 mg for *irbesartan.* Therefore, *candesartan* is more potent than is *irbesartan* (it has a lower EC_{50} value, similar to Drug A in Figure 2.7). Since the range of drug concentrations (from 1% to 99% of the maximal response) usually spans several orders of magnitude, semilogarithmic plots are used so that the complete range of doses can be graphed. As shown in Figure 2.7B, the curves become sigmoidal in shape, which simplifies the interpretation of the dose–response curve.

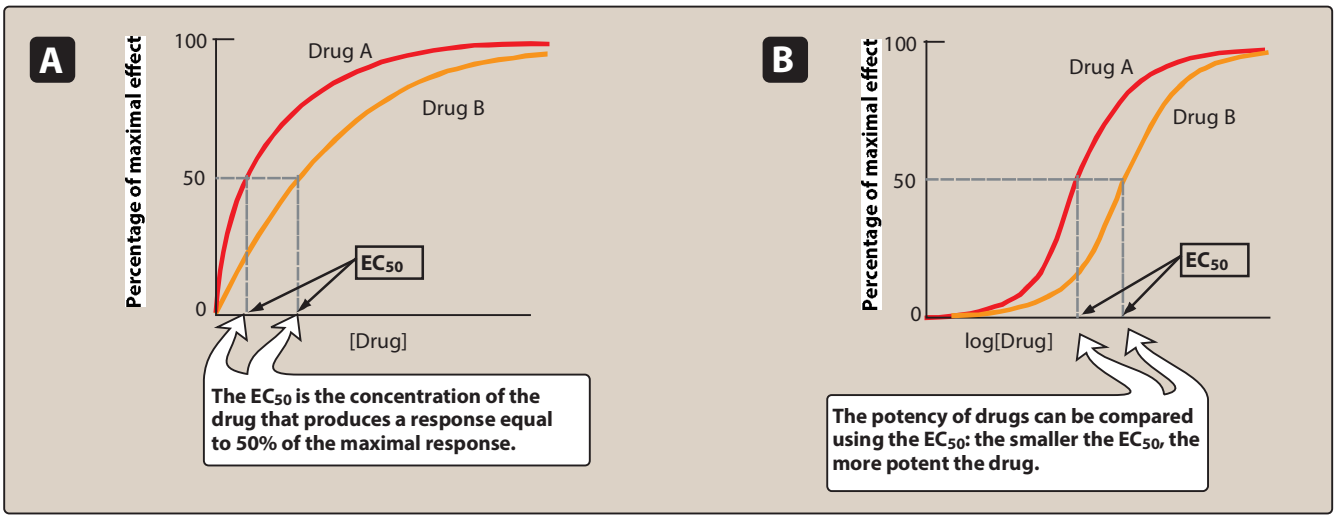

Figure 2.7
The effect of dose on the magnitude of pharmacologic response. **Panel A** is a linear graph. **Panel B** is a semilogarithmic plot of the same data. EC_{50} = drug dose causing 50% of maximal response.

2. **Efficacy:** Efficacy is the magnitude of response a drug causes when it interacts with a receptor. Efficacy is dependent on the number of drug–receptor complexes formed and the intrinsic activity of the drug (its ability to activate the receptor and cause a cellular response). Maximal efficacy of a drug (E_{max}) assumes that all receptors are occupied by the drug, and no increase in response is observed if a higher concentration of drug is obtained. Therefore, the maximal response differs between full and partial agonists, even when 100% of the receptors are occupied by the drug. Similarly, even though an antagonist occupies 100% of the receptor sites, no receptor activation results and E_{max} is zero. Efficacy is a more clinically useful characteristic than is drug potency, since a drug with greater efficacy is more therapeutically beneficial than is one that is more potent. Figure 2.8 shows the response to drugs of differing potency and efficacy.

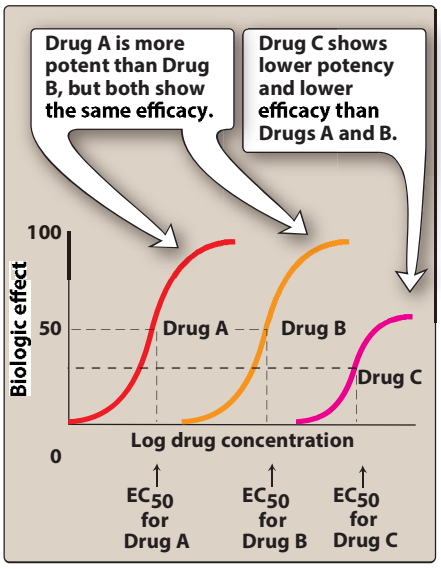

Figure 2.8
Typical dose–response curve for drugs showing differences in potency and efficacy. EC_{50} = drug dose that shows 50% of maximal response.

B. Effect of drug concentration on 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:

$$\text{Drug} + \text{Receptor} \rightleftarrows \text{Drug–receptor complex} \rightarrow \text{Biologic effect}$$

By making the assumption that the binding of one drug molecule does not alter the binding of subsequent molecules and applying the law of mass action, we can mathematically express the relationship between the percentage (or fraction) of bound receptors and the drug concentration:

$$\frac{[DR]}{[R_t]} = \frac{[D]}{K_d + [D]} \qquad (1)$$

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 = the equilibrium 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, and vice versa. Equation (1) defines a curve that has the shape of a rectangular hyperbola (Figure 2.9A). As the concentration of free drug increases, the ratio of the concentrations of bound receptors to total receptors approaches unity. The binding of the drug to its receptor initiates events that ultimately lead to a measurable biologic response. Thus, it is not surprising that the curves shown in Figure 2.9 and those representing the relationship between dose and effect (Figure 2.7) are similar.

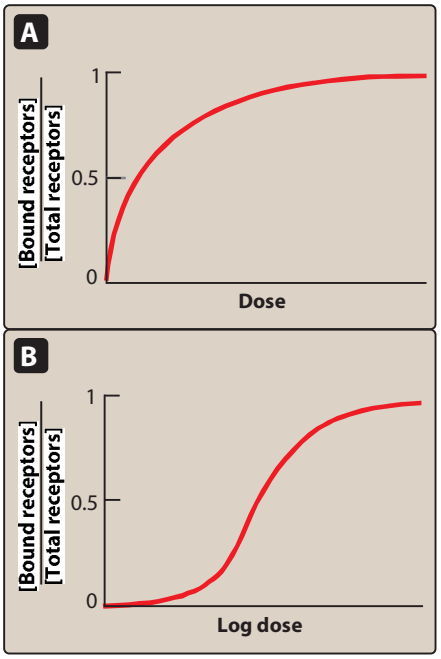

Figure 2.9
The effect of dose on the magnitude of drug binding.

C. Relationship of drug binding to pharmacologic effect

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,

$$\frac{[E]}{[E_{max}]} = \frac{[D]}{K_d + [D]} \quad (2)$$

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

Thus, it follows that if a specific population of receptors is vital for mediating a physiological effect, the affinity of an agonist for binding to those receptors should be related to the potency of that drug for causing that physiological effect. It should be remembered that many drugs and most neurotransmitters can bind to more than one type of receptor, thereby causing both desired therapeutic effects and undesired side effects. In order to establish a relationship between drug occupation of a particular receptor subtype and the corresponding biological response, correlation curves of receptor affinity and drug potency are often constructed (Figure 2.10).

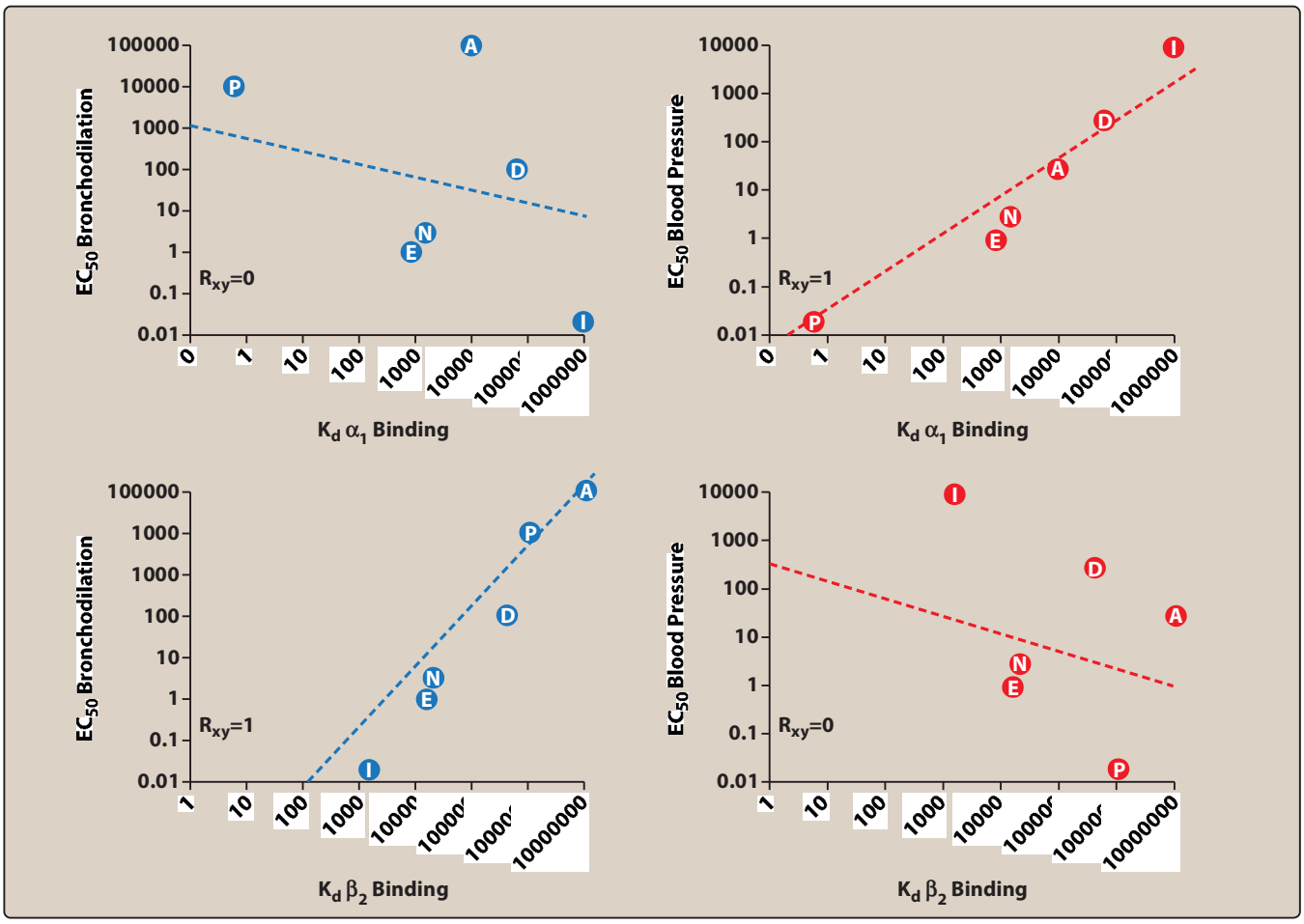

Figure 2.10
Correlation of drug affinity for receptor binding and potency for causing a physiological effect. A positive correlation should exist between the affinity (K_d value) of a drug for binding to a specific receptor subtype and the potency (EC_{50} value) of that drug to cause physiological responses mediated by that receptor population. For example, many drugs have affinity for both α_1 and β_2 adrenergic receptors. The circled letters in the figure represent agonists with varying affinities for α_1 and β_2 receptors. However, from the data provided, it becomes clear that α_1 receptors only mediate changes in blood pressure, while β_2 receptors only mediate changes in bronchodilation.

IV. INTRINSIC ACTIVITY

As mentioned above, an agonist binds to a receptor and produces a biologic response based on the concentration of the agonist and the fraction of activated receptors. The intrinsic activity of a drug determines its ability to fully or partially activate the receptors. Drugs may be categorized according to their intrinsic activity and resulting E_{max} values.

A. Full agonists

If a drug binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous ligand, it is a full agonist (Figure 2.11). Full agonists bind to a receptor, stabilizing the receptor in its active state and are said to have an intrinsic activity of one. All full agonists for a receptor population should produce the same E_{max}. For example, *phenylephrine* is a full agonist at α_1-adrenoceptors, because it produces the same E_{max} as does the endogenous ligand, norepinephrine. Upon binding to α_1-adrenoceptors on vascular smooth muscle, *phenylephrine* stabilizes the receptor in its active state. This leads to the mobilization of intracellular Ca^{2+}, causing interaction of actin and myosin filaments and shortening of the muscle cells. The diameter of the arteriole decreases, causing an increase in resistance to blood flow through the vessel and an increase in blood pressure. As this brief description illustrates, an agonist may have many measurable effects, including actions on intracellular molecules, cells, tissues, and intact organisms. All of these actions are attributable to interaction of the drug with the receptor. For full agonists, the dose–response curves for receptor binding and each of the biological responses should be comparable.

B. Partial agonists

Partial agonists have intrinsic activities greater than zero but less than one (Figure 2.11). Even if all the receptors are occupied, partial agonists cannot produce the same E_{max} as 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. When a receptor is exposed to both a partial agonist and a full agonist, the partial agonist may act as an antagonist of the full agonist. Consider what would happen to the E_{max} of a receptor saturated with an agonist in the presence of increasing concentrations of a partial agonist (Figure 2.12). 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 as both an agonist and antagonist may be therapeutically utilized. For example, *aripiprazole,* an atypical antipsychotic, is a partial agonist at selected dopamine receptors. Dopaminergic pathways that are overactive tend to be inhibited by *aripiprazole*, whereas pathways that are underactive are stimulated. This might explain the ability of *aripiprazole* to improve symptoms of schizophrenia, with a small risk of causing extrapyramidal adverse effects (see Chapter 11).

C. Inverse agonists

Typically, unbound receptors are inactive and require interaction with an agonist to assume an active conformation. However, some

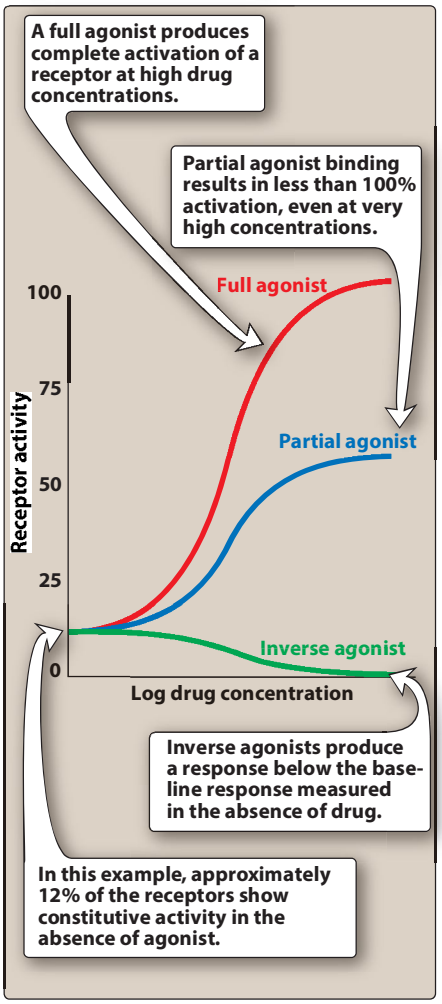

Figure 2.11
Effects of full agonists, partial agonists, and inverse agonists on receptor activity.

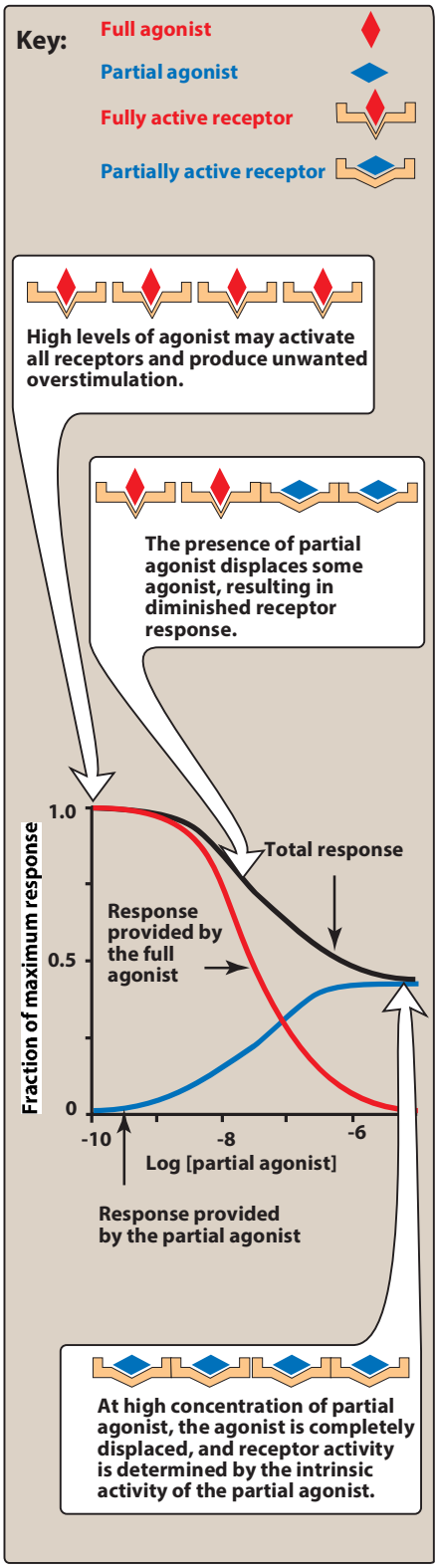

Figure 2.12
Effects of partial agonists.

receptors show a spontaneous conversion from R to R* in the absence of an agonist. Inverse agonists, unlike full agonists, stabilize the inactive R form and cause R* to convert to R. This decreases the number of activated receptors to below that observed in the absence of drug (Figure 2.11). Thus, inverse agonists have an intrinsic activity less than zero, reverse the activity of receptors, and exert the opposite pharmacological effect of agonists.

D. Antagonists

Antagonists bind to a receptor with high affinity but possess zero intrinsic activity. An antagonist has no effect in the absence of an agonist but can decrease the effect of an agonist when present. Antagonism may occur either by blocking the drug's ability to bind to the receptor or by blocking its ability to activate the receptor.

1. **Competitive antagonists:** If both the antagonist and the agonist bind to the same site on the receptor in a reversible manner, they are said to be "competitive." The competitive antagonist prevents an agonist from binding to its receptor and maintains the receptor in its inactive state. For example, the antihypertensive drug *terazosin* competes with the endogenous ligand norepinephrine at α_1-adrenoceptors, thus decreasing vascular smooth muscle tone and reducing blood pressure. However, this inhibition can be overcome by increasing the concentration of agonist relative to antagonist. Thus, competitive antagonists characteristically shift the agonist dose–response curve to the right (increased EC_{50}) without affecting E_{max} (Figure 2.13).

2. **Irreversible antagonists:** Irreversible antagonists bind covalently to the active site of the receptor, thereby reducing the number of receptors available to the agonist. An irreversible antagonist causes a downward shift of the E_{max}, with no shift of EC_{50} values (unless spare receptors are present). In contrast to competitive antagonists, the effect of irreversible antagonists cannot be overcome by adding more agonist (Figure 2.13). Thus, irreversible antagonists and allosteric antagonists (see below) are both considered noncompetitive antagonists. A fundamental difference between competitive and noncompetitive antagonists is that competitive agonists reduce agonist potency (increase EC_{50}) and noncompetitive antagonists reduce agonist efficacy (decrease E_{max}).

3. **Allosteric antagonists:** An allosteric antagonist also causes a downward shift of the E_{max}, with no change in the EC_{50} value of an agonist. This type of antagonist binds to a site ("allosteric site") other than the agonist-binding site and prevents the receptor from being activated by the agonist. An example of an allosteric agonist is picrotoxin, which binds to the inside of the GABA-controlled chloride channel. When picrotoxin is bound inside the channel, no chloride can pass through the channel, even when the receptor is fully activated by GABA.

4. **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 functional antagonism by epinephrine to histamine-induced bronchoconstriction. Histamine binds to H_1 histamine receptors on bronchial smooth muscle, causing

bronchoconstriction of the bronchial tree. Epinephrine is an agonist at β_2-adrenoceptors on bronchial smooth muscle, which causes the muscles to relax. This functional antagonism is also known as "physiologic antagonism."

V. QUANTAL DOSE–RESPONSE RELATIONSHIPS

Another important dose–response relationship is that between the dose of the drug and the proportion of a population that responds to it. These responses are known as quantal responses, because, for any individual, the effect either occurs or it does not. Graded responses can be transformed to quantal responses by designating a predetermined level of the graded response 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 a fall of at least 5 mm Hg in diastolic blood pressure. Quantal dose–response curves are useful for determining doses to which most of the population responds. They have similar shapes as log dose–response curves, and the ED_{50} is the drug dose that causes a therapeutic response in half of the population.

A. Therapeutic index

The therapeutic index (TI) of a drug is the ratio of the dose that produces toxicity in half the population (TD_{50}) to the dose that produces a clinically desired or effective response (ED_{50}) in half the population:

$$TI = TD_{50} / ED_{50}$$

The TI 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. Clinical usefulness of the therapeutic index

The TI 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 high TI values are required for most drugs, some drugs with low therapeutic indices are routinely used to treat serious diseases. In these cases, the risk of experiencing side effects is not as great as the risk of leaving the disease untreated. Figure 2.14 shows the responses to *warfarin*, an oral anticoagulant with a low therapeutic index, and *penicillin,* an antimicrobial drug with a large therapeutic index.

1. **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- to threefold increase in the international normalized ratio [INR]) until, eventually, all patients respond (Figure 2.14A). However, at higher doses of *warfarin*, anticoagulation resulting in hemorrhage occurs in a small percent of patients. Agents with a low TI (that is, drugs for which dose is critically important) are those drugs for which bioavailability critically alters the therapeutic effects (see Chapter 1).

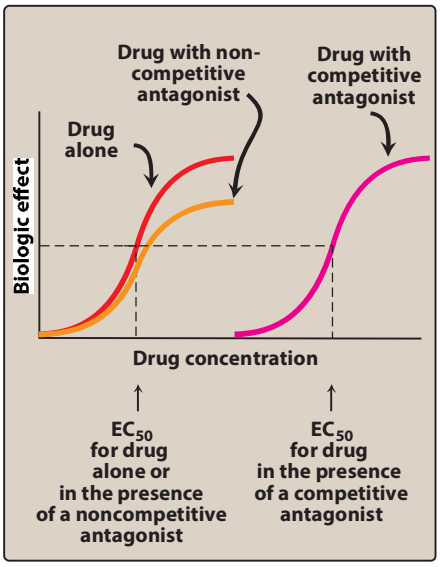

Figure 2.13
Effects of drug antagonists. EC_{50} = drug dose that shows 50% of maximal response.

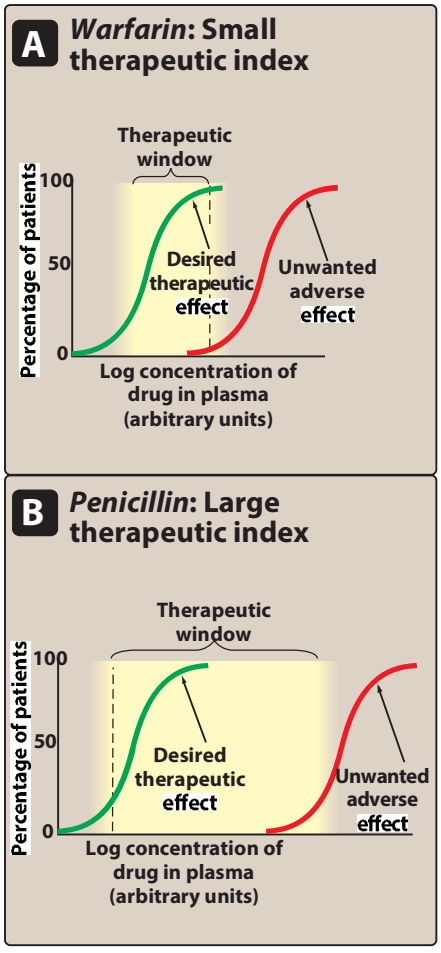

Figure 2.14
Cumulative percentage of patients responding to plasma levels of *warfarin* and *penicillin.*

2. **Penicillin (example of a drug with a large therapeutic index):** For drugs such as *penicillin* (Figure 2.14B), it is safe and common to give doses in excess of that which is minimally required to achieve a desired response without the risk of adverse side effects. In this case, bioavailability does not critically alter the therapeutic or clinical effects.

Study Questions

Choose the ONE best answer.

2.1 Isoproterenol produces maximal contraction of cardiac muscle in a manner similar to epinephrine. Which of the following best describes isoproterenol?

A. Full agonist.
B. Partial agonist.
C. Competitive antagonist.
D. Irreversible antagonist.
E. Inverse agonist.

Correct answer = A. A full agonist has an E_{max} similar to the endogenous ligand. A partial agonist would only produce a partial effect. An antagonist would block the effects of an endogenous agonist. An inverse agonist would reverse the constitutive activity of receptors and exert the opposite pharmacological effect.

2.2 If 10 mg of naproxen produces the same analgesic response as 100 mg of ibuprofen, which of the following statements is correct?

A. Naproxen is more efficacious than is ibuprofen.
B. Naproxen is more potent than ibuprofen.
C. Naproxen is a full agonist, and ibuprofen is a partial agonist.
D. Naproxen is a competitive antagonist.
E. Naproxen is a better drug to take for pain relief than is ibuprofen.

Correct answer = B. Without information about the maximal effect of these drugs, no conclusions can be made about efficacy or intrinsic activity. E is false because the maximal response obtained is often more important than the amount of drug needed to achieve it.

2.3 If 10 mg of morphine produces a greater analgesic response than can be achieved by ibuprofen at any dose, which of the following statements is correct?

A. Morphine is less efficacious than is ibuprofen.
B. Morphine is less potent than is ibuprofen.
C. Morphine is a full agonist, and ibuprofen is a partial agonist.
D. Ibuprofen is a competitive antagonist.
E. Morphine is a better drug to take for pain relief than is ibuprofen.

Correct answer = E. Based on the information presented here, since morphine is more efficacious than is ibuprofen, it is going to provide more pain relief. As long as the situation warrants the necessity of such efficacious pain relief and without any information about differences in side effects caused by the two drugs, morphine is the better choice. Choice C would only be true if both drugs bound to the same receptor population, and that is not the case. The other choices are incorrect statements.

2.4 In the presence of naloxone, a higher concentration of morphine is required to elicit full pain relief. Naloxone by itself has no effect. Which of the following is correct regarding these medications?

A. Naloxone is a competitive antagonist.
B. Morphine is a full agonist, and naloxone is a partial agonist.
C. Morphine is less efficacious than is naloxone.
D. Morphine is less potent than is naloxone.
E. Naloxone is a noncompetitive antagonist.

Correct answer = A. Since naloxone has no effect by itself, B and C are incorrect. Since it decreases the effect of an agonist but this inhibition can be overcome by giving a higher dose of morphine, naloxone must be a competitive antagonist. No information is given about potency of either drug.

2.5 In the presence of pentazocine, a higher concentration of morphine is required to elicit full pain relief. Pentazocine by itself has a smaller analgesic effect than does morphine, even at the highest dose. Which of the following is correct regarding these medications?

A. Pentazocine is a competitive antagonist.
B. Morphine is a full agonist, and pentazocine is a partial agonist.
C. Morphine is less efficacious than is pentazocine.
D. Morphine is less potent than is pentazocine.
E. Pentazocine is a noncompetitive antagonist.

Correct answer = B. Pentazocine has a lower E_{max} value than does morphine but still has some efficacy. Thus, pentazocine is a partial agonist. Even though pentazocine blocks some of the actions of morphine, since it has some efficacy, it cannot be an antagonist. No information is given about the potency of either drug.

2.6 In the presence of picrotoxin, diazepam is less efficacious at causing sedation, regardless of the dose. Picrotoxin by itself has no sedative effect even at the highest dose. Which of the following is correct?

A. Picrotoxin is a competitive antagonist.
B. Diazepam is a full agonist, and picrotoxin is a partial agonist.
C. Diazepam is less efficacious than is picrotoxin.
D. Diazepam is less potent than is picrotoxin.
E. Picrotoxin is a noncompetitive antagonist.

Correct answer = E. Picrotoxin has no efficacy alone, so B and C are false. Since it decreases the maximal effect of diazepam, it is a noncompetitive antagonist. No information is given about potency of either drug.

2.7 Which of the following statements most accurately describes a system having spare receptors?

A. The number of spare receptors determines the maximum effect.
B. Spare receptors are sequestered in the cytosol.
C. A single drug–receptor interaction results in many cellular response elements being activated.
D. Spare receptors are active even in the absence of an agonist.
E. Agonist affinity for spare receptors is less than their affinity for “non-spare” receptors.

Correct answer = C. One explanation for the existence of spare receptors is that any one agonist–receptor binding event can lead to the activation of many more cellular response elements. Thus, only a small fraction of the total receptors need to be bound to elicit a maximum cellular response. The other choices do not accurately describe spare receptor systems.

2.8 Which of the following would up-regulate postsynaptic β_1 adrenergic receptors?

A. Daily use of amphetamine that causes norepinephrine to be released.
B. A disease that causes an increase in the activity of norepinephrine neurons.
C. Daily use of isoproterenol, a β_1 receptor agonist.
D. Daily use of formoterol, a β_2 receptor agonist.
E. Daily use of propranolol, a β_1 receptor antagonist.

Correct answer = E. Up-regulation of receptors occurs when receptor activation is lower than normal, such as when the receptor is continuously exposed to an antagonist for that receptor. Down-regulation of receptor number occurs when receptor activation is greater than normal because of continuous exposure to an agonist.