Pharmacology: is the study of drugs and the action of drugs on living organisms.

Toxicology: is the branch of pharmacology that deals with the undesirable effects of chemicals on living systems.

Drug: is a natural product, chemical substance, or pharmaceutical preparation intended for administration to a human or animal to diagnose, prevent or treat a disease.

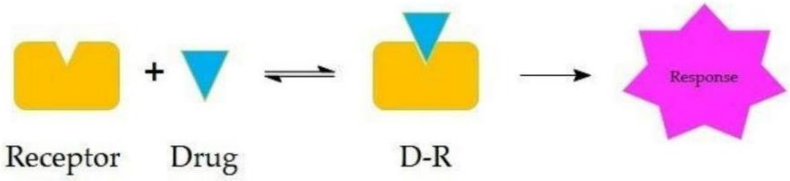
Drugs may be hormones, neurotransmitters, or peptides produced by the body; conversely a **xenobiotic** is a drug produced outside the body, either synthetic or natural.

Poison: is a drug that can kill.

Toxin: is a drug that can kill and is produced by a living organism (poisons of biologic origin, i.e., synthesized by plants or animals).

Receptors: Receptors are macromolecules (proteins) present either on the cell surface, cytoplasm or in the nucleus with which the drug binds and interacts to produce cellular changes.

Drug (D) + Receptor (R) ↔ Drug–receptor complex → Response



Formation of the drug-receptor complex is usually reversible and the proportion of the receptors occupied (and thus the response) is directly related to the concentration of the drug.

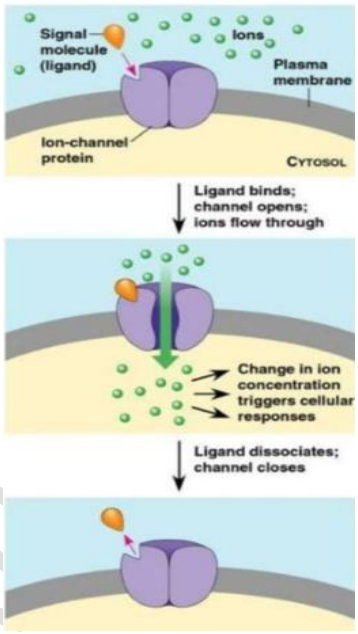
Ligands: molecules capable of ligating themselves to the receptor protein leading to a series of biochemical reactions inside the cell (signal transduction). Ligands are either exogenous compounds like drugs, or endogenous like neurotransmitters, hormones and growth factors.

It is important to know that not all drugs exert effects by interacting with a receptor. Antacids, for instance, chemically neutralize excess gastric acid, thereby reducing stomach upset.

Types and locations of receptors:

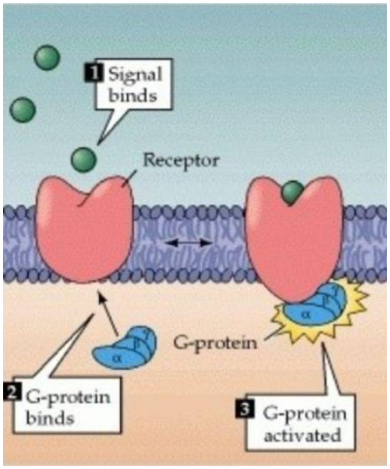
1. Transmembrane ligand-gated ion channels.
2. Transmembrane G protein–coupled receptors.
3. Enzyme-linked receptors.
4. Intracellular receptors.

1. **Transmembrane ligand-gated ion channels:**



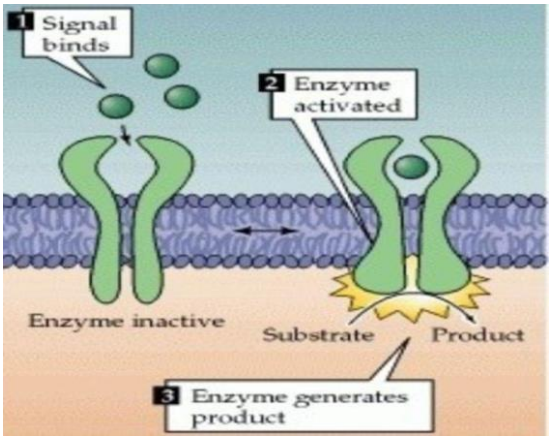
- Ionotropic receptors.
- The extracellular portion of ligand-gated ion channels contains the drug-binding site. This site regulates the opening of the pore through which ions can flow across cell membranes (like Na^{+}, K^{+}, Ca^{+2}, and/or Cl^{-}).
- The channel is usually closed until the receptor is activated by an agonist, which opens the channel for a few milliseconds.
- 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.
- Ion channels are located within the membrane of all excitable cells (like neurons and muscle cells).

2. Transmembrane G protein–coupled receptors:



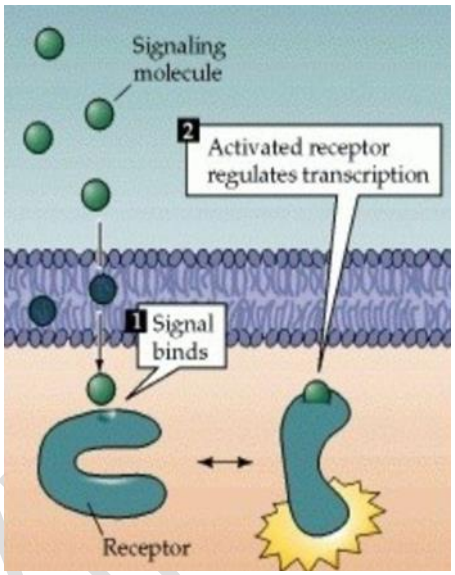
- Metabotropic receptors.
- The extracellular portion of this receptor contains the ligand-binding site.
- The intracellular portion interacts (when activated) with a G protein which then interacts with specific cellular effectors, usually an enzyme or an ion channel, that cause further actions within 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:



- These are receptors for insulin and other growth factors, which are directly linked to tyrosine kinase (an enzyme).
- They have large extracellular and intracellular domains.
- The extracellular domain is the binding site for hormone and the intracellular domain includes tyrosine kinase.
- The binding of hormone results in activation of tyrosine kinase.
- Tyrosine kinase then activates cellular enzymes, which in turn stimulate transcription of particular genes. This brings about the cellular response to the original hormone, for example growth factors.

4. Intracellular receptors:



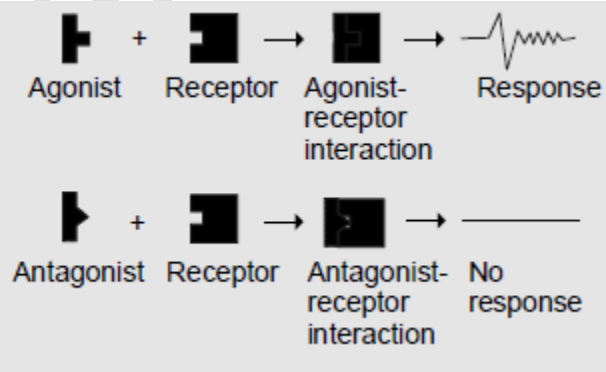
These are receptors for steroid hormones and thyroid hormone.

- They are located in the nucleus or the cytoplasm of the cell.
- The hormone first has to enter the cell. Steroid hormones and thyroid hormones pass easily across the cell membrane, as they are lipid soluble.
- Once the hormone binds to its receptor, the receptor is thought to unfold exposing a DNA-binding domain. The receptor molecule then binds to a particular region of DNA and activates certain genes. The result is increased protein synthesis that mediates the cellular response.

Agonist: A drug that is capable of producing pharmacological action after binding to the receptor.

Partial agonist: A drug that binds to the receptor but produces an effect less than that of an agonist.

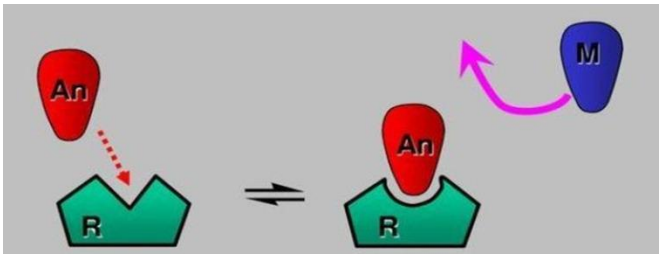
Antagonist: A drug that binds to receptors but is not capable of producing pharmacological action.



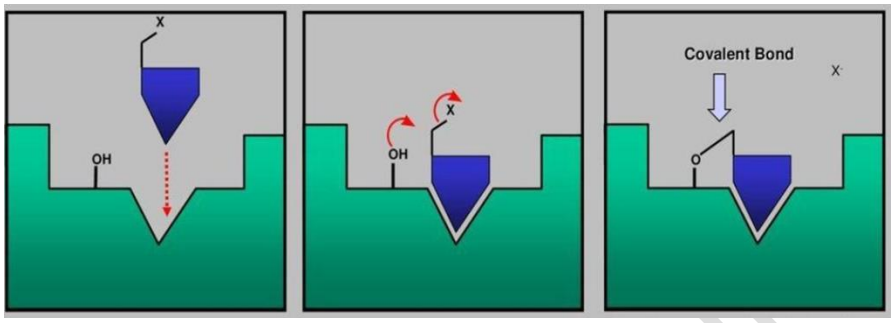
An antagonist has no effect on biological function in the absence of an agonist, but can decrease the effect of an agonist when present. Antagonism may occur either by blocking the drug's ability to bind to the receptor or by blocking its ability to activate the receptor.

Types of Antagonism:

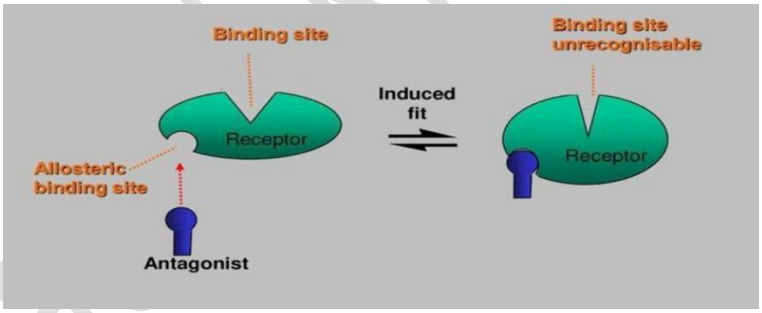
- **Competitive antagonism**: In competitive antagonism, both agonist and the antagonist bind reversibly to the same site on the receptor. This type of antagonism can be overcome (reversible) by increasing the concentration of agonist.



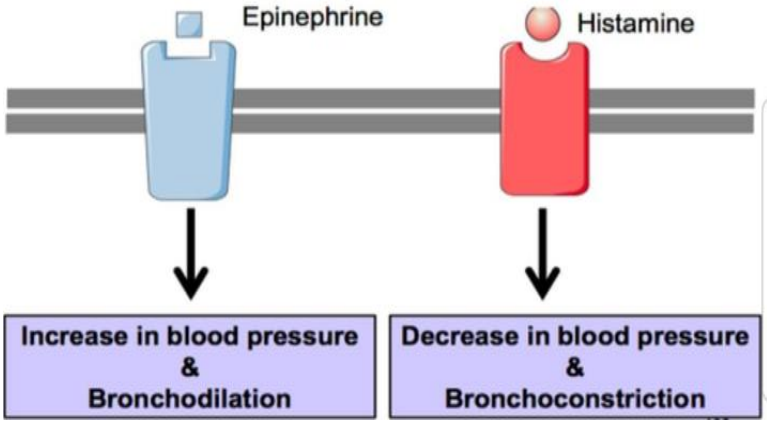
- **Noncompetitive antagonism**: could be
  - ✓ Irreversible antagonists: in which the antagonist binds covalently to the active site of the receptor, thereby permanently reducing the number of receptors available to the agonist. In contrast to competitive antagonists, addition of more agonist does not overcome the effect of irreversible antagonists.



  - ✓ Allosteric antagonists: An allosteric antagonist binds to a site (allosteric site) other than the agonist-binding site and prevents receptor activation by the agonist.



- **Physiological (functional) antagonism**: Here, two drugs act at different receptors or by different mechanisms on the same physiological system and produce opposite effects. For example, insulin and glucagon on blood sugar, adrenaline and histamine on bronchial smooth muscle—histamine produces bronchoconstriction (via histamine receptors), whereas adrenaline produces bronchodilatation by acting through adrenergic β_2 receptors—hence adrenaline helps to reverse bronchospasm in anaphylactic shock.

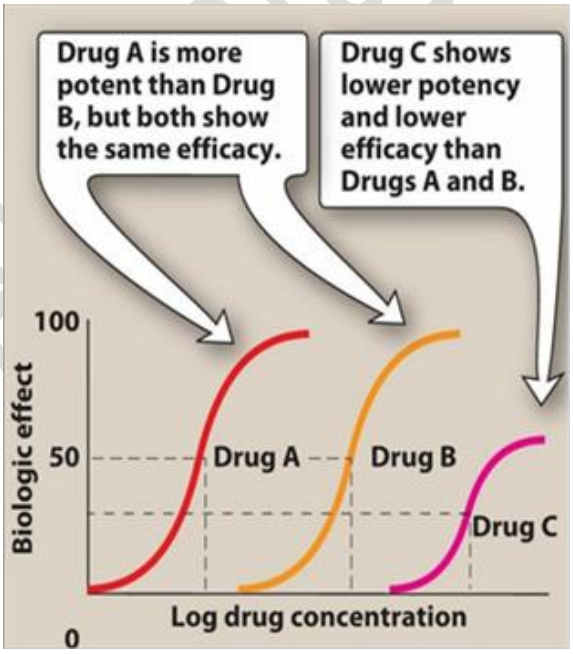


Relation Between Drug Dose and Clinical Response:

1/ Graded Dose–Response Relationships

The pharmacological effect of a drug depends on its concentration at the site of action, which, in turn, is determined by the dose of the drug administered. Such a relationship is called '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. Two important drug characteristics, potency and efficacy, can be determined by graded dose–response curves.

1. Potency: The amount of a drug required to produce a desired response is called the potency of the drug. The lower the dose required for a given response, the more potent is the drug. For example, the analgesic dose of morphine is 10 mg and that of pethidine is 100 mg. Therefore, morphine is ten times more potent than pethidine as an analgesic.



2. Efficacy: Efficacy is the magnitude of response a drug causes when it interacts with a receptor. Efficacy is dependent on the number of drug–receptor complexes formed and the intrinsic activity of the drug (its ability to activate the receptor and cause a cellular response). 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.

2/ Quantal Dose–Response Relationships: Another important dose–response relationship is that between the dose of the drug and the proportion of a population of patients that responds to it. These responses are known as quantal responses. Quantal dose–response curves are useful for determining doses to which most of the population responds. They have similar shapes as log dose–response curves, and the ED_{50} is the drug dose that causes a therapeutic response in half of the population.

Therapeutic index:

The therapeutic index (TI) of a drug is the ratio of the dose that produces toxicity in half the population (TD_{50}) to the dose that produces a clinically desired or effective response (ED_{50}) in half the population:

$$TI = TD_{50} / ED_{50}$$

The TI is a measure of a drug's safety, because a larger value indicates a wide margin between doses that are effective and doses that are toxic.

A. Warfarin (example of a drug with a small therapeutic index).
B. Penicillin (example of a drug with a large therapeutic index).