Pharmacodynamics

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.

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.

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.

Note: not all drugs exert effects by interacting with a receptor. Antacids, for instance, chemically neutralize excess gastric acid, thereby reducing stomach upset.

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*.

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:

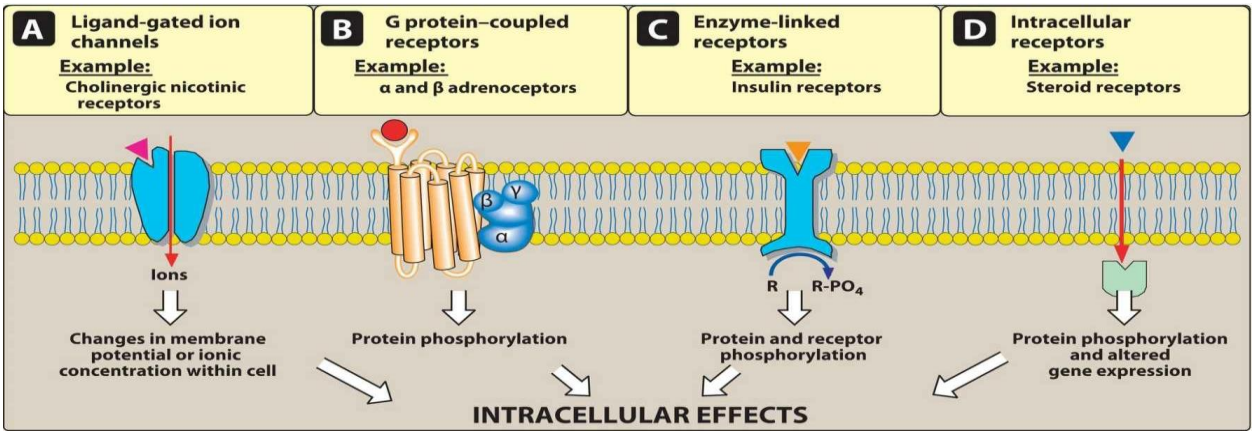
1) ligand-gated ion channels

2) G protein–coupled receptors

3) enzyme-linked receptors

4) intracellular receptors

Generally, hydrophilic ligands interact with receptors that are found on the cell surface. In contrast, hydrophobic ligands enter cells through the lipid bilayers of the cell membrane to interact with receptors found inside cells.

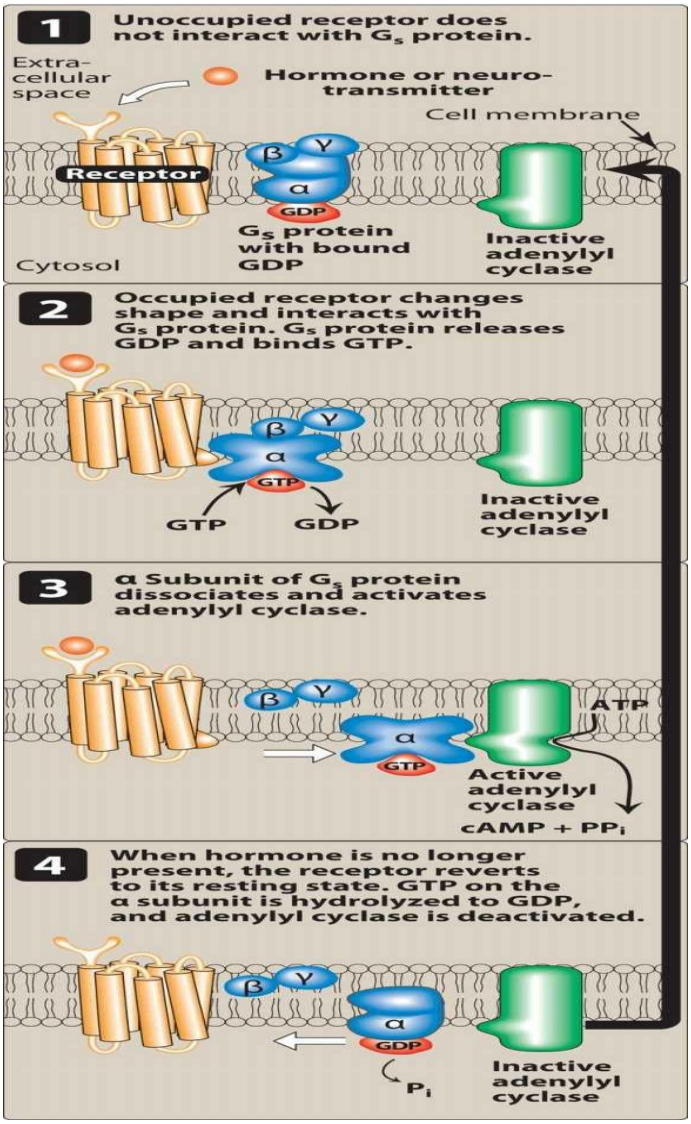


1. Transmembrane ligand-gated ion channels

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. 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.

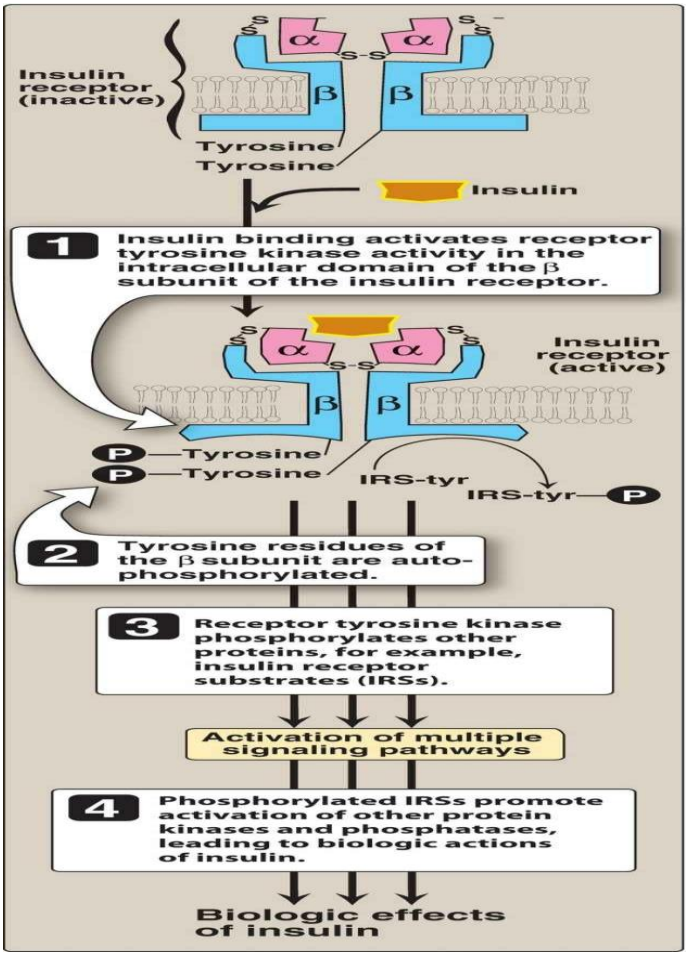
2. Transmembrane G protein–coupled receptors

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, Gs , Gi, and Gq), 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 . 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.



3. Enzyme-linked receptors

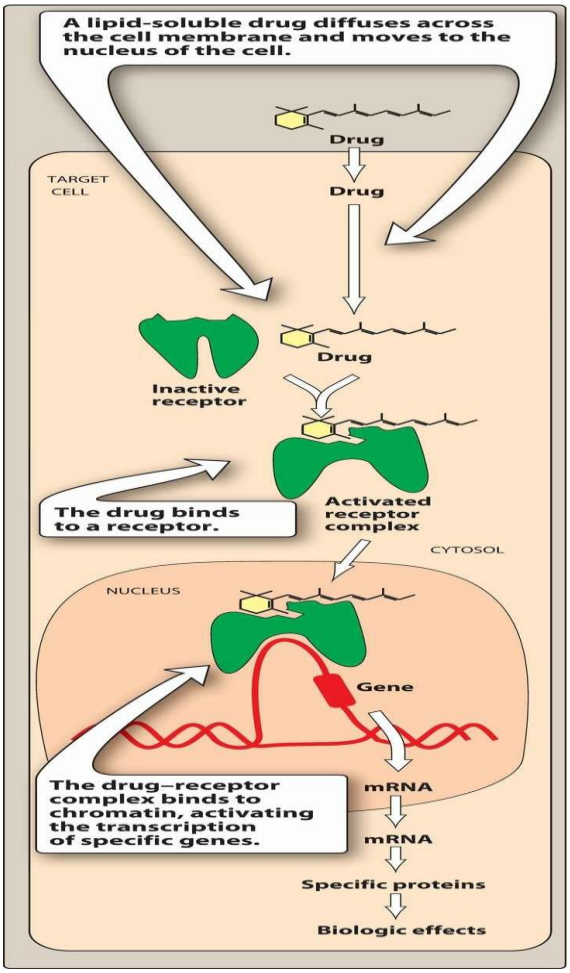
This family of receptors undergoes conformational changes when activated by a ligand, resulting in increased intracellular enzyme activity. This response lasts for minutes to hours. The most common enzymelinked receptors (for example, growth factors and insulin) possess tyrosine kinase activity. When activated, the receptor phosphorylates tyrosine residues on itself and other specific proteins. 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

This type of the receptors have the following properties:

- Found intracellularly
- Bind with ligand inside the cell (example steroid hormone)
- Must have sufficient lipid solubility to diffuse into the cell and bind with receptor.
- Binding of ligand with this receptor causes activation or inactivation of transcription factors alters the transcription of DNA into RNA and subsequently translation of RNA into proteins.
- Activation of this receptor 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 paclitaxel, the enzyme dihydrofolate reductase is the target of antimicrobials such as trimethoprim, and the 50S subunit of the bacterial ribosome is the target of macrolide antibiotics such as erythromycin.



Characteristics of signal transduction

1) the ability to amplify small signals

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

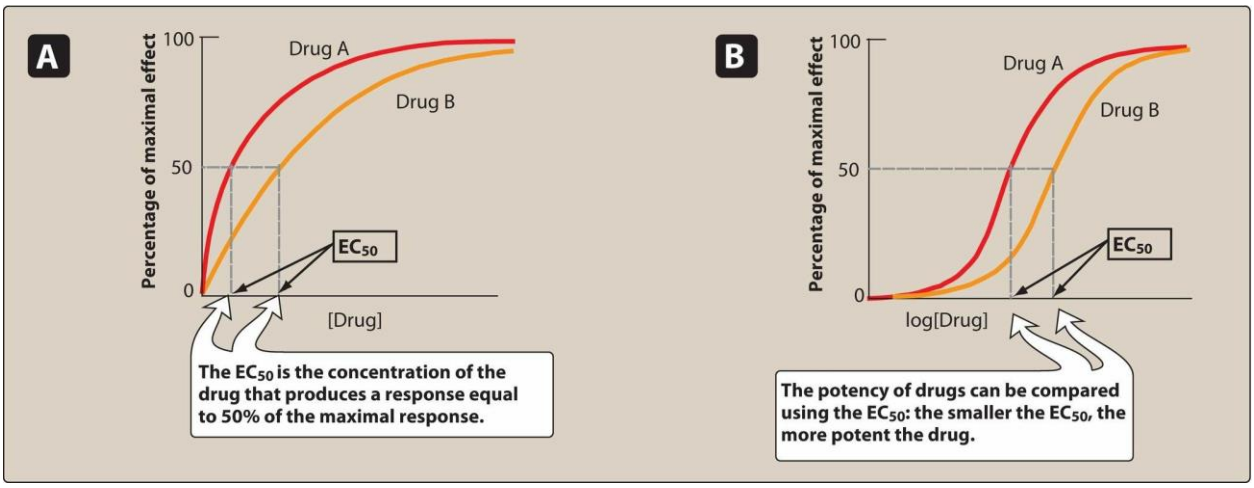
1. **Tachyphylaxis:** Repeated or continuous administration of an agonist or antagonist often leads to changes in the responsiveness of the receptor. The receptor may become desensitized due to too much agonist stimulation, resulting in a diminished response. It is often due to phosphorylation that renders receptors unresponsive to the agonist.
2. **Down-regulation of receptor:** Receptors may be internalized within the cell, making them unavailable for further agonist interaction. 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."
3. **Up-regulation of receptors:** It is an increase in the number of the receptor occur upon repeated exposure of a receptor to an antagonist, 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.

Dose–Response Relationships

Agonist drugs mimic the action of the endogenous ligand for the receptor (for example, isoproterenol mimics norepinephrine on β1 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.

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 the following figure. 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 (EC50) is often used to determine potency. In Figure 2.7, the EC50 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 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 EC50 value).

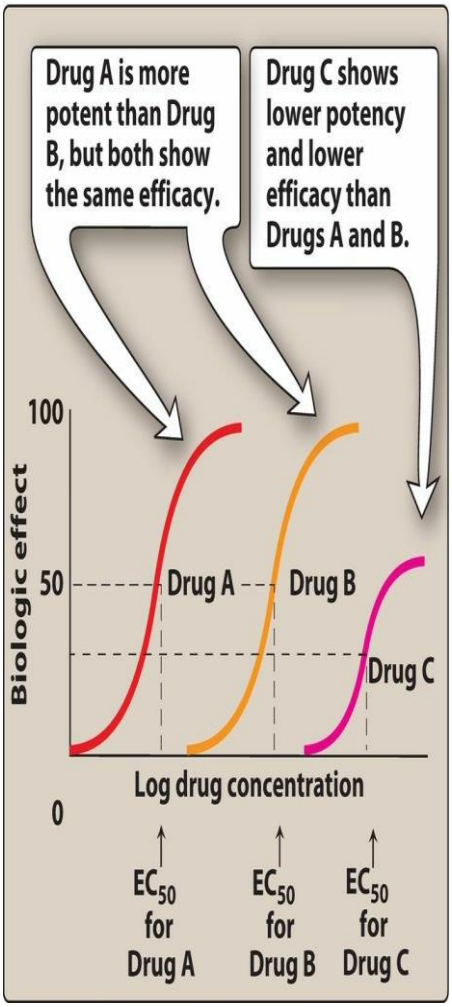
2. Efficacy

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.

Intrinsic activity of the drug: Its ability to activate the receptor and cause a cellular response. So intrinsic activity of drug determines its ability to fully or partially activate the receptors.

Maximal efficacy of a drug (Emax) 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 Emax 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.



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:

Drug + Receptor **Drug-Receptor** ⟶ **Biological effect**

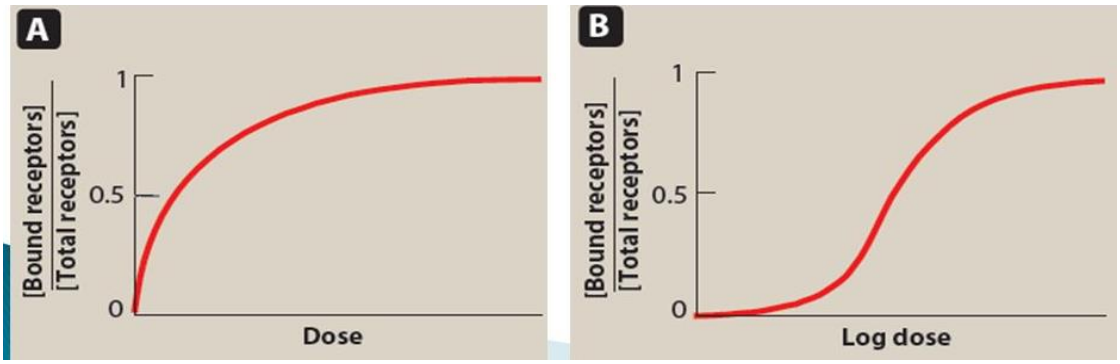
By making the assumption that the binding of one drug molecule does not alter the binding of subsequent molecules and applying the law of mass action, we can mathematically express the relationship between the percentage (or fraction) of bound receptors and the drug concentration:

$$\frac{[DR]}{[Rt]} = \frac{[D]}{Kd + [D]}$$

where [D] = the concentration of free drug, [DR] = the concentration of bound drug, [Rt] = the total number of receptors, and Kd = the equilibrium dissociation constant for the drug from the receptor. The value of Kd 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 Kd value, the weaker the interaction and the lower the affinity, and vice versa.

In the following figure we can see 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.



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 Emax occurs when all receptors are bound

3) one molecule of drug binds to only one molecule of receptor.

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.

Intrinsic Activity

Biologic response of an agonist based on:

1. The concentration of the agonist
2. Agonist's affinity for the receptor
3. The fraction of occupied receptors.

The intrinsic activity of a drug further determines its ability to fully or partially activate the receptors. Accordingly, drugs may be categorized according to their intrinsic activity and resulting Emax values into:

A. Full agonist
B. Partial agonist
C. Inverse agonist
D. Antagonist

Full agonist

Agonist drugs are known to activate receptors because they resemble the natural transmitters or hormones. Their value depends on their capacity to resist degradation inside the body and to act for longer than the natural substances they mimic e.g. bronchodilation produced by salbutamol lasts longer than that induced by adrenalin.

Characteristics of agonist

1. A drug that interacts and bind with a receptor.
2. Elicits (or causes) a maximal biological response (Emax).
3. It has affinity for the receptor.
4. It has efficacy (intrinsic activity equal 1). i.e stabilize the receptor in active state
5. It has fast rate of association and dissociation from the receptor.

Partial agonists

Are drugs that can activate receptors but are unable to elicit the maximal response of the receptor system. It has the following characteristics:

1. Agonist acts on the same receptors as full agonists.
2. Cannot produce the same maximum response (Emax) as a full agonist even when all the receptor occupied or when its concentration increase
3. Have high affinity.
4. Have low efficacy.
5. **Example on partial agonist:** aripiprazole, an atypical antipsychotic

Q) A partial agonist may also act as a partial antagonist of a full agonist, explain that?

Answer: 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 Emax would decrease until it reached the Emax of the partial agonist.

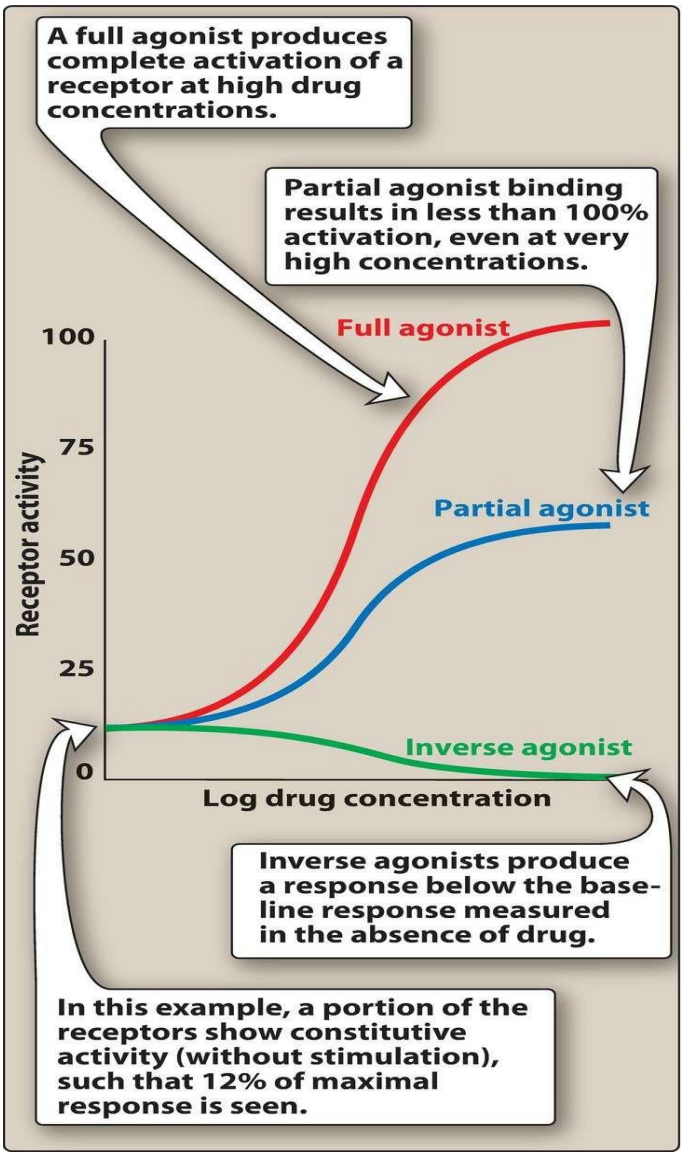
Note ***Sometimes partial agonist is said to have characteristics of both agonist and antagonist.*** In other words, in addition to capacity of blocking access of natural agonist to receptor they have low degree of activation.

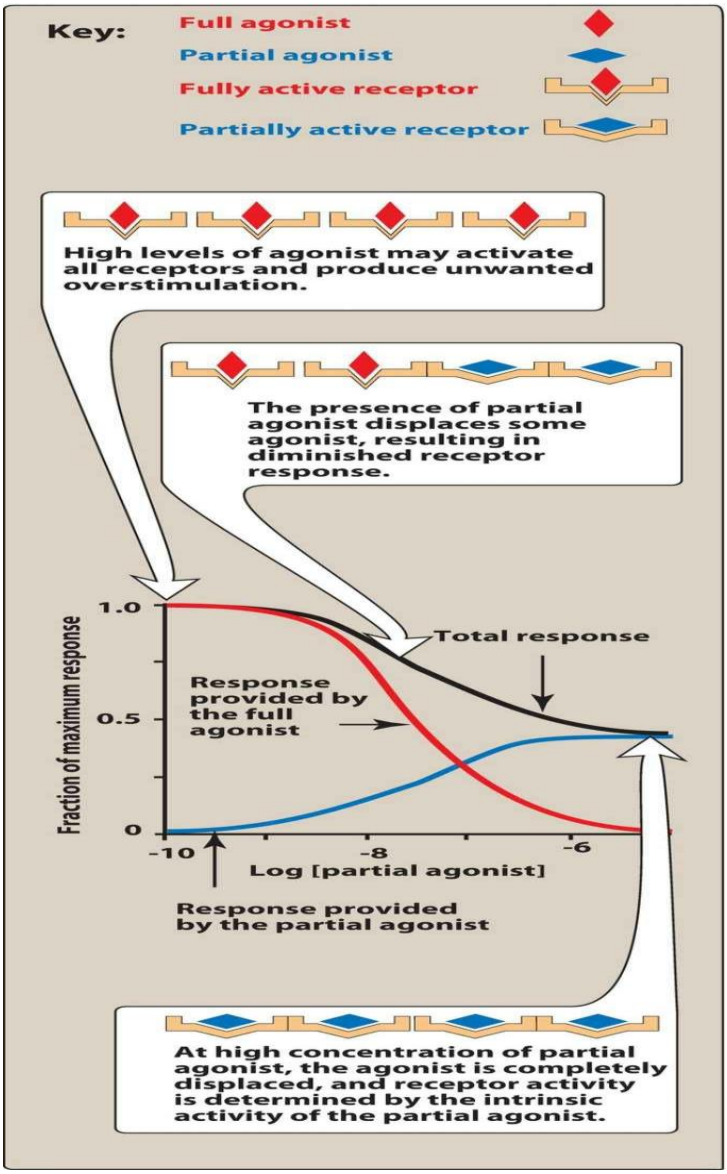
Inverse agonists

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.

Characteristics of inverse agonist

1. Have intrinsic activity less than zero.
2. Reverse the activation state of receptors
3. Exert the opposite pharmacological effect of agonists





Antagonists

1. Antagonists have the ability to bind to a receptor.
2. Have high affinity but possess zero intrinsic activity.
3. An antagonist has no effect on biological function in the absence of an agonist, but can decrease the effect of an agonist when present.
4. Antagonism may occur either by blocking the drug's ability to bind to the receptor or by blocking its ability to activate the receptor.

Types of antagonists:

1. Competitive antagonists
2. Irreversible antagonists
3. Allosteric antagonists
4. Functional antagonism
5. Chemical antagonist

Competitive antagonists

1. Binds to the same site on the receptor as the agonist in a reversible manner.
2. It is “competitive which mean as the concentration of agonist increase relative to antagonist can overcome this inhibition.
3. interferes with an agonist binding to its receptor and maintains the receptor in its inactive state.
4. Shift the agonist dose–response curve to the right (increased EC50) without affecting Emax.

Note: EC50 = drug dose that shows 50% of maximal response.

Irreversible antagonists

Bind covalently to the active site of the receptor, thereby permanently reducing the number of receptors available to the agonist.

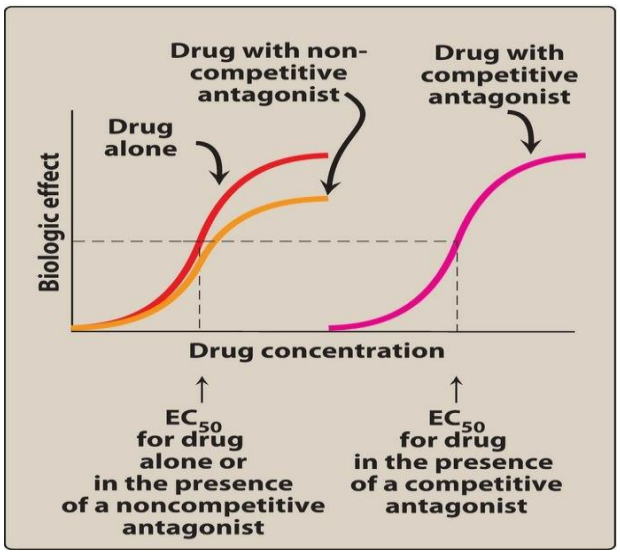
It causes a downward shift of the Emax , with no shift of EC50 values

Addition of more agonist does not overcome the effect of irreversible antagonists (so it is noncompetitive)

Q) What is the differences between competitive and noncompetitive antagonists?

Answer:

Competitive antagonists reduce agonist potency (increase EC50) while noncompetitive antagonists reduce agonist efficacy (decrease Emax)



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 Emax of an agonist, with no change in the EC50 value.** An example of an allosteric agonist is picrotoxin, which binds to the inside of the GABAcontrolled chloride channel. When picrotoxin binds inside the channel, no chloride can pass through the channel, even when GABA fully occupies the receptor.

Functional antagonism (physiologic 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 H1 histamine receptors on bronchial smooth muscle, causing bronchoconstriction of the bronchial tree. Epinephrine is an agonist at β2 -adrenoceptors on bronchial smooth muscle, which causes the muscles to relax.

Quantal Dose–Response Relationships (Response occur or does not occur)

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.

ED50 is the drug dose that causes a therapeutic response in half of the population.

Therapeutic index

The therapeutic index (TI) of a drug is the ratio of the dose that produces toxicity in half the population (TD50) to the dose that produces a clinically desired or effective response (ED50) in half the population:

$$TI = \frac{TD50}{ED50}$$

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.

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. The following figure shows the responses to warfarin, an oral anticoagulant with a low TI, and penicillin, an antimicrobial drug with a large TI.