Drug action-Receptor Theory

DRUG

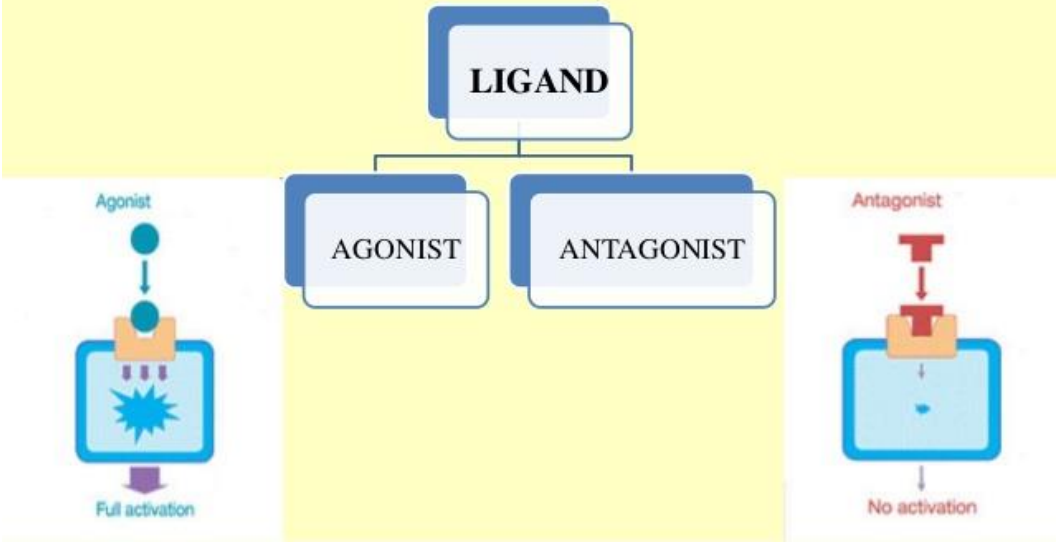
It is a natural or synthetic substances which has a physiological effects when administered into the body.

RECEPTOR

It is a specific binding site present on the cell surface made up of protein or nucleic acid where a ligand can bind and initiates a characteristic response.

CLASSIFICATION OF LIGANDS

Ligands are classified by effects upon binding to the receptor



Molecules (eg, drugs, hormones, neurotransmitters) that bind to a receptor are called ligands. The binding can be specific and reversible. A ligand may activate or inactivate a receptor; activation may increase or decrease a particular cell function. Each ligand may interact with

multiple receptor subtypes. Few if any drugs are absolutely specific for one receptor or subtype, but most have relative selectivity. Selectivity is the degree to which a drug acts on a given site relative to other sites; selectivity relates largely to physicochemical binding of the drug to cellular receptors.

A drug's ability to affect a given receptor is related to the drug's affinity (probability of the drug occupying a receptor at any given instant) and intrinsic efficacy (intrinsic activity—degree to which a ligand activates receptors and leads to cellular response). A drug's affinity and activity are determined by its chemical structure.

The pharmacologic effect is also determined by the duration of time that the drug-receptor complex persists (residence time). The lifetime of the drug-receptor complex is affected by dynamic processes (conformation changes) that control the rate of drug association and dissociation from the target. A longer residence time explains a prolonged pharmacologic effect. Drugs with long residence times include finasteride and darunavir. A longer residence time can be a potential disadvantage when it prolongs a drug's toxicity. For some receptors, transient drug occupancy produces the desired pharmacologic effect, whereas prolonged occupancy causes toxicity.

Ability to bind to a receptor is influenced by external factors as well as by intracellular regulatory mechanisms. Baseline receptor density and the efficiency of stimulus-response mechanisms vary from tissue to tissue. Drugs, aging, genetic mutations, and disorders can increase (upregulate) or decrease (downregulate) the number and binding affinity of receptors. Receptor upregulation and downregulation affect adaptation to drugs (eg, desensitization, tachyphylaxis, tolerance, acquired resistance, postwithdrawal supersensitivity).

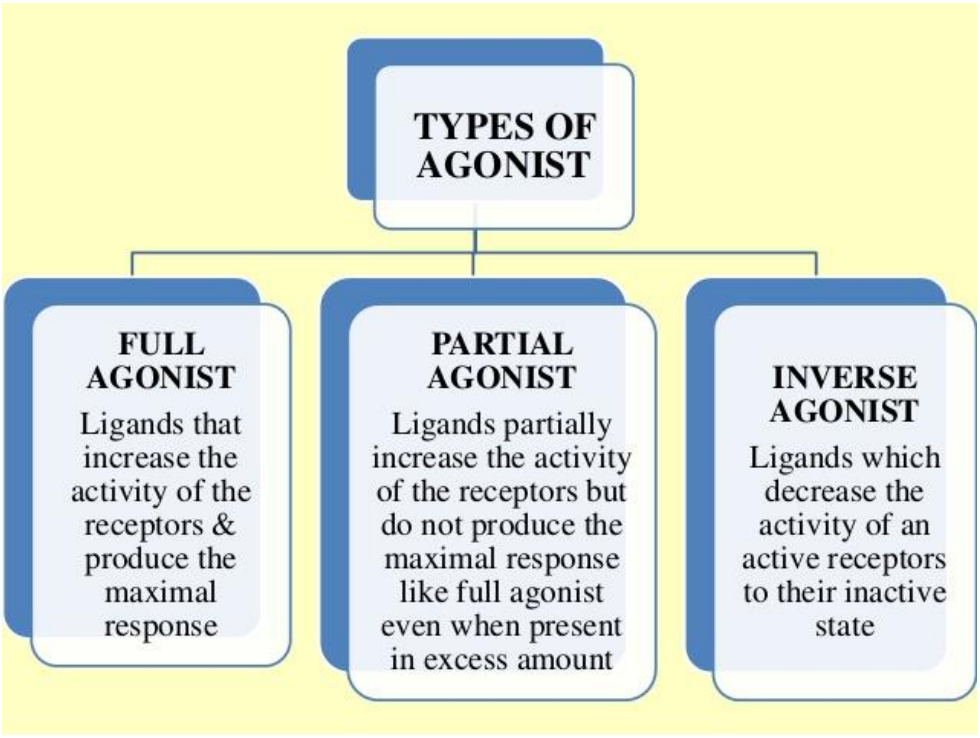
Ligands bind to precise molecular regions, called recognition sites, on receptor macromolecules. The binding site for a drug may be the same as or different from that of an endogenous agonist (hormone or neurotransmitter). Agonists that bind to an adjacent site or a different site on a receptor are sometimes called allosteric agonists. Nonspecific drug binding also occurs—ie, at molecular sites not designated as receptors (eg, plasma proteins). Drug binding to such nonspecific sites, such as binding to serum proteins, prohibits the drug from binding to the receptor and thus inactivates the drug. Unbound drug is available to bind to receptors and thus have an effect.

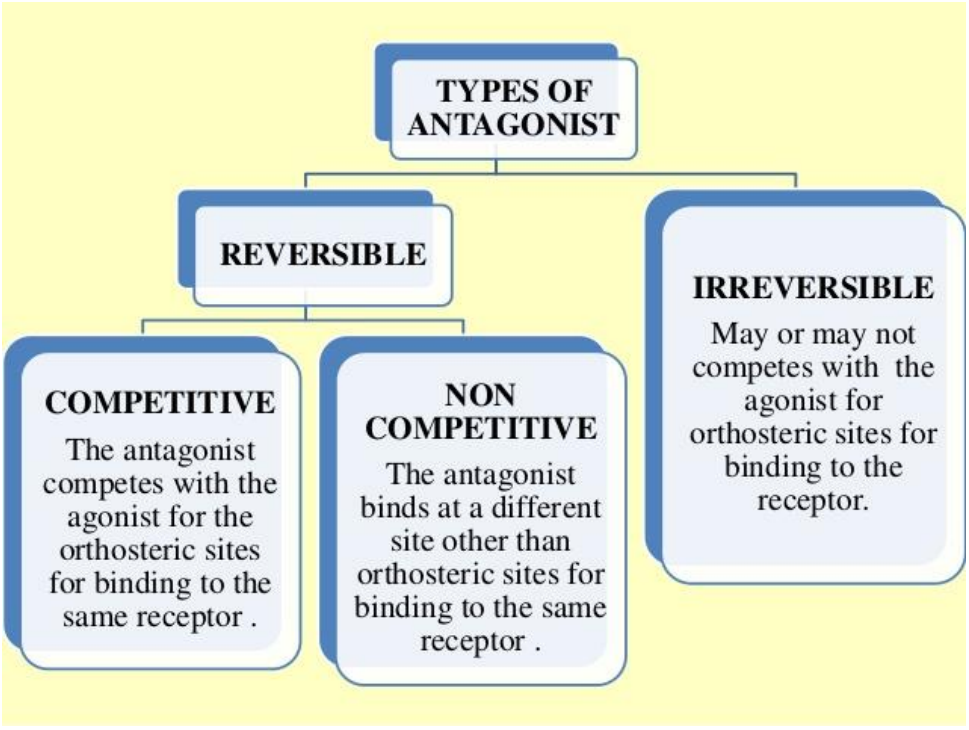
an **endogenous agonist** for a particular receptor is a compound naturally produced by the body which binds to and activates that receptor. For example, the primary **endogenous agonist** for serotonin receptors is serotonin,

Agonists and antagonists

Agonists activate receptors to produce the desired response. Conventional agonists increase the proportion of activated receptors. Inverse agonists stabilize the receptor in its inactive conformation and act similarly to competitive antagonists. Many hormones, neurotransmitters (eg, acetylcholine, histamine, norepinephrine),and drugs
(eg, morphine, phenylephrine, isoproterenol, benzodiazepines, barbiturates) act as agonists.

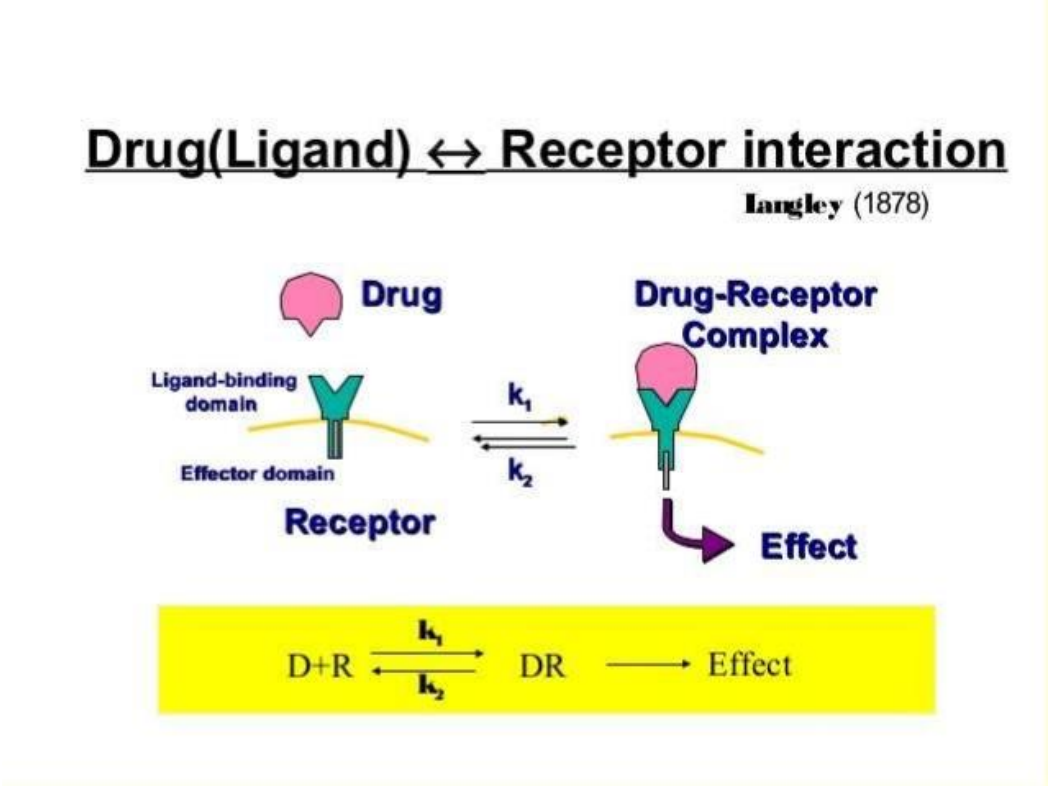
Antagonists prevent receptor activation. Preventing activation has many effects. Antagonists increase cellular function if they block the action of a substance that normally decreases cellular function. Antagonists decrease cellular function if they block the action of a substance that normally increases cellular function.





Receptor antagonists can be classified as reversible or irreversible. Reversible antagonists readily dissociate from their receptor; irreversible antagonists form a stable, permanent or nearly permanent chemical bond with their receptor (eg, by alkylation). Pseudo-irreversible antagonists slowly dissociate from their receptor.

In **competitive antagonism,** binding of the antagonist to the receptor prevents binding of the agonist to the receptor.
In **noncompetitive antagonism,** agonist and antagonist can be bound simultaneously, but antagonist binding reduces or prevents the action of the agonist.
In **reversible competitive antagonism,** agonist and antagonist form short-lasting bonds with the receptor, and a steady state among agonist, antagonist, and receptor is reached. Such antagonism can be overcome by increasing the concentration of the agonist. For example, naloxone (an opioid receptor antagonist that is structurally similar to morphine), when given shortly before or after morphine, blocks morphine's effects. However, competitive antagonism by naloxone can be overcome by giving more morphine.



FORCES INVOLVED IN DRUG RECEPTOR INTERACTION

$$Kd = \frac{[drug][receptor]}{[drug - recptor\ complex]}$$

$$Drug + receptor \underset{K_{off}}{\overset{Kon}{\longleftrightarrow}} \text{Drug-receptor complex}$$

Where k_{on} is the rate constant for formation of the drug-receptor complex, which depends on the concentration of the drug and the receptor

k_{off} is the rate constant for breakdown of the complex, which depends on the concentration of the drug-receptor complex as well as other forces.

The biological activity of drug is related to its affinity for the receptor, i.e., the stability of the drug-receptor complex.

This stability is commonly measured by how difficult is for the complex to dissociate, which is measured by **its kd, the dissociation constant** for the drug-receptor complex at equilibrium.

INTERACTIONS INVOLVED IN THE DRUG-RECEPTOR COMPLEX

1. Ionic interactions
2. Ion-dipole and dipole-dipole interactions,
3. Hydrogen bonding
4. Hydrophobic interactions
5. Vander waals interactions
6. Covalent bonding

THEORIES OF DRUG RECEPTOR INTERACTIONS

1. Occupation theory
2. Rate Theory
3. The induced-fit theory of enzyme-substrate interaction
4. Macromolecular perturbation theory
5. Activation-aggregation theory
6. Two state model of receptor activation

OCCUPATION THEORY

Drugs act on binding sites and activate them, resulting in a biological response that is proportional to the amount of drug-receptor complex formed.
The response ceases when this complex dissociates.

Intensity of pharmacological effect is directly proportional to number of receptors occupied

$$D + R \leftrightarrow DR \Rightarrow RESPONSE$$

Response is proportional to the fraction of occupied receptors
Maximal response occurs when all the receptors are occupied

RATE THEORY

The response is proportional to the rate of drug-Receptor complex formation.

Activation of receptors is proportional to the total number of encounters of a drug with its receptor.

According to this view, the duration of Receptor occupation determines whether a molecule is **agonist, partial agonist.**

THE INDUCED-FIT THEORY

According to this theory, binding produces a mutual plastic molding of both the ligand and the receptor as a dynamic process.

The conformational change produced by the mutually induced fit in the receptor macromolecule is then translated into the biological effect, eliminating the rigid and **obsolete " lock and key" concept of earlier times**

Agonist induces conformational change – response

Antagonist does not induce conformational change – no response

Partial agonist induces partial conformational change-partial response

MACROMOLECULAR PERTURBATION THEORY

Suggests that when a drug-receptor interaction occurs, one of two general types of Macromolecular perturbation is possible:

a specific conformational perturbation leads to a biological response (Agonist),

whereas a non specific conformational perturbation leads to no biological response (Antagonist)

ACTIVATION AGGREGATION THEORY

Receptor is always in a state of dynamic equilibrium between activated form (Ro) and inactive form (To).

$R_o \rightleftharpoons T_o$

biological response — no biological response

Agonists shift equilibrium to R_o

Antagonists shift equilibrium to T_o

Partial agonists bind to both R_o and T_o

SAR

- **SAR** is the relationship between the chemical or 3D structure of a molecule and its biological activity.
- Determination of the chemical groups ➔responsible for evoking a target biological effect in the organism.
- Quantitative SARs (QSAR)as a special case of SARs (when relationships become quantified)

Structure Activity Relationships (SAR) can be used to predict biological activity from molecular structure. This powerful technology is used in drug discovery to guide the acquisition or synthesis of desirable new compounds, as well as to further characterize existing molecules.

The biological effects of a new chemical compound can often be predicted from its molecular structure using data about other similar compounds. This is because similar compounds may have similar physical and biological properties. There is a relationship between molecular structures and their biological activity, and this principle is referred to as Structure Activity Relationship (SAR).

Structure- Activity Relationships (SAR)

- Although there has been a great deal of success in understanding the relationship between chemical structure and biological activity in a number of areas, especially for antibacterial drugs, there are still many human afflictions that require new and improved drugs. Cancer, viral infections, cardiovascular diseases, and mental diseases need new agents and approaches for treating and preventing these illnesses.
- Most drugs act at a specific site such as an enzyme or receptor. Compounds with similar structures often tend to have similar pharmacological activity. However, they usually exhibit difference in potency and unwanted side effects and in some cases different activities. ***These structurally related differences are commonly referred to as Structure-Activity Relationships (SAR)***

Structure- Activity Relationships (SAR)

- A study of the Structure- Activity Relationships (SAR) of a lead compound (***the original pharmacologically active compound from which these synthetic analogues are developed is known as lead compound***) and it's analogues can be used to determine the parts of the structure of the lead that are responsible for it's biological activity, that is, it's **pharmacophore** and also it's unwanted side effects. This information is subsequently used to develop a new drug that has
- increased activity (optimize it's SAR),
- a different activity from an existing drug,
- fewer unwanted side effects and
- Improved ease of administration to the patient.

Structure- Activity Relationships (SAR)

- Structure- Activity Relationships are usually determined by making minor changes to the structure of the lead and assessing the effect that this has on biological activity.
- Traditional SAR investigations are carried out by making large numbers of analogues of the lead and testing them for biological activity.
- Over the years numerous lead compounds have been investigated and from the mass of data it is possible to make some broad generalizations about biological effects of specific structural changes. These changes may be conveniently classified as:
  1. **the size and shape of the carbon skeleton,**
  2. **the nature and degree of substitution, and**
  3. **the stereochemistry of the lead.**
- The selection of the changes required to produce analogues of a particular lead is made by considering the activities of compounds with similar structures and also the possible chemistry and biochemistry of the intended analogue.

Structure- Activity Relationships (SAR)

- For example, replacing a hydroxyl group with a methyl group could reduce the water solubility of the analogue and it's ability to form hydrogen bonding.
- The former could reduce it's ease of absorption whereas the latter could affect it's ability to bind to it's target site.
- It could improve the transport of the drug through membranes and also introduce changes in the metabolism of the drug.
- For example, oxidation of the methyl group to a carboxylic group could increase the rate of metabolism.
- All these effects could result in loss of activity or a reduction in unwanted side effects.
- A further consideration is the size of the analogue. Changing the structure of the lead could result in an analogue that is too big to fit it's intended target site.
- Computerized molecular modeling can be used to check this provided that the structure of the target is known or can be simulated with some degree of accuracy.
- Traditional SAR investigation procedures are useful tools in the search for new drugs. However, they are expensive in both personnel and materials. Consequently, a number of attempts have been made to improve on traditional Structure- Activity investigations with varying degree of success.

Pharmacophore-based drug design

Design method 1: Chemical modification

Probing specific functional groups in a molecule

Binding role of hydroxy groups: H-bond donor or acceptor

Convert to:

•methyl ether (no H-bond donor now; maybe steric problem)

•an ester (no H-bond donor now; poor H-bond acceptor; maybe steric problem)

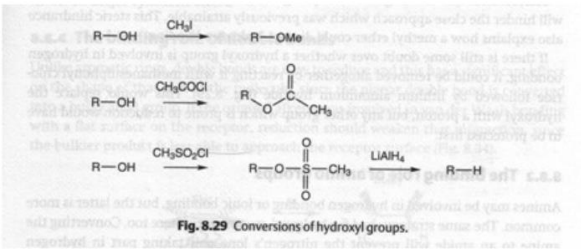


Fig. 8.29 Conversions of hydroxyl groups.

Probing specific functional groups in a molecule

Binding role of amino groups: H-bond donor (if N-H is present) or acceptor; ionic (protonation of N to form a salt; recall pKa)

Convert to:

•amide (no protonation; no H-bond acceptor now; steric problem?)

•Tertiary amine (no H-bond donor now; still H-bond acceptor; sterics?)

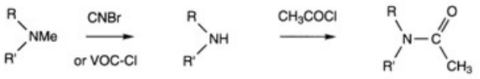


Fig. 8.32 Dealkylation of tertiary amines.

Binding role of aromatic rings, alkenes: hydrophobic; cation-pi

Convert to:

•Saturated compound (not effective overlap; no pi system; more flexible)

Fig. 8.34 Hydrogenation of alkenes.