

Objectives

After completing this chapter, the reader should be able to

- Describe the various mechanisms in which drug molecules elicit their effects.
- Illustrate the effects of receptor-mediated agonists and antagonists.
- Describe the differences between competitive, non-competitive, and allosteric antagonism.
- Compare and contrast the differences and similarities between ionophoric and metabophoric receptors.
- Compare current and historic mechanisms of anesthetic action in the body.

Introduction

The branch of pharmacology that relates drug concentration to biologic effect is known as pharmacodynamics. Major goals of this area of study are determining the proper dose to administer to elicit the desired effect while avoiding toxicity. Although pharmacokinetics can be used to determine dosing requirements necessary to maintain a particular drug concentration, it is the relationship between drug concentration and effect that ultimately decides appropriate dosing. The ultimate goal is to maintain a drug concentration within the proper therapeutic window thereby avoiding toxicity while providing an adequate concentration of the drug to provide the desired effect.

Most drug effects are induced by the interaction of a drug molecule with specific molecular structures in the body known as receptors.¹ However, some drug effects are non-receptor mediated and are caused by the particular physical or chemical properties of the drug molecule. To firmly grasp the concepts of how effects, both desired and deleterious, are induced in the body by a drug molecule requires an understanding of where and how these molecules interact.

Receptor Theory

The idea that drug molecules interact at specific sites in the body is not new. The initial idea of materials within the body to which administered drugs interact has been attributed to the work of Langley and Ehrlich in the late 1800s and early 1900s.² Proof of the receptor concept lagged

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Pharmacodynamics: The Study of Drug Action

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behind theory, and it would take the introduction of the β -adrenergic antagonist, propranolol, in 1965 to provide the data necessary to completely convince the scientific community that receptors truly exist. Since then, specific molecular targets of action have been identified for nearly all drugs, and evidence for the receptor theory continues to grow. However, a few drugs, such as osmotic laxatives, do not appear to require receptor interactions to provide their effects. Another class of compounds of particular interest, the general anesthetics, apparently exhibit such a wide array of effects that some in the scientific community still do not subscribe to the idea that a receptor-mediated response is necessary for action, even though multiple receptor interactions have been identified.³

The basic concept of drug-receptor interactions can be described by the “lock and key” model in which a receptor structure (the lock) has a region with a particular shaped pocket at which an appropriately shaped molecule (the key) can interact (Figure 2-1). The substance that interacts at the receptor binding site is known as a ligand. It is important to remember that receptors evolved over the ages to provide particular functions within the body. Although a particular drug may be identified as interacting with a particular receptor, the reason that a receptor exists is to interact with some normal endogenous ligand or common environmental material. Therefore drug molecules that interact at receptors either mimic or inhibit normal body compounds. In addition, because both receptors and the compounds with which they interact are chemical entities, they behave according to chemical principles. Receptors themselves are normally characterized as protein structures, either a single protein or a complex comprised

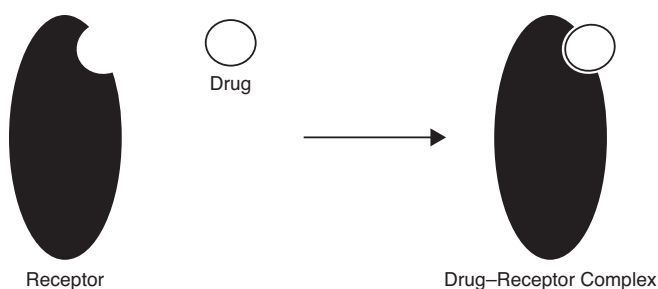


Figure 2-1 “Lock and key” representation of drug–receptor binding.

of multiple protein subunits. The binding site on the receptor complex where the ligand interacts may only be a small portion of the molecule. The interaction of a drug molecule with its receptor can be represented in the manner shown in Figure 2-2, where D is the drug concentration, R is the free receptor concentration, and DR is the concentration of receptor molecules occupied by drug molecules. The interaction of the ligand at its binding site on the receptor complex is governed by two important concepts: affinity and intrinsic activity.

Affinity is best described as how well a particular compound is drawn into and held at the binding site. A relative affinity constant can be determined from the relationship outlined in Figure 2-2. At equilibrium, the dissociation constant (K_D) of a drug–receptor complex is equal to $k_{\text{off}}/k_{\text{on}}$. The equilibrium affinity constant (K_A) is the reciprocal of the equilibrium dissociation constant ($1/K_D$). Therefore the smaller the equilibrium dissociation constant is, the greater the affinity of the drug for the receptor. This is useful when examining how well different drugs bind to a specific receptor complex. To understand how individual molecules, such as drug molecules, move around a receptor zone, it is important to remember that these molecules are present in a mix of other molecules and move in a random manner driven by Brownian motion. The interaction of a molecule, whether it is a drug molecule or the normal receptor ligand, with its receptor is primarily a matter of chance. The likelihood that a particular type of compound will interact at a given receptor is based on the number of molecules (concentration) located near the receptor site. The greater the concentration, the more likely it is that the

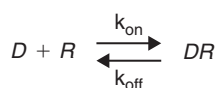


Figure 2-2 Drug–receptor formation showing the rate of drug binding and release from the receptor.

random motion of a particular molecule will bring it close enough to a receptor site to interact. If a molecule is able to interact with the receptor site, it is said to have affinity for that site. The stronger it interacts, the greater its affinity for that receptor site.

The concept of interaction at the receptor site is based mainly on the ligand’s shape and chemical makeup. The receptor site may have particular chemical functional groups that interact at specific places. For example, a positively charged group at a specific location within the binding pocket may interact with a negatively charged region on a ligand, thus increasing the binding force between the two compounds and increasing the affinity. Most ligands bind very briefly with the receptor site and then are knocked out of the site by collisions with other molecules that are jostling around in the surrounding area. Therefore even a drug with high affinity may only interact with a receptor zone briefly. However, if the concentration of the ligand molecules in the surrounding area is high, the likelihood of continued receptor–ligand interaction increases. This idea is critical to understanding drug action. The greater the drug concentration at a receptor zone, the more likely it is that a drug molecule will be occupying the receptor site at any given time. As the drug concentration goes down, the percentage of time the receptor is occupied also decreases.

The other important factor governing how a ligand interacts at a receptor zone is known as intrinsic activity. Whereas affinity describes how well a particular compound interacts with the binding site of a receptor complex, intrinsic activity is used to describe the effect the ligand has when it interacts with a receptor site. A ligand may have good affinity, but if it has no intrinsic activity it will elicit no response when it binds to the receptor zone. On the other hand, a ligand that has good intrinsic activity will elicit a strong response at the receptor zone if it also has good affinity. But if the affinity of the compound for the receptor site is low, even a high level of intrinsic activity will not elicit much of a response.

The response generated from a receptor interaction can be plotted against the dose of a drug to produce the classic dose–response curve known so well in pharmacology (Figure 2-3). In a typical dose–response curve, the dose of the drug is assumed to be proportional to the concentration of the drug at the receptor zone. Data for dose–response curves depend on the effect of the drug being examined. An appropriate response to the drug is chosen, and different drug doses are plotted against the response generated. One example is changes in muscle strength when different doses of a particular muscle stimulant are administered. At low doses, little response is observed. However, at some

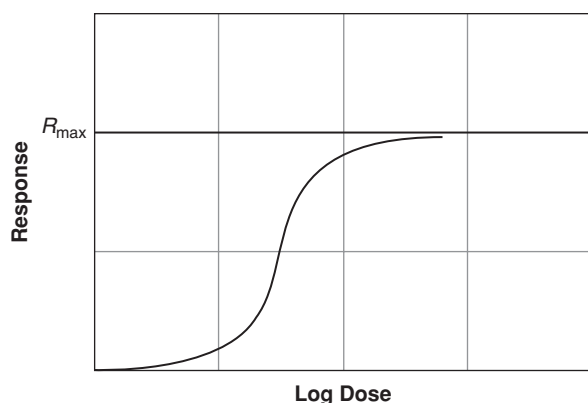


Figure 2-3 Log dose–response curve. R_{\max} is the maximal response.

particular dose, the response begins to increase suddenly. This is because a certain number of receptors need to be occupied before a response is observed. Once a critical number of receptors are occupied, increasing the dose increases the response. However, this increase in response is not linear but is instead logarithmic.

Dose–response curves are normally plotted as the log of the dose on the x axis versus the linear response on the y axis. In this type of plot, the log of the dose is directly proportional to the response and is seen as a straight line through the middle range of the plot. This represents the most appropriate dose range to produce the observed effect. As the dose increases further, the curve again loses its logarithmic relationship between dose and response. Every response has a maximum, and as this maximal response is neared, increases in occupied receptors produce less and less of an increase in response. At some point the response reaches its maximum, and no further increases in drug dose produce a greater effect. This does not mean that all available receptors have been occupied, just that the tissue is unable to produce a greater response. In fact, the number of receptors that are occupied when the response becomes maximal may only be a small percentage of available receptors. This apparent excess of receptors seen at most receptor zones allows small concentrations of a ligand to elicit a graded response.

Receptor Interactions

The ways in which ligands interact with receptors vary greatly among different compounds and receptors. Most receptors are large, complex protein structures that are held in a particular shape or conformation based on their

specific environment. Proteins are made up of amino acids, and some amino acids are affected by the pH of the micro-environment surrounding the compound. If the local pH changes slightly, certain amino acids within the receptor protein may become charged (or uncharged). This change can cause the protein complex to alter its conformation and thereby alter the shape of a ligand binding zone on the protein. This could either enhance or diminish the ability of a specific ligand to bind to the zone. This concept illustrates the importance of the microenvironment surrounding the receptor protein. Just as pH changes may affect the shape of the receptor complex, other compounds that interact with the protein may also alter the receptor protein conformation. These changes in molecular shape may occur at various places within the receptor complex, not only at the receptor binding site. In fact, these conformational changes in the receptor complex explain how most drugs and endogenous ligands elicit their effects upon binding to a receptor site. The interaction of the ligand at the specific binding site causes some conformational change in the receptor complex, thereby altering the function of the protein complex.

Proteins have many functions within the body, including enzymes, channels, and transporters. If a particular receptor zone is located on one of these proteins, the normal effect of that specific protein may be altered by the induced conformational change. Therefore an enzyme whose normal conformation does not allow it to interact with its substrate may be activated when a specific ligand binds to a receptor site. Or, conversely, an enzyme that is normally active may be shut off when a specific ligand interacts at a receptor zone on the molecule. The same idea can be applied to other protein structures such as channel proteins or transport proteins. These may also be activated or inactivated by ligand interactions at specific receptor zones. In the body this provides a means of controlling normal function and allows the organism a means to fine tune its biologic processes based on specific needs. The discovery that exogenous compounds interact at specific receptor sites and can be used to alter biologic function has led to major changes in the ways that new drugs are designed. Determining the specific functions of a compound in the body, such as an enzyme, and then designing a chemical compound that can interact with the substance provides a means to alter various biologic processes.

There are several different ways in which drug molecules may interact with complex protein molecules in the body. It is through these different mechanisms that the ability to control various biologic processes has been developed.

Agonists and Antagonists

For every receptor in the body, there is an endogenous compound that is believed to be able to act. Sometimes, however, the receptor is identified by actions of an exogenous compound before the normal endogenous ligand is identified. Such has been the case in the discovery of the benzodiazepine receptor and the search for an endogenous ligand.^{4,5} Many compounds have been identified in the body that appear to act on this receptor zone (the endozepines, for *endogenous benzodiazepines*), but none has been conclusively proven to be secreted specifically to interact at this receptor zone.^{6,7} The interaction of compounds with the receptor zone has been based on the way in which they interact with the receptor complex and the results of their interactions. These interactions can be roughly classified as receptor agonists and receptor antagonists.

Receptor Agonists

The interaction of a ligand with a receptor zone that invokes some functional change in the receptor complex is an example of an agonist reaction. Most drug molecules that elicit an agonistic effect mimic the effects of an endogenous compound at the receptor. The strength of binding to the receptor and the overall effect elicited depend on the compound's affinity and intrinsic activity. To be a good agonist at a specific receptor site requires good affinity and good intrinsic activity. When an exogenous molecule interacts with a specific receptor, it blocks the body's endogenous ligand from interacting with the receptor for as long as the exogenous compound occupies the receptor. Usually, however, exogenous agonists are given to increase the normal agonistic stimulation of the receptor and blocking the endogenous agonist is of no consequence. Drugs with good receptor affinity but intrinsic activity that is less than the normal endogenous agonist are termed partial agonists because their response at the receptor is less than the endogenous agonist or less than a particular response from an exogenously administered standard agonist (Figure 2-4). An example of a partial agonist is the action of buprenorphine at the opioid μ -receptor where its agonist effect is less than morphine. Some drugs have been classified as superagonists, which are compounds that elicit greater effects at the specific receptor zone than the defining receptor agonist. Fentanyl is an example of a superagonist, being approximately 100 times more potent at opioid μ -receptors than morphine.

Other types of agonists are the physiologic agonists, which are compounds that produce the same bodily effects but through an entirely different receptor system and

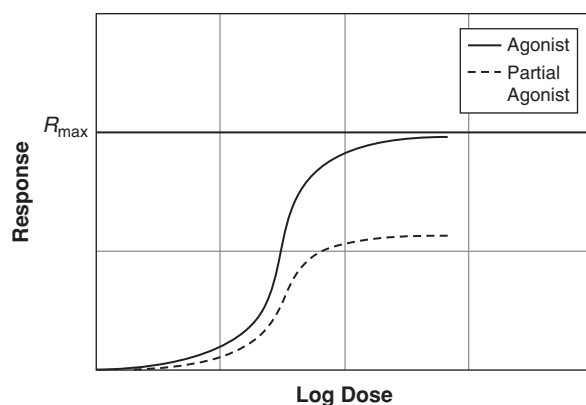


Figure 2-4 Comparison of full and partial agonists.

mechanism. An example of physiologic agonists is the anesthetic effect of ketamine, which acts at *N*-methyl-D-aspartate (NMDA) receptors, and the effect of propofol, which acts at the γ -aminobutyric acid (GABA)_A receptor complex. Both agents produce a loss of consciousness but act at different receptor sites. Other agonistic drugs may not be able to elicit a specific response on their own but instead require the action of multiple compounds to produce an effect. These types of agonist drugs are often referred to as coagonists because more than one is required for effect. An example of coagonists is the stimulation of some NMDA receptors that require binding of both glycine and glutamate.

Agonist drugs are also characterized on their selectivity. Selective agonists act primarily at only one specific receptor zone, whereas nonselective agonists may act at many different receptor types. An example involves the β -adrenergic agonist isoproterenol, which stimulates both β_1 and β_2 receptors, and albuterol, which is considered a selective β_2 agonist.

Receptor Antagonists

Some drugs produce their effects by interaction at the receptor complex, but instead of stimulating the receptor or mimicking the normal endogenous ligand for that receptor, they block or decrease agonist interaction at the receptor zone. This causes a loss of the effect that is normally produced by the receptor agonist. Although many drug molecules have been designed with this type of function, there are only a few known instances of endogenous compounds capable of this form of receptor interaction. The most common type of antagonism produced by drug molecules is referred to as competitive antagonism (Figure 2-5), in which the antagonist interacts at the same receptor site as the normal agonist. The antagonist therefore must possess affinity to allow it to interact with the receptor site.

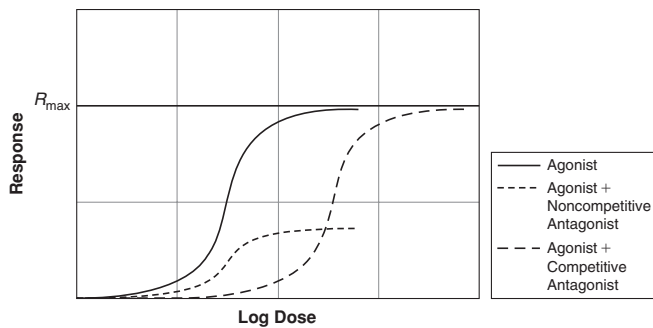


Figure 2-5 Comparison of responses generated following administration of a competitive antagonist or noncompetitive antagonist.

However, the antagonist does not appreciably stimulate the receptor and thus has little to no intrinsic activity. Interaction of compounds with the receptor site on molecules is based on the law of mass action, which in this case means that the more molecules in the area around the receptor that can bind to a receptor (greater concentration), the greater the likelihood that the receptor will be occupied by one of the molecules at any given time. If molecules of an antagonist are added to the area around the receptor where there are already agonist molecules, then the more molecules of antagonist present, the greater the likelihood that an antagonist molecule will be bound to the receptor at any given time. If the antagonist concentration is increased even further, it becomes even less likely that an agonist molecule can “compete” for receptor binding (Figure 2-6).

What makes competitive antagonism particularly interesting is that a competitive antagonist can be used to decrease the normal effects at a particular receptor zone and then an agonist that acts at that specific site can later be added to compete away the added competitive antagonist. This is the principle used often in anesthesia with neuromuscular

blocking drugs. A neuromuscular blocking drug, such as vecuronium, which is a competitive antagonist at the neuromuscular nicotinic receptor site, acts to block the normal endogenous agonist, acetylcholine, from binding to the receptor. The effect of the competitive antagonist can be decreased by increasing the agonist at the receptor, and drugs such as neostigmine are administered to decrease the metabolism of acetylcholine, allowing more of it to exist around the receptor zone and thus reversing the effect of the administered neuromuscular blocker.⁸

Another important type of receptor antagonism, referred to as noncompetitive antagonism (see Figure 2-5), can actually occur by two different mechanisms. The first mechanism is seen by compounds that bind irreversibly or for such a long time as to be effectively irreversible. Once a receptor site has been occupied by an irreversible agent, no concentration of agonist molecules around the site will allow the site to be reclaimed by an agonist. In effect, it appears as if the receptor has been removed from the system. If many receptors on a particular tissue are irreversibly inhibited, then the maximal response of the tissue to the agonist will be decreased because there are not enough noninhibited receptors remaining to elicit a maximal response, even if all were stimulated with an agonist. Once the receptors have become inhibited by the irreversible antagonist, even if the antagonist concentration in the area around the receptor zone decreases, the effect of antagonism will continue. This type of antagonism can be demonstrated through the administration of phenoxybenzamine, an irreversible inhibitor of α -adrenergic receptors.

The second way in which noncompetitive antagonism can occur is when a compound interacts with the receptor complex at a different binding site from the agonist site, called the allosteric site. If the binding of the antagonist

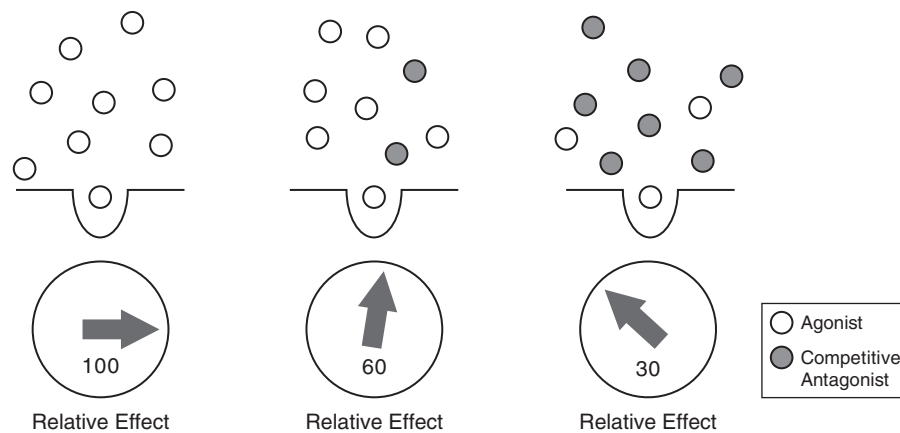


Figure 2-6 Representation of decreasing receptor effect as the concentration of a competitive antagonist increases around a receptor zone.

molecule to its binding site causes a conformational change in the receptor complex, that may alter the conformation of the binding site of the normal agonist. If this occurs, the agonist may no longer be able to bind to its site and elicit its effect. As seen with irreversible antagonism, increasing the concentration of the agonist molecule will not increase the effect because the binding site is unavailable, thus making this type of inhibition noncompetitive and therefore decreasing the maximal response of the tissue to its normal agonist. However, unlike irreversible antagonism, the binding to the allosteric site is not necessarily irreversible, and as the concentration of the allosteric antagonist decreases, the receptor complex may return to its previous conformation and again function normally.

An example of allosteric inhibition is the decrease in affinity of glycine at the glycine receptor complex when strychnine binds to an allosteric site. In certain neuronal pathways in the spinal cord, glycine receptors act with glycine to inhibit the pathway. The binding of strychnine to its allosteric site decreases the affinity of glycine for its binding site, thus diminishing the glycine-based inhibition of the pathway. Therefore the action of strychnine increases the stimulation of the pathway, leading to convulsions.⁹

Related to the concept of allosteric inhibition is the opposite, or allosteric potentiation. This is not a form of antagonism but actually appears more like a form of agonism. In allosteric potentiation a compound acts at an allosteric site and enhances the affinity of the normal agonist at its binding site. The classic example of this is the way the benzodiazepines and some anesthetics act at allosteric sites on the GABA_A complex to increase the affinity of GABA for its binding site. Because GABA causes an inhibitory response through the GABA_A complex, increasing the affinity of GABA causes a greater degree of inhibition.¹⁰

Inverse agonists are another group of compounds that produce effects that appear as if an antagonist has been delivered to a receptor zone. However, unlike other antagonists, the effect of these compounds can be reversed by the addition of a competitive antagonist. To understand the action of the inverse agonists, the concept of a receptor and its associated effector (e.g., enzyme, ion channel) as existing in an on or off state based on whether the receptor site is occupied with an agonist or not needs to be modified. Many ion channels are not completely open or closed without their receptor agonist present. In such a state, some ions pass through the channel normally because it is neither fully open nor fully closed. An agonist will cause the channel to either open or close more than normal. An inverse agonist produces the opposite effect. If an agonist opens an ion channel more than seen at rest, then an inverse agonist

closes the channel more than at rest. Receptors that act this way are classified as constitutive receptors and are capable of wide-ranging effects. As the concept of constitutive receptor activity has been more broadly accepted, it has become apparent that many drugs once thought to be competitive antagonists should now be classified as inverse agonists.¹¹

Two other types of receptor antagonism are based in part on agonistic effects. As discussed, some agonist drugs may exhibit less agonistic effects than the normal endogenous agonist or some drugs used as the reference standard. These drugs appear to have less intrinsic activity at the receptor site. Therefore they are labeled partial agonists. However, while they occupy the receptor site, they are keeping the normal agonist from interacting with the receptor. If the normal agonist possesses more intrinsic activity, then as long as the partial agonist is present on the receptor, less effect is seen than if the normal agonist were interacting with the receptor. In effect, it appears as if an antagonist is interacting at the receptor. Therefore these drugs are frequently referred to as partial agonists/antagonists. The final type of antagonist to be presented is also a type of agonist. However, in this case the compounds act as agonists at one type of receptor and antagonists at other receptors. These compounds are referred to as agonist/antagonists. One example of such a compound is the analgesic nalbuphine, which acts as an antagonist at opioid μ -receptors and as an agonist at opioid κ -receptors.¹²

Receptor Regulation

As discussed, most receptors are proteins and as such are synthesized by protein synthesis mechanisms inside the cell nucleus and cell body. After synthesis, these receptor molecules may be functional on their own or may require further assembly with other components, such as other protein subunits, to produce a functional receptor complex. The receptor proteins may be stored in an inactive form inside the cell or in the cell membrane until needed. The number of active receptors present appears to be controlled and can be increased or decreased as needed by the cell. A common experiment to demonstrate this regulation is the destruction of a nerve leading to a receptor zone on the surface of a muscle cell. Normally, the receptors on the muscle cell receive signals to initiate muscle contraction from the release of the neurotransmitter, acetylcholine, from the presynaptic neuron. If this neuron leading to the receptor zone is destroyed, no acetylcholine is present at the receptor zone. The cell, in an apparent attempt to sense the missing acetylcholine, increases the number of acetylcholine receptors on the

surface of the receptor zone. This is termed up-regulation and is seen whenever a normally present receptor agonist decreases at a receptor zone below some point. After up-regulation, a cell becomes hypersensitive to the receptor agonist. Any sudden release or application of a receptor agonist to a highly up-regulated zone can lead to overstimulation and potential cell injury or death.

Cells can also regulate the number of receptors in the other direction. If a receptor zone is experiencing excessive stimulation from an agonist, it can decrease the number of available receptors. If the receptors were located on the cell membrane, these receptors may be internalized and stored for future use or destroyed. This process of decreasing the number of available receptors is termed down-regulation. The administration of many compounds over a long period of time can lead to down-regulation of some receptors. If the administered agent is suddenly discontinued, there may be inadequate receptor stimulation, which can lead to problems. For this reason many drugs that have been provided to a patient for a prolonged period should not be suddenly discontinued but should instead be tapered off over a period of several days to allow the patient's receptor sites and systems to adjust to the lack of the previously supplied compound. A special related condition, known as physiologic tolerance, can be seen with the administration of some drugs. In this situation administration of a drug may lead to physiologic changes in the number of receptors to the compound (down-regulation). As the number of receptors decreases, larger doses of the drug may be required to elicit the same effect. The exact cause of tolerance development to various drugs is still unclear, however, and morphine, which frequently causes tolerance, does not appear to do so by simply down-regulating receptors.^{13,14}

Receptor Types

As more and more receptors have been discovered in the body, it has become clear that most drug effects are due to some type of receptor interaction. When drug receptors were first identified, major research efforts were made into identifying specific receptors to known therapeutic agents. With the current ability to decipher large sections of the genetic code, receptors have been identified before an endogenous ligand has been located. This has led to an explosion in the number of known receptor types and subtypes in recent years, the importance of which will be under study for many years. Some identified receptor subtypes differ only in a few amino acids in their overall protein structure, which may

prove inconsequential. In addition, individual variations and population genetic differences provide other modified receptors in some people (see Chapter 3). Most specific receptors fall into one of several broad classes of receptors based on their structure and general mechanism of action.

Ligand-Gated Ion Channels

Cellular membranes are studded with many different types of ion channels. Some ion channels, such as the inward rectifier potassium channel, are permanently open, thereby providing a means for ion conductance across the membrane based entirely on concentration and electrical gradients. Other ion channels may be voltage gated, opening and closing in response to particular cellular voltage differentials, such as voltage-gated sodium and potassium channels. Another group of ion channels are controlled by a chemical receptor zone that interacts with specific ligand molecules (Figure 2-7). These ligand-gated ion channels (also known as ionophores) are formed from multiple (usually five) protein subunits that span the entire cellular membrane in their active state. The protein subunits surround a central ion passageway or pore through which specific ions can pass. Many different forms of ligand-gated ion channels exist; however, all appear to be developmentally related and are structurally similar. The pore may be normally open or normally closed, with the action of a ligand binding to an associated location on the structure forcing the pore into the opposite state. The ligand binding site may be intracellular, extracellular, or located within the channel and may require more than one molecule of ligand to bind to different binding sites on the complex to fully activate the channel.

Of the different varieties of ligand-gated ion channels known, most are activated by specific neurotransmitters (e.g., acetylcholine, glycine, GABA, glutamic acid, serotonin)

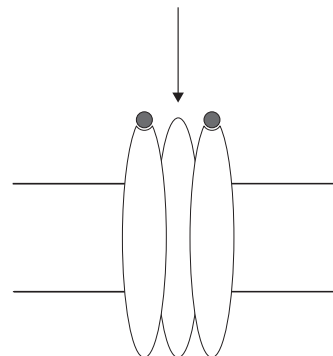


Figure 2-7 Cross-sectional diagram of ligand-gated ion channel embedded in cell membrane. The channel is in the open state with two molecules of ligand bound to extracellular receptor sites.

binding to extracellular binding sites. Different varieties also gate different ions (e.g., sodium, potassium, calcium, or chloride). One specific example is the neuromuscular nicotinic acetylcholine receptor¹ located on skeletal muscle at the neuromuscular junction. Acetylcholine released from somatic cholinergic nerve terminals at the synapse binds to two receptor sites on the nicotinic receptor on the postsynaptic membrane, stimulating an allosteric change in the pentameric receptor complex that opens the ion channel and allows sodium ions to enter the cell from the extracellular fluid. This initiates a local depolarization, which can then lead to the initiation of muscle contraction.

Metabophores

Metabophores are transmembrane receptors that are composed of an external binding site and an internal enzymatic component. Interaction of an extracellular ligand to the binding site causes a modification of the intracellular component of the protein that then initiates one of several known metabolic conversions of intracellular compounds, such as the direct conversion of GTP to cGMP. This then acts as a second messenger inside the cell, triggering additional biochemical processes (Figure 2-8).

G-Protein Coupled Receptors

This class of receptor is responsible for detecting specific extracellular ligands and initiating an intracellular response. In some ways these receptors are similar to metabophores in that they may control biochemical pathways inside the cell in response to an external signal. However, the mechanism by which these receptor complexes act is quite different and considerably more complex. A metabophore directly links some enzymatic function to the ligand interaction, whereas the G-protein coupled receptor complex initiates a series of changes that may eventually lead to control of a specific enzyme. The G-protein coupled receptor family is the most common type of receptor structure found on cell membranes. They comprise a large transmembrane protein with

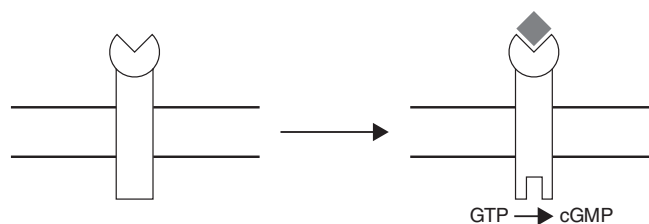


Figure 2-8 Example metabophoric receptor embedded in cell membrane. Binding of the receptor agonist activates the intracellular enzymatic domain, producing cGMP from GTP.

seven transmembrane loops. The extracellular region forms the binding site for the specific ligand.

Many drugs, hormones, neurotransmitters, and other signaling compounds act as ligands at specific G-protein coupled receptors. The intracellular side of the transmembrane protein is linked to the G-protein complex. When a ligand binds to the extracellular binding site, a conformational change occurs that triggers the substitution of GTP on the G-protein in place of GDP. This then activates the G-protein complex, allowing the separation of the G-protein from the transmembrane protein. The G-protein can then migrate and interact with various effector macromolecules, leading to their activation or inhibition. The G-protein then undergoes hydrolysis, converting the GTP to GDP and deactivating the effector molecule. The G-protein complex then recombines with the transmembrane protein in preparation for another round of activation.

Many internal effectors such as ion channels and enzymes (e.g., phospholipase C, adenylyl cyclase, phosphodiesterase) have been shown to be activated or inhibited by variants of the G-protein subunits, leading to a wide range of intracellular effects (Figure 2-9). An example of G-protein coupled receptors are the β -adrenergic receptors that, when stimulated by a β -adrenergic agonist, initiate the activation of adenylyl cyclase, allowing the intracellular production of cAMP, which acts as an intracellular second messenger capable of initiating other biochemical changes within the cell.¹⁵

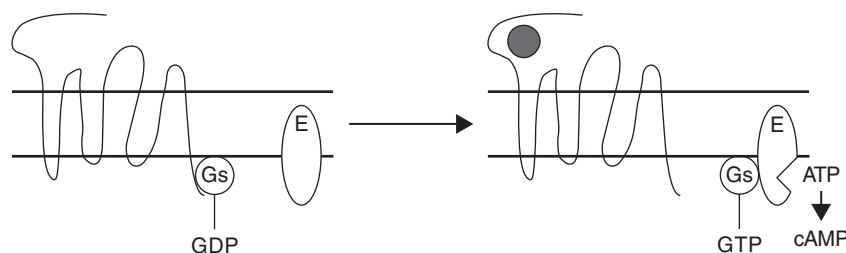


Figure 2-9 G-Protein coupled receptor example. The binding of a specific ligand to the seven-transmembrane loop protein initiates the activation of the G-protein complex (Gs = G stimulatory protein) by allowing GTP substitution for GDP. The G-protein then migrates to interact with effector molecules (E), here represented as adenylyl cyclase, which then catalyzes the conversion of ATP to cAMP, a cellular second messenger.

Intracellular Receptors

Although all receptors discussed to this point have been associated with the cell membrane, there are some receptors located inside the cell. This should not really be surprising given the wide variety and number of processes that occur inside a cell. Many intracellular biochemical reactions are controlled by the concentration of their products or reactants acting on the enzymes responsible for the reaction. Locating the binding sites that provide control of specific enzymes and developing drugs that can interact at those binding sites is a common goal of new drug design.

One class of intracellular receptors has been fairly well characterized. These are the steroid receptors.¹⁶ Most steroid molecules are very lipid soluble and easily cross the cell membrane and enter the cell via passive diffusion. Once inside the cell, the steroid molecule binds to a specific inactive protein complex. The binding of the steroid to the complex causes an attached inactivating protein to dissociate from the complex. The activated complex is then transported into the nucleus of the cell where it usually forms a dimer with another activated receptor complex. This dimer then binds to specific regions of the nucleic DNA and can increase or decrease transcription of specific genes into RNA for translation into proteins. Unlike receptor-mediated ion channel interactions, which are nearly instantaneous in response, steroid receptor-induced effects are slower to begin and tend to last longer due to the lag time for protein synthesis.

Transporters

Although very small compounds can cross cell membranes via water pores and lipid-soluble agents can cross membranes by passive membrane diffusion, many molecules are either too large or not lipid soluble enough to enter cells by these mechanisms. The movement of these molecules across membranes involves the use of various transport proteins. These transporters may or may not require energy to move select molecules from one side of the membrane to the other. Many different types of transporter protein have been characterized. Some are very selective for the compounds that can be transported and others less so. Several transporter proteins have become the targets of drug therapy, especially the neurotransmitter reuptake proteins.¹⁷ One specific example involves the serotonin selective reuptake inhibitors, such as fluoxetine. These agents act on a transport protein known as SERT which is found on serotonin nerve terminals and is responsible for serotonin reuptake back into the nerve terminal. Inhibition of serotonin reuptake leads to altered function of serotonergic neurons and is commonly used to treat depression. Due

to their function, many other transport proteins are now or will become targets for drug therapy.

Non-Receptor-Mediated Effects

Although receptor-mediated effects account for most of the actions known to be elicited by current drugs, a few agents produce their therapeutic effects without receptor interactions. Most agents that do not rely on receptors for effect seem to instead rely on their physical or chemical properties to alter normal body function. Consider the use of dextran 70 as a plasma expander. It is used primarily because of its osmotic properties and relatively slow elimination. Another example is the use of ammonium chloride to decrease the pH of urine. This is occasionally useful to enhance the elimination rate of some basic compounds and is based entirely on the acid-base chemistry of the compounds in urinary fluid.

Mechanisms of General Anesthesia

For many years the inhalational general anesthetic agents were believed to produce anesthesia entirely due to their high degree of lipid solubility and alteration of cellular membrane function (Meyer-Overton rule, Mullins hypothesis). This suggested a mechanism that was due to the physical properties of the agents and not a receptor-mediated function. Like other areas of science (i.e., physics), a single unified theory explaining the action of all anesthetics was particularly attractive. Additional research has unfortunately complicated the picture. Current theories place increasing importance on evidence of receptor interactions as the primary mechanism of the general anesthetic agents, both inhalational and parenteral. Although lipid solubility of the agents is undoubtedly important, it may be more related to getting the agents to their required site of action than actual effect. The general anesthetics appear to elicit their primary effects by increasing inhibitory signals or decreasing excitatory signals in the brain and/or spinal cord. Examples of agents that appear to increase inhibitory pathways are the agents that act on the GABA_A ionophoric complex. This ligand-gated ion channel opens in response to GABA, allowing chloride ions to enter the cell. The increasing negative charge due to the chloride ions lowers the local intracellular voltage (hyperpolarized), making the cell more resistant to depolarization. Many of the general anesthetic agents (e.g., the barbiturates, propofol, etomidate, isoflurane, desflurane, and sevoflurane) all appear to act, in large part, by binding to the GABA_A receptor complex at specific sites and causing an allosteric potentiation

of GABA binding to its receptor site. This causes increased inhibitory activity believed to induce an anesthetized state. Other general anesthetic agents (e.g., nitrous oxide, xenon, ketamine) appear to act to decrease excitatory signaling through NMDA glutamate receptors and nicotinic acetylcholine receptors in the brain or spinal cord.

The exact mechanism of the general anesthetics is still unclear. It is believed to be more likely due to a variety of causes linked to physical properties and multiple receptor zone effects.

Key Points

- Drug–Receptor Theory
- Agonists and Antagonists
- Receptor Types
- Receptor Location and Function
- Mechanisms of General Anesthetics

Chapter Questions

1. Explain how different types of drug–receptor interactions can elicit physiologic effects.
2. How can drug-induced allosteric changes affect receptor activity?
3. Why does doubling the dose of a drug not double the response even if the original and doubled doses are in the “linear” range of the log dose–response curve?
4. In what ways are metabotropic and G-protein coupled receptors similar? How do they differ?
5. Explain the concept of receptor antagonism and how this relates to neuromuscular blockade?

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