Drug–Receptor Interactions and Pharmacodynamics

2

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I. OVERVIEW

Pharmacodynamics describes the actions of a drug on the body. Most drugs exert effects, both beneficial and harmful, by interacting with specialized target macromolecules called receptors, which are present on or in 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 receptors act as signal detectors. A drug is termed an "agonist" if it binds to a site on a receptor protein and activates it to initiate a series of reactions that ultimately result in a specific intracellular response. "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-adrenergic receptors that bind and respond to epinephrine or norepinephrine. Cardiac cells also contain muscarinic receptors that bind and respond to acetylcholine. These two receptor populations dynamically interact to control the heart's vital functions.

The magnitude of the cellular response is proportional to the number of drug–receptor complexes. This concept is conceptually similar to the formation of complexes between enzyme and substrate and shares many common features, such as specificity of the receptor for a given agonist. Although much of this chapter centers on the interaction of drugs with specific receptors, it is important to know that not all drugs exert effects by interacting with a receptor. Antacids, for instance, chemically neutralize excess gastric acid, thereby reducing stomach upset.

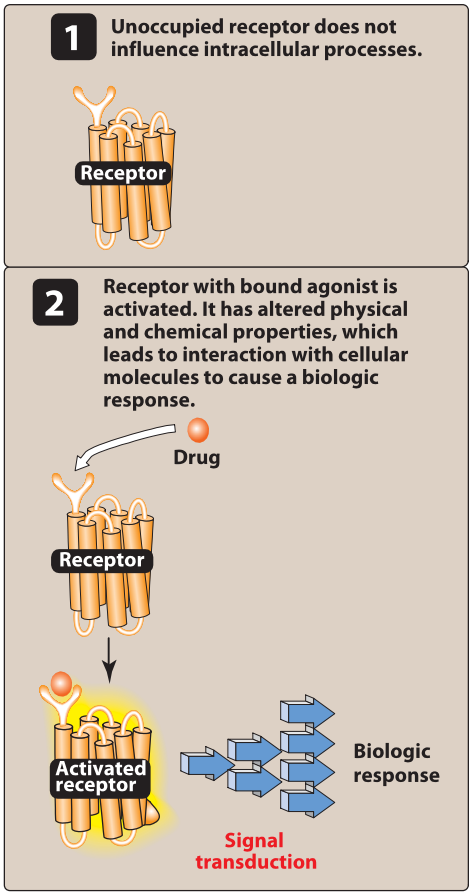

Figure 2.1
The recognition of a drug by a receptor triggers a biologic response.

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 are drugs that bind to the receptor but do not increase the fraction of R*, instead stabilizing the fraction of R. Some drugs (partial agonists) shift the equilibrium from R to R*, but the fraction of R* is less than that caused by an agonist. The magnitude of biological effect is directly related to the fraction of R*. In summary, agonists, antagonists, and partial agonists are examples of molecules or ligands that bind to the activation site on the receptor and can affect the fraction of R*.

C. Major receptor families

A receptor is defined 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 receptors are membrane-bound 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). Generally, hydrophilic ligands interact with receptors that are found on the cell surface (Figure 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).

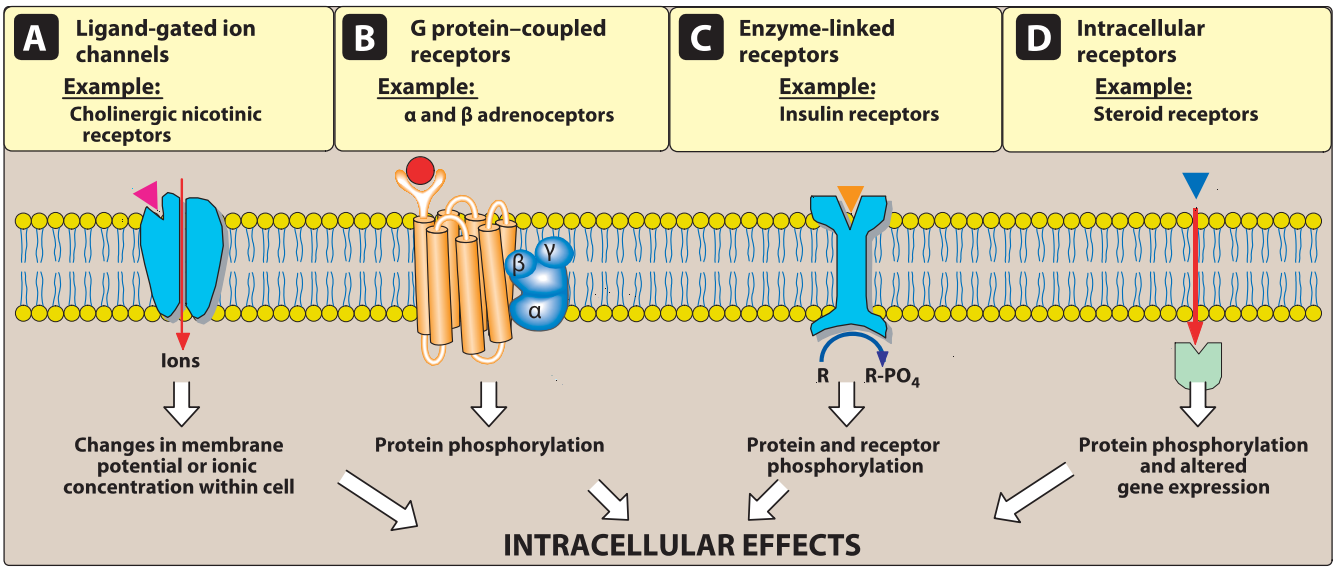

Figure 2.2
Transmembrane signaling mechanisms. **A.** Ligand binds to the extracellular domain of a ligand-gated channel. **B.** Ligand binds to a domain of a transmembrane receptor, which is coupled to a G protein. **C.** Ligand binds to the extracellular domain of a receptor that activates a kinase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

1. **Transmembrane ligand-gated ion channels:** The extracellular portion of ligand-gated ion channels contains the drug-binding site. This site regulates the opening 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 for a few milliseconds. Depending on the ion conducted through these channels, these receptors mediate diverse functions, including neurotransmission and muscle contraction. For example, stimulation of the nicotinic receptor by acetylcholine opens a channel that allows sodium influx and potassium outflux across the cell membranes of neurons or muscle cells. This change in ionic concentrations across the membrane generates an action potential in a neuron and contraction in skeletal and cardiac muscle. On the other hand, agonist stimulation of the A subtype of the γ-aminobutyric acid (GABA) receptor increases chloride influx, resulting in hyperpolarization of neurons and less chance of generating an action potential. Drug-binding sites are also found on many voltage-gated ion channels where they 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 portion of this receptor contains the ligand-binding site, and the intracellular portion interacts (when activated) with a G protein. There are many kinds of G proteins (for example, G_s, G_i, and G_q), but all types 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. The α and βγ subunits are then free to interact with specific cellular effectors, usually an enzyme or an ion channel, that cause further actions within the cell. These responses usually last several seconds to minutes. Often, the activated effectors produce "second messenger" molecules 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). The effector phospholipase C, when activated by G_q, generates two second messengers: inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). DAG and cAMP activate specific protein kinases within the cell, leading to a myriad of physiological effects. IP_3 increases intracellular calcium concentration, which in turn activates other protein kinases.

3. **Enzyme-linked receptors:** This family of receptors undergoes conformational changes when activated by a ligand, resulting in

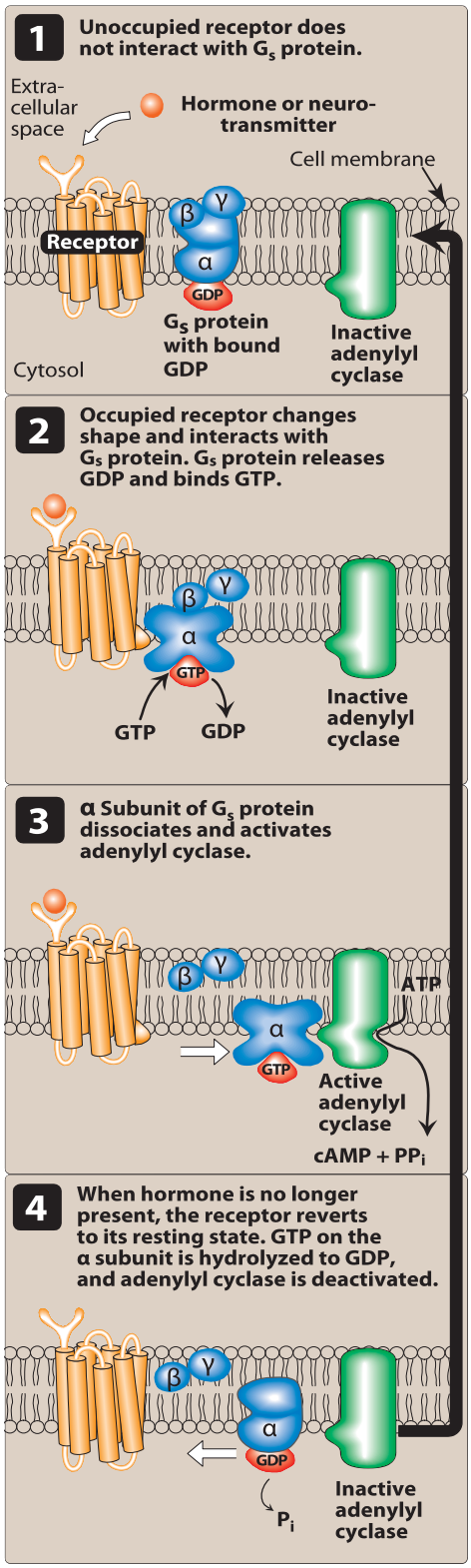

Figure 2.3
The recognition of chemical signals by G protein–coupled membrane receptors affects the activity of adenylyl cyclase. PP_i = inorganic pyrophosphate.

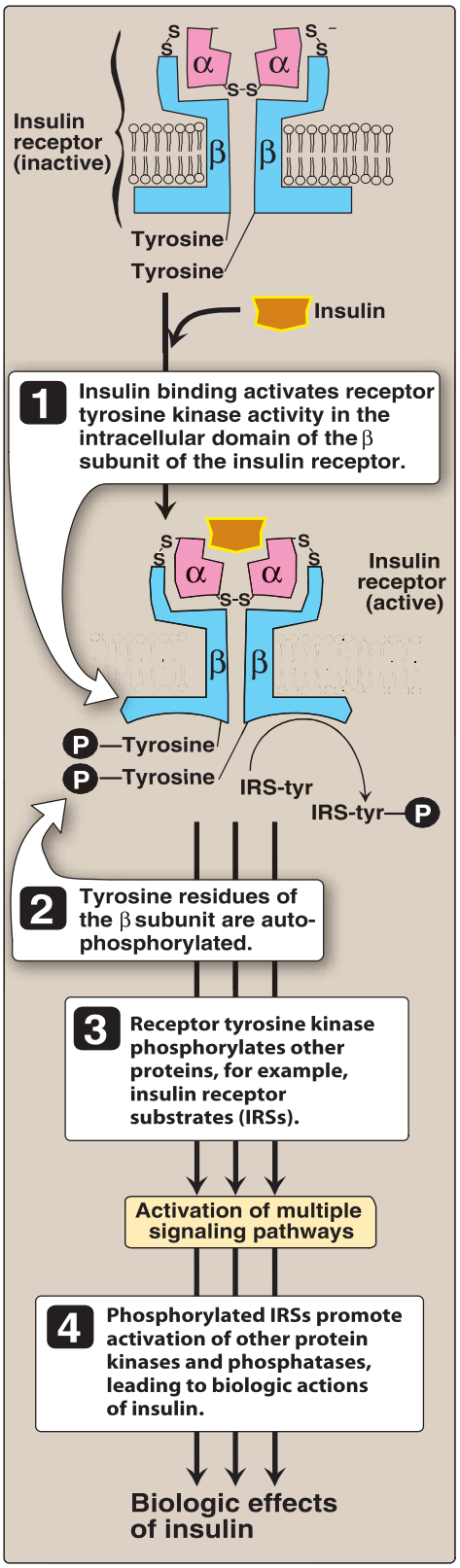

Figure 2.4
Insulin receptor.

increased intracellular enzyme activity (Figure 2.4). This response lasts for minutes to hours. The most common enzyme-linked receptors (for example, growth factors and insulin) possess tyrosine kinase activity. When activated, the receptor phosphorylates tyrosine residues on itself and other specific proteins (Figure 2.4). Phosphorylation can substantially modify the structure of the target protein, thereby acting as a molecular switch. For example, the phosphorylated insulin receptor in turn phosphorylates other proteins that now become active. Thus, enzyme-linked receptors often cause a signal cascade effect like that caused by 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 (for example, steroid hormones) must have sufficient lipid solubility to diffuse into the cell to interact with the receptor (Figure 2.5). The primary targets of activated intracellular receptors are transcription factors in the cell nucleus that regulate gene expression. The activation or inactivation of transcription factors alters the transcription of DNA into RNA and subsequently translation of RNA into proteins. The effect of drugs or endogenous ligands that activate intracellular receptors takes hours to days to occur. 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 35), the enzyme dihydrofolate reductase is the target of antimicrobials such as *trimethoprim* (see Chapter 31), and the 50S subunit of the bacterial ribosome is the target of macrolide antibiotics such as *erythromycin* (see Chapter 30).

D. 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 the ability to amplify signal intensity and duration via the signal cascade effect. 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. About 99% of insulin receptors are “spare,” providing an immense functional reserve that ensures that adequate amounts of glucose enter the cell. On the other hand, only

about 5% to 10% of the total β-adrenoceptors in the heart are spare. Therefore, 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 antagonist often leads to changes in the responsiveness of the receptor. The receptor may become desensitized due to too much agonist stimulation (Figure 2.6), resulting in a diminished response. This phenomenon, called tachyphylaxis, is often due to phosphorylation that renders receptors unresponsive to the agonist. In addition, receptors may be internalized within the cell, making them unavailable for further agonist interaction (down-regulation). 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." Repeated exposure of a receptor to an antagonist, on the other hand, results in up-regulation of receptors, in which receptor reserves are inserted into the membrane, increasing the number of receptors available. Up-regulation of receptors can make cells more sensitive to agonists and/or more resistant to effects of the antagonist.

III. DOSE–RESPONSE RELATIONSHIPS

Agonist drugs mimic the action of the 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 receptor sensitivity to the drug and 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.

A. Graded dose–response relationship

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. Two important drug characteristics, 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. The concentration of drug producing 50% of the maximum effect (EC_{50}) is often 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 to obtain 50% effect. Therapeutic preparations of drugs reflect their potency. For example, *candesartan* and *irbesartan*

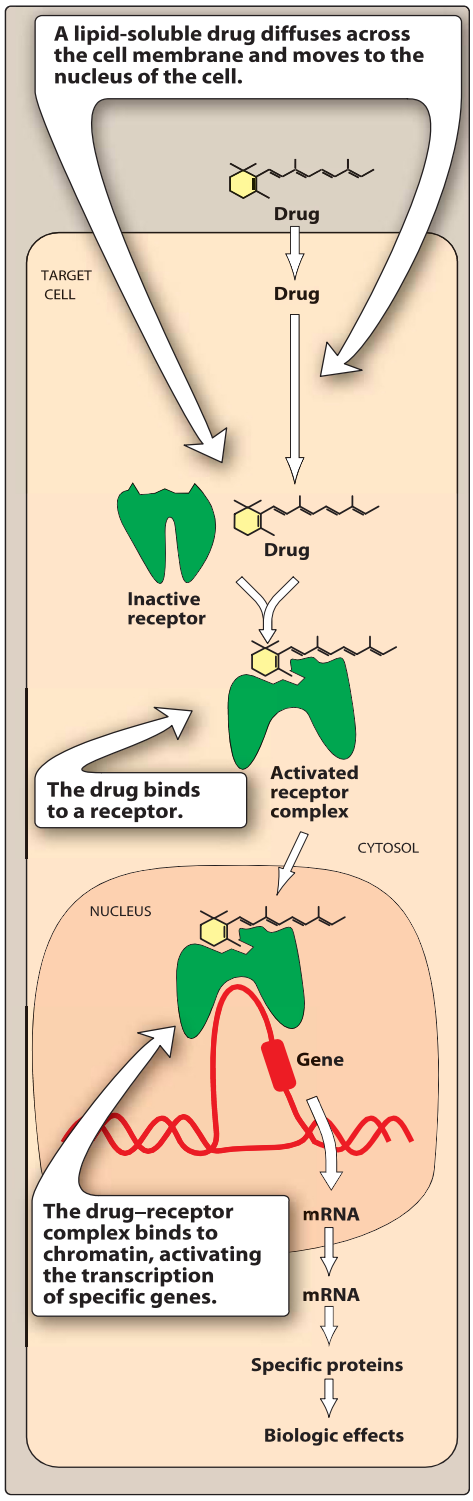

Figure 2.5
Mechanism of intracellular receptors. mRNA = messenger RNA.

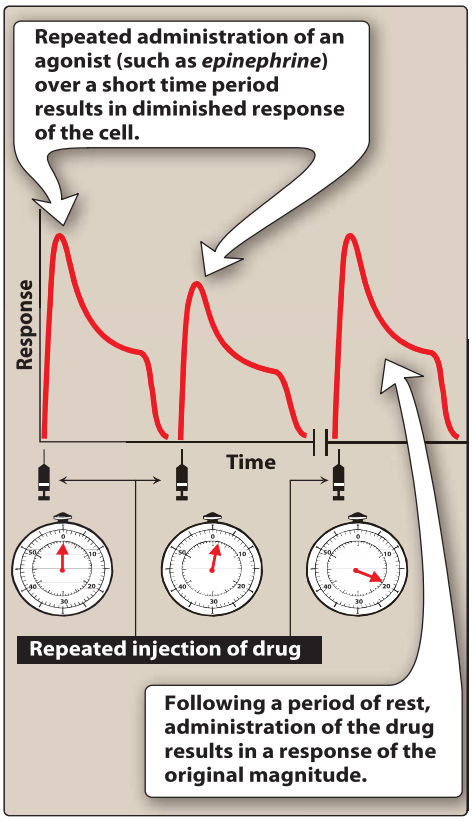

Figure 2.6
Desensitization of receptors.

are angiotensin receptor blockers 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 *irbesartan* (it has a lower EC_{50} value). Since the range of drug concentrations that cause from 1% to 99% of maximal response usually spans several orders of magnitude, semilogarithmic plots are used to graph the complete range of doses. As shown in Figure 2.7B, the curves become sigmoidal in shape, which simplifies the interpretation of the dose–response curve.

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 the drug occupies all receptors, and no increase in response is observed in response to higher concentrations of drug. The maximal response differs between full and partial agonists, even when the drug occupies 100% of the receptors. 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 potency, since a drug with greater efficacy is more therapeutically beneficial than one that is more potent. Figure 2.8 shows the response to drugs of differing potency and efficacy.

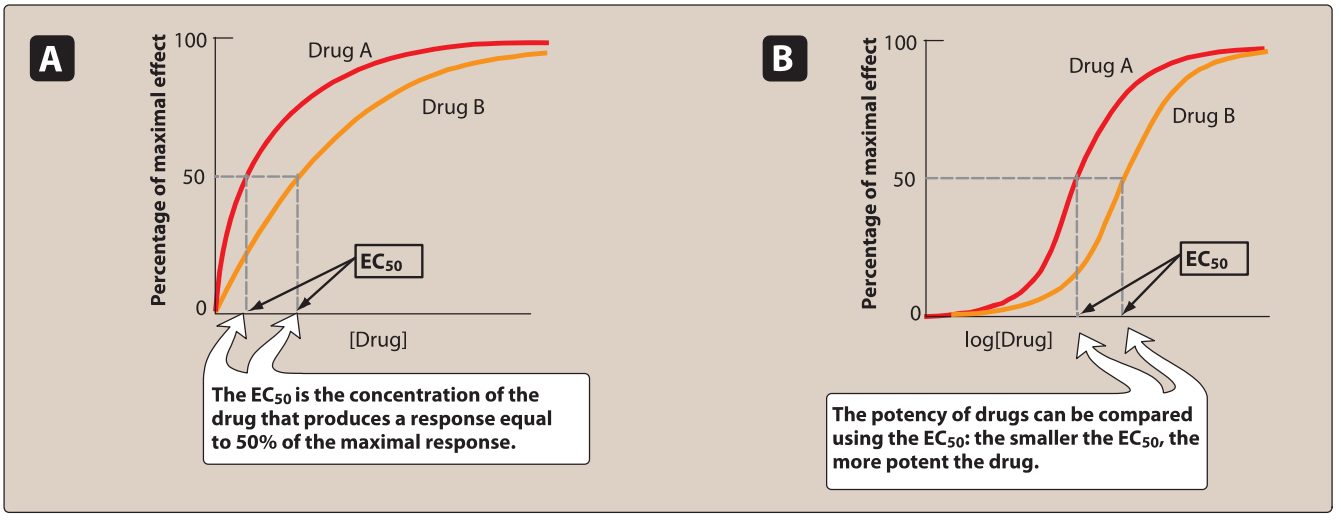

Figure 2.7
The effect of dose on the magnitude of pharmacologic response. **Panel A** is a linear plot. **Panel B** is a semilogarithmic plot of the same data. EC_{50} = drug dose causing 50% of maximal response.

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:

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

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:

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

where [D] = the concentration of free drug, [DR] = the concentration of bound drug, $[R_t]$ = the total number of 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 shapes shown in Figure 2.9 when plotted against drug concentration (Panel A) or log drug concentration (Panel B). As the concentration of free drug increases, the ratio of the concentrations of bound receptors to total receptors approaches unity, thereby producing the maximal effect. 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.

C. Relationship of drug binding to pharmacologic effect

The law of mass action can be applied to drug concentration and response providing the following assumptions are met: 1) The magnitude of the response is proportional to the amount of receptors occupied by drug, 2) the E_{max} occurs when all receptors are bound, and 3) one molecule of drug binds to only one molecule of receptor. 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. Many drugs and most neurotransmitters can bind to more than one type of receptor, thereby causing

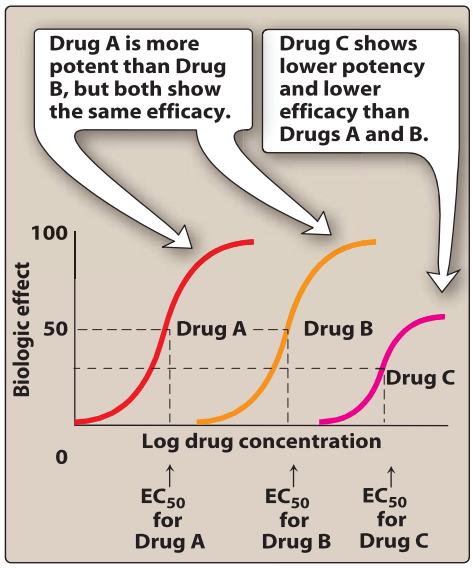

Figure 2.8
Typical dose–response curve for drugs showing differences in potency and efficacy. EC_{50} = drug dose that shows 50% of maximal response.

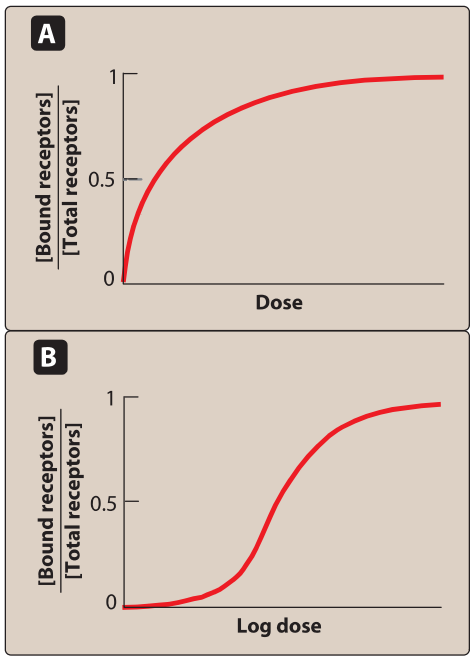

Figure 2.9
The effect of dose on the magnitude of drug binding.

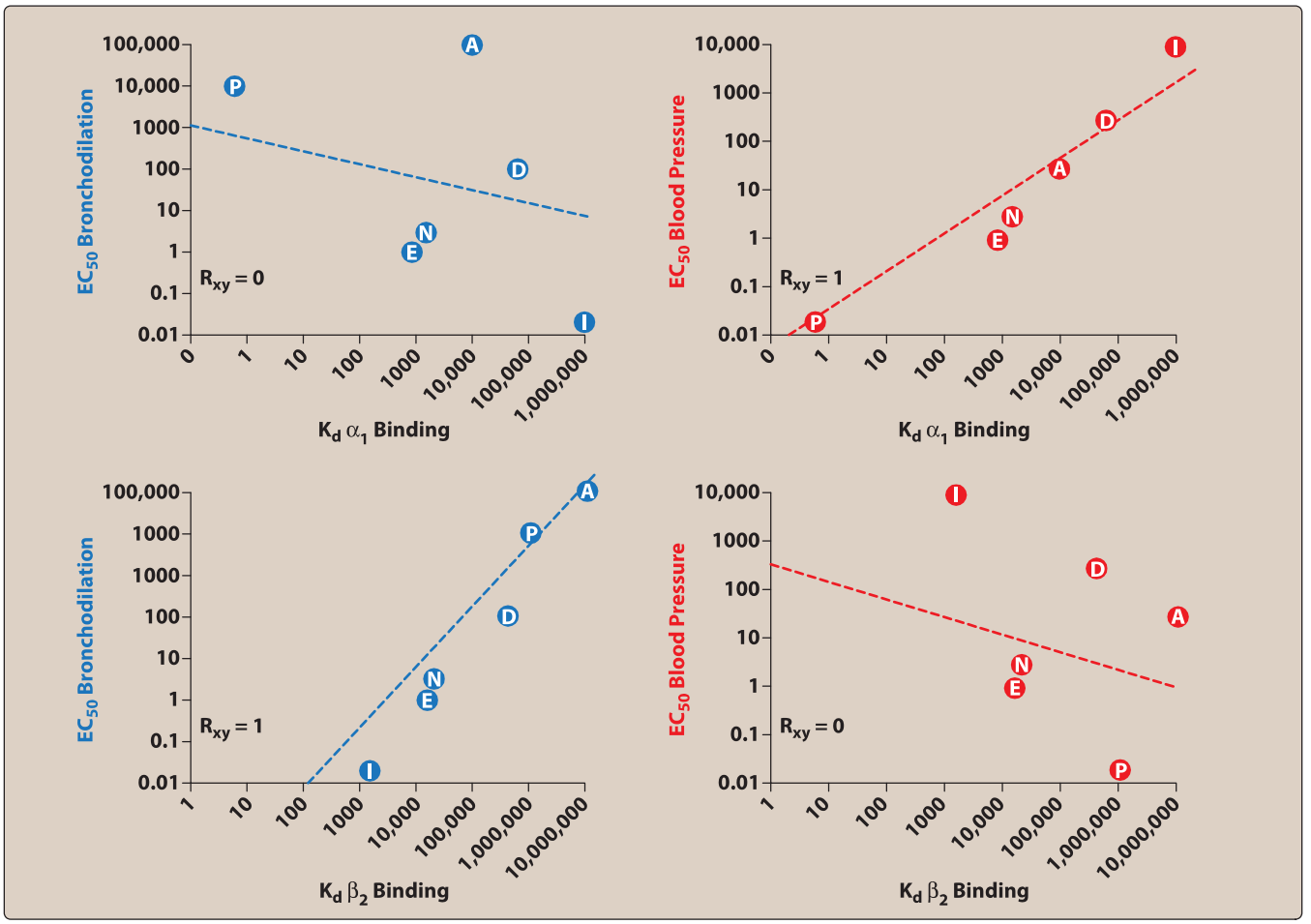

Figure 2.10
Correlation of drug affinity for receptor binding and potency for causing a physiological effect. A positive correlation should exist between the affinity (K_d value) of a drug for binding to a specific receptor subtype and the potency (EC_{50} value) of that drug to cause physiological responses 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.

both desired therapeutic effects and undesired adverse effects. In order to establish a relationship between drug occupation of a particular receptor subtype and the corresponding biological response to that drug, correlation curves of receptor affinity and drug potency are often constructed (Figure 2.10).

IV. INTRINSIC ACTIVITY

As mentioned above, an agonist binds to a receptor and produces a biologic response based on the concentration of the agonist, its affinity for the receptor and, hence, the fraction of occupied receptors. However, the intrinsic activity of a drug further 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 the endogenous ligand, norepinephrine. Upon binding to α_1-adrenoceptors on vascular smooth muscle, both norepinephrine and *phenylephrine* stabilize the receptor in its active state, thereby increasing G_q activation. Activation of G_q increases 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. Thus, effects of agonists on intracellular molecules, cells, tissues, and intact organisms are all 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 when all the receptors are occupied, partial agonists cannot produce the same E_{max} as a full agonist. Even so, a partial agonist may have an affinity that is greater than, less than, or equivalent to that of a full agonist. A partial agonist may also act as a partial antagonist of a full agonist (Figure 2.12). As the number of receptors occupied by the partial agonist increases, the number of receptors that can be occupied by the full agonist decreases and therefore 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 have therapeutic utility. For example, *aripiprazole*, an atypical antipsychotic, is a partial agonist at selected dopamine receptors. Overactive dopaminergic pathways tend to be inhibited by *aripiprazole*, whereas underactive pathways 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 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 activation state of receptors, and exert the opposite pharmacological effect of agonists.

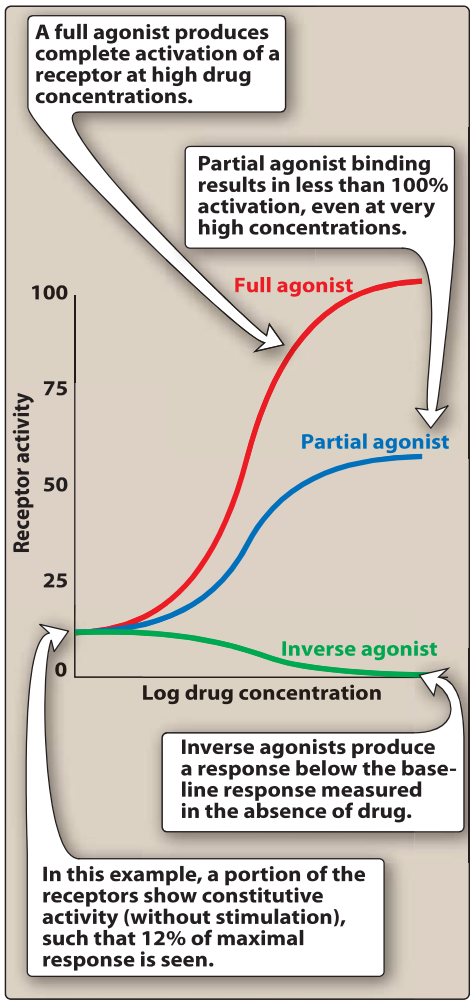

Figure 2.11
Effects of full agonists, partial agonists, and inverse agonists on receptor activity.

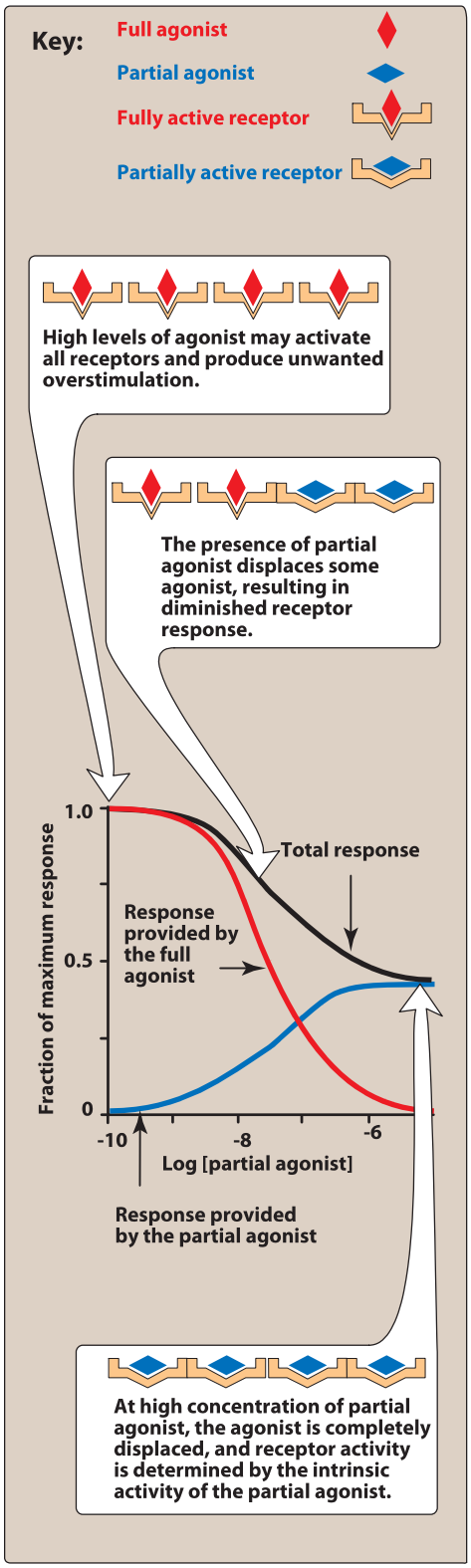

Figure 2.12
Effects of partial agonists.

D. Antagonists

Antagonists bind to a receptor with high affinity but possess zero intrinsic activity. An antagonist has no effect on biological function 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 the antagonist binds to the same site on the receptor as the agonist in a reversible manner, it is "competitive." A competitive antagonist interferes with an agonist 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, increasing the concentration of agonist relative to antagonist can overcome this inhibition. 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 permanently 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 (Figure 2.13). In contrast to competitive antagonists, addition of more agonist does not overcome the effect of irreversible antagonists. Thus, irreversible antagonists and allosteric antagonists (see below) are both considered noncompetitive antagonists. A fundamental difference between competitive and noncompetitive antagonists is that competitive antagonists reduce agonist potency (increase EC_{50}) and noncompetitive antagonists reduce agonist efficacy (decrease E_{max}).

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

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 of patients that responds to it. These responses are known as quantal responses, because, for any individual, either the effect 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.

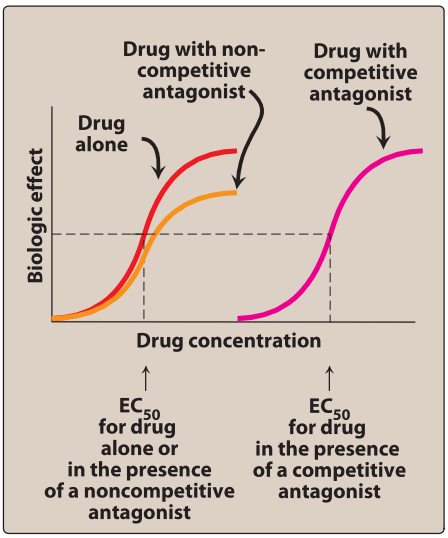

Figure 2.13
Effects of drug antagonists. EC_{50} = drug dose that shows 50% of maximal response.

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 adverse 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 TI, and *penicillin*, an antimicrobial drug with a large TI.

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).

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 effects. In this case, bioavailability does not critically alter the therapeutic or clinical effects.

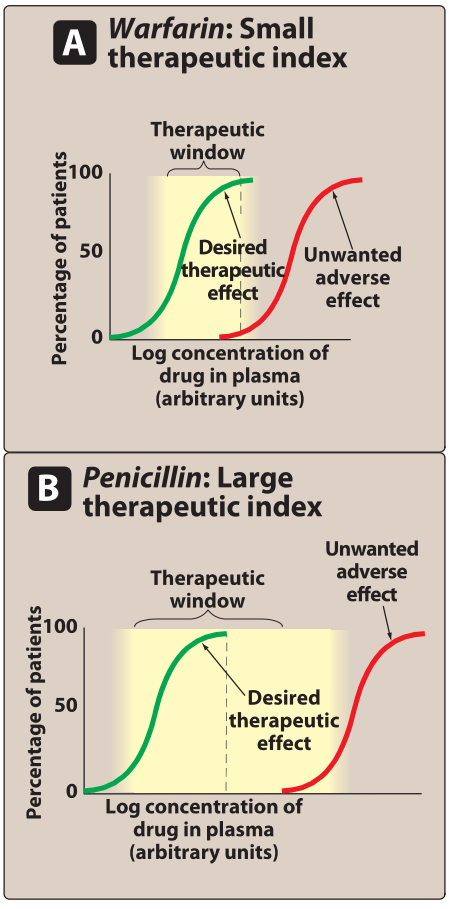

Figure 2.14
Cumulative percentage of patients responding to plasma levels of *warfarin* and *penicillin*.

Study Questions

Choose the ONE best answer.

2.1 Which of the following best describes how a drug that acts as an agonist at the A subtype of GABA receptors affects signal transduction in a neuron?

A. Activation of this receptor subtype alters transcription of DNA in the nucleus of the neuron.
B. Activation of this receptor subtype opens ion channels that allow sodium to enter cells and increases the chance of generating an action potential.
C. Activation of this receptor subtype opens ion channels that allow chloride to enter cells and decreases the chance of generating an action potential.
D. Activation of this receptor subtype results in G protein activation and increased intracellular second messenger levels.

Correct answer = C. The GABA-A receptor is a ligand-gated ion channel selective for chloride. Agonists for the GABA-A receptor increase opening of channels, resulting in chloride entry into the neuron, hyperpolarization, and decreased action potential events.

2.2 If 1 mg of lorazepam produces the same anxiolytic response as 10 mg of diazepam, which is correct?

A. Lorazepam is more potent than is diazepam.
B. Lorazepam is more efficacious than is diazepam.
C. Lorazepam is a full agonist, and diazepam is a partial agonist.
D. Lorazepam is a better drug to take for anxiety than is diazepam.

Correct answer = A. A drug that causes the same effect at a lower dose is more potent. B and C are incorrect because without information about the maximal effect of these drugs, no conclusions can be made about efficacy or intrinsic activity. D is incorrect because the maximal response obtained is often more important than the amount of drug needed to achieve it.

2.3 If 10 mg of oxycodone produces a greater analgesic response than does aspirin at any dose, which is correct?

A. Oxycodone is more efficacious than is aspirin.
B. Oxycodone is less potent than is aspirin.
C. Aspirin is a full agonist, and oxycodone is a partial agonist.
D. Oxycodone and aspirin act on the same drug target.

Correct answer = A. Drugs with greater response at maximally effective concentrations are more efficacious than drugs with a lower maximal response. Choice B is incorrect since no information is given about the half maximal concentrations of either drug. Choices C and D are incorrect since it is not known if both drugs bind to the same receptor population.

2.4 In the presence of propranolol, a higher concentration of epinephrine is required to elicit full antiasthmatic activity. Propranolol has no effect on asthma symptoms. Which is correct regarding these medications?

A. Epinephrine is less efficacious than is propranolol.
B. Epinephrine is a full agonist, and propranolol is a partial agonist.
C. Epinephrine is an agonist, and propranolol is a competitive antagonist.
D. Epinephrine is an agonist, and propranolol is a noncompetitive antagonist.

Correct answer = C. Since propranolol decreases the effect of epinephrine but the inhibition can be overcome by giving a higher dose of epinephrine, propranolol must be a competitive antagonist. If D were correct, even very high concentrations of epinephrine would not be able to elicit a maximal effect in the presence of propranolol. Since propranolol has no effect by itself, A and B are incorrect.

2.5 In the presence of picrotoxin, diazepam is less efficacious at causing sedation, regardless of the dose. Picrotoxin has no sedative effect, even at the highest dose. Which of the following is correct regarding these agents?

A. Picrotoxin is a competitive antagonist.
B. Picrotoxin is a noncompetitive antagonist.
C. Diazepam is less efficacious than is picrotoxin.
D. Diazepam is less potent than is picrotoxin.

Correct answer = B. Since picrotoxin decreases the maximal effect of diazepam regardless of the diazepam dose, it is a noncompetitive antagonist. Picrotoxin has no efficacy alone, so C is incorrect. No information is provided about potency of either drug.

2.6 Haloperidol, chlorpromazine, and clozapine are antipsychotic medications that bind to the D2 subtype of dopamine receptors, with a binding affinity of haloperidol > chlorpromazine > clozapine. Which statement would have to be correct to conclude that the mechanism of antipsychotic effects for these drugs is via binding to D2 receptors?

A. Haloperidol should have the lowest potency of the three antipsychotic drugs.
B. D2 receptor binding should also be related to the potency of these drugs in causing Parkinson's-like adverse effects.
C. A positive correlation should exist between the affinity of these drugs to bind to D2 receptors and their potency for antipsychotic actions.
D. Clozapine would have to be more potent than chlorpromazine for decreasing psychosis.

Correct answer = C. To conclude that the mechanism of antipsychotic effect for these drugs is via binding to D2 receptors, there should be a positive correlation between the affinity of the drugs for D2 receptors and their potency for antipsychotic actions. Haloperidol should have the highest antipsychotic potency and clozapine the lowest. There is no guarantee the therapeutic effects and adverse effects are mediated by the same receptor population; therefore, a different correlation may exist for the adverse effects and D2 receptor affinity.

2.7 If there were spare β_1-adrenergic receptors on cardiac muscle cells, which statement would be correct?

A. The number of spare β_1-adrenergic receptors determines the size of the maximum effect of the agonist epinephrine.
B. Spare β_1 adrenergic receptors make the cardiac tissue less sensitive to epinephrine.
C. A maximal effect of epinephrine is seen when only a portion of β_1 adrenergic receptors are occupied.
D. Spare receptors are active even in the absence of epinephrine.

Correct answer = C. Only a fraction of the total receptors need to be bound to elicit a maximum cellular response when spare receptors are present. The other choices do not accurately describe the effects of having spare receptors.

2.8 Which of the following up-regulates postsynaptic α_1-adrenergic receptors?

A. Daily use of amphetamine that causes release of norepinephrine
B. A disease that causes an increase in the activity of norepinephrine neurons
C. Daily use of phenylephrine, an α_1 receptor agonist
D. Daily use of prazosin, an α_1 receptor antagonist

Correct answer = D. 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 receptors occurs when receptor activation is greater than normal because of continuous exposure to an agonist, as described in A, B, and C.

2.9 Methylphenidate helps patients with attention deficit hyperactivity disorder (ADHD) maintain attention and perform better at school or work, with an ED_{50} of 10 mg. However, methylphenidate can also cause significant nausea at higher doses (TD_{50} = 30 mg). Which is correct regarding methylphenidate?

A. The therapeutic index of methylphenidate is 3.
B. The therapeutic index of methylphenidate is 0.3.
C. Methylphenidate is more potent at causing nausea than treating ADHD.
D. Methylphenidate is more efficacious at causing nausea than treating ADHD.

Correct answer = A. Therapeutic index is calculated by dividing TD_{50} by ED_{50} (30/10), making B incorrect. C is incorrect because methylphenidate is more potent at treating ADHD (it takes a lower dose) than causing nausea. D. No information about efficacy is provided.

2.10 Which is correct concerning the safety of using warfarin (with a small therapeutic index) versus penicillin (with a large therapeutic index)?

A. Warfarin is a safer drug because it has a low therapeutic index.
B. Warfarin treatment has a high chance of resulting in dangerous adverse effects if bioavailability is altered.
C. The high therapeutic index makes penicillin a safe drug for all patients.
D. Penicillin treatment has a high chance of causing dangerous adverse effects if bioavailability is altered.

Correct answer = B. Agents with a low TI (that is, drugs for which dose is critically important) are those drugs for which bioavailability critically alters the therapeutic and adverse effects. A is incorrect, because a drug with a low TI is not generally considered to be safe. C is incorrect because a high TI does not ensure safety across the entire patient population. D is incorrect because the high TI makes it unlikely that bioavailability alters the incidence of therapeutic or adverse effects.