Pharmacodynamics

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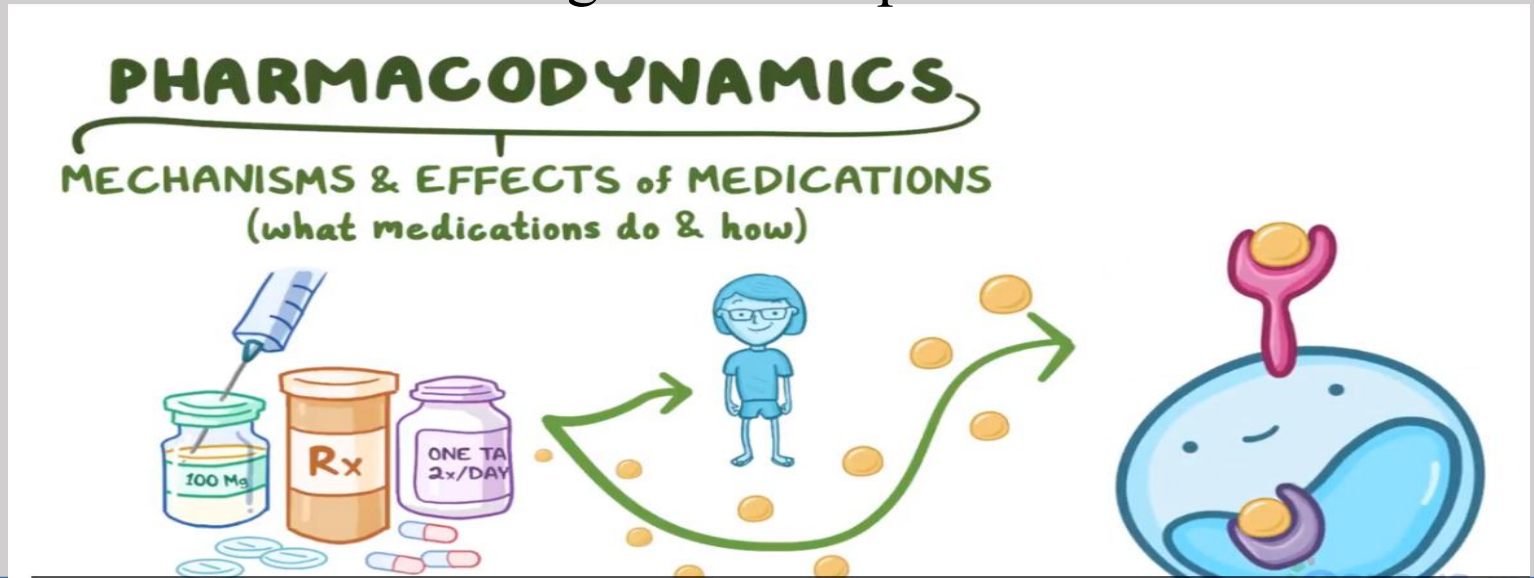
Pharmacodynamics

- Pharmacodynamics refers to the mechanisms and effects of medications within the body. Or more simply, it’s what medications do to the body and how they do it.
- Pharmacodynamics (sometimes described as what a drug does to the body) is the study of the biochemical, physiologic, and molecular effects of drugs on the body and involves receptor binding (including receptor sensitivity), postreceptor effects, and chemical interactions. Pharmacodynamics, with pharmacokinetics (what the body does to a drug, or the fate of a drug within the body), helps explain the relationship between the dose and response, (the drug's effects). The pharmacologic response depends on the drug binding to its target. The concentration of the drug at the receptor site influences the drug’s effect.



What is Pharmacodynamics

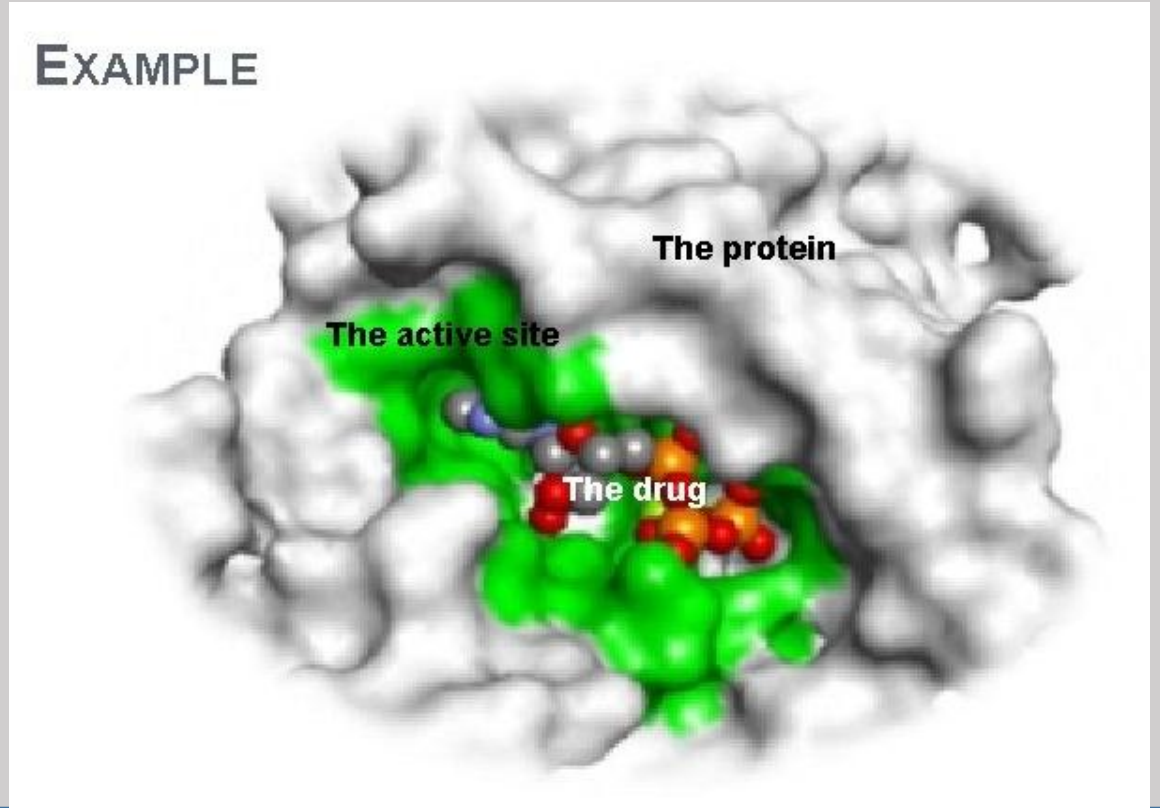
Pharmacodynamics: the study of the relationship between drug concentration in the body, and the physiological response to that concentration of drug

Two key principles:

- The dose of the drug is directly linked to the magnitude of the body's response to that drug
- Drugs act through receptors

RECEPTOR-DRUG INTERACTION

- Receptors are mostly membrane-bound proteins that selectively bind small molecules called ligands which results in physiological response. They are difficult to isolate because they exist in tiny amount and if isolated it will be difficult to purify.



MECHANISMS OF DRUG ACTION

1. Physical action
- Physical mass- bulk laxatives
- Osmotic property- mannitol
- Radioactivity

2. Chemical action
- Acidity or alkalanity- aluminium hydroxide, sodium bicarbonate

3. Through enzymatic mechanisms
- Enzyme stimulation
- Enzyme inhibition

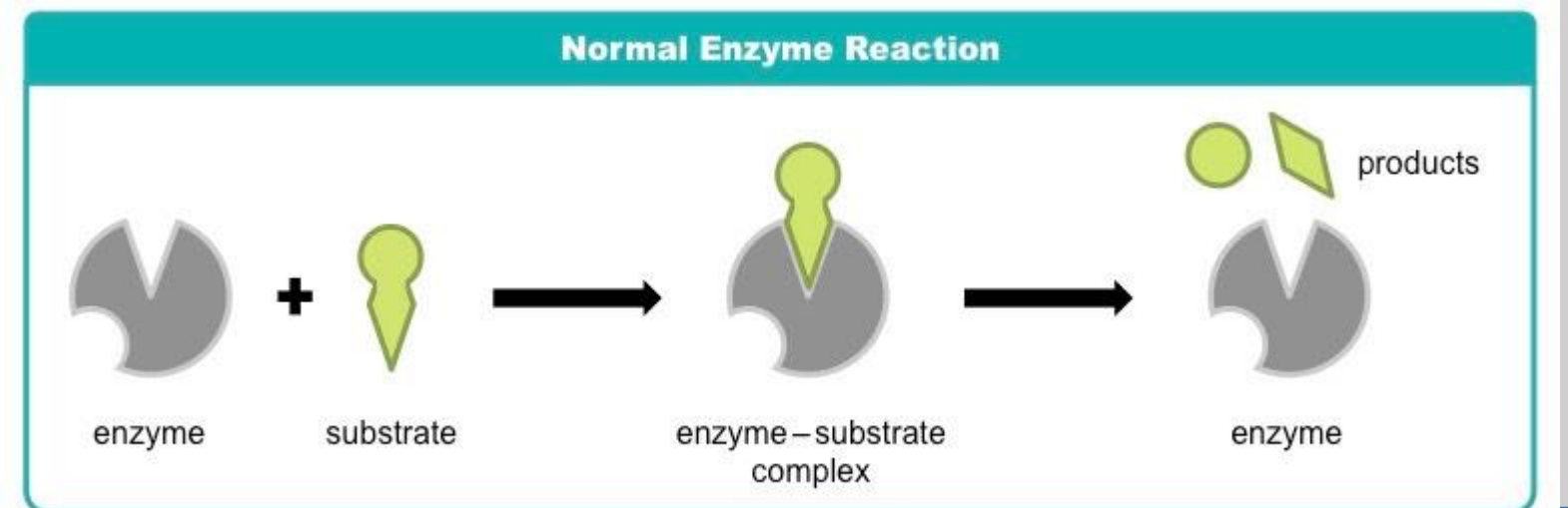
4. Through receptors

Enzyme induction

- Enzyme induction refers to an increase in the rate of hepatic metabolism, mediated by increased transcription of mRNA encoding the genes for drug-metabolizing enzymes.
- This leads to a decrease in the concentrations of drugs metabolized by the same enzyme.
- Rifampicin is a potent inducer of CYP3A4 and can result in clinically significant decreases in plasma concentrations of many concomitant medications.

Enzyme inhibitor

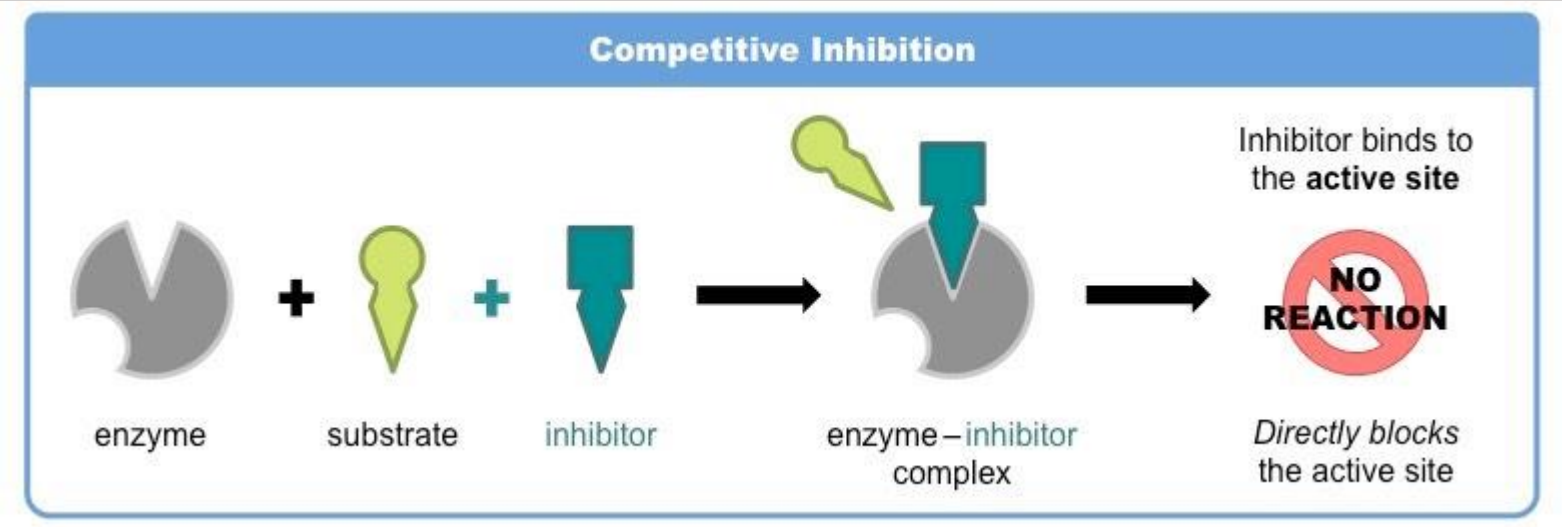
- An **enzyme inhibitor** is a molecule that binds to an enzyme and decreases its activity.
- By binding to enzymes' active sites, inhibitors reduce the compatibility of substrate and enzyme and this leads to the inhibition of Enzyme-Substrate complexes' formation, preventing the catalysis of reactions and decreasing (at times to zero) the amount of product produced by a reaction.
- Enzyme inhibitors can be either competitive or non-competitive depending on their mechanism of action.



Types of Enzyme inhibitor

1. Competitive Inhibition

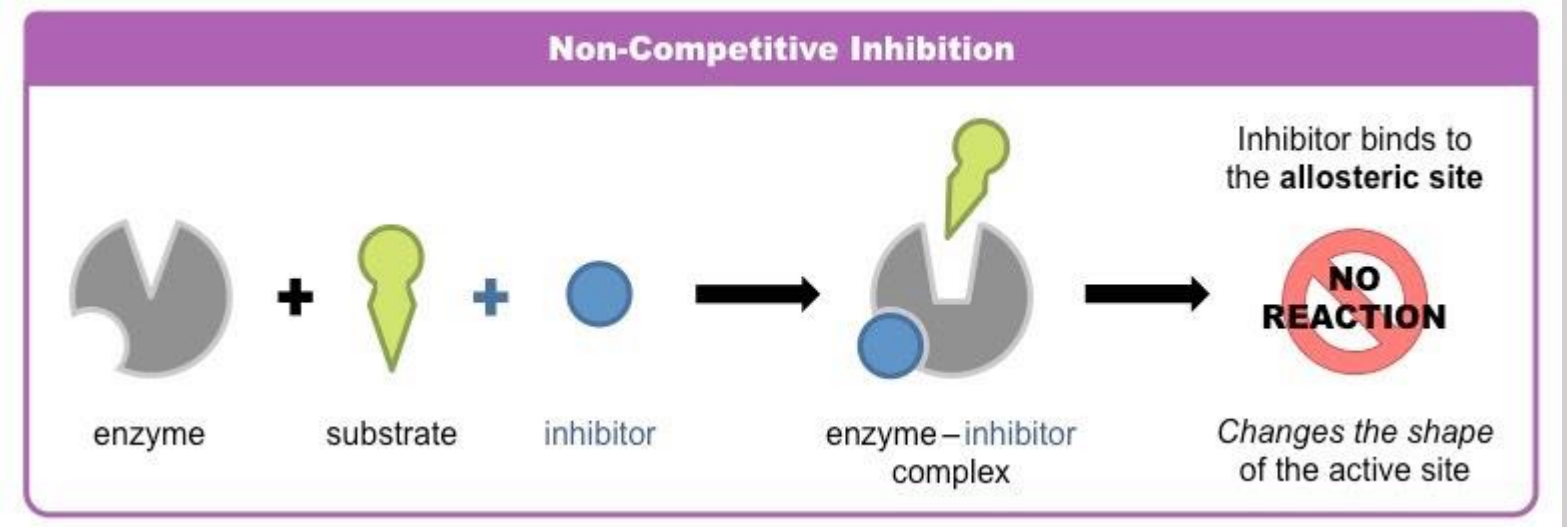
- Competitive inhibition involves a molecule, other than the substrate, binding to the enzyme's *active site*
- The molecule (inhibitor) is structurally and chemically similar to the substrate (hence able to bind to the active site)
- The competitive inhibitor blocks the active site and thus prevents substrate binding
- As the inhibitor is in competition with the substrate, its effects can be reduced by increasing substrate concentration



Types of Enzyme inhibitor

2. Noncompetitive Inhibition

- Non-competitive inhibition involves a molecule binding to a site other than the active site (an *allosteric site*)
- The binding of the inhibitor to the allosteric site causes a conformational change to the enzyme's active site
- As a result of this change, the active site and substrate no longer share specificity, meaning the substrate cannot bind
- As the inhibitor is **not** in direct competition with the substrate, increasing substrate levels cannot mitigate the inhibitor's effect



Pharmacodynamics / Receptors

- Receptors : Sensing elements in the system of chemical communication that co-ordinate the function of all the different cells in the body.
- Receptors are macromolecules involved in chemical signaling between and within cells; they may be located on the cell surface membrane or within the cytoplasm.
- Most medications have to reach their target cells and bind to a receptor.
- Receptors are specialized proteins both on the **cell membrane** and **inside the cell**, that can bind to a ligand and get triggered to alter their shape or activity.

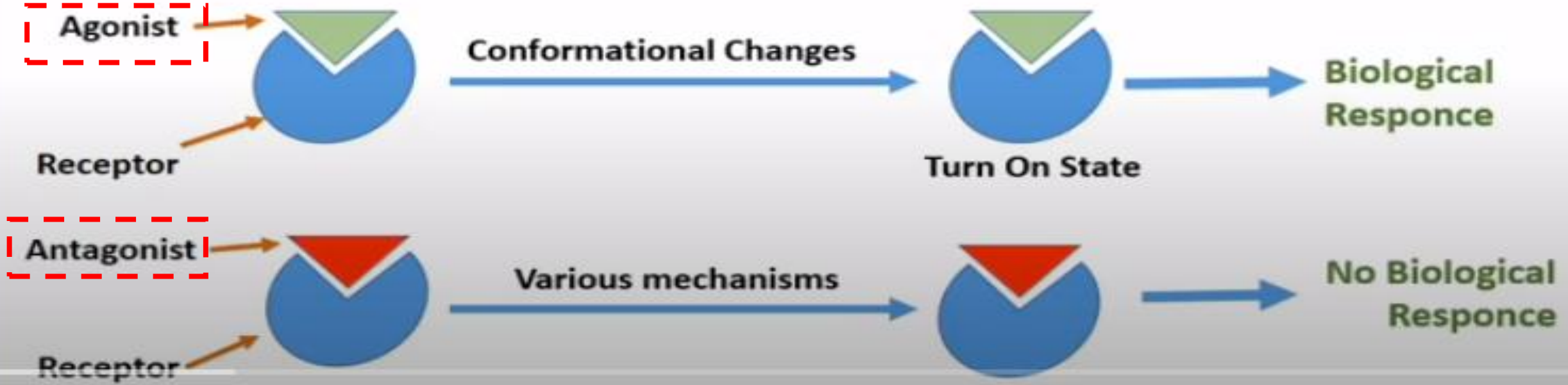
- **Function of receptors :**

- To propagate regulatory signal from outside & within effective cell
- To amplify the signal
- To integrate various extra cellular & intracellular regulatory signalling To adapt to short & long term changes in regulatory system
- To maintain homeostasis

Pharmacodynamics / Receptors

responsible for biological activities. When any signalling molecules (ligand Molecules) binds with these receptors, the receptors, they produces some conformational changes in receptors. These changes turns any receptor in "TURN ON" or "TURN OFF" condition. These conditions are responsible for progression or suppression of any biological process.

These ligands can be exogenous (drug / Chemical) or endogenous (biological molecules or hormones).

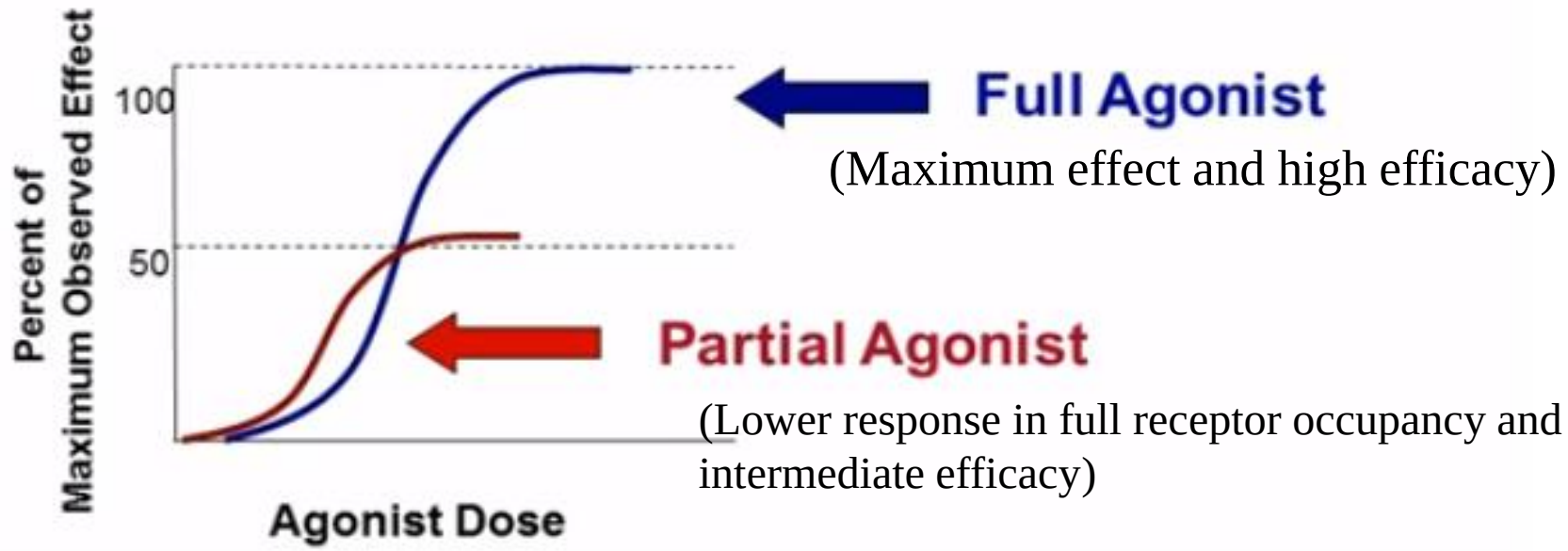


Agonists

Agonists: initiate changes in cell function through their actions at receptors

Potency: range of doses over which a chemical produces increasing responses

- **Affinity:** tendency to bind to receptors
- **Efficacy:** ability to initiate changes once bound



(Maximum effect and high efficacy)

(Lower response in full receptor occupancy and intermediate efficacy)

Types of agonist- Full Agonist

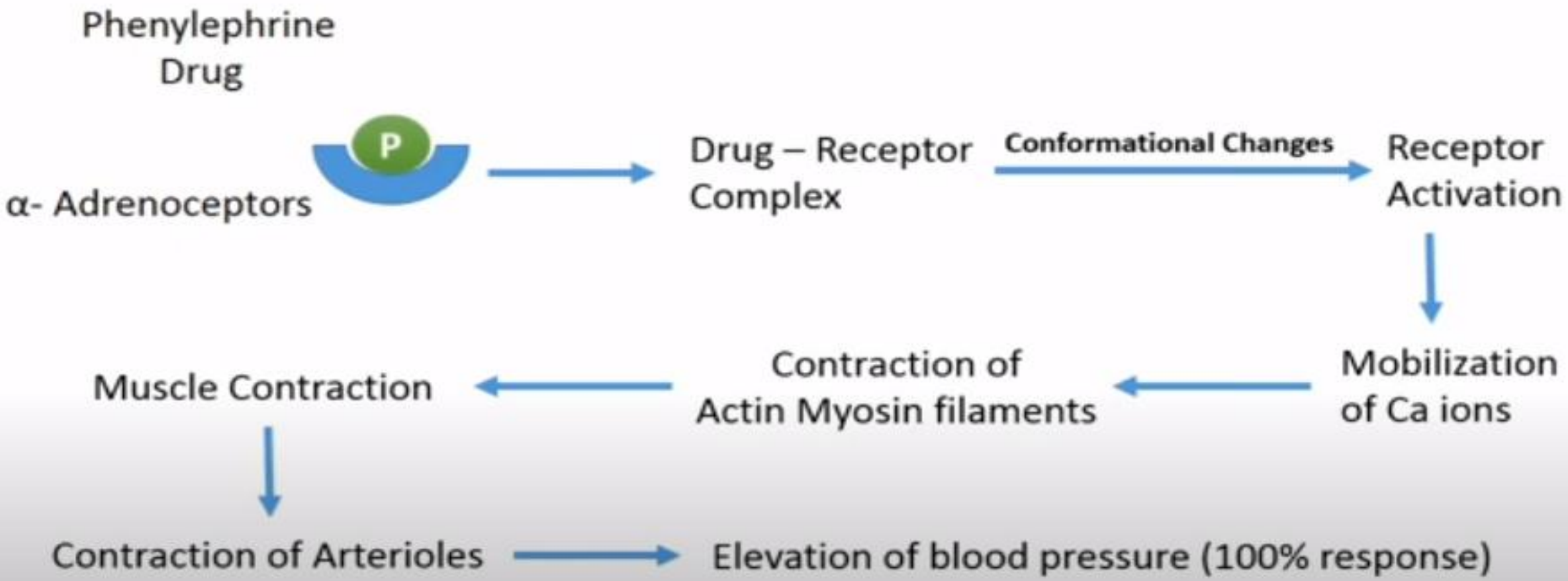
Agonist are of many types, as:

FULL AGONIST-

When a drug binds to a receptor and produces the similar maximum effect as the endogenous ligand (natural agonist) generates. Then the drug turned as full agonist.

The receptors are in active or in inactive state and these states interchanged together reversibly. When a agonist drug binds with inactive receptor, it converts the receptor state from Inactive to active, and also keep the receptor stabilize in this condition. Until the receptor is in active form it shows its biological response.

Full agonist example



Same effect generated by endogenous(biological) ligand Norepinephrine

Types of agonist- Partial Agonist

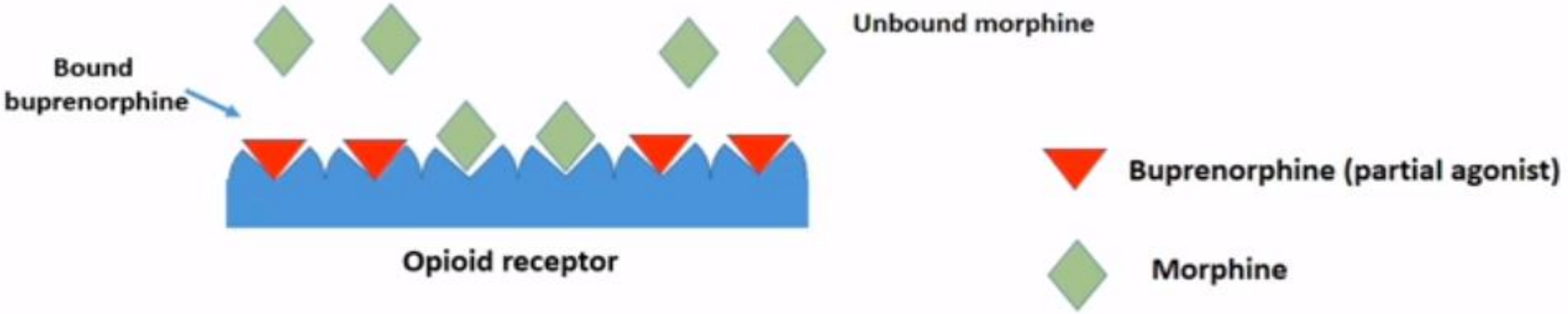
PARTIAL AGONIST

Partial agonist activate the receptor, but not upto that extent comparable to full agonist. The activation of partial agonist is lesser than the full agonist.

Partial agonist reduces the action of full agonists. Partial agonist can occupy or binds with some receptors, so that few or reduced number of receptors become available for binding with full agonist. Due to reduced binding of full agonist to the receptor, biological response gets reduced accordingly.

Sometime full agonist generates overstimulation partial agonist use to reduce over response generated by agonists.

Partial agonist example



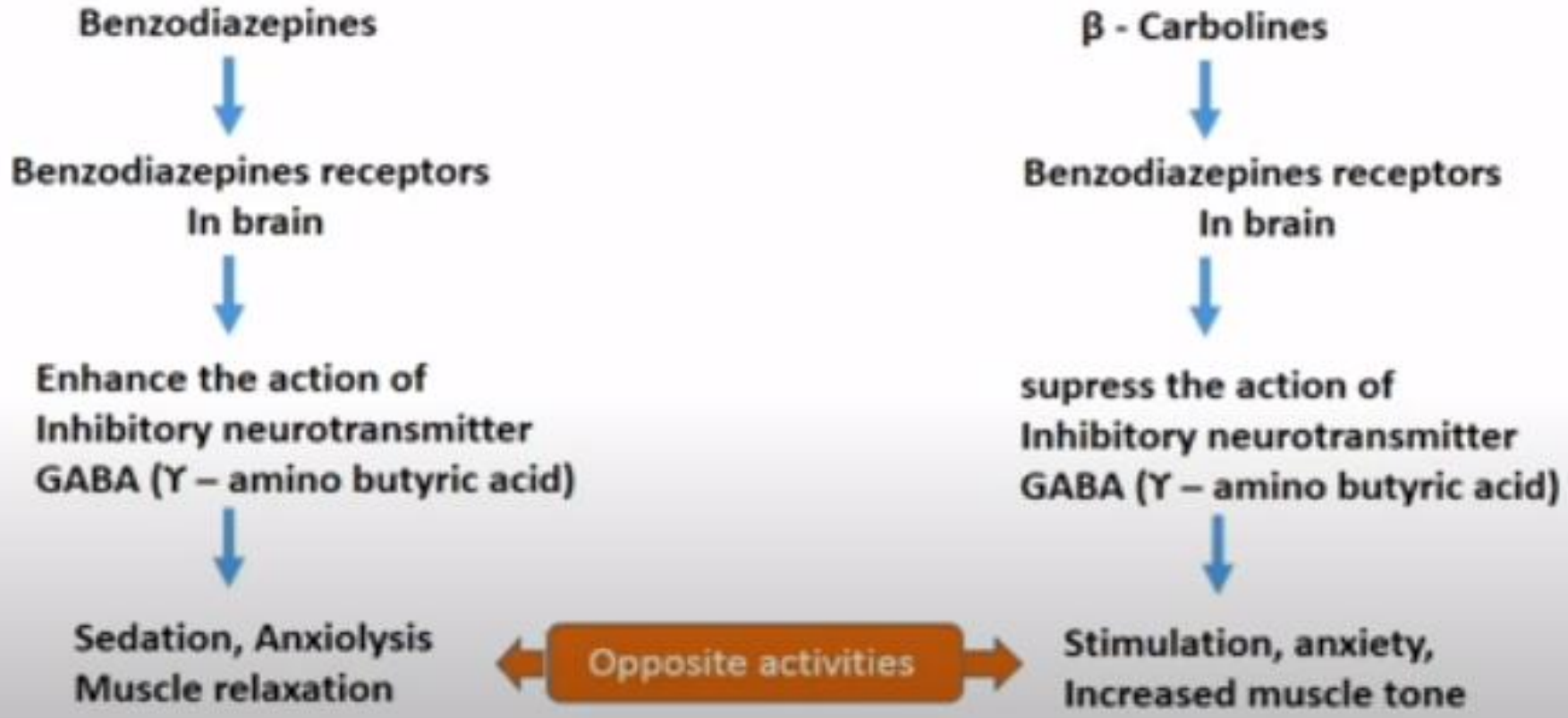
Due to reduced number of receptor bound morphine, the effect of morphine gets reduced

Another example of partial agonist is Aripiprazol, which has affinity to bind on dopamine Receptors. Aripiprazol is partial agonist against dopamine. This drug binds with dopamine receptors and blocks the binding of dopamine to receptor and helps to improve in shizophrania.

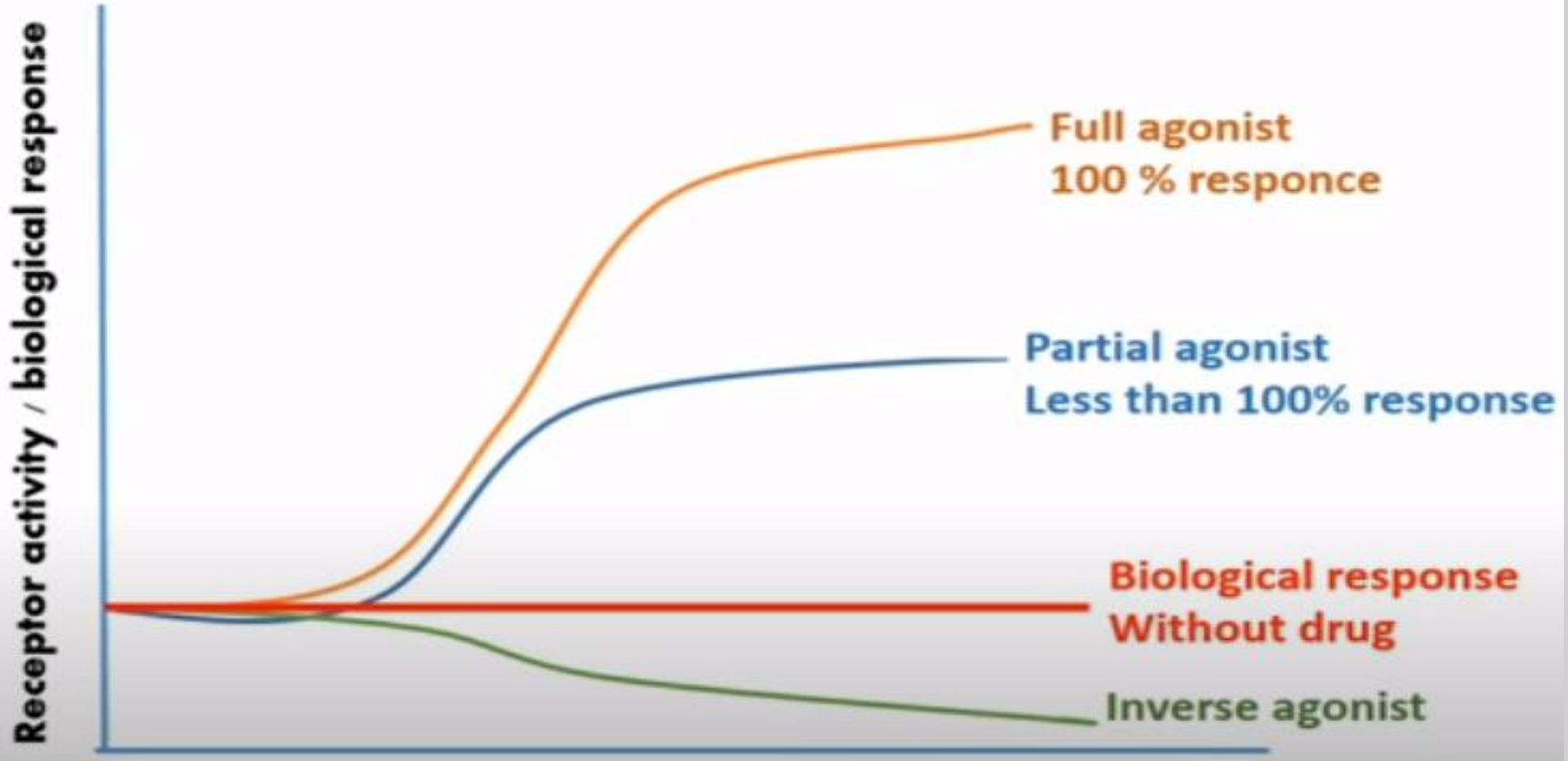
Types of agonist- Inverse Agonist

INVERSE AGONIST

Some substances produces effects, that are specifically opposite of the agonist action.



Biological responses with different types of agonist



ANTAGONIST

- Antagonist drugs interfere in the natural operation of receptor proteins.
- They are sometimes called **blockers**; examples include alpha blockers, beta blockers, and calcium channel blockers.

- In pharmacology, **antagonists** have affinity but no efficacy for their cognate receptors, and binding will disrupt the interaction and inhibit the function of an agonist or inverse agonist at receptors.

- Antagonists mediate their effects by binding to the active site or to the allosteric site on a receptor, or they may interact at unique binding sites not normally involved in the biological regulation of the receptor's activity.

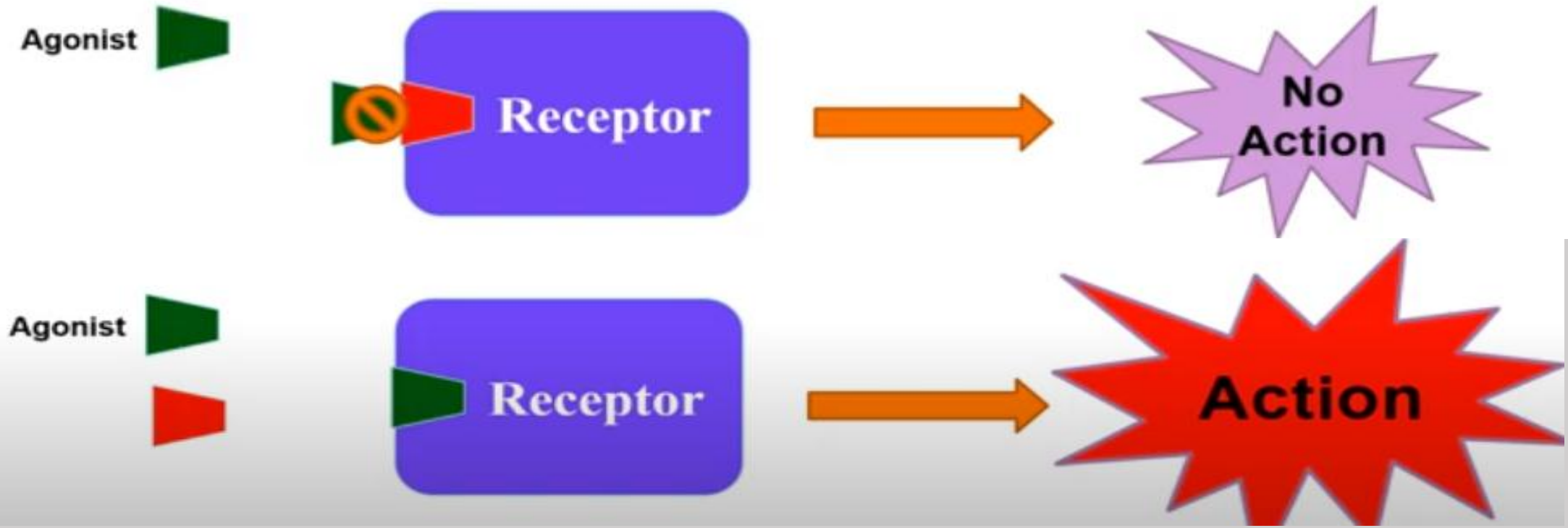
Types of antagonists

- Competitive antagonist
- Irreversible antagonist
- Functional antagonist
- Chemical antagonist

Competitive / Reversible antagonism

Competitive / Reversible antagonism

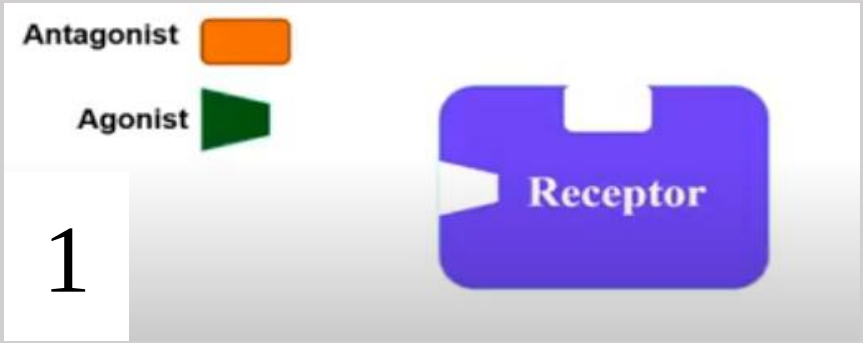
- Agonist and antagonist compete for the same receptor.
- An antagonist bind with receptor thereby preventing the agonist from binding and initiating a response.
- It is reversible. It is totally dependent on the concentration of agonist and antagonist.
- Antagonist can be replaced by agonist, if agonist is in more concentration.
- Eg.- Acetylcholine and atropine

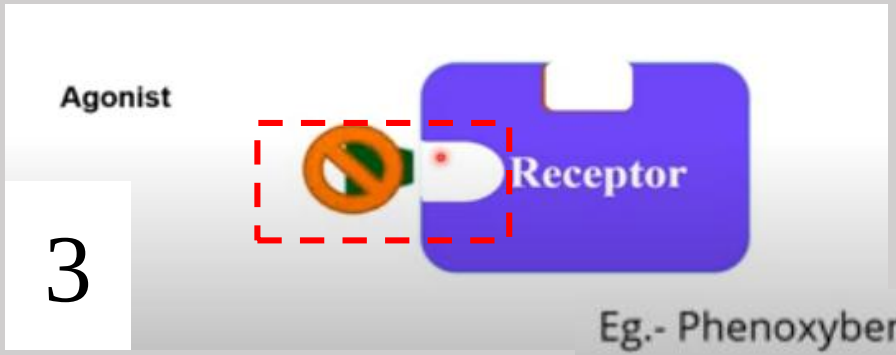


Non competitive / irreversible antagonism

Non-competitive / Irreversible antagonism

- In this type, agonist and antagonist bind with different binding sites of the same receptor.
- Since binding sites are different, there is no competition for binding with receptor.
- Antagonist bind with receptor and changes the structure of receptor.
- As a result, agonist can not bind with receptor.





Eg.- Phenoxybenzamine and nor-adrenaline

Physiological antagonism

Physiological antagonism

- In this type, agonist and antagonist bind with different receptors of the same physiological system and produce opposite effects.

- Eg.- Adrenaline binds with adrenergic receptor and produce bronchodilation
  Histamine binds with histaminic receptor and produce bronchoconstriction
  If both drugs are given together, they cancel actions of each other

Chemical Antagonism

Chemical antagonism

- It is observed when two drugs are given together, they react with each other and produce inactive product.
- Eg.- Acid and alkali if given in combination, they neutralizes each other.

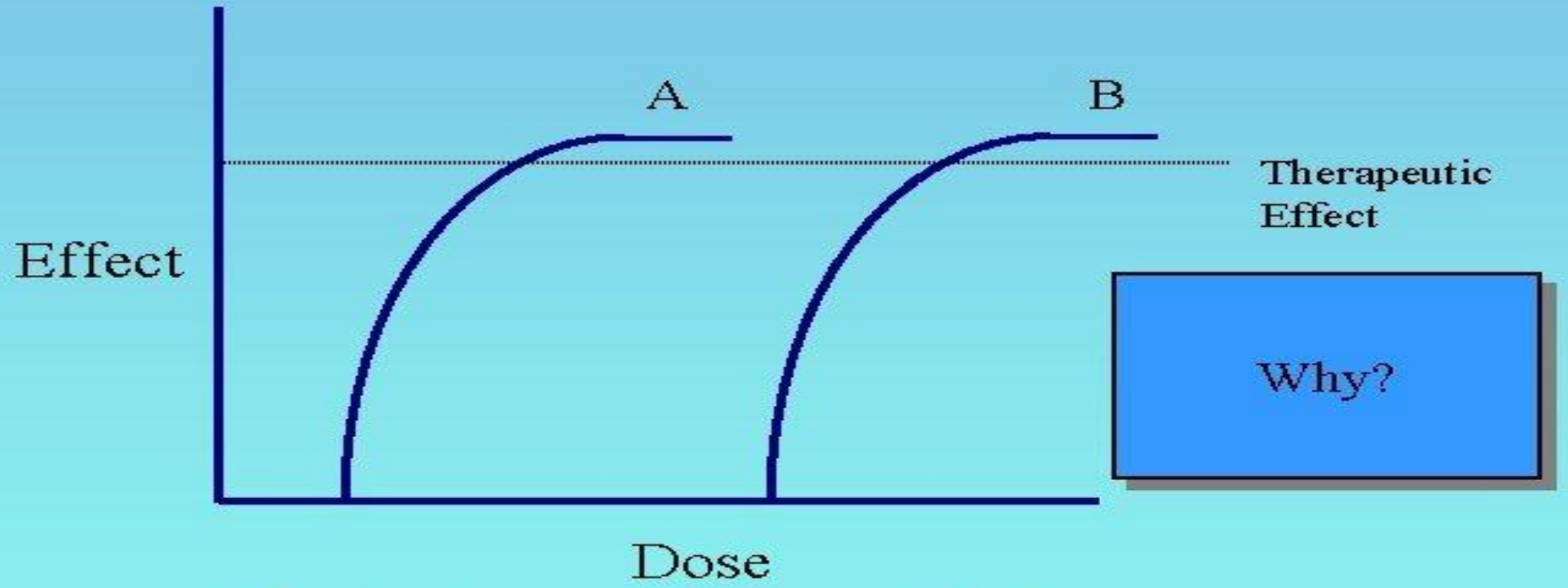
Affinity, Efficacy and Potency

- **Affinity** - the ability of a drug to get bound to a receptor. how strongly the drug binds to the receptor; depends on the molecular complementarily of drug and receptor.

- **Efficacy or intrinsic activity** - Drug efficacy maximal response that can be elicited by the drug or the ability of the drug to elicit a pharmacological response after its interaction with its receptor. A compound with high affinity does not necessarily have high efficacy (e. g. antagonists).

- **Potency**: the amount of drug needed to achieve a defined biological effect and produce a certain response . The smaller dose required, the more potent the drug. It is possible to have potent drugs with low efficacy. **Potency depends in** part on the affinity of the receptor for binding the drug, and in part on the efficiency with which the drug-receptor interactions is coupled to response.

Potency



Which drug is more potent?

- **Therapeutic Index (TI) = Margin of Safety:**

$$TI = \frac{LD50}{ED50}$$

- **LD50** = lethal dose to 50% of the population in animal experiments.
- **ED50** = the effective dose in 50% of animals.

- The higher the TI, the safer the drug e.g. barbiturate (TI=10)

- The lower the TI, the greater the possibility of toxicity e.g. digitalis (TI=3), so death may occur if only 3mg has been administered because the usual therapeutic dose of cardiac glycoside is one mg.

RECEPTOR TYPES OR FAMILIES

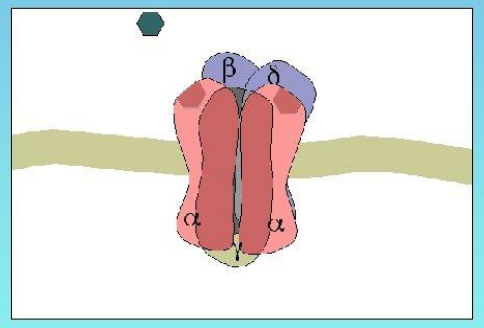
1.Channel linked or ionotropic

2. G-protein coupled

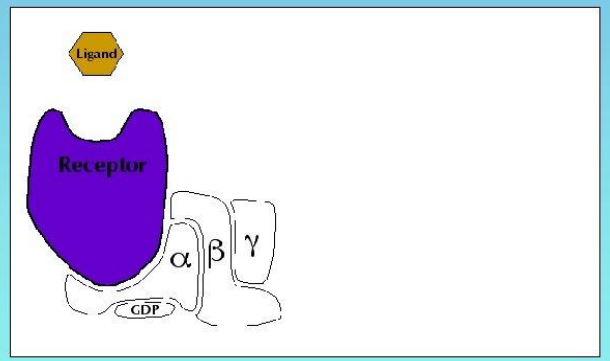
3. Enzymatic or kinase linked

4. Receptors regulating gene expression

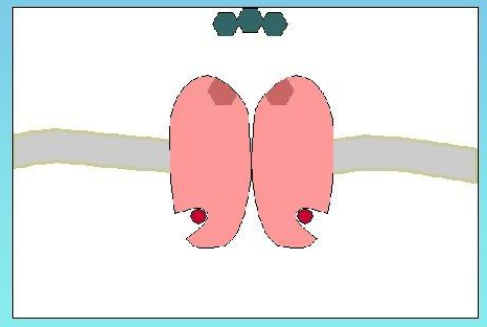
Channel linked or ionotropic



G-protein coupled Receptor



Enzymatic or kinase linked receptor

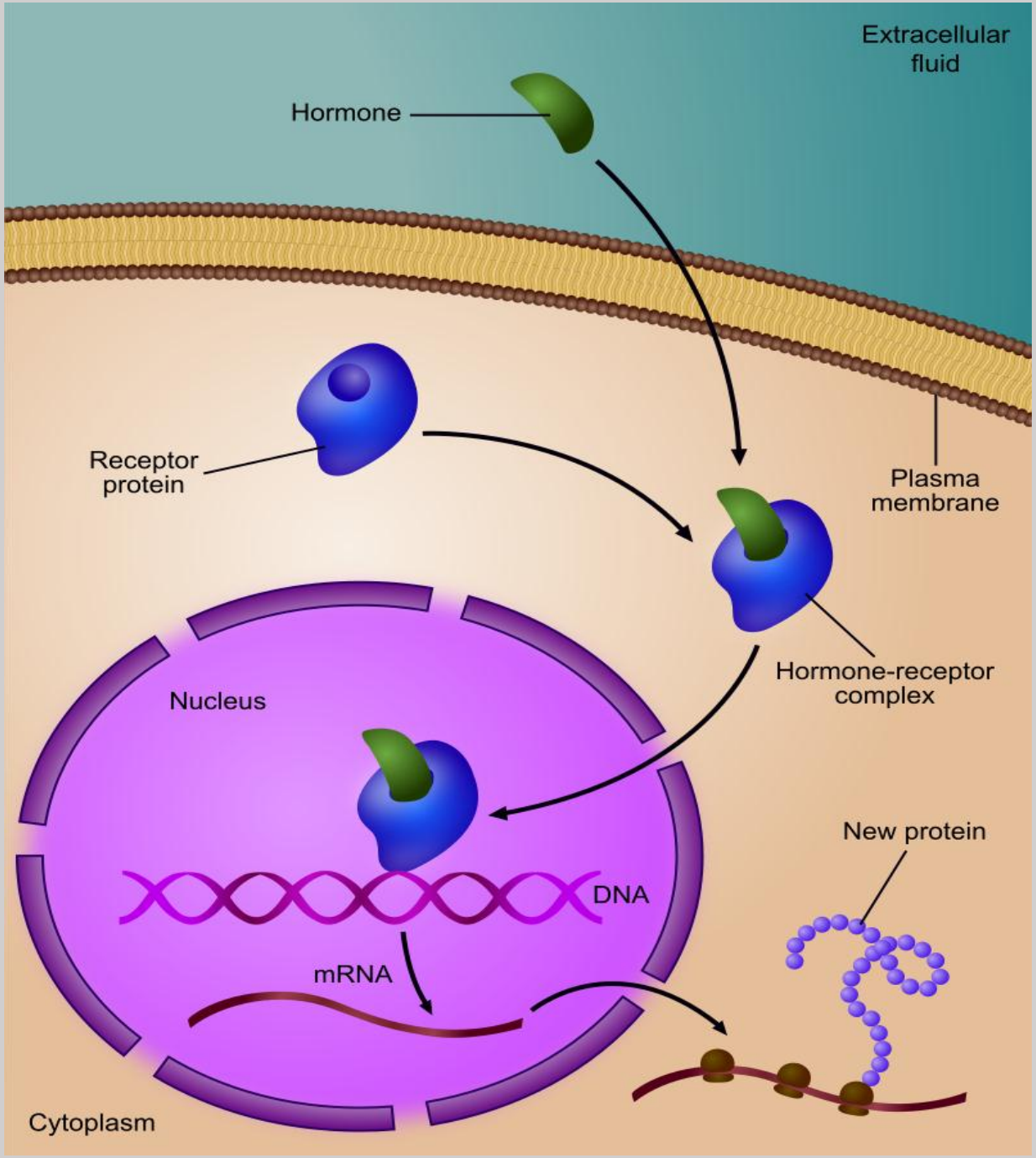


G proteins and their receptors and effectors

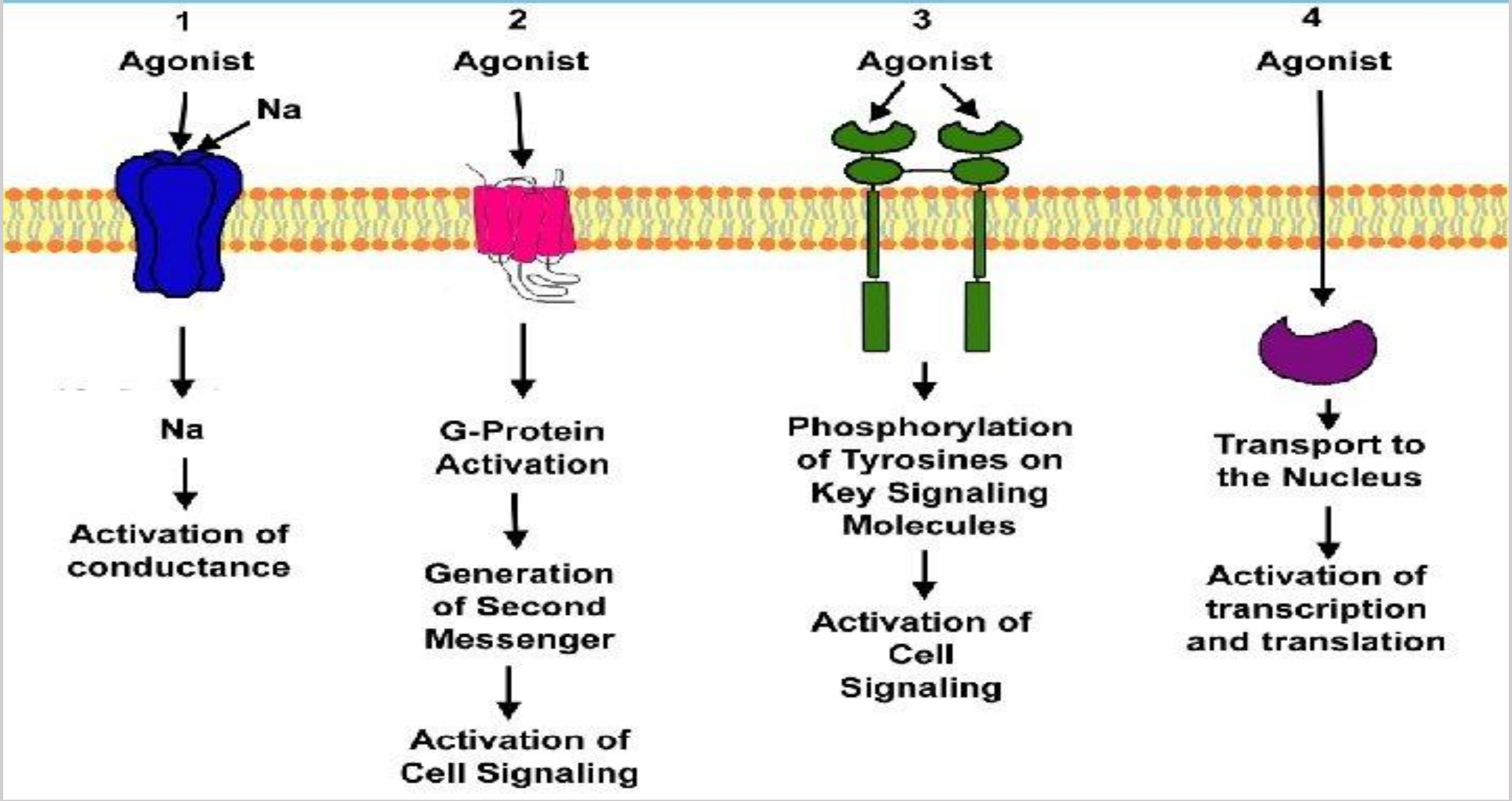
G Protein	Receptors for:	Effector/Signaling Pathway
G_s	β-Adrenergic amines, glucagon, histamine, serotonin, and many other hormones	↑ Adenylyl cyclase , ↑ cAMP
G_{i1}, G_{i2}, G_{i3}	α_2-Adrenergic amines, acetylcholine (muscarinic), opioids, serotonin, and many others	Several, including: ↓ Adenylyl cyclase , ↓ cAMP Open cardiac K^+ channels , ↓ heart rate
G_{olf}	Odorants (olfactory epithelium)	↑ Adenylyl cyclase , ↑ cAMP
G_o	Neurotransmitters in brain (not yet specifically identified)	Not yet clear
G_q	Acetylcholine (eg, muscarinic), bombesin, serotonin ($5\text{-}HT_{1C}$), and many others	↑ Phospholipase C, ↑ IP_3, ↑ diacylglycerol, cytoplasmic Ca^{2+}
G_{t1}, G_{t2}	Photons (rhodopsin and color opsins in retinal rod and cone cells)	↑ cGMP phosphodiesterase (phototransduction)

Receptors regulating gene expression

- Intracellular soluble proteins
- Steroidal hormones, thyroxine, vit D, vit A



Activation through different types of receptors



COMBINED EFFECTS OF DRUGS

- SYNERGISM: When the action of one drug is increased by the other, they are said to be synergistic

- Additive : Additive Action

1 + 1= 2 (Paracetamol + Diclofenac)

- Potentiation / Supra-additive

1 + 1= 3 (Levodopa + Carbidopa)

COMBINED EFFECTS OF DRUGS

❑ANTAGONISM

(1+1= 0)

- Physical
- Chemical
- Physiological/functional
- Receptor

FACTORS MODIFYING DRUG ACTION

- **Body size**
- **Age**
- **Sex**
- **Species and race**
- **Genetics**
- **Route of administration**
- **Emotional factors**
- **Diet and environment**
- **Pathological states**
- **Other drugs**
- **Cumulation**
- **Tolerance**

FACTORS MODIFYING DRUG ACTION

- **Differences in body weight**: the adult dose is calculated to produce specific effect in population between ages 18 -65 and weighing about 70 kg, so very thin or obese individuals have to receive special doses to give the same response.
- **Age**: the immature liver or kidney of the chid may delay drug metabolism and excretion. • On the other hand delayed distribution, metabolism and excretion are common in elderly because of disease condition or normal deterioration of body system
- **Sex:** males need higher doses than females owing to the higher bulky muscles androgen which is an enzyme inducer. Drugs should be administered cautiously during pregnancy and lactation.
- **Disease states**: long duration of action or toxic effect of a drug may be related to liver or kidney disease and long period of time for absorption and distribution related to heart disease.
- **Psychological factors:** the hopes, fears and expectation of the individual often affect the drug action. Patients may even improve with placebo (tablet or capsule containing sucrose or lactose). This may be due to release of endogenous substances like endorphins and enkephalins in the brain and other body parts

Timing of dosage

- Timing of dosage:
- A single dose of antacid or ranitidine taken at bedtime is more effective than two or three doses taken during the day.
- Absorption is better on empty stomach.
- Irritant drugs should be given after meals.
- CNS stimulants never be given at bed time.

Cumulation

- Cumulation: . A drug is designated as cumulative when its elimination and/or detoxification are slow.
- e. g. digitalis, diazepam, amiodarone and large doses of aspirin or phenytoin.
- The toxicity could be avoided by decreasing the dose

Tolerance

- Tolerance It is a decrease or failed response to the usual therapeuticdose of a drug.
- **Types of Tolerance:**
- Congenital tolerance: existing from birth examples:
- Negroes are tolerant to the mydriatic action of ephedrine.
- Eskimos are highly tolerant to fat diet (not develop acidosis).
- Biological variation i. e. individual tolerance within any population. This may be related to genetic factors.
- Rabbits are tolerant to large doses of atropine , probably due to the presence of atropine esterase in the liver (species tolerance).
- Cross-tolerance: tolerance to a drug may extend to the related drugs. Example: nicotine/lobeline, morphine / pethidine, and between members of barbiturates. Bacterial resistance: it is a sort of tolerance to the action of antimicrobial drugs