DOCTOR 2020 | JU

PHARMACOLOGY

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In the previous sheet, we have discussed about some terms and definitions related to pharmacology, and now we are going to continue these definitions.

- ✓ **Drug misuse**: It is the improper use of common medications in a way that lead to acute and chronic toxicity, It means that people don't use the drugs for its intended purposes, for example; antacid, vitamins as well as **"laxative"** that is a drug that is used for increasing the frequency of evacuation in cases of constipation, but some people use it for losing weight, So that is a misuse of that drug.

- ✓ **Drug abuse:** usually referred to drugs that causes addiction, and these drugs are used to relieve the pain such as **morphine**, so when people continually or periodically have these drugs even when it is not needed, it causes drug abuse!

- ✓ **Pharmacotherapeutics:** it is the use of drugs for the prevention and treatment of a disease, it is related to the study of choosing the appropriate drug for each particular patient.

- ✓ **Chemotherapeutics**: It is the use of drugs to stop the growth or kill microorganisms (like antibiotics and antiviral drugs) or that kill cancer cells.

- ✓ **Pharmacogenomics:** The relation between the individual's genetic makeup to his/her response to specific drugs (**entire genome**).

- ✓ **Pharmacogenetics:** There are several drugs that are affected by certain genes in our body, so due to the genetic variation among individuals, the metabolic mechanism for drugs will be different. Some people have high metabolic rate while others don't and subsequently, not all people will need the same dose of drug, That is what pharmacogenetics does! It studies how this specific gene affect the drug, accordingly the dose that is needed for this individual depending on the presence of Mutations or polymorphism in this gene. (**Specific gene**)

- There is no need to differentiate between Pharmacogenomics and Pharmacogenetics as both terms are used interchangeably.

- ✓ **Idiosyncratic drug response:** unusual response, infrequently observed in most patients, usually caused by **genetic differences in metabolism of drug** or **by immunologic mechanisms including allergic reactions** (unusual side effect).

- ✓ **Tolerance:** It is s a decrease in the responsiveness to the drug with continued drug administration, occurs when the drug is used repeatedly and the body adapts to the continued presence of the drug, So the body will need larger amounts to get the same effect. However, this doesn't apply for all drugs as we will discuss later on.

- ✓ **Tachyphylaxis:** Similar to tolerance but more rapid.

There are several procedures that should be done before a drug can be used on humans, it starts by doing experiments in the lab by cell culturing, then studying this drugs on animals. These experiments take years and years before the drug can be proved to be safe to use on humans. Still, there are four phases of **clinical investigation** that should be done.

Phase I The drug is given for healthy volunteers (men) between the age of 18 and 45, the purpose of this phase is to study the dose level at which signs of toxicity first appear (the optimal dose of the drug that doesn't cause toxicity) This phase is done on a small number of individuals (between 20-100 subjects).	**Phase II** This is the first experiment on real patients, drugs are given to larger group [100-300] to confirm effectiveness, monitor side effects & further evaluate safety.
Phase III The main difference between phase 2&3 is that we increase the number of subjects [1,000-3,000] & Compare the new drug to commonly used drugs that are already approved to be safe. After phase 3 the drug can be released to the market, but researches must continue on the effectiveness of the drug, and this is phase IV.	**Phase IV** After new drug has been marketed, studies continue to test and to collect data about effects in various populations & side effects from long term use.

NOTE: phase I can't be applied to all drugs, some drugs have serious side effects like cancer drugs, while we can try mild drugs like painkillers that tend to be relatively safe.

These phases are summarized further in the tables below.

	# Subs.	Length	Purpose	% Drugs Successfully Tested
Phase I	20 – 100	Several months	Mainly Safety	70%
Phase II	Up to several 100	Several months- 2 yrs.	Short term safety; mainly effectiveness	33%
Phase III	100s – several 1000	1-4 yrs.	Safety, dosage & effectiveness	25-30%

TABLE 1.1 Phases of Clinical Investigation

Phase	Purpose
I	Establish safety
II	Establish efficacy and dose
III	Verify efficacy and detect adverse affects
IV	Obtain additional data following approval

Area of pharmacology

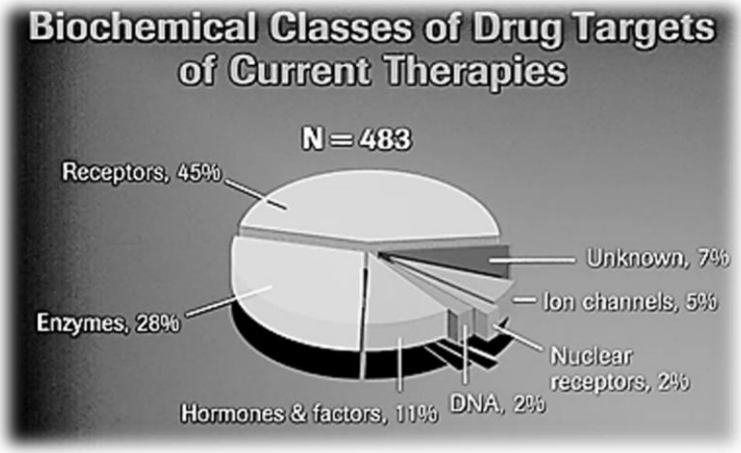
There are two areas of pharmacology,

1. **Pharmacokinetics:** it is the movement of the drug in the body and how the body deals with this drug starting from absorption to distribution, metabolism (biotransformation) and finally excretion.

2. **Pharmacodynamics**: It is what the drug does to the body, which includes the biochemical and physiological effects of the drug, including the mechanism of action, interaction with receptors as well as the adverse (side) effects.

❖So how do drugs work?

By studying pharmacodynamics, drugs work by interacting with **endogenous proteins** (mostly enzymes). Some drugs antagonize, block or inhibit certain enzymes and some drugs activate them. However, there are few drugs that have unconventional mechanisms of action, so they don't interact with proteins.
There are many targets for current therapy that drugs interact with, such as receptors, enzymes, and ion channels, as shown in this figure.



Some targets of the drugs are unknown until now. Recall that penicillin has been used since 1940 to treat patients, but the mechanism of action stayed unknown till 20 years later. Although these drugs targets are known, but we use them in clinic because they have been found to be beneficial for patients long time ago, and there is no better alternatives for them.

Side note: due to the development of molecular techniques, scientists could discover new receptors that exist in our body, but we still don't know the function of them. These receptors are called "***orphan receptors***".

Mechanism of drug action

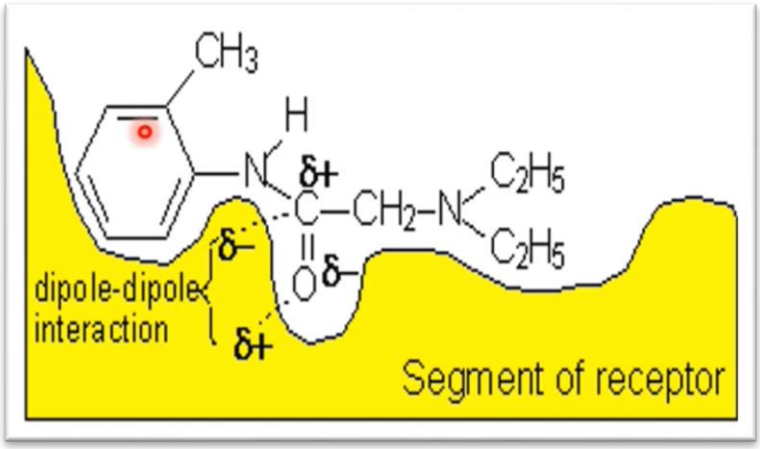
Most drugs exert their effect by interacting with specialized target macromolecules, called **receptors**, that are present **on the cell surface or intracellularly**.

The function of the receptor is to transduce signal from outside of the cell to the inside by activation of certain signal cascade that will give physiological effect.

Why are receptors the major group of drug targets?

Receptors are large macromolecules with a well-defined 3D shape, this allows us to have specificity with which ligand can bind to them. There are two fundamental properties of receptors underlying specificity in drug-receptor interactions:

1. Complementarity of **shape** and **chemical structure** between drug and receptor.
2. Complementarity between the **electrostatic**, **hydrophobic** and **hydrogen bonding** surfaces of each component.



Receptors are proteins, and proteins get further post-translation modification which gives the proteins more specificity to the ligand.

- **HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?**

Recall that there are many targets for drugs such as cell surface receptors, intracellular receptors (nuclear receptors), enzymes, etc. so, to inhibit endogenous proteins, drugs could be antagonists of cell surface receptors, antagonists of nuclear receptors, enzyme Inhibitors and so on.

Remember: Antagonist is a substance that acts against and blocks an action. Antagonist is the opposite of agonist.

Other important properties of the receptors are (3**S**: **S**pecificity, **S**electivity, **S**ensitivity)

Selectivity of the receptor, which means that there are different receptors in the body like alpha and beta adrenergic receptors, these subcategories allows us to synthesize drugs that targets one receptor but not the other. So drugs are **selective** to activate or inhibit certain type of receptor.

Sensitivity: one molecule of drug can bind to a receptor and then, the signal is amplified to make a huge physiological response. For example, when adrenaline binds to the adrenergic receptor and activates G-protein coupled receptor which will activate adenylyl cyclase to produce more cAMP which help in cell signaling. One molecule of adrenaline will give you about 100 of cAMP, so the signal is amplified through a cascade of reactions, that's what sensitivity means.

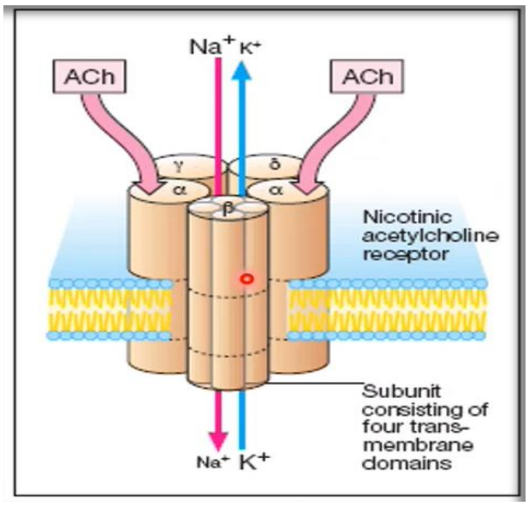
Major receptor families

- **Ligand-gated ion channels**
- **G protein-coupled receptors**
- **Enzyme-linked receptors**
- **Intracellular receptors**

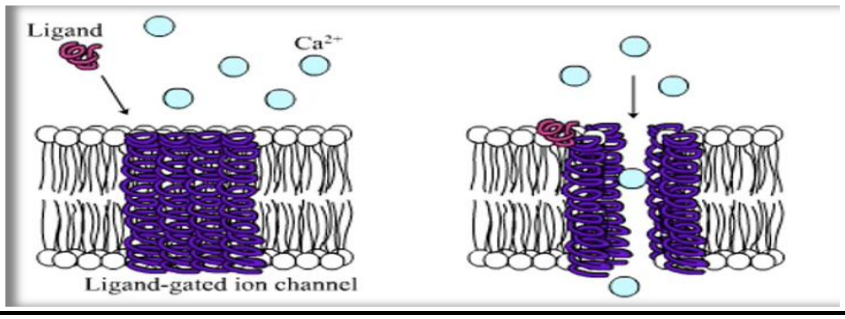
1. Ligand-gated ion channels

Responsible for regulation of the flow of ions across cell membranes and it is regulated by binding of the ligand to the channels.
The best example being, **the nicotinic receptor**, in which the binding of the acetylcholine results in sodium influx and the activation of contraction of skeletal muscle.

Muscle relaxants are group of drugs that act as nicotinic antagonists that bind to the nicotinic receptors and block the binding of acetylcholine to it, causing relaxation of the skeletal muscles (not because of the binding of the antagonist, but due to the inhibition of the binding of acetylcholine)



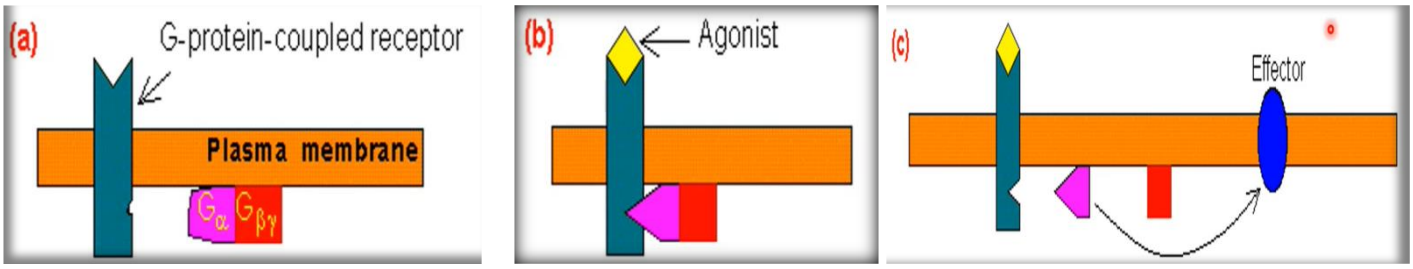
Muscle relaxants don't do a new action rather than preventing acetylcholine from doing its action.



One group of muscle relaxants called **Tubocurarine**, is used a lot in surgical procedures. Muscles need to be relaxed during surgeries to easy up the process of intubation, this indicates how important antagonists are.

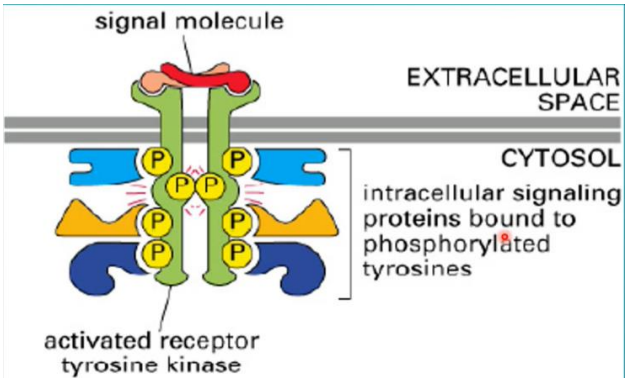
2. G protein-coupled receptors

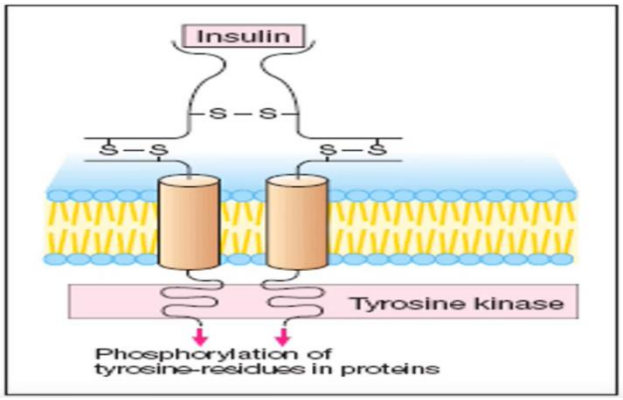
Receptors on the inner face of the plasma membrane regulate or facilitate effector proteins through a group of guanosine triphosphate (GTP) proteins known as **G proteins**, these receptors may be **hormones peptide receptors and neurotransmitter receptors** (e.g. adrenergic and muscarinic receptors depend on the G proteins) mediate their action on cells. The importance of these receptors like adrenergic and muscarinic receptors is best illustrated in the autonomic nervous system that they regulate most body functions and treat many conditions.



3. Enzyme-linked receptors

Receptor that has an intracellular domain that is attached to an enzyme. The most common are the receptors that have a tyrosine kinase activity as part of their intracellular structure, in which the binding results in the phosphorylation of tyrosine residues of specific protein. The addition of phosphate group can modify the three-dimensional structure of the target protein, and so resulting in molecular switch.

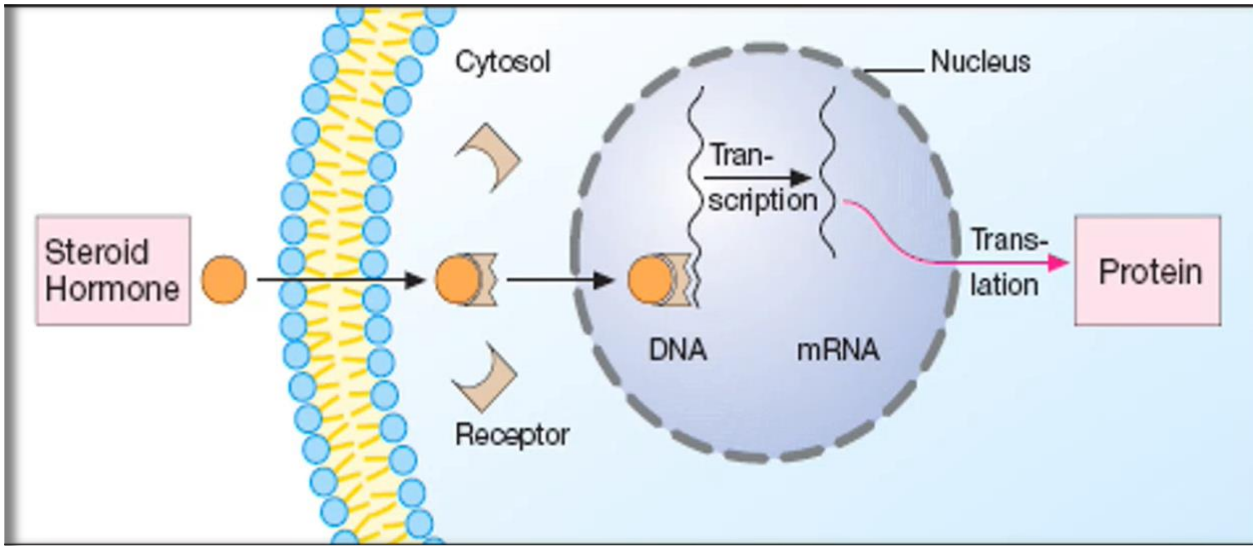




An example of tyrosine enzyme-linked receptors is **insulin receptors,** when insulin binds, phosphorylation of tyrosine residues happens and the receptor gets activated, then the linked enzyme will phosphorylate other molecules which induces changes in the cell, like **translocation of glucose transporters to the cell surface**, **so glucose can enter the cell**.

4. Intracellular receptors (nuclear receptors)

In this family the ligand must be hydrophobic (lipid soluble) to diffuse into the cell to interact with cytoplasmic receptors. After the formation of drug-receptor complex, this complex will move to the nucleus and bind the DNA and modulate the expression of certain genes, **steroid hormones** are examples of lipid soluble ligands.



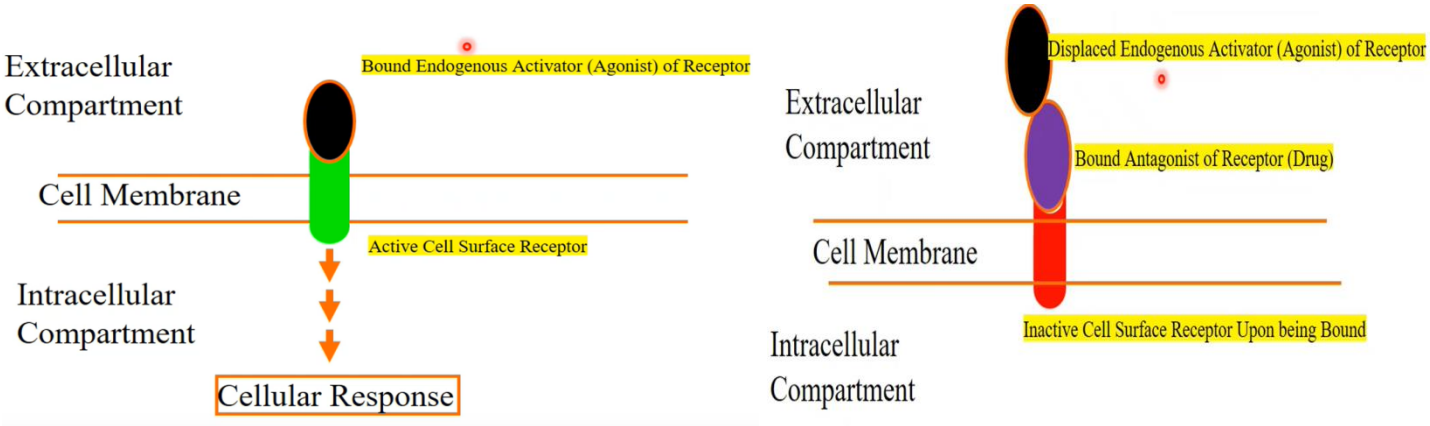
Steroid hormones due to their hydrophobic structure can diffuse through plasma membrane and interact with intracellular receptors, and then the complex will move to the DNA and activate or inhibit gene expression.

- HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?

Cell surface receptors exist to transmit chemical signals from the outside to the inside of the cell. However, some compounds bind to cell surface receptors, yet do not activate the receptors to trigger a response.

When cell surface receptors bind these compounds, the endogenous chemical (normal ligand for this receptor) cannot bind to the receptor and cannot trigger a response. **In this case the compound is said to "antagonize" or "block" the receptor and is referred to as a receptor antagonist.**

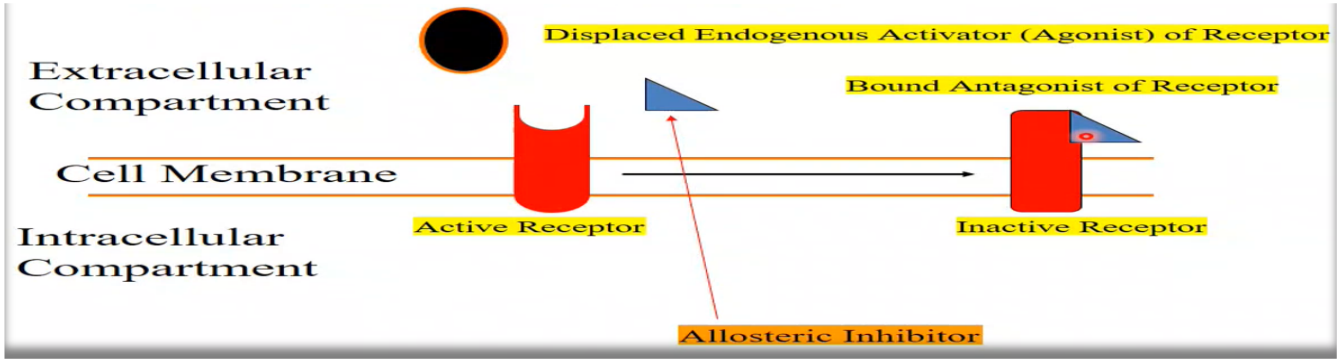
The receptor will not be activated until the normal ligand (black) binds to it, once this **endogenous compound** binds to it, it will be activated and turn on cascades of cell signaling which causes cellular response, but when an **antagonist** (purple) binds to the receptor it occupies the binding site of the ligand, so **it prevents the activation of the receptor by displacing the endogenous activator.**



Most antagonists attach to binding site on receptor for endogenous agonist and prevent endogenous agonist from binding.

- ✓ If binding is **reversible** - **Competitive antagonists**
- ✓ If binding is **irreversible** - **Noncompetitive antagonists**

However, antagonists may bind to another remote site on receptor and cause **allosteric effects** that displace endogenous agonist or prevent endogenous agonist from activating receptor are known as (**Noncompetitive allosteric antagonists**).



In this case the antagonist doesn't fit in the same site of the ligand, but it can cause conformational changes in the receptor thus inhibiting the binding of any ligands. (**Noncompetitive inhibition**).

To sum up: If the ligand and the antagonist bind to different sites, it is considered **noncompetitive allosteric antagonism**. If the ligand and the antagonist bind to the same site and it is **reversible**, it is considered **competitive antagonism**. If the binding on the same site is **irreversible** it is considered **noncompetitive antagonism**.

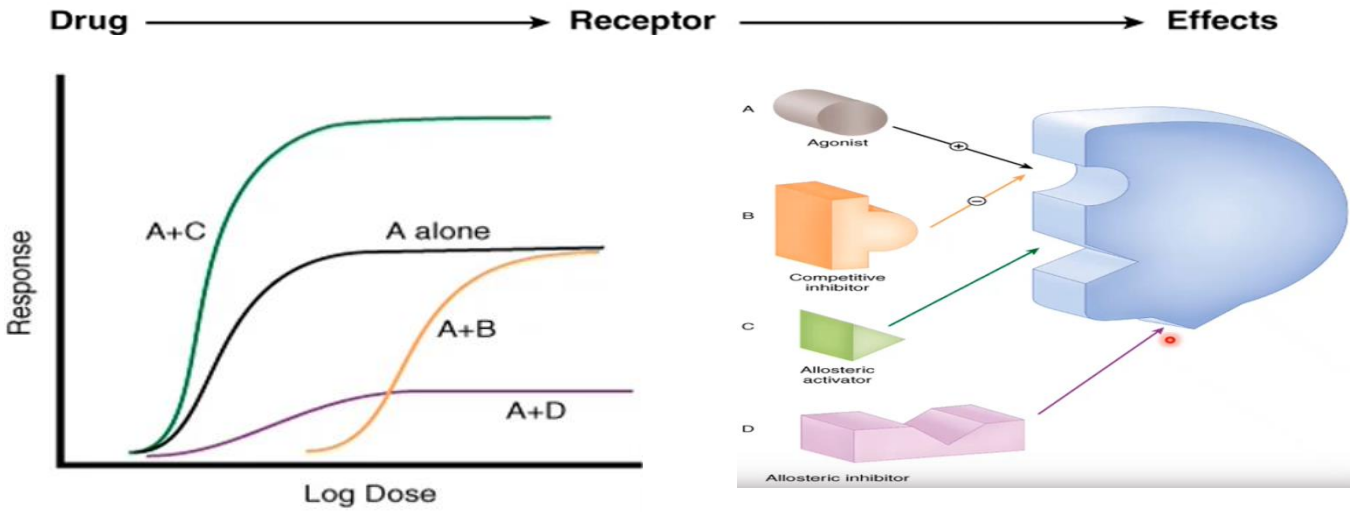
- Most drugs act in a reversible manner (bind for milliseconds and leave).
- Allosteric inhibition could be reversible or irreversible but it is always noncompetitive.
- Even irreversible drugs will leave the body eventually but it will take hours or even days to go out the body by other mechanisms of action.

❖ Some important examples of antagonists;

- **Angiotensin** is a peptide that has a receptor on the surface of the cell (example : endothelial cells), so normally when it binds, it will cause contraction of the blood vessels and increase the blood pressure. **So, in cases of high blood pressure**, **heart failure, chronic renal insufficiency:** patients will be given **Angiotensin Receptor Blockers (ARBs)**, like losartan, valsartan to decrease these symptoms.

- Beta adrenergic receptors when bound to **adrenaline**, it gets activated, and the heart muscle will contract. **So, in cases of angina, myocardial infraction, heart failure, high blood pressure, anxiety**, patients will be given **Beta-adrenoceptors Blockers** to decrease these issues.

The figures below show how the endogenous agonist and the competitive inhibitor are similar in shape, different binding sites for allosteric activator and inhibitor and show the effect of binding of each one (will be discussed later).



The End