

THEORIES FOR DRUG RECEPTOR
INTERACTION
AND TYPES OF DRUG RECEPTOR
INTERACTION

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RECEPTORS –

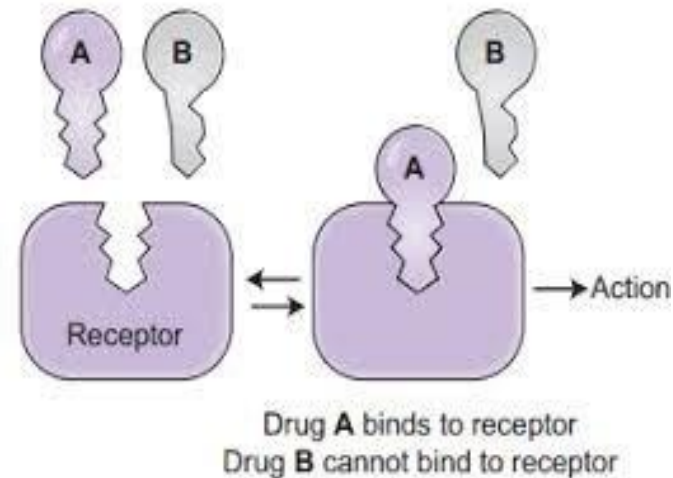
- ☐ A receptor is the specific chemical constituent of the cell with which a drug interacts to produce its Pharmacological effects.
- ☐ Some receptor sites have been identified with specific parts of proteins and nucleic acids.
- ☐ The term drug receptor or drug target denotes the cellular macromolecule or macromolecular complex with which the drug interacts to elicit a cellular response, i.e., a change in cell function.



A Receptor is analogous to a switch that it has two configurations: “ON” and “OFF”

☐ Four Primary Receptor Families

- ☐ Ligand-gated Ion Channel
- ☐ G –protein coupled Receptor Systems
- ☐ Enzyme-linked receptors
- ☐ Intracellular receptors



❓ **Receptor:** Any cellular macromolecule that a drug binds to initiate its effects.

❓ **Drug:** A chemical substance that interacts with a biological system to produce a physiologic effect. All drugs are chemicals but not all chemicals are drugs.

❓ The ability to bind to a receptor is mediated by the chemical structure of the drug that allows it to interact with complementary surfaces on the receptor.

❓ Once bound to the receptor an agonist activates or enhances cellular activity. Examples of agonist action are drugs that bind to beta receptors in the heart and increase the force of myocardial contraction or drugs that bind to alpha receptors on blood vessels to increase blood pressure.

❓ The binding of the agonist often triggers a series of biochemical events that ultimately leads to the alteration in function.

INTERACTION

Over the years a number of hypotheses have been proposed to account for the ability of a drug to interact with a receptor and elicit a biological response. Several of the more important proposals are:

1. Occupancy Theory

- ☐ The occupancy theory of Gaddum and Clark states that the intensity of the pharmacological effect is directly proportional to the number of receptors occupied by the drug.
- ☐ Maximal response occurs when all the receptors are occupied.



- ☐ The concept of drug–receptor interactions involve two stages: **first**, there is a complexation of the drug with the receptor, which termed the **affinity**; **second**, there is an initiation of a biological effect, which termed the **intrinsic activity and the efficacy**.

□ **Affinity**, is a measure of the capacity of a drug to bind to the receptor.

□ **Intrinsic activity** (α) or **Efficacy** is the property of a compound that produces the maximum response or the ability of the drug–receptor complex to initiate a response.

□ **Examples** of affinity and efficacy are given in **Figure 1A** shows the theoretical dose–response curves for five drugs with the same affinity for the receptor ($pK_D = 8$), but having efficacies varying from 100% of the maximum to 20% of the maximum. The drug with 100% efficacy is a full agonist; the others are partial agonists.

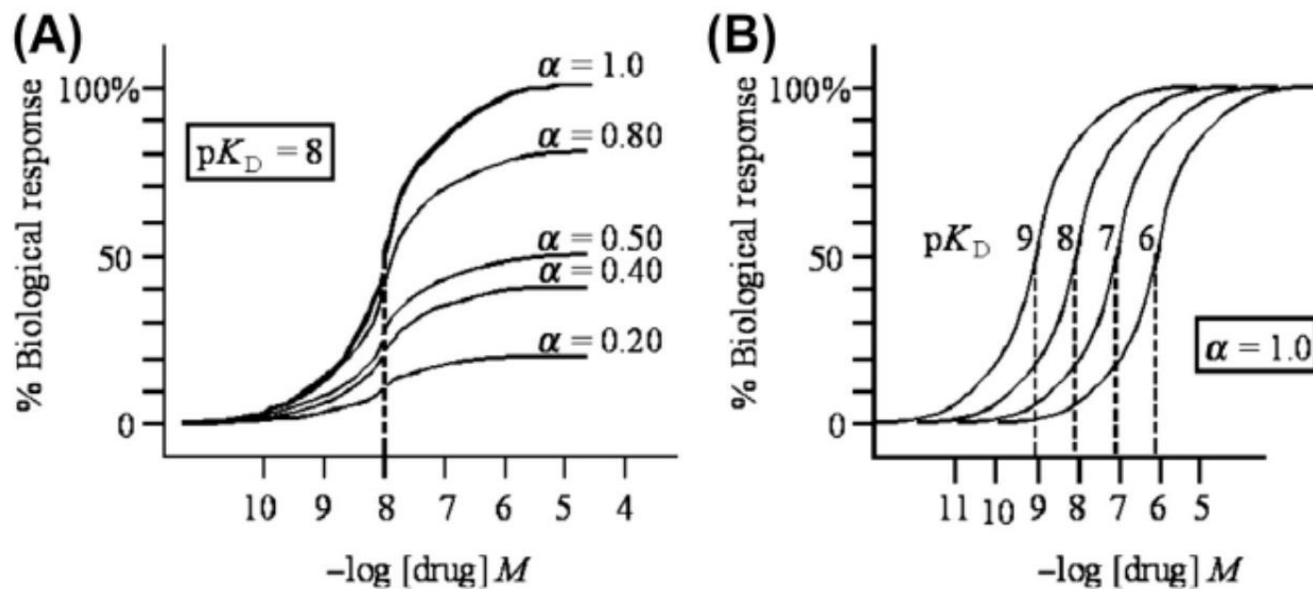


FIGURE 1. Theoretical dose–response curves illustrate (A) drugs with equal affinities and different efficacies (the top compound is a full agonist, and the others are partial agonists) and (B) drugs with equal efficacies (all full agonists) but different affinities.

Figure 1B shows dose–response curves for four drugs with the same efficacy (all full agonists), but having different affinities varying from a pK_d of 9 to 6.

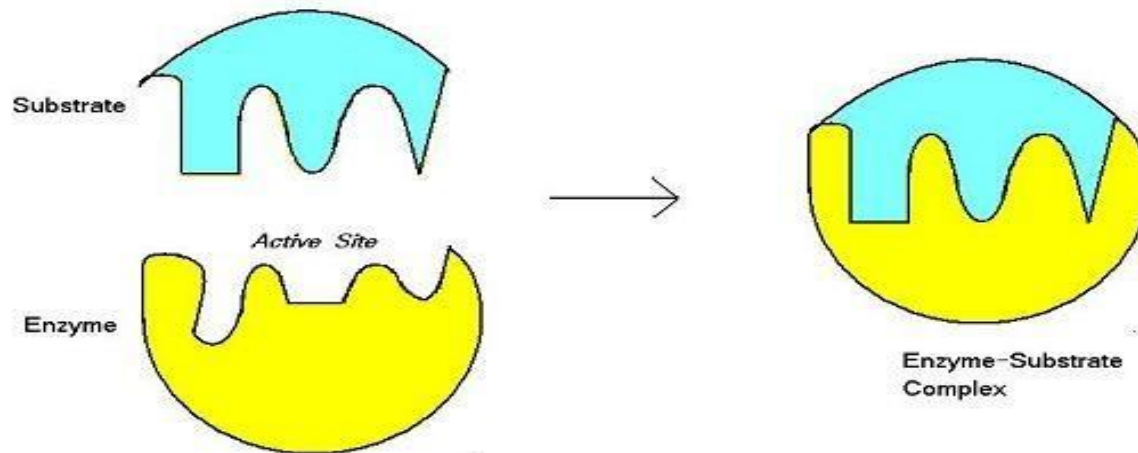
- ❑ Antagonists can bind tightly to a receptor (great affinity), but be devoid of activity (no efficacy).
- ❑ A compound that is an agonist for one receptor may be an antagonist or inverse agonist for another receptor.
- ❑ The response ceases when the drug–receptor complex dissociates. However, not all agonists produce a maximal response.
- ❑ Does not rationalize how two drugs can occupy the same receptor and act differently.

2. Rate theory

- ☐ The response is proportional to the rate of drug-Receptor complex formation.
- ☐ Effect is produced by the drug molecules based on the rates of association and dissociation of drugs to and from the receptors.
- ☐ As an alternative to the occupancy theory, Paton proposed that the activation of receptors is proportional to the total number of encounters of the drug with its receptor per unit time.
- ☐ Therefore, the **rate theory** suggests that the pharmacological activity is a function of the rate of association and dissociation of the drug with the receptor and not the number of occupied receptors. Each association would produce a quantum of stimulus.
- ☐ In the case of **agonists**, the rates of both association and dissociation would be fast.
- ☐ The rate of association of an **antagonist** with a receptor would be fast, but the dissociation would be slow.
- ☐ **Partial agonists** would have intermediate drug-receptor complex dissociation rates.

3. Induced-Fit Theory

- The induced-fit theory of Koshland was originally proposed for the action of substrates with enzymes, but it could apply to drug–receptor interactions as well.
- According to this theory, the receptor need not necessarily exist in the appropriate conformation required to bind the drug. As the drug approaches the receptor, a conformational change is induced, which orients the essential binding sites (Figure 2).



Induced-fit Model. - The enzyme active site forms a complementary shape to the substrate after binding.

- ❑ The conformational change in the receptor could be responsible for the initiation of the biological response (movement of residues to interact with the substrate).
- ❑ The receptor (enzyme) was suggested to be elastic, and could return to its original conformation after the drug (product) was released.
- ❑ The conformational change need not occur only in the receptor (enzyme), the drug (substrate) also could undergo deformation, even if this resulted in strain in the drug (substrate).
- ❑ According to this theory, an **agonist** would induce a conformational change and elicit a response, an **antagonist** would bind without a conformational change, and a **partial agonist** would cause a partial conformational change.
- ❑ The induced- fit theory can be adapted to the rate theory. An agonist would induce a conformational change in the receptor, resulting in a conformation to which the agonist binds less tightly and from which it can dissociate more easily.
- ❑ If drug–receptor complexation does not cause a conformational change in the receptor, then the drug–receptor complex will be stable, and an antagonist will result.

4. *Macromolecular Perturbation Theory*

▣ Having considered the conformational flexibility of receptors, Belleau suggested that in the interaction of a drug with a receptor two general types of macromolecular perturbations could result:

▣ A **specific** conformational perturbation makes possible the binding of certain molecules that produce a biological response (an agonist)

▣ A **non-specific** conformational perturbation accommodates other types of molecules that do not elicit a response (e.g., an antagonist).

▣ If the drug contributes to both macromolecular perturbations, a mixture of two complexes will result (a partial agonist).

▣ This theory offers a physicochemical basis for the rationalization of molecular phenomena that involve receptors, but does not address the concept of inverse agonism.

5. Activation–Aggregation Theory

According to this theory, even in the absence of drugs, a receptor is in a state of dynamic equilibrium between an activated form (R_o), which is responsible for the biological response, and an inactive form (T_o).

Using this theory, agonists bind to the R_o form and shift the equilibrium to the activated form, antagonists bind to the inactive form (T_o), and partial agonists bind to both conformations.

In this model, the agonist binding site in the R_o conformation can be different from the antagonist binding site in the T_o conformation.

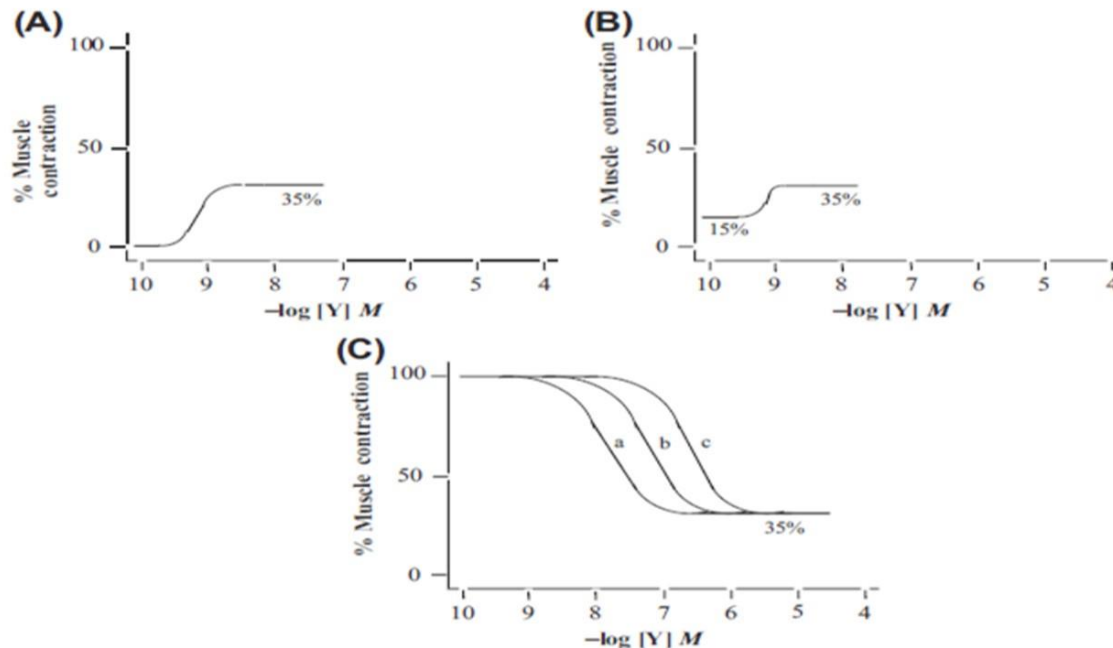


Figure 3

- ❑ This theory can explain the ability of partial agonists to possess both the agonistic and antagonistic properties as depicted in Figure 3.
- ❑ In Figure 3.B, as the partial agonist interacts with the remaining unoccupied receptors, there is an increase in the response up to the maximal response for the partial agonist interaction.
- ❑ In Figure 3.C, the partial agonist competes with the neurotransmitter for the receptor sites. As the partial agonist displaces the neurotransmitter, it changes the amount of R_0 and T_0 receptor forms (T_0 increases and therefore, the response decreases) until all the receptors have the partial agonist bound.

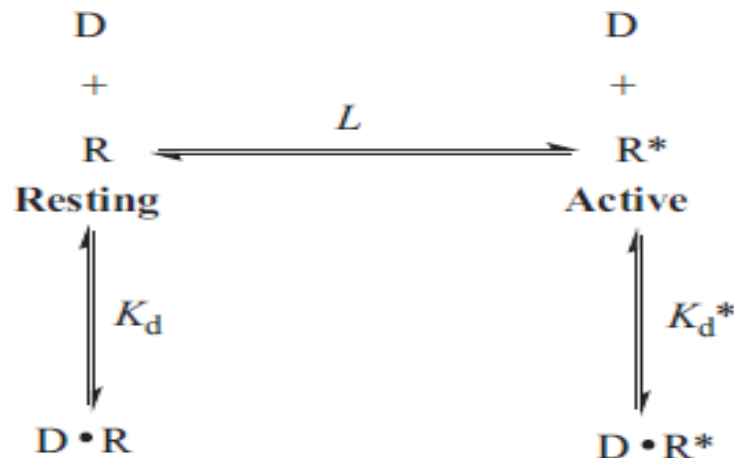
- ❑ This theory, however, also does not address inverse agonists.

6. The Two-State (Multistate) Model of Receptor Activation

▣ Was developed on the basis of the kinetics of competitive and allosteric inhibition as well as through interpretation of the results of direct binding experiments.

▣ It postulates that a receptor, regardless of the presence or absence of a ligand, exists in two distinct states: the **R (relaxed, active or on)** and **T (Tense, inactive or off)** states, which are in equilibrium with each other.

▣ In the absence of the natural ligand or agonist, receptors exist in equilibrium (defined by equilibrium constant L ; Figure 4) between an active state (R^*), which is able to initiate a biological response, and a resting state (R), which cannot.



? In the absence of a natural ligand or agonist, the equilibrium between R^* and R defines the basal activity of the receptor.

? A drug can bind to one or both of these conformational states, according to equilibrium constants K_d and K^*_d for formation of the drug–receptor complex with the resting ($D \cdot R$) and active ($D \cdot R^*$) states, respectively.

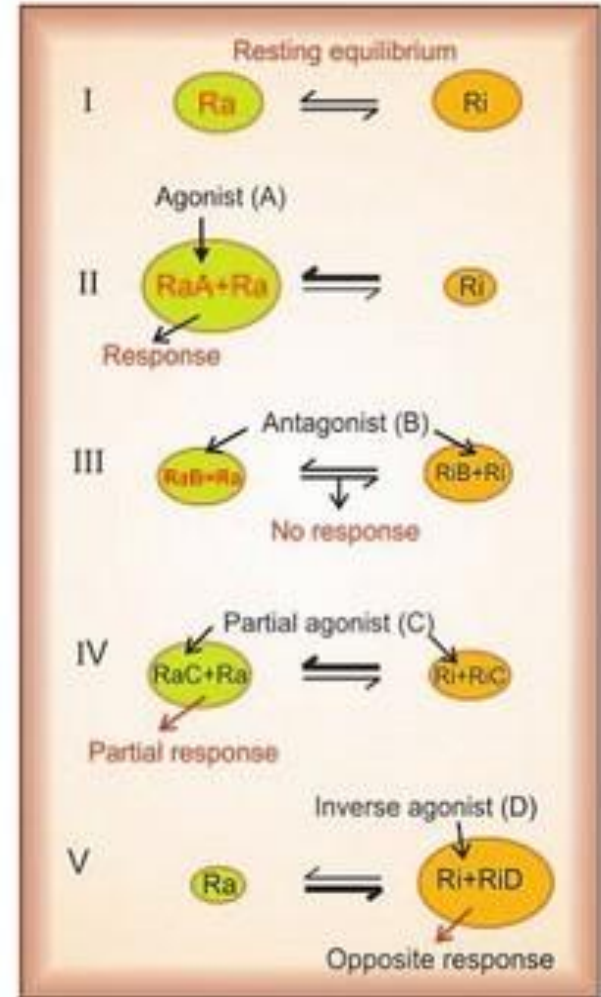
? Full agonists bind only to R^*

? Partial agonists bind preferentially to R^*

? Full inverse agonists bind only to R

? Partial inverse agonists bind preferentially to R

? Antagonists have equal affinities for both R and R^* (no effect on basal activity)



IMPORTANT INTERACTIONS (FORCES) INVOLVED IN THE DRUG-RECEPTOR COMPLEX

- ☐ Interactions involved in the drug-receptor complex are the same forces experienced by all interacting organic molecules.
- ☐ **These include:-** covalent bonding, ionic (electrostatic) interactions, ion-dipole and dipole-dipole interactions, hydrogen bonding, charge-transfer interactions, hydrophobic interactions, halogen bonding, and van der Waals interactions.

1. Covalent Bonds

- ☐ The covalent bond is the strongest bond, generally formed by sharing of electrons between two atoms. It is formed by a drug-receptor interaction, except with enzymes and DNA.
- ☐ The majority of drugs combine with their receptor by weak molecular interactions.
- ☐ These interactions form a strong link between the drug and its receptor but individually the interactions are reversible.
- ☐ The covalent bonds are important as compared to other bonds.

2. Ionic (or Electrostatic) Interactions

For protein receptors at physiological pH (pH 7.4), basic groups such as the amino side chains of arginine, lysine are protonated and, therefore, provide a cationic environment. Acidic groups, such as the carboxylic acid side chains of aspartic acid and glutamic acid, are deprotonated to give anionic groups.

Drug and receptor groups will be mutually attracted provided they have opposite charges. This ionic interaction can be effective at distances farther than those required for other types of interactions, and they can persist longer.

3. Ion–Dipole and Dipole–Dipole Interactions

As a result of the greater electronegativity of atoms such as oxygen, nitrogen, sulfur, and halogens relative to that of carbon, C–X bonds in drugs and receptors, where X is an electronegative atom, will have an asymmetric distribution of electrons; this produces electronic dipoles.

These dipoles in a drug molecule can be attracted by ions (ion–dipole interaction) or by other dipoles (dipole–dipole interaction) in the receptor, provided charges of opposite sign are properly aligned.

Because the charge of a dipole is less than that of an ion, a dipole–dipole interaction is weaker than an ion– dipole interaction.

4. Hydrogen Bonds

- Hydrogen bonds are a type of dipole–dipole interaction formed between the proton of a group X–H, where X is an electronegative atom, and one or more other electronegative atoms (Y) containing a pair of non-bonded electrons.
- The most significant hydrogen bonds occur in molecules where X and Y are N and O .
- X removes electron density from the hydrogen so it has a partial positive charge, which is strongly attracted to the non-bonded electrons of Y. The interaction is denoted as a dotted line, $-X-H\cdots Y-$
- X is referred to as the hydrogen bond donor and Y is the hydrogen bond acceptor. When X and Y are equivalent in electronegativity and degree of ionization, the proton can be shared equally between the two groups, i.e. $-X\cdots H\cdots Y-$.

5. Charge–Transfer Complexes

When a molecule (or group) that is a good electron donor comes into contact with a molecule (or group) that is a good electron acceptor, the donor may transfer some of its charge to the acceptor. This forms a charge-transfer complex.

Donor groups contain π -electrons, such as alkenes, alkynes, and aromatic moieties with electron-donating substituents, or groups that contain a pair of non-bonded electrons, such as oxygen, nitrogen, and sulfur moieties.

Acceptor groups contain electron-deficient π -orbitals, such as alkenes, alkynes, and aromatic moieties having electron-withdrawing substituents, and weakly acidic protons.

There are groups on receptors that can act as electron donors, such as the aromatic ring of tyrosine or the carboxylate group of aspartate.

6. Halogen Bonding

It has now been well established that a covalently bonded halogen atom can act as an electron acceptor (Lewis acid) to undergo halogen bonding with an electron-rich donor atom, such as O, N, or S.

These interactions can govern the conformation of molecules in the binding site of proteins.

7. Van der Waals or London Dispersion Forces

☐ Atoms in nonpolar molecules may have a temporary non-symmetrical distribution of electron density, which results in the generation of a temporary dipole.

☐ As atoms from different molecules (such as a drug and a receptor) approach each other, the temporary dipoles of one molecule induce opposite dipoles in the approaching molecule. Consequently, intermolecular attractions, known as van der Waals forces, result.

☐ These weak universal forces only become significant when there is a close surface contact of the atoms.

AGONIST :

- ☐ Agonist are molecules that activates receptors, a drug that has both affinity and high intrinsic activity.
- ☐ Many drugs produce their effects by acting as an agonist.

For example: *Dobutamine* - it mimics the action of norephenephrine at the receptors on the heart. Thereby causing the heart to contract and increase the heart beat.

- ☐ An agonist binds to a receptor and produces a biological response.

- ☐ Full agonists
- ☐ Partial agonists
- ☐ Inverse agonists

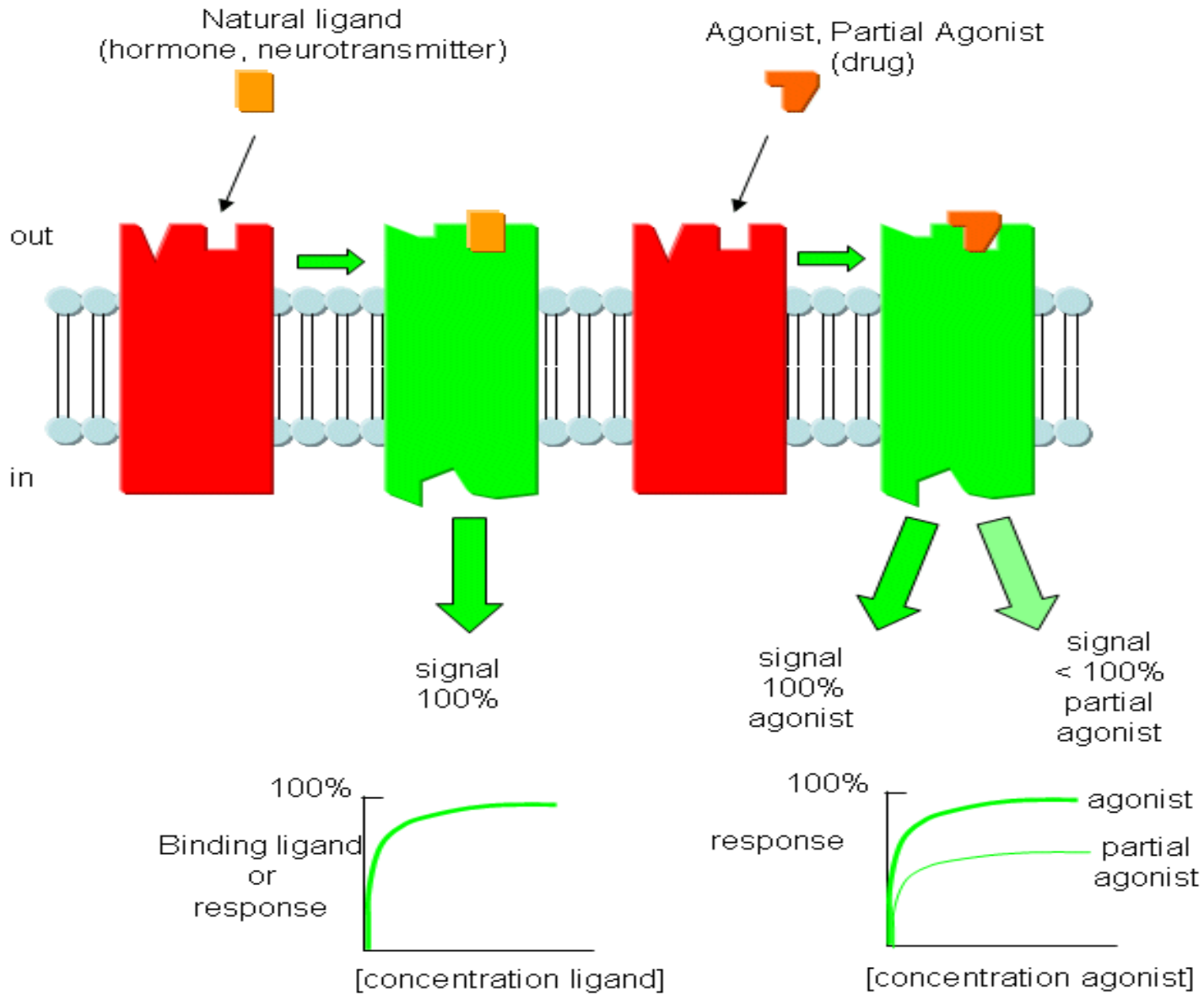
1. **Full agonist:** If a drug binds to a receptor and produces a *maximal* biological response that mimics the response to the endogenous ligand, it is known as a full agonist.

- ☐ Full agonist stabilizes the receptor in its active state.

2. **Partial agonist:** Have efficacies greater then zero but less then that of a full agonist.

- ☐ A partial agonist may have an *affinity* that is greater than, less than or equivalent to that of a full agonist.

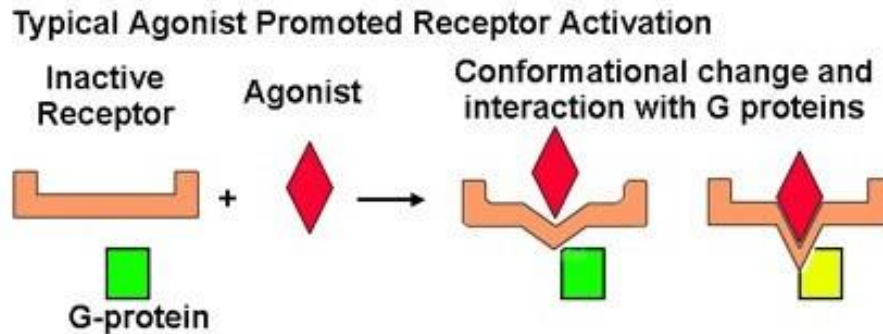
Agonists



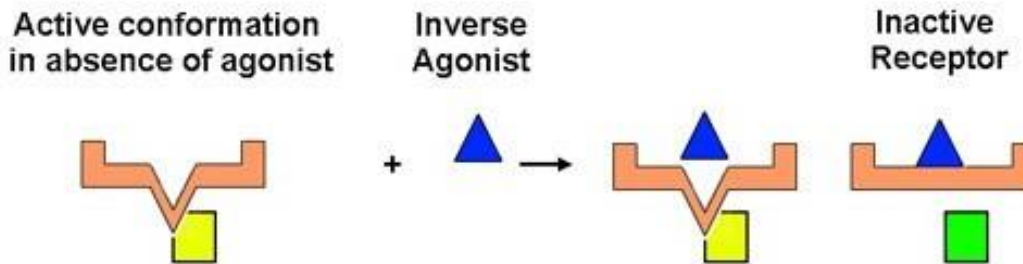
3. **Inverse agonists:** They produce a response below the baseline responses measured in the absence of drug.

☐ This decreases the number of activated receptors to below observed in the absence of the drug.

☐ They exert the opposite pharmacological effect of receptor agonists.



Constitutively Active Receptor and an Inverse Agonist



ANTAGONIST:

- ☐ Antagonists are drugs that decrease the actions of another drug or an endogenous ligand.
- ☐ An antagonist has no effect if an agonist is not present.
- ☐ Antagonists produce no effect by themselves.
 - ☐ Competitive antagonists
 - ☐ Non-competitive (irreversible) antagonists
 - ☐ *Competitive antagonists*: both the antagonist and agonist bind to the same site on the receptor.
 - ☐ *Non-competitive antagonists*: An irreversible antagonist causes a downward shift of the maximum. And can not be overcome by adding more agonist.
 - i. Covalent binding to the active site of the receptor
 - ii. Allosteric binding

COMPETITIVE AND NON-COMPETITIVE ANTAGONIST

Sr. no	Competitive antagonist	Non-competitive antagonists
1.	Antagonist binds with the same receptor as the agonist	Binds to another site of receptor
2.	Antagonist resembles chemically with the agonist	Does not resemble
3.	The same maximal response can be attained by increasing dose of agonist	Maximal response is supported
4.	Right shift of agonist DRC	Flattening of agonist DRC
5.	Intensity of response depends on conc. of both agonist and antagonist	Depends only on conc. of antagonist
6.	Examples: ACh- Atropine Morphine- Naloxone	Diazepam-Bicuculline

