Pharmacodynamics

The purpose of the pharmacodynamics is to study the rules of drugs in the body and interpret their mechanisms of prevention and treatment.

Drugs can treat diseases just because they exert the periaqueductal gray stimulation and inhibitory action, resulting in adjustment and recovery of the balance which is destructed by the pathological factors.

II. Ways of the drug action

- **Direct action and indirect action**

In view of the order of the drug action; the direct action is defined as the primary action generated when the drug directly contacts tissues and organs. The indirect action is defined as the secondary action caused by the direct action of drugs. For example; digitalis affects the heart directly enhancing the myocardial contractile force, decreasing the heart rate, improving the cardiac function and blood circulation; the direct action results in the increasing of renal the blood flow; generating the diuretic effect, making Edema; induced by the congestive heart failure weakened or eliminated.

- **Local effect and the absorptive action**

The local action is defined as the direct action generated in the position where the drug is affected before it enters the blood. For example; procaine exerts local anesthesia in the part where it is given, losing the sensory function of the nerve ending. The absorptive action is defined as the general action after the drug enters the blood. For example; after the antipyretic analgesic enters the blood; it effects

on the body temperature regulating center; enhancing the body heat loss by the respiration; showing the effect of relieving fever and pain.

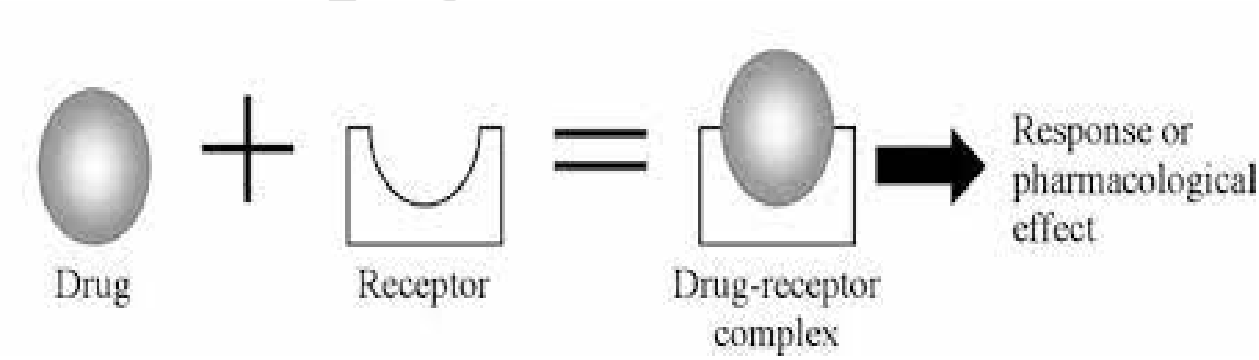
III. Selectivity of the drug action

When the majority of drugs are used at the proper dose; they only show the obvious effect on some tissues and organs having the little effect on other ones, even; we define the situation as the selectivity of the drug action.

IV. The therapeutic action and adverse effects of drugs

When we use drugs to prevent and treat diseases in the clinic; drugs may generate many pharmacological or physiological effects. Some effects are good for the health in the animals; which are defined as the therapeutic actions of drugs; other effects are bad for health; which are defined as adverse effects (including the side effects and toxic effects).

A drug receptor is a specialized target macromolecule that binds a drug and mediates its pharmacological action. The formation of the drug-receptor complex leads to a biological response.



Its important to know that not all drugs exert their effects by interacting with receptor:

●**Changing the physical and chemical conditions** for instance Antacid chemically neutralize excess gastric acid; thus reducing stomach upset.

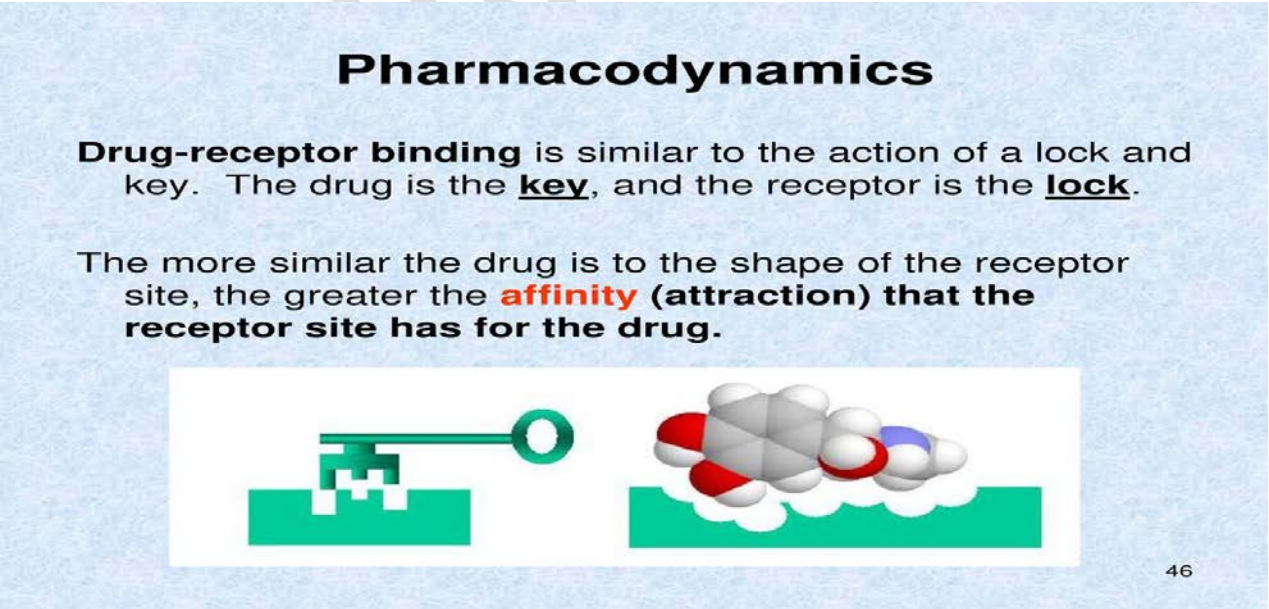
●**Affecting on the enzymes** for instance Phenobarbital induces liver microsomal enzyme.

● **Effecting on the ion channels** Some drugs can directly act on Na+, K+, Ca2+ channels on the cell membrane and produce pharmacological effects; for instance Procaine to block Na+ channels and have a role of local anesthesia.

●**Effecting on neurotransmitters or the active substance in the body** Any interference or block in the links of biosynthesis, storage, release or eliminate of neurotransmitters or auto-active substances in the body can induce significant pharmacological effects; for instance Ephedrine would promote the release of noradrenaline.

Lock and Key Theory:

Metaphor **Lock and Key** is a useful concept for understanding the interaction of receptors with their ligands.



The successful binding of a drug requires an exact fit of the ligand with the receptor. The theory presume that the drug must be able to show the role of receptor-binding; which is a combination of chemical that is through combination of a variety of chemical bonds and the receptor active groups .

This combination is consistent and it is reversible that is when the concentration of the drugs reduces or lower, its bands break, this time the role of the drug is to stop.

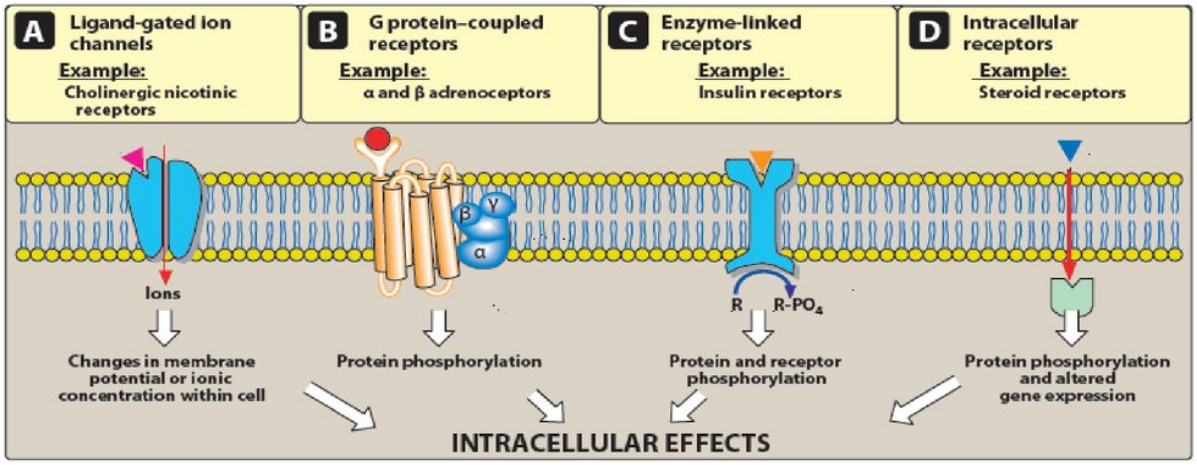
After the receptor-binding, receptor may be excited, also be blocked which mainly depends on the "intrinsic activity" of drugs, that is drugs could have a certain strength of the effect after receptor-binding which is known as agonists. If one drug with affinity of combination with receptor has no internal activity it does not only have a clear effect but also interfere with agonist or medium to exert effects because the receptor is taken up and sheltered by the drug such a drug is known as the antagonist.

Receptor Types:

Receptor can be defined as any biologic molecule to which a drug binds and produces a measurable response.

Receptor Types

➢ **Receptor types can be divided into four families (from A-D):**

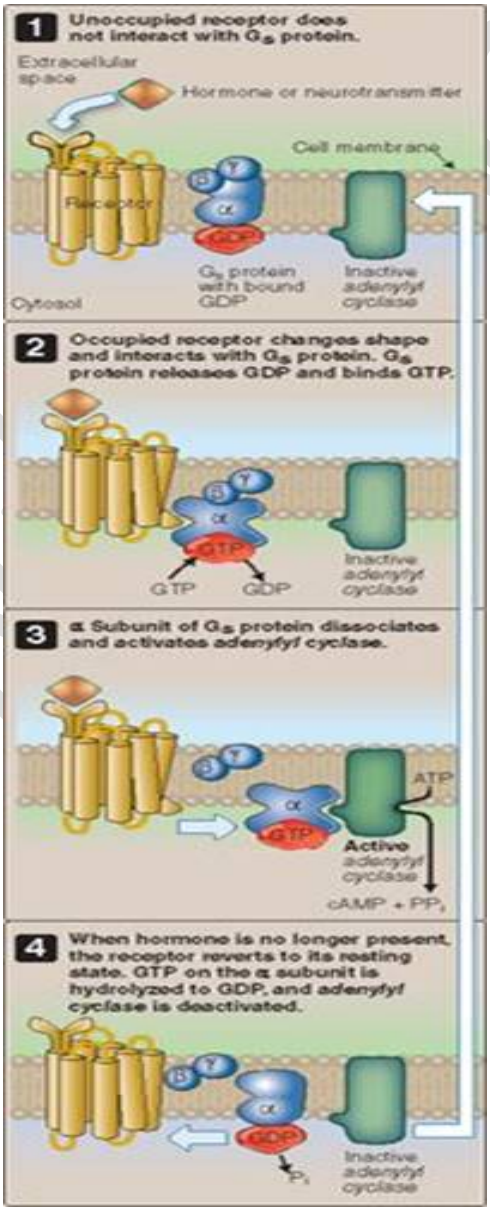


1. **Transmembrane ligand-gated ion channels:** The extracellular portion of ligand-gated ion channels contains the drug-binding site. This site regulates the opening of the pore through which ions can flow across cell membranes. The action usually last milliseconds.
2. **Transmembrane G protein-coupled receptors:** The extracellular portion of this receptor contains the ligand-binding site and the intracellular portion interacts (when activated) with a G protein. Binding to extracellular portion lead to intracellular portion become 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.

G protein coupled receptors (GPCRs) are integral membrane proteins **(that contain seven membrane-spanning helices)** are used by cells to convert extracellular signals into intracellular responses; including responses to hormones, neurotransmitters. The receptor is coupled with heterotrimeric G proteins on the intracellular side of the cell membrane. Heterotrimeric G proteins are important molecular switches in signal transduction pathways and consist of a trimer of three subunits: alpha (Gα), beta (Gβ), and gamma (Gγ).

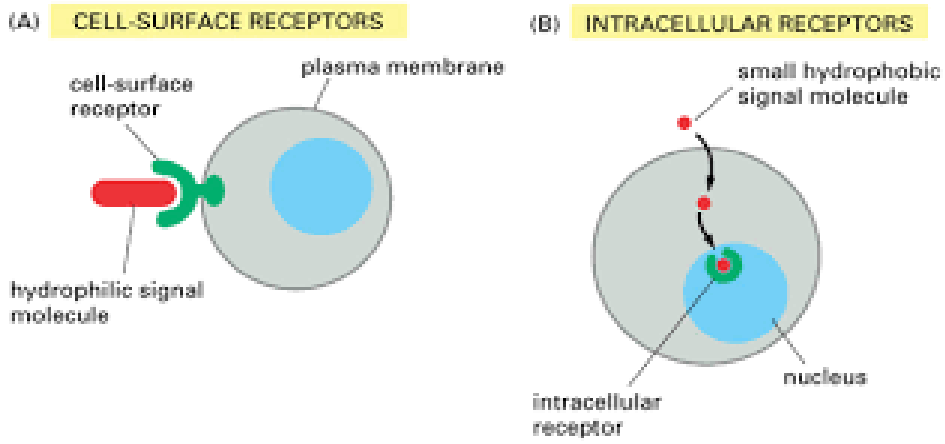


3. **Enzyme-linked receptors:** This family of receptors undergoes conformational changes when activated by a ligand resulting in increased intracellular enzyme activity. The most common enzyme-linked receptors are growth factors and insulin.

This response lasts for minutes to hours.

4. **Intracellular receptors:** The fourth family of receptors differs considerably from the other three in that the receptor is entirely intracellular therefore; the ligand (steroid hormones) must have sufficient lipid solubility to diffuse into the cell to interact with the receptor.

Activate intracellular receptors takes hours to days to occur.



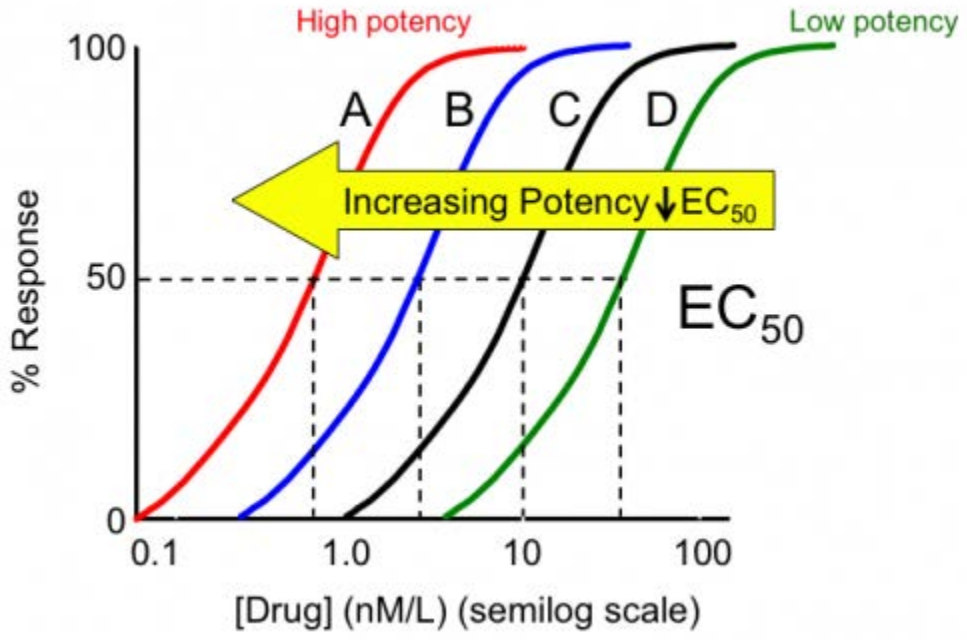
Spare receptors: A characteristic of many receptors; particularly those that respond to hormones, neurotransmitters and peptides is their ability to amplify signal duration and intensity. Only a fraction of the total receptors for a specific ligand may need to be occupied to elicit a maximal response for instance; about 99% of insulin receptors are "spare" providing an immense functional reserve that

ensures that adequate amounts of glucose enter the cell and 5% to 10% of the total β-adrenoceptors in the heart are spare.

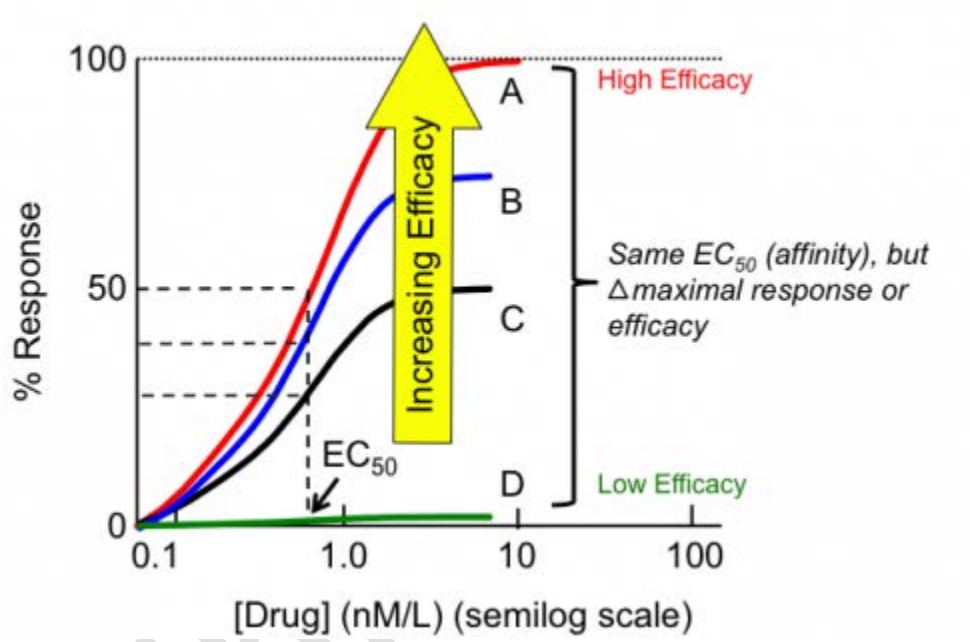
DOSE-RESPONSE RELATIONSHIPS

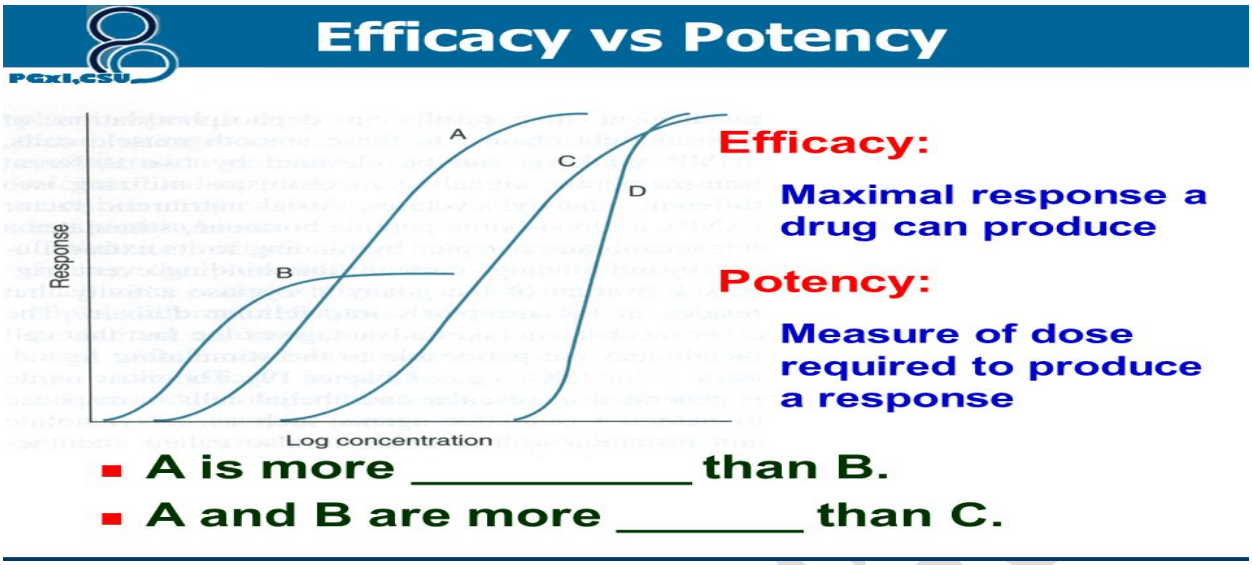
Agonist drugs mimic the action of the endogenous ligand for the receptor. As the concentration of a drug increases; its pharmacologic effect also gradually increases until all the receptors are occupied (**the maximum effect**).

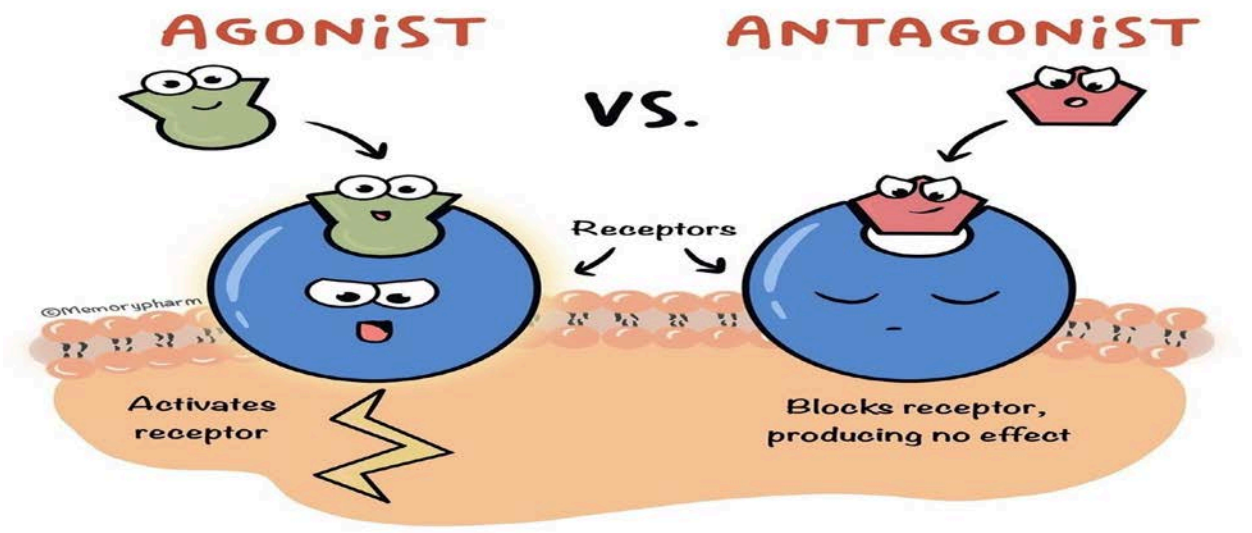
1. **Potency:** Potency is a measure of the amount of drug necessary to produce an effect. The concentration of drug producing 50% of the maximum effect (EC50) is often used to determine potency.



2. Efficacy: Efficacy is the magnitude of response a drug causes when it interacts with a receptor. 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.







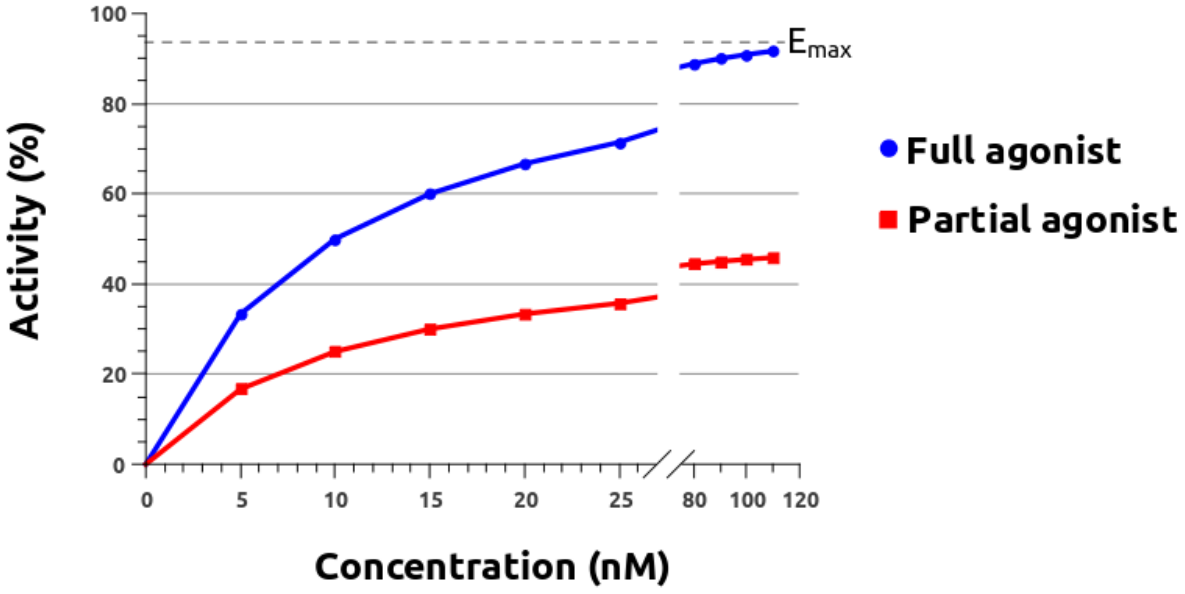
Full agonists

If a drug binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous ligand; it is a full agonist. All full agonists for a

receptor population should produce the same Emax· For example; phenylephrine is a full agonist at α1-adrenoceptors because it produces the same Emax as the endogenous ligand norepinephrine.

Partial agonists

Partial agonists have intrinsic activities greater than zero but less than one. Even when all the receptors are occupied; partial agonists cannot produce the same Emax as a full agonist.



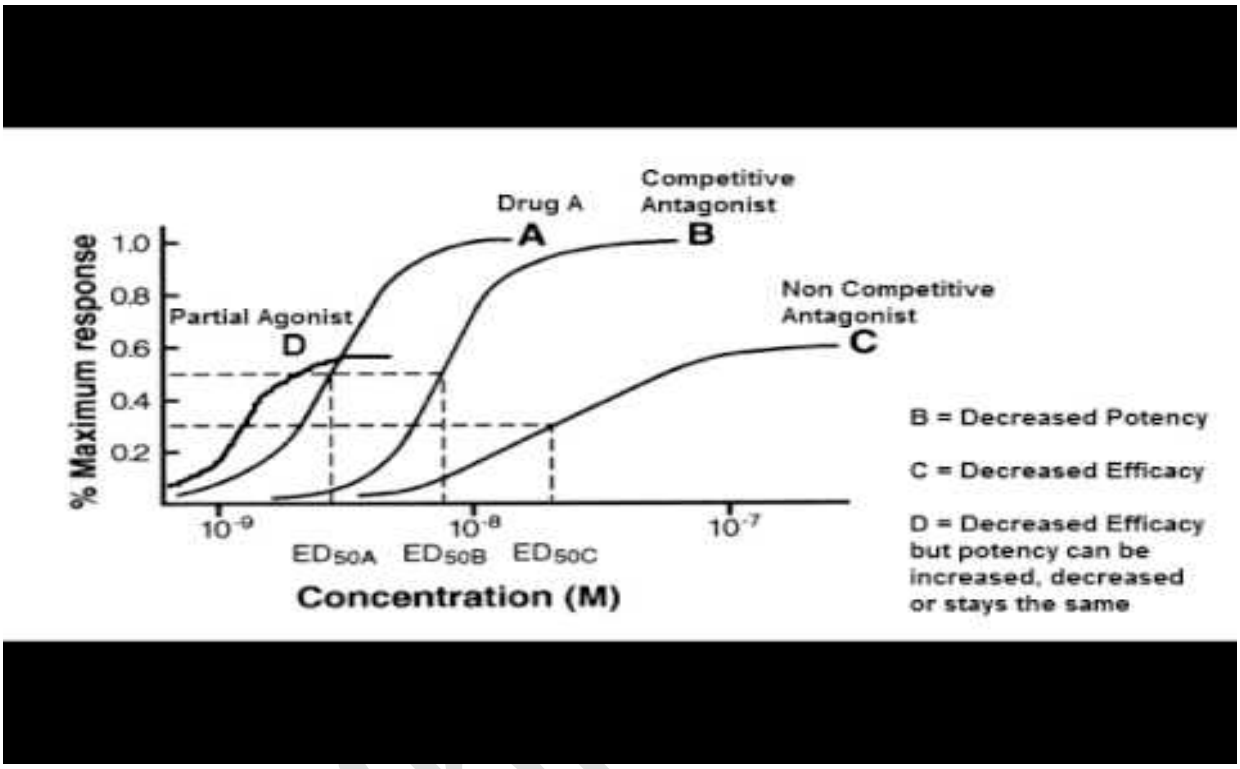
Antagonists

Antagonists bind to a receptor with high affinity but possess zero intrinsic activity. Antagonism may occur either by blocking the drug's ability to bind to the receptor or by blocking its ability to activate the receptor.

Competitive antagonists:

A competitive antagonist interferes with an agonist binding to its receptor and maintains the receptor in its inactive state.

However; increasing the concentration of agonist relative to antagonist can overcome this inhibition.



Irreversible antagonists:

Irreversible antagonists bind 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.

Functional 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 H1histamine receptors on bronchial smooth muscle; causing bronchoconstriction of the bronchial tree. Epinephrine is an agonist at β2-adrenoceptors on bronchial smooth muscle; causes muscles to relax. This functional antagonism is also known as "physiologic antagonism."

Therapeutic index

The therapeutic index (**TI**) of a drug is the ratio of the dose that produces toxicity lethality in half the population (**TD50** in human **or LD50** in animals) to the dose that produces a clinically desired or effective response (ED50) in half the population

Tl = TD50 or LD50/ ED50

The Tl 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 or lethal.

Penicillin (example of a drug with a large therapeutic index): It is safe and common to give doses in excess of that which is minimally required to achieve a desired response without the risk of adverse effects.