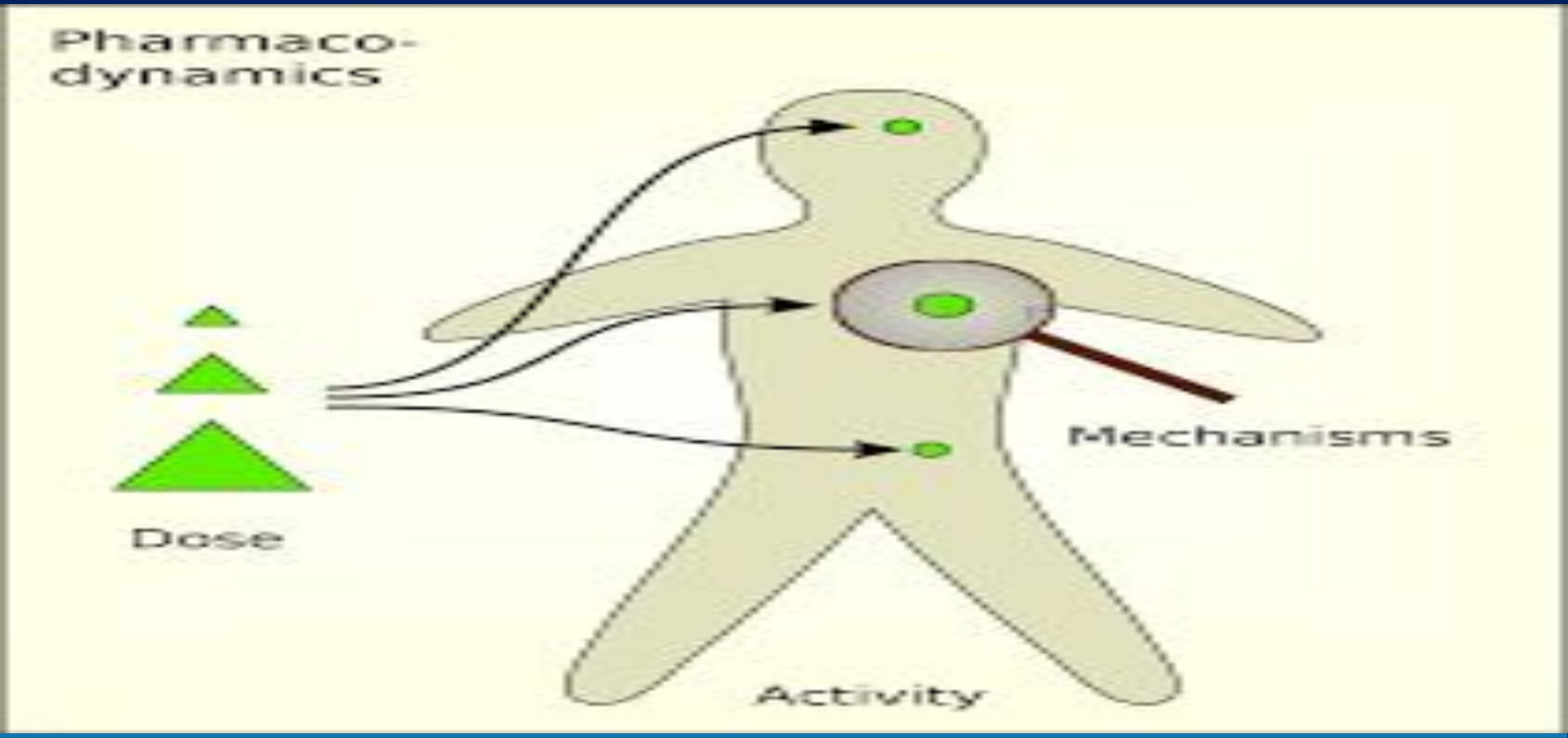
Pharmacodynamics L1



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objectives

- Know the meaning of pharmacodynamics, mechanism of action, pharmacological terms, types and location of receptors and its binding, dose response curve.
- Know possible duration of action and time of termination the effects of drug binding to each types of receptor
- Importance of methods and benefit of drug selectivity.

Pharmacodynamics

- In Greek

Pharmacon = Drug Dynamics = Action/Power

Is the action of drugs upon the body regarding their biological effects and response (including mechanism of .action)

Types of Drug Action (Type of effects or responses):-

1. Stimulation
2. Inhibition/Depression
3. Replacement
4. Irritation
5. Cytotoxic

Receptor: is a macromolecule, protein in chemical nature have specific **configuration** and specific **affinity** to a certain .ligand (ligand = drug, hormone, toxin,…)

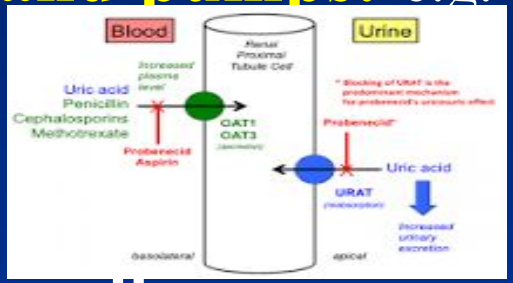
Principle mechanisms of drug actions:

1-Drugs acting on cell membrane:

a- On specific receptors: e.g. agoinsts on adrenoceptors.

b- Interference with selective passage of ions across membrane: e.g. Ca or Na channel blocker.

c- Inhibition of membrane-bound enzymes and pumps: e.g. digoxin (inhibits **ATPase**).

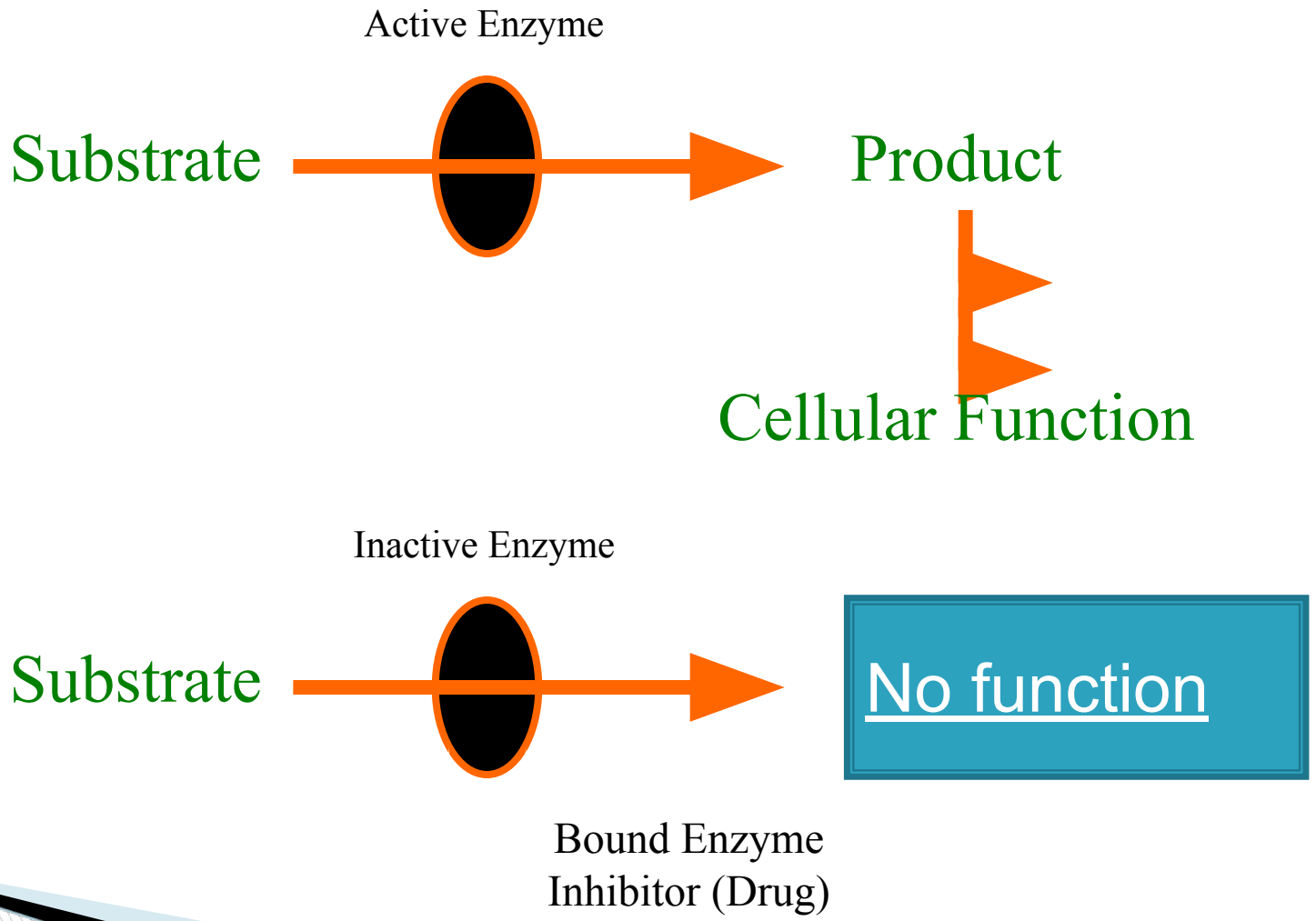


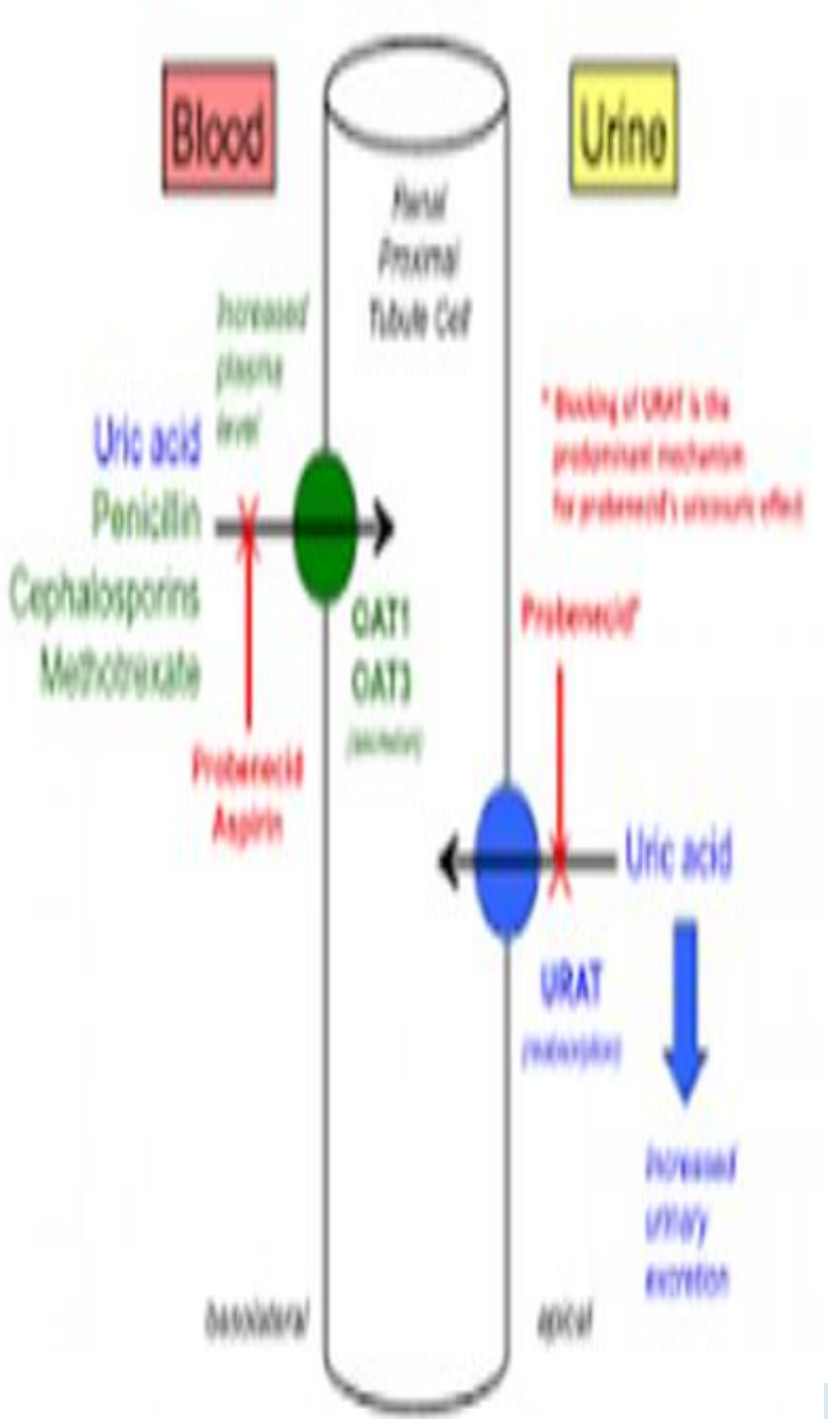
2- Drugs act on metabolic process within the cell.

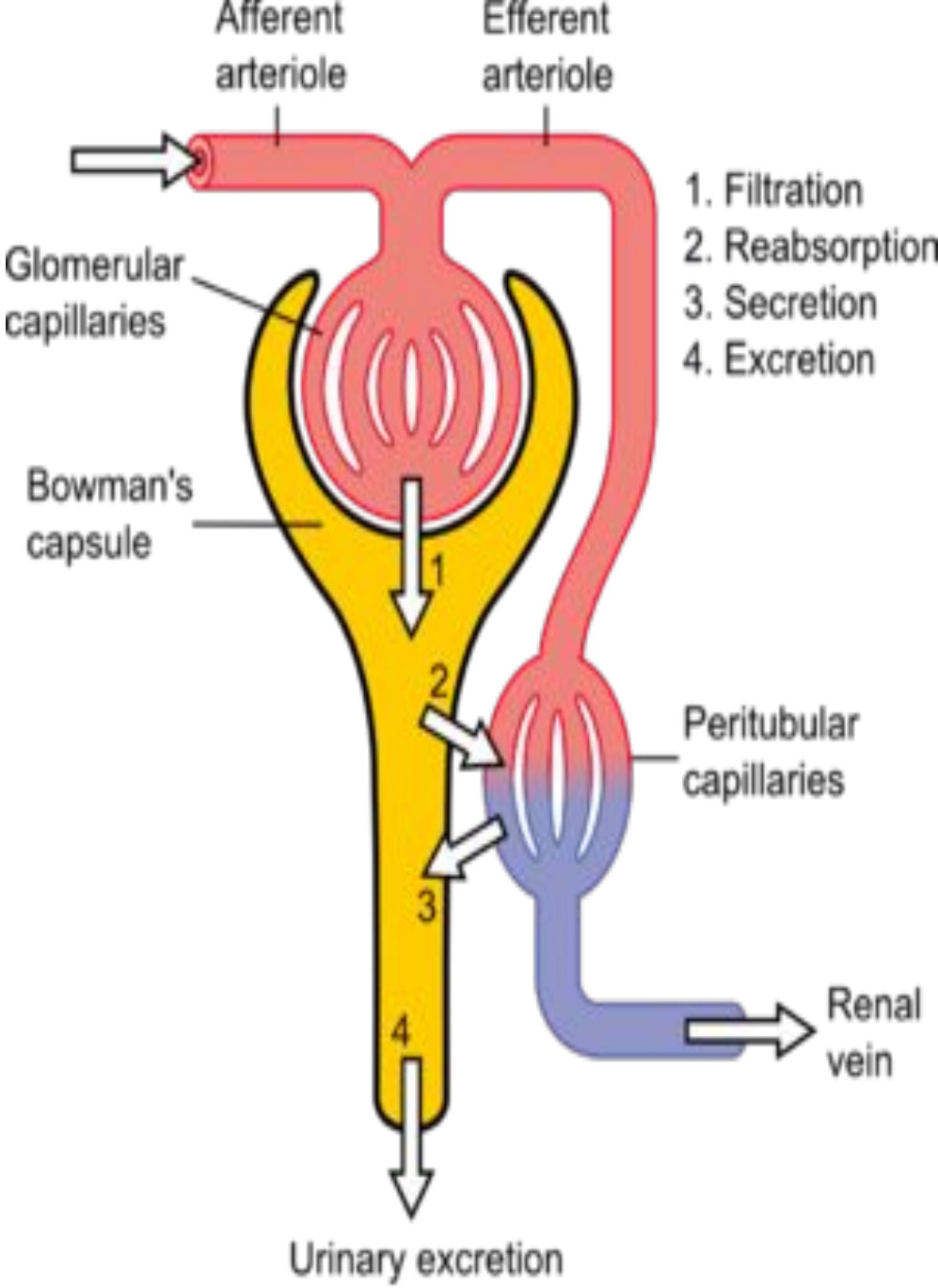
.Enzyme inhibition: e.g. paracetamol (COX enzyme inhibitor).

b. Inhibition of transport processes across cell: e.g. probencid block renal tubular secretion transporter(thereby decreasing renal clearance and elevating their plasma concentrations)

HOW DO DRUGS WORK BY INHIBITING ENZYMES?







Excretion = Filtration – Reabsorption + Secretion

C .Incorporation into large molecules: e.g. 5 Flurouracil (an anticancer which is incorporated into mRNA in place of uracil).

D. Altering metabolic processes unique to microorganisms: e.g. penicillin interferes with the formation of peptidoglycans layers of the bacterial cell wall.

3-Drugs act out side the cell:

a- Direct chemical interaction: e.g. antacid (acid-base interaction).

b- Osmosis: e.g. diuretics and purgatives……. Ex: (manitol)

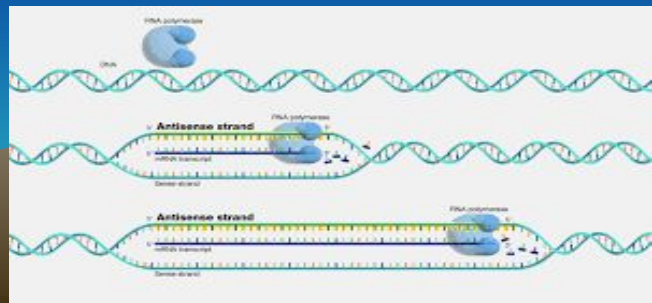
4- other drugs work by unconventional mechanism of action

•Being Nutrients
•e.g. vitamins, minerals

Being Enzymes
e.g. streptokinase for thrombolysis

• Binding Free Molecules or Atoms
•e.g. drugs for heavy metal poisoning, infliximab (anti-TNF)
• Working Via an Antisense Action

• Being Antigens
e.g. vaccines



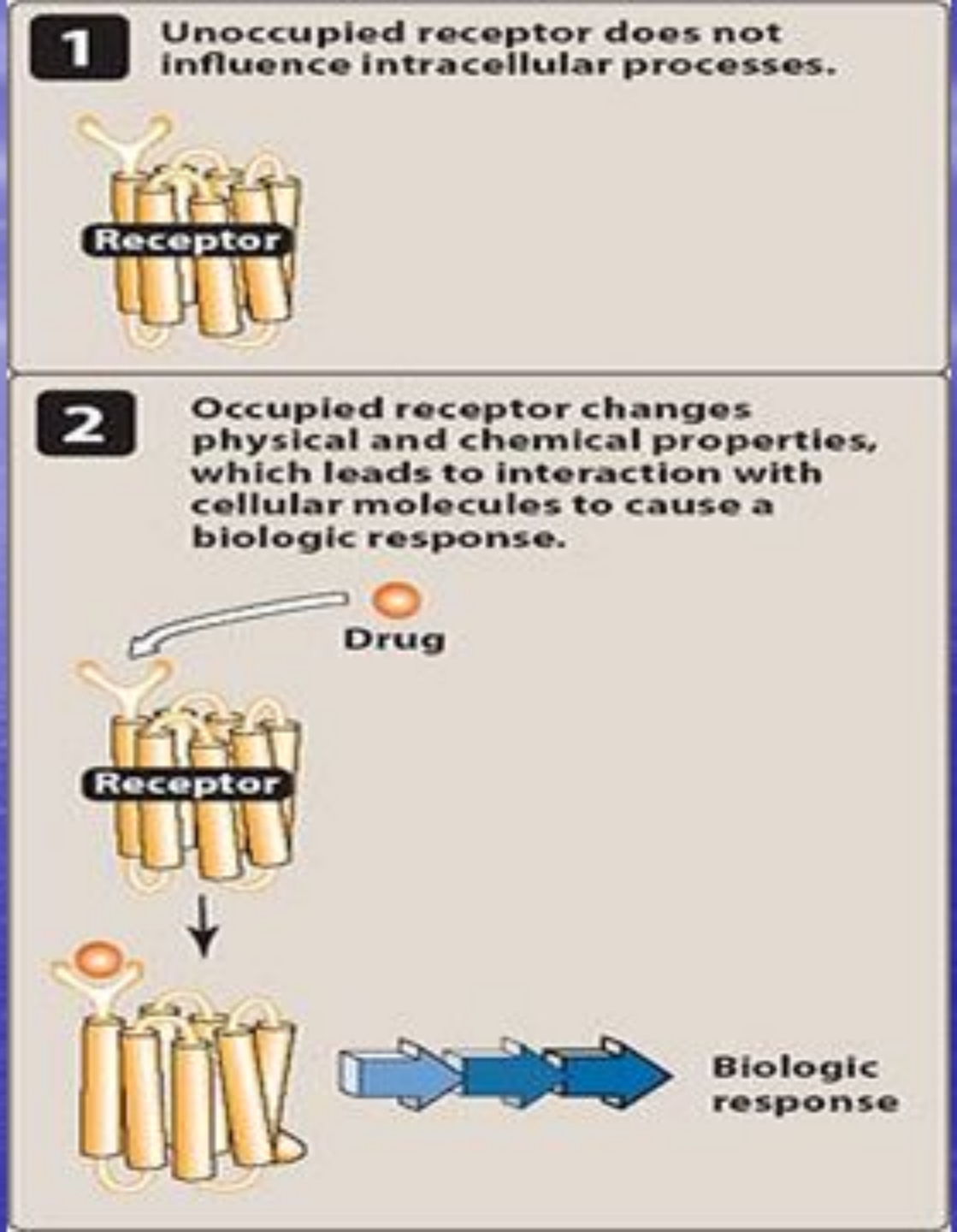
:Location of receptor

Cell membrane (ex. Catecholamine receptors: alpha and -1 beta R …..)

.Cytoplasm (ex. Steroid receptor) -2

.Nuclear membrane(ex. Thyroid Receptor) -3

Binding of drug(D) to receptor(R) → drug receptor **interaction** → drug-receptor complex formation → intracellular events or **.response**


1
Unoccupied receptor does not influence intracellular processes.
Receptor
2
Occupied receptor changes physical and chemical properties, which leads to interaction with cellular molecules to cause a biologic response.
Drug
Receptor
Biologic response

Drug- receptor interaction:

Interaction of the receptors with ligands involves the formation of **chemical bonds**, most commonly

1-electrostatic

2-hydrogen bonds

3- weak interactions involving **van der waal** forces.

…….

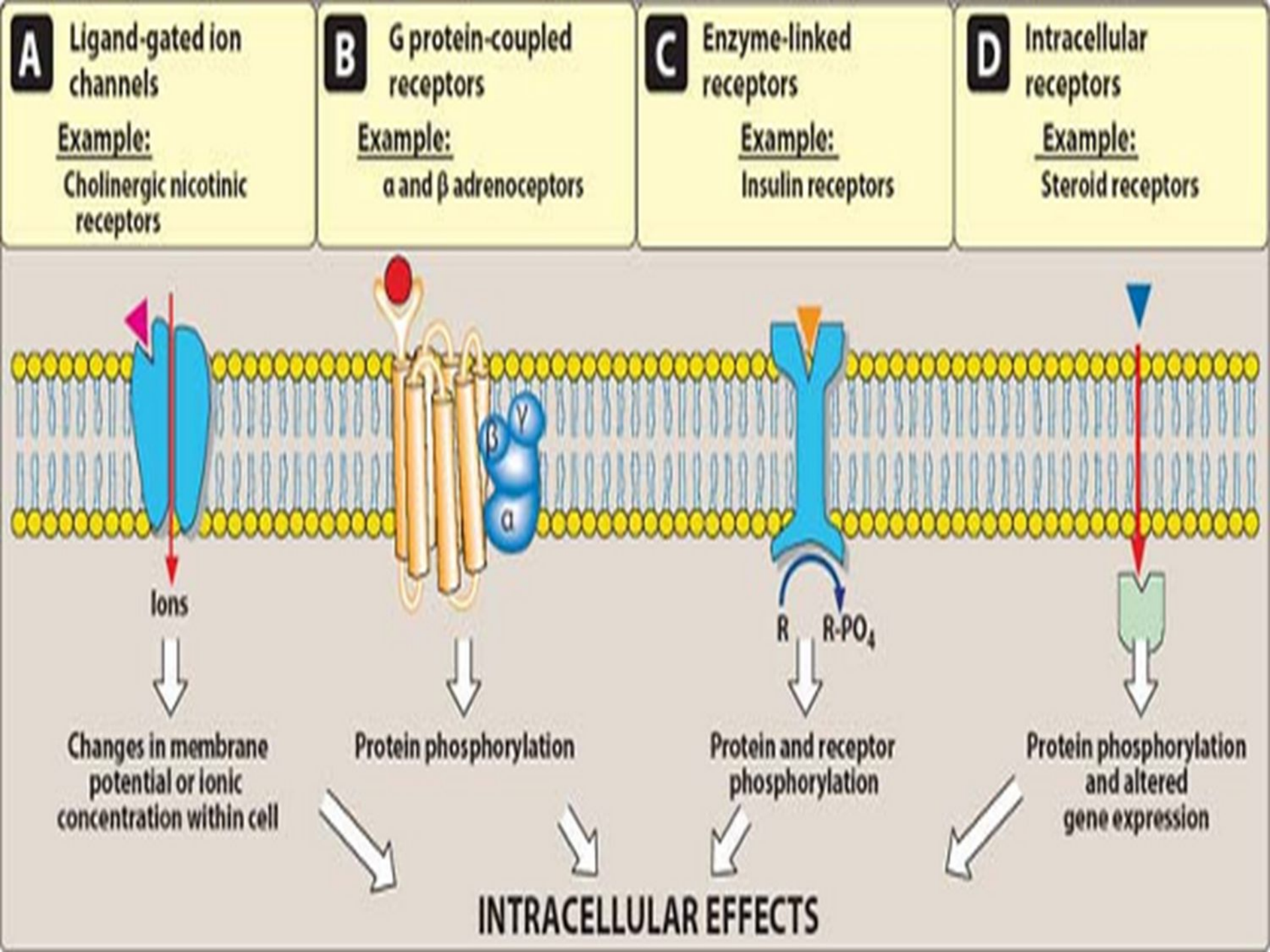
……..

- The **bonds** are usually **reversible** except for some drugs that **covalently** bond to their targets (**irreversible**).

- **Successful binding** of a drug requires an **exact fit** of the ligand atoms with the complementary receptors atoms Which is determined by
- Size
- Shape
- Charge distribution of the drug molecule

Transduction mechanisms of D-R interaction (**Types of receptors**):

A: ligand-gated ion channels: these are **responsible** for the **regulation of the flow** of ions across cell membrane **by** **binding of a ligand to the channel**. The **response** is very rapid with short duration of action e.g. nicotinic receptors .

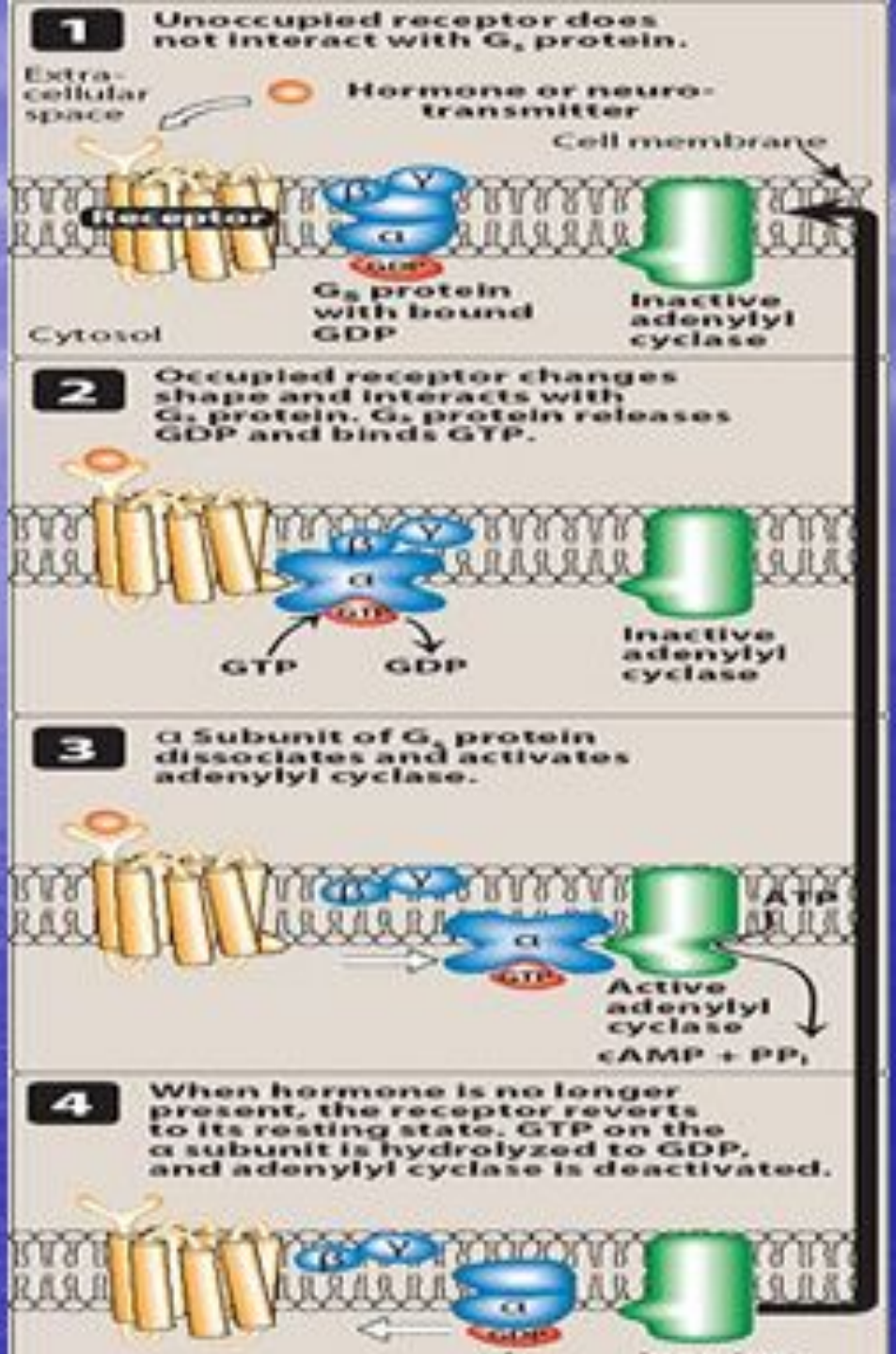

A
Ligand-gated ion channels
Example:
Cholinergic nicotinic receptors
B
G protein-coupled receptors
Example:
α and β adrenoceptors
C
Enzyme-linked receptors
Example:
Insulin receptors
D
Intracellular receptors
Example:
Steroid receptors
β
γ
α
Ions
R
R-PO4
Changes in membrane potential or ionic concentration within cell
Protein phosphorylation
Protein and receptor phosphorylation
Protein phosphorylation and altered gene expression
INTRACELLULAR EFFECTS

B: G protein-coupled receptors:

comprised of a single peptide that has seven membrane-spanning regions, these receptors are linked to a G protein(Gs) having 3 subunits an α subunit that binds guanosine triphosphate GTP and a β γ subunit.

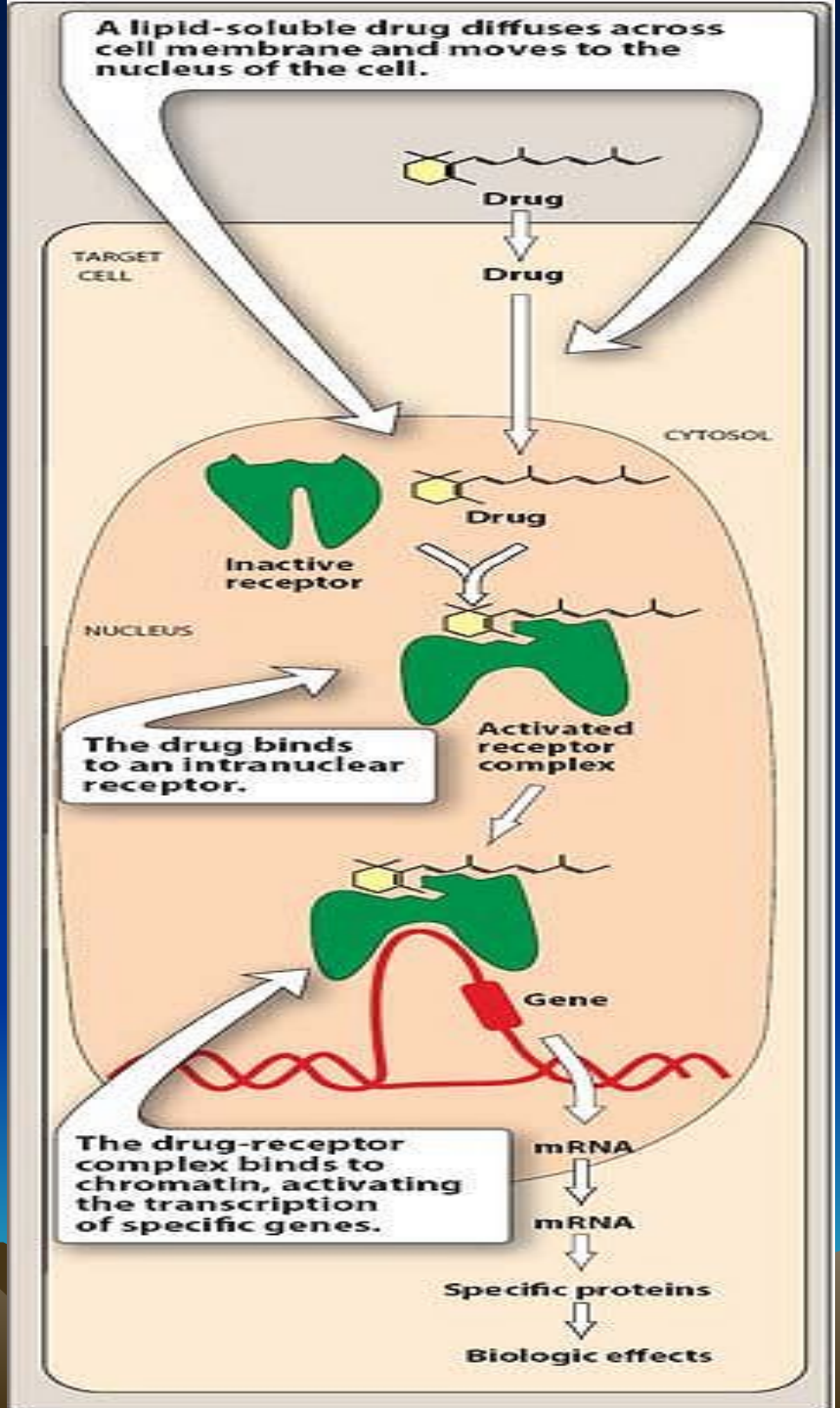
It lead lastly to activation of adenylyl cyclase and protein phosphorylation as in diagram.

G proteins also activate **phospholipase C** which is responsible for the generation of two other **second messengers**, namely inositol 1,4,5 triphosphate(IP3) and **diacylglycerol**. These effectors are responsible for the regulation of free calcium concentration within the cell.


1
Unoccupied receptor does not interact with G_s protein.
Extra-cellular space
Hormone or neuro-transmitter
Cell membrane
Receptor
β
γ
α
GDP
G_s protein with bound GDP
Inactive adenylyl cyclase
Cytosol
2
Occupied receptor changes shape and interacts with G_s protein. G_s protein releases GDP and binds GTP.
GTP
GDP
Inactive adenylyl cyclase
3
α Subunit of G_s protein dissociates and activates adenylyl cyclase.
ATP
Active adenylyl cyclase
cAMP + PP_i
4
When hormone is no longer present, the receptor reverts to its resting state. GTP on the α subunit is hydrolyzed to GDP, and adenylyl cyclase is deactivated.

C: Enzyme-linked receptors: these receptors have cytosolic enzymetic activity as an integral component of their structure or function. Binding of a ligand to an extracellular domain activates or inhibits enzyme activity. Duration of responses is long. E.X: insulin receptors..

D : Intracellular receptors: ligand must diffuse into the cell to interact with the receptor (must be **phospholipid** drugs), it take longer time for action and response bs protein synthesis and gene expression are modified (see the following diagram)


A lipid-soluble drug diffuses across cell membrane and moves to the nucleus of the cell.
Drug
Drug
TARGET CELL
CYTOSOL
Drug
Inactive receptor
NUCLEUS
Activated receptor complex
The drug binds to an intranuclear receptor.
Gene
The drug-receptor complex binds to chromatin, activating the transcription of specific genes.
mRNA
mRNA
Specific proteins
Biologic effects

:Theories of response to drugs

Occupational theory -1

Response depends on Number of receptor occupied

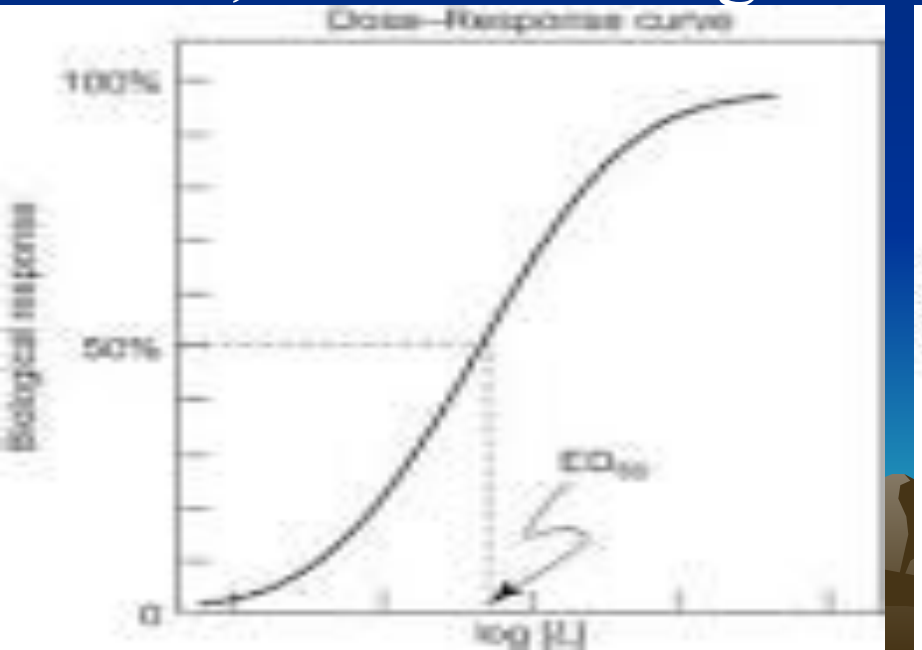
Rate theory -2

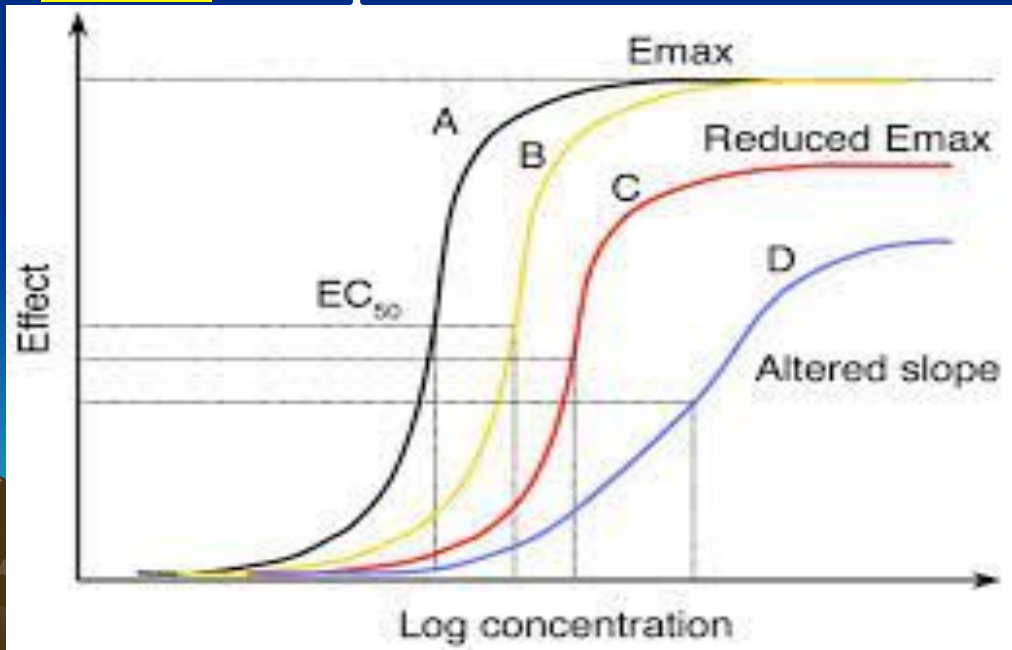
Response depends on Rate of association between drug and receptor

Quantal dose response curve

It represent the **relation** between % of **population** responding to a certain drug and the **dose** of this drug and it measure the variability of response with .different doses

The majority of drugs have **S shape** or sigmoid shape .curve, but some drugs has **liner** shape curve





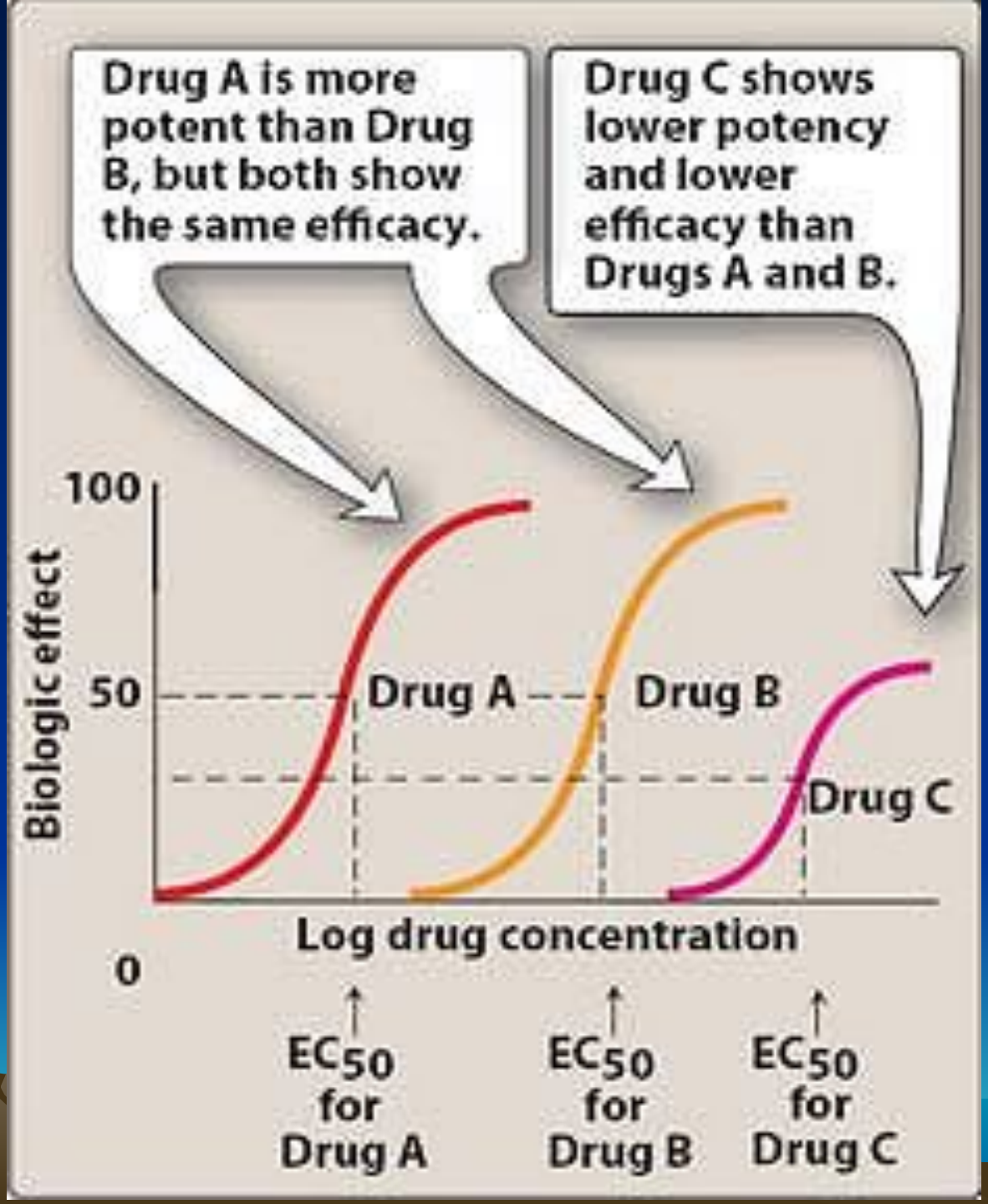
Benefit of dose response curve

To **compare** the potencies of different drugs by -1 measuring ED50 (the dose of drug that give 50% .response)

.**Doupling** of dose not mean doubling of response -2

The response may reach a **platue** phase, so any-3 further increase in dose not increase the response but .cause **toxicity**

??Types of dose response curve**


Drug A is more potent than Drug B, but both show the same efficacy.
Drug C shows lower potency and lower efficacy than Drugs A and B.
100
50
0
Biologic effect
Drug A
Drug B
Drug C
Log drug concentration
EC50 for Drug A
EC50 for Drug B
EC50 for Drug C

Efficacy(intrinsic activity) : is the maximal response of drug **regardless** the dose

.**Affinity** : is the ability of drug to bind the receptor

Ligand: name given to a molecule that binds to a receptor.

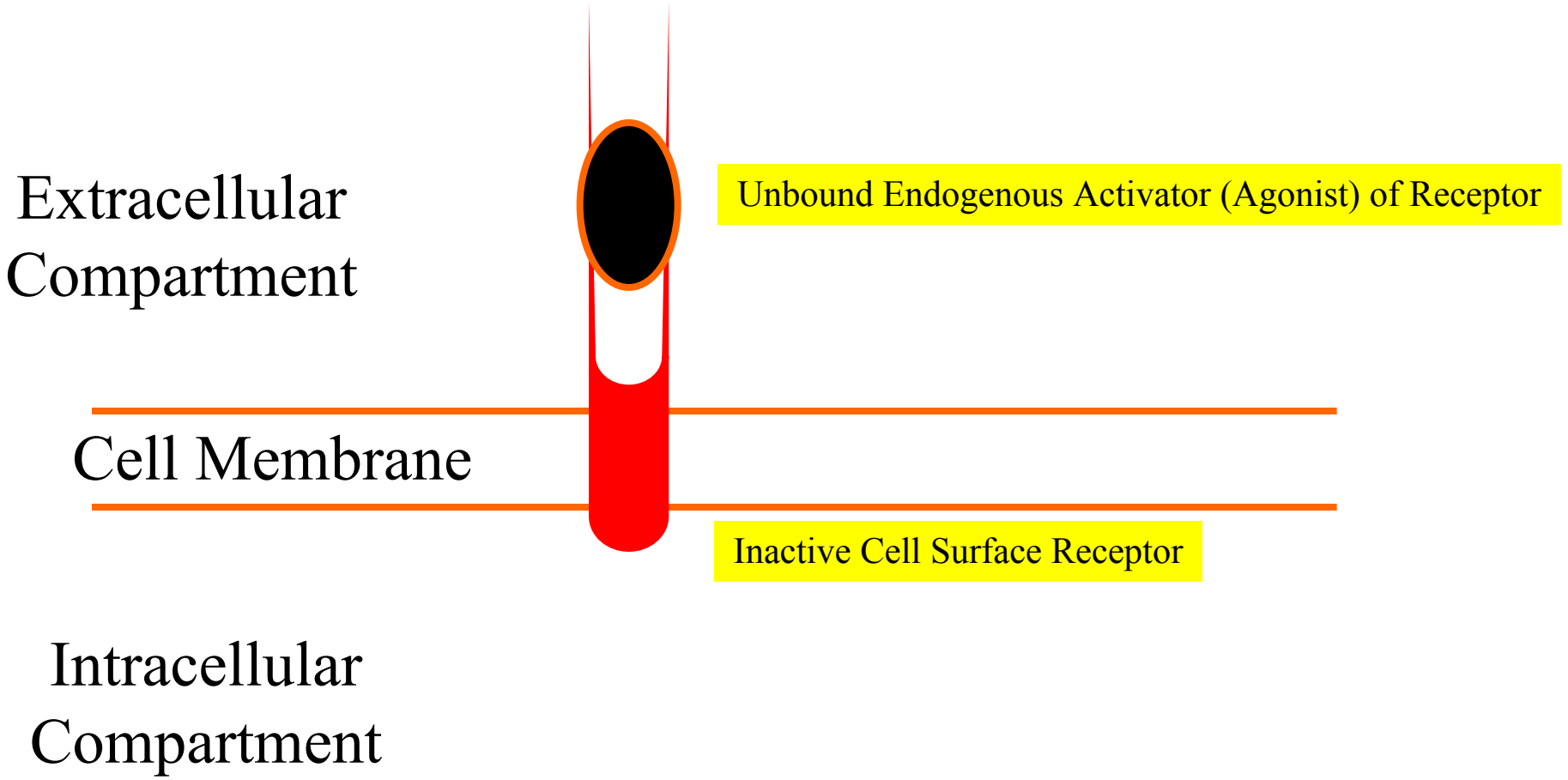
Agonist :is a ligand which has affinity + intrinsic activity and give dose response curve, and give 100% response(100% .efficacy)

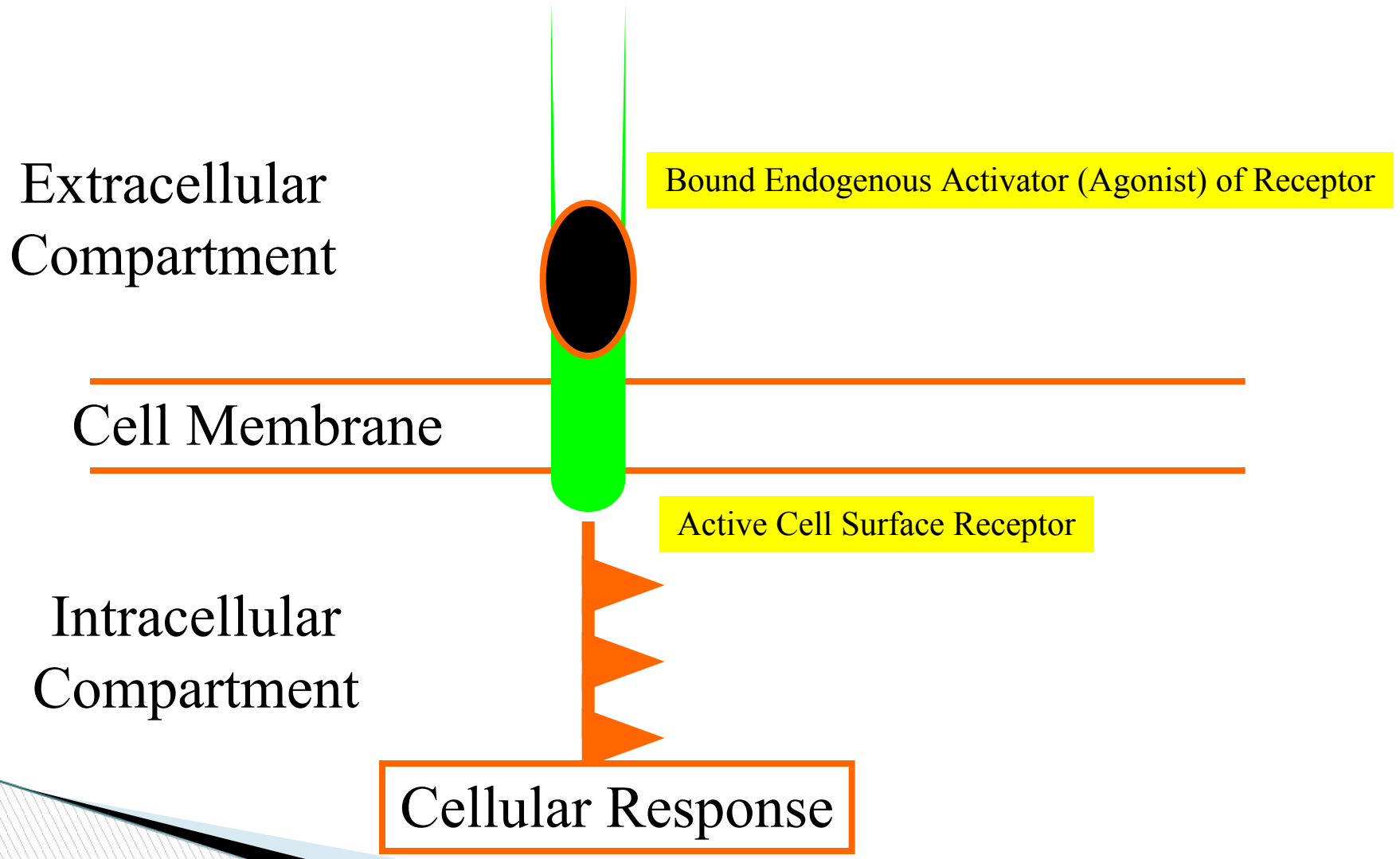
Antagonist :a ligand which has affinity but no intrinsic .activity

Partial agonist: a ligand which has **affinity +little intrinsic** activity and give 50 % response, and act as antagonist in presence of full agonist (e.x: nalorphine is a partial agonist, .act as antagonist to morphine(full agonist))

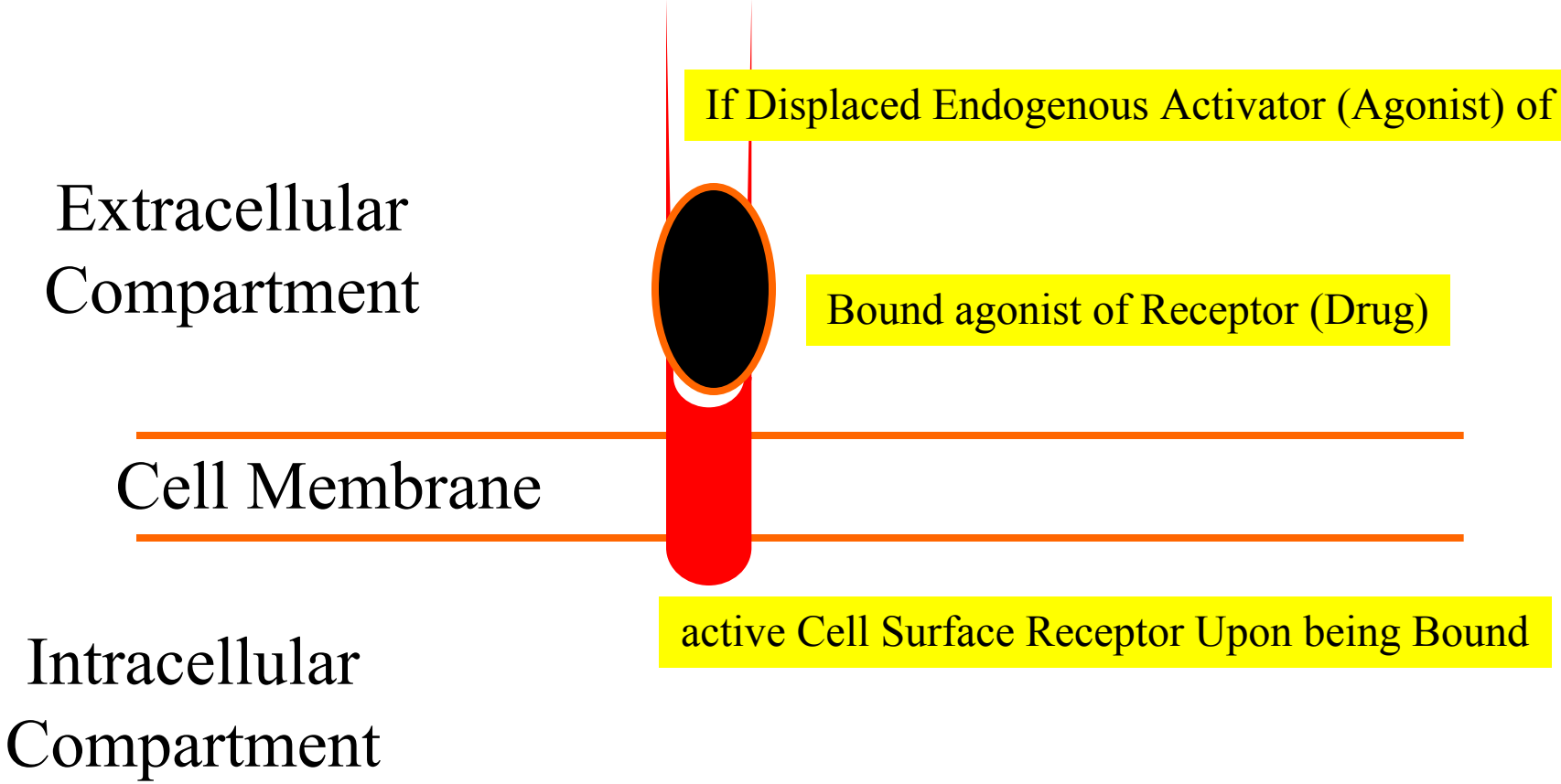
Superagonist: is a compound that is capable of producing a greater maximal response than the agonist for the target receptor, and thus has an efficacy of more than 100%.

HOW DO DRUGS WORK BY BEING AGONIST TO CELL SURFACE RECEPTORS?




Extracellular Compartment
Bound Endogenous Activator (Agonist) of Receptor
Cell Membrane
Active Cell Surface Receptor
Intracellular Compartment
Cellular Response

HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?



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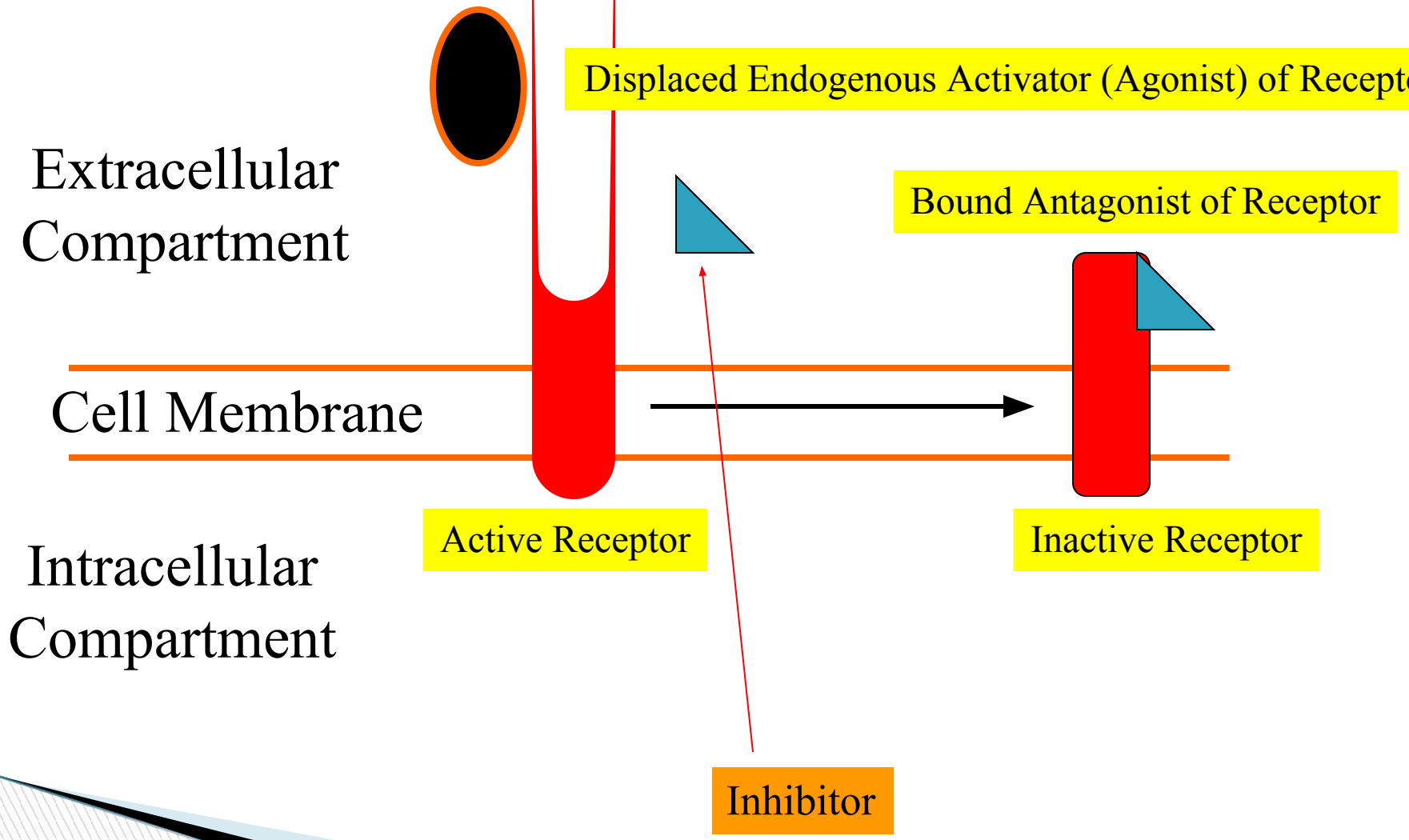


Types of antagonist

Pharmacological: in which both agonist and antagonist act **-1** on the **same** receptor (if **same orthosteric** site named as **competitive** ex. Acetylcholie (act on cholinergic receptor)and .atropine(acts on cholinergic receptor)

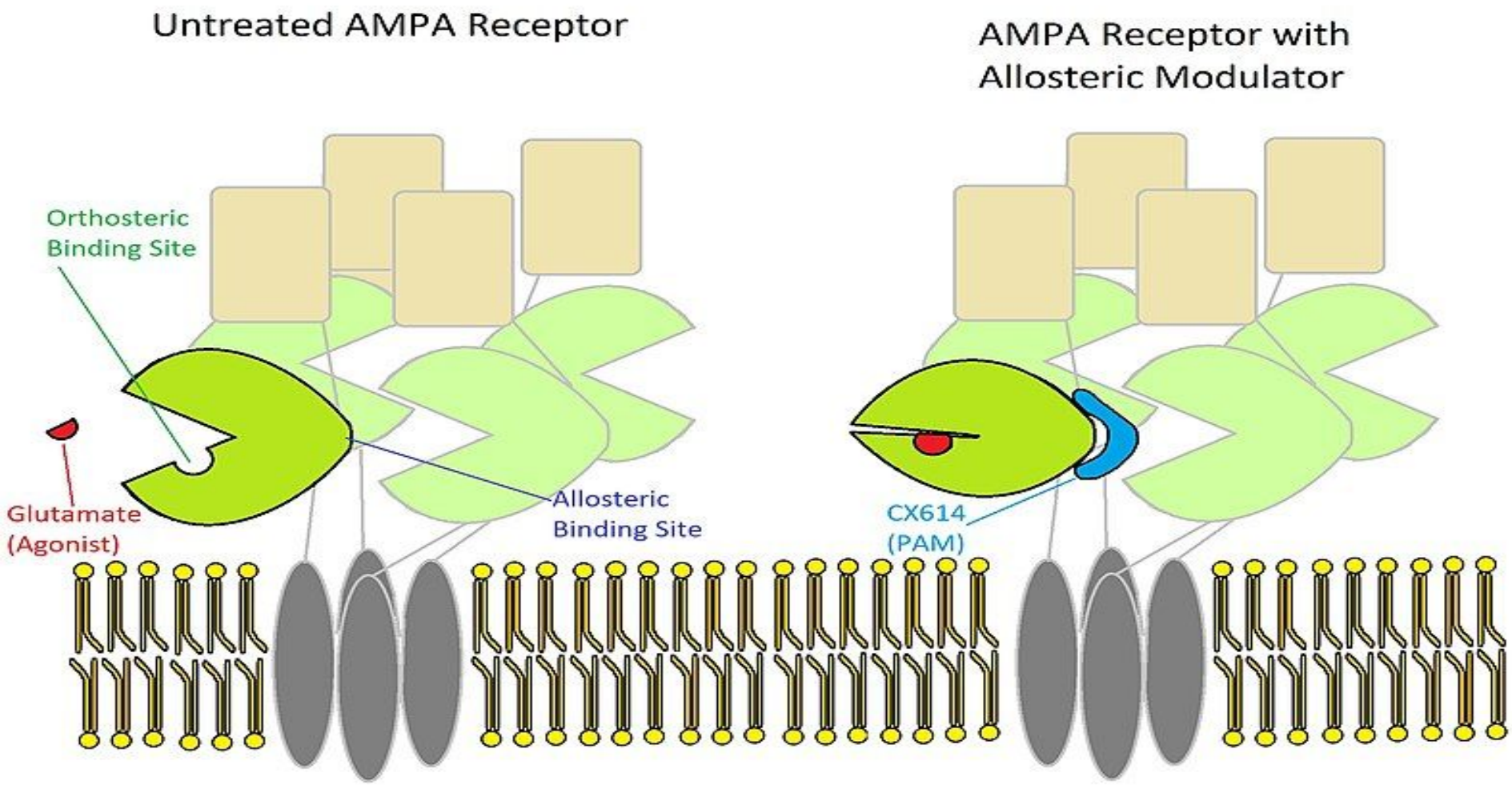
:Allosteric antagonists (non competitive) -2

This type of antagonist binds to a site ("**allosteric site**")other than the agonist-binding site on the **same** receptor and prevents the receptor from .being activated by the agonist

Physiological(functional):in which both agonist and **-3** antagonist act on **different receptor** ex: histamine (act on histaminergic receptors and adrenaline (act on adrenergic .receptor)

Chemical: act by direct local chemical interaction like antacid **-4**

Allosteric and orthosteric sites of receptor



:NOTE

The difference between competitive and noncompetitive antagonists is that

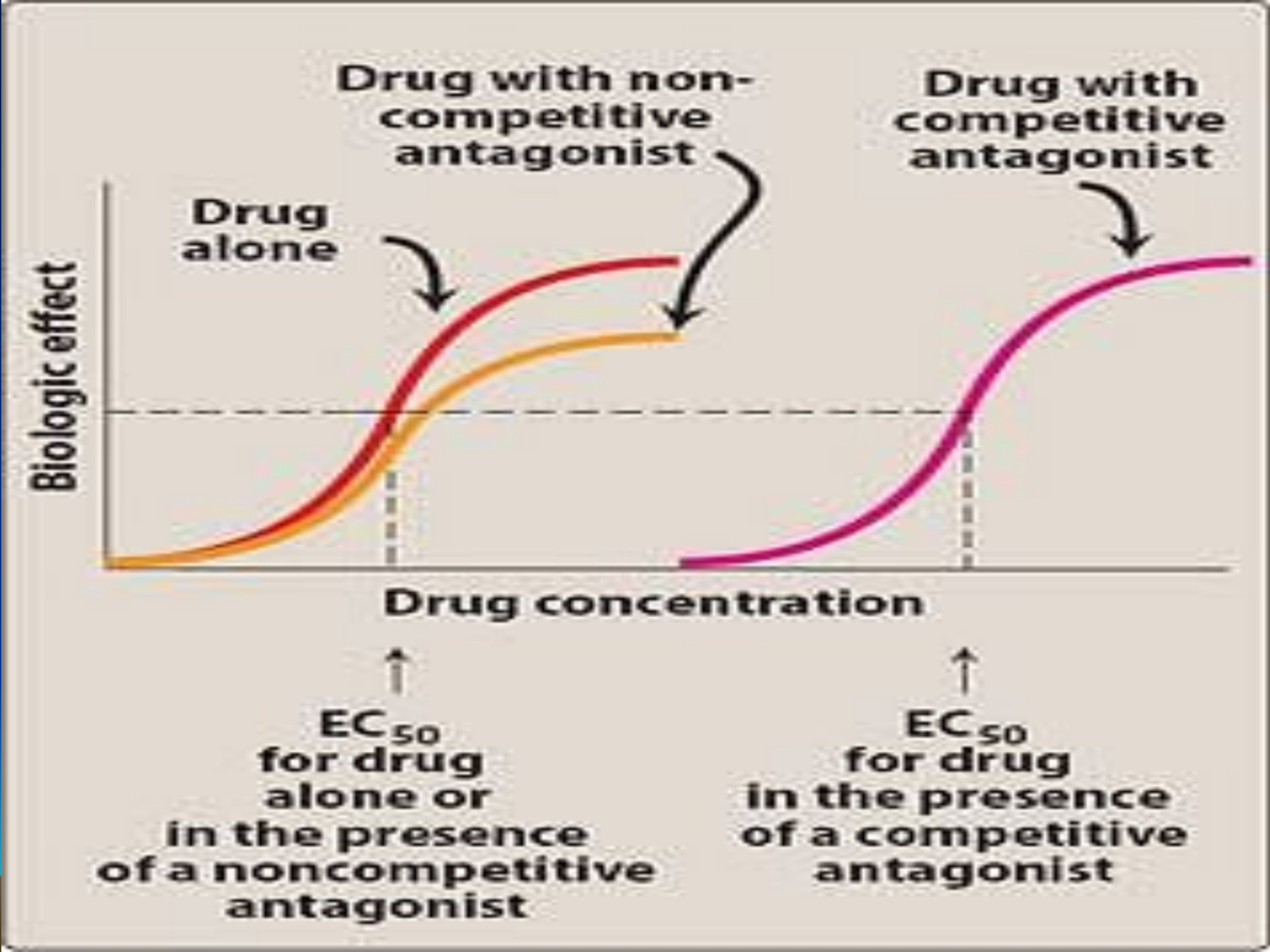
competitive antagonists reduce agonist potency (increase EC50)

noncompetitive antagonists reduce agonist efficacy (decrease .Emax)

Types of antagonism

Reversible: bind to receptor reversibilly and can be over**-1** .commed by increase the dose of agonist

Irreversible: bind to receptor irreversibilly and cannot over **-2** commed by increase the dose of agonist till synthesis of new receptors

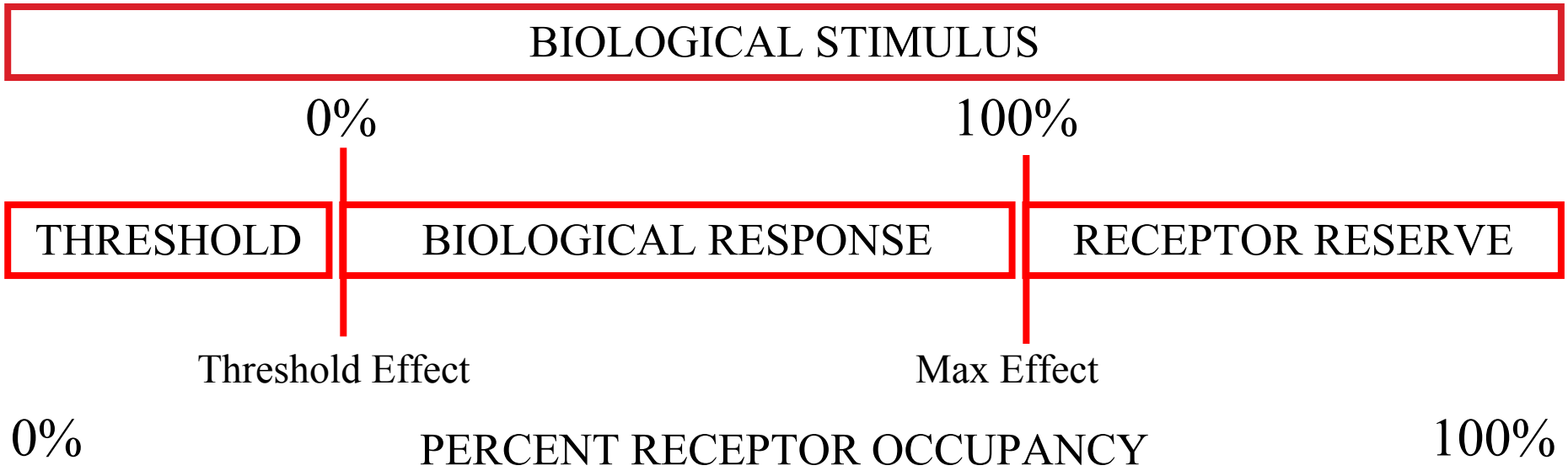

Drug with non-competitive antagonist
Drug with competitive antagonist
Drug alone
Biologic effect
Drug concentration
EC50 for drug alone or in the presence of a noncompetitive antagonist
EC50 for drug in the presence of a competitive antagonist

Spare Receptors

Response is a **FUNCTION** of occupancy

Maximum response can be produced **WITHOUT** 100% occupation,

i.e. tissues have *spare receptors*



Note: The receptor numbers do not remain constant.

*When tissues are continuously exposed to an **agonist**:

1-Decrease **number** of receptors

2- Decrease **sensitivity** of receptor.

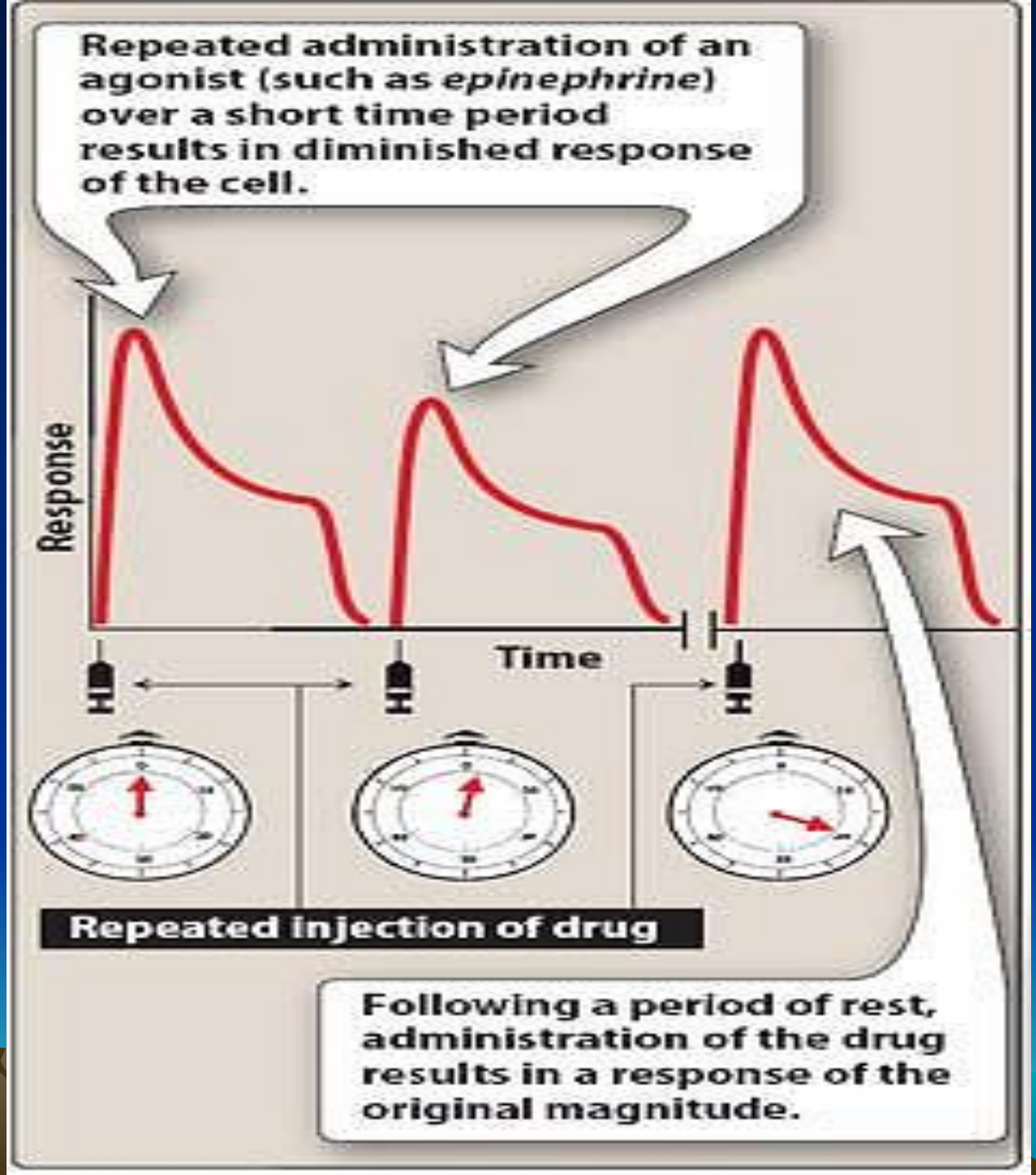
This means **desensitization** (**down-regulation**) and this may be a cause of **tachyphylaxis** (rapid loss of efficacy with frequently repeated doses) e.g. in **asthmatics** on adrenoceptor agonist bronchodilator.

*Prolonged contact with an **antagonist** leads to:

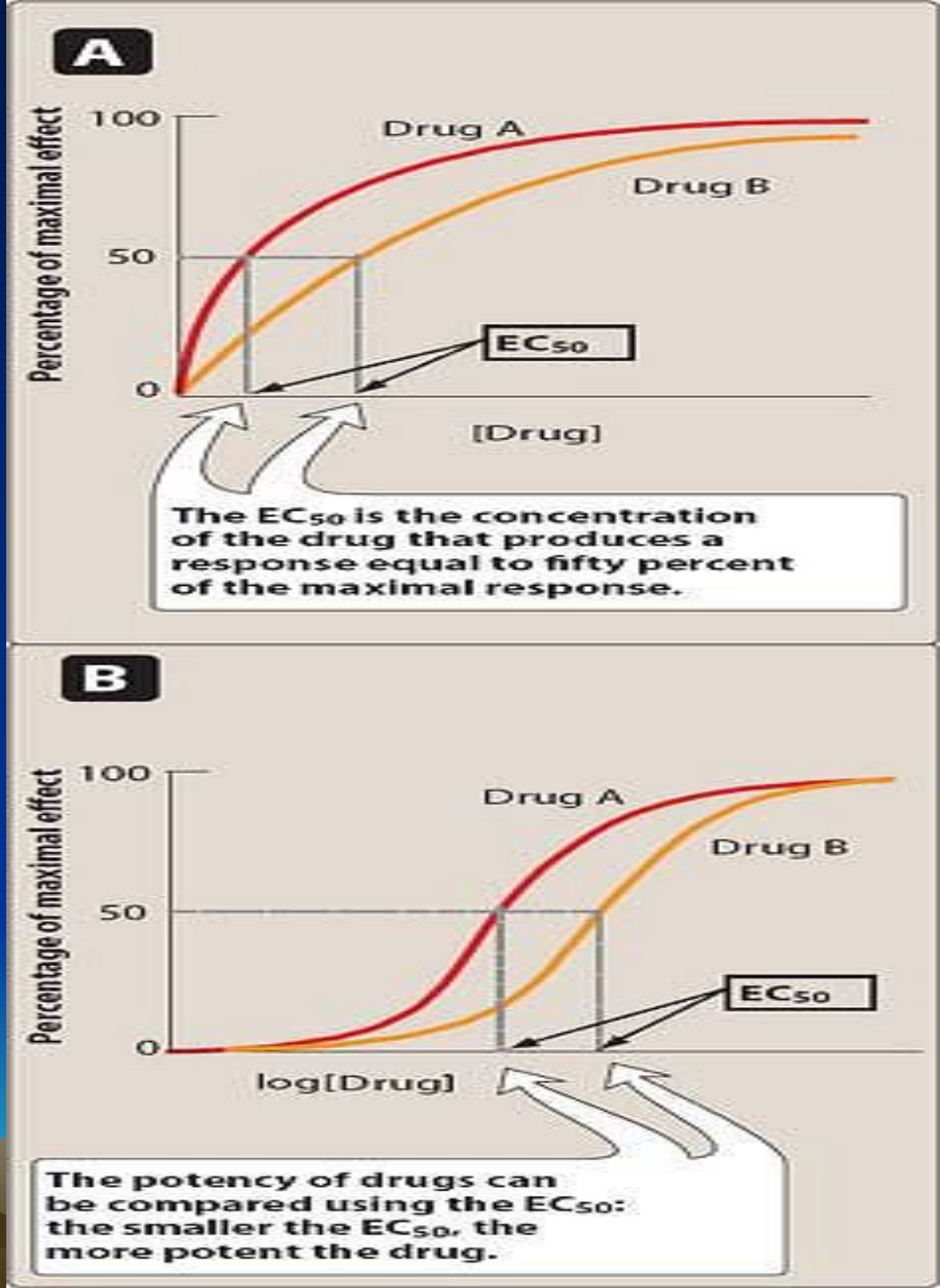
1-Formation of **new** receptors

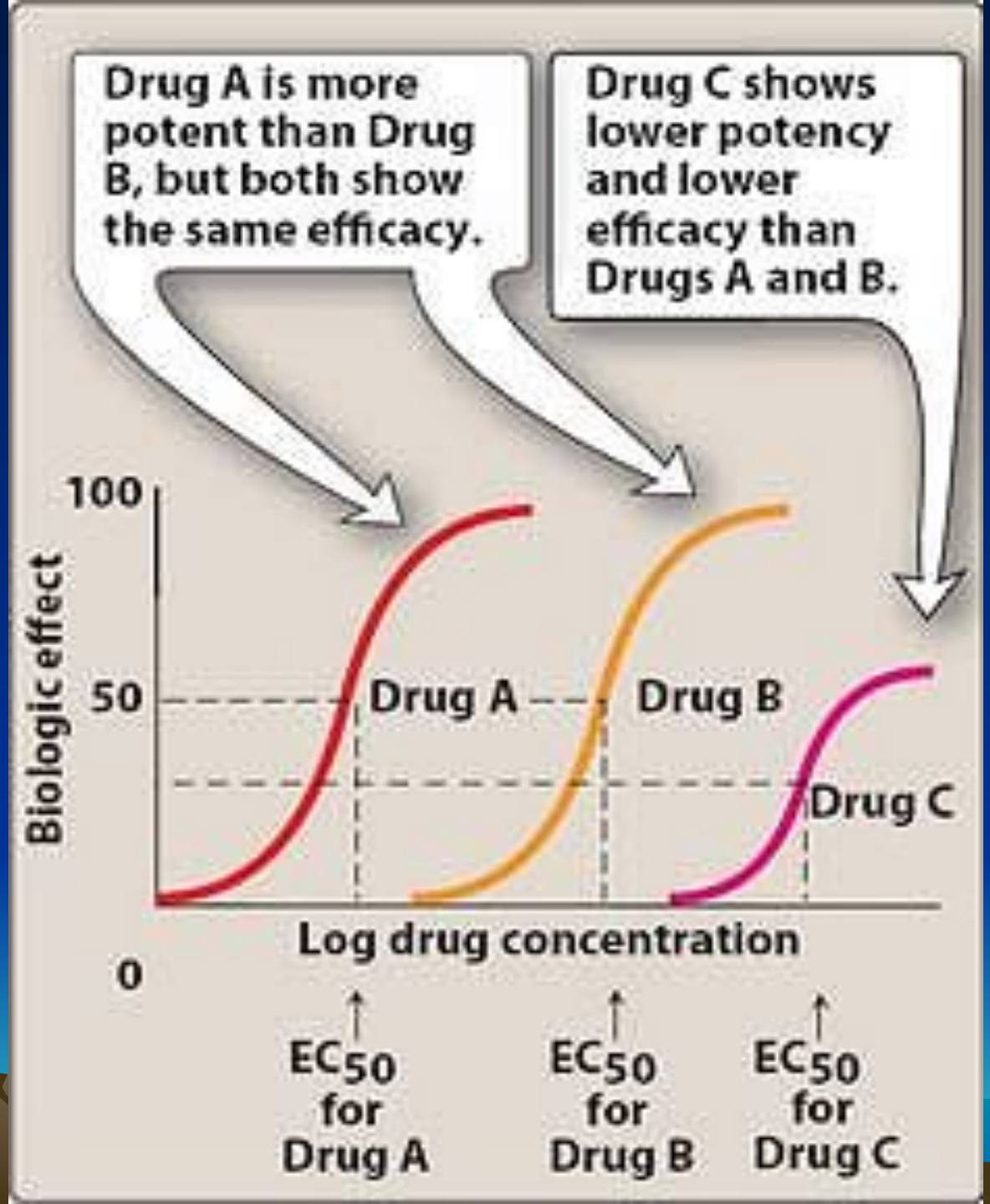
2-Increase **sensitivity** of receptor

This mean (**up-regulation**) e.g. sudden withdrawal of long term use of **β-adrenoceptor blockers** in hypertensive patients may lead to ventricular arrhythmias.


Repeated administration of an agonist (such as *epinephrine*) over a short time period results in diminished response of the cell.
Response
Time
Repeated injection of drug
Following a period of rest, administration of the drug results in a response of the original magnitude.

Potency: is the amount (weight) of drug in relation to its effect **e.g.** if 10 mg of drug (A) produce the **same** response produces by 60 mg of drug (B), then drug (A) is more potent than drug (B), **although** the maximum therapeutic effect obtainable may be similar with both drugs

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Drug C shows lower potency and lower efficacy than Drugs A and B.
100
50
0
Biologic effect
Drug A
Drug B
Drug C
Log drug concentration
EC50 for Drug A
EC50 for Drug B
EC50 for Drug C

Selectivity: mean deliver drug to the patient with :

1- Maximal efficacy .

2- Minimal unwanted effects.

This can be achieved by:

- **Modification** of drug **structure**.
- Selective **delivery system** (drug targeting) e.g. by topical application and certain delivery systems,…….


Thank
You!