بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | Lecture 4

Pharmacodynamics pt.2

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Pharmacodynamics

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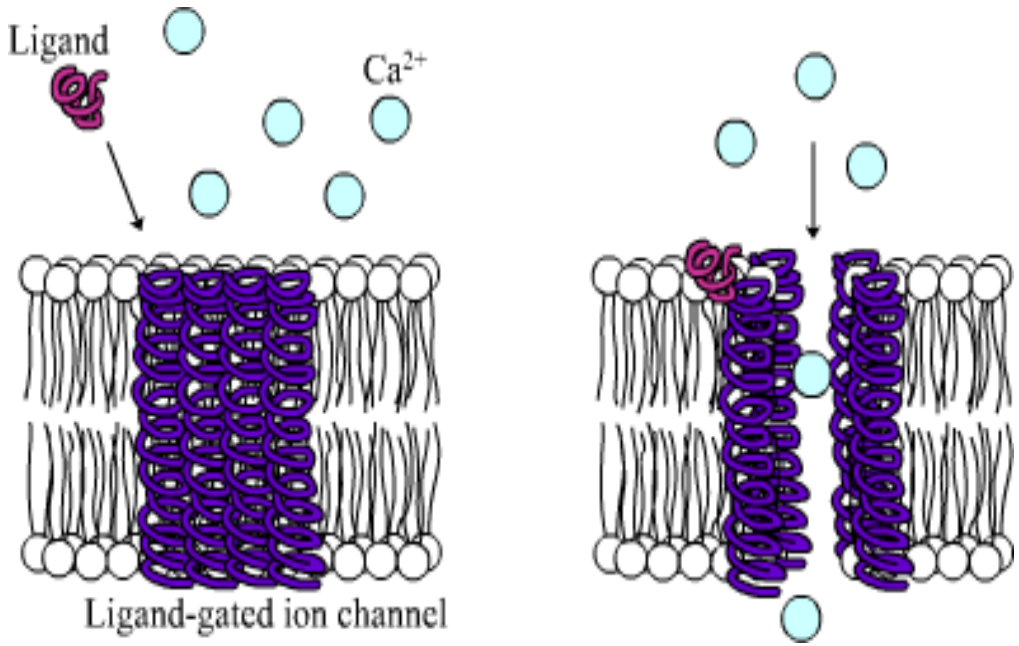
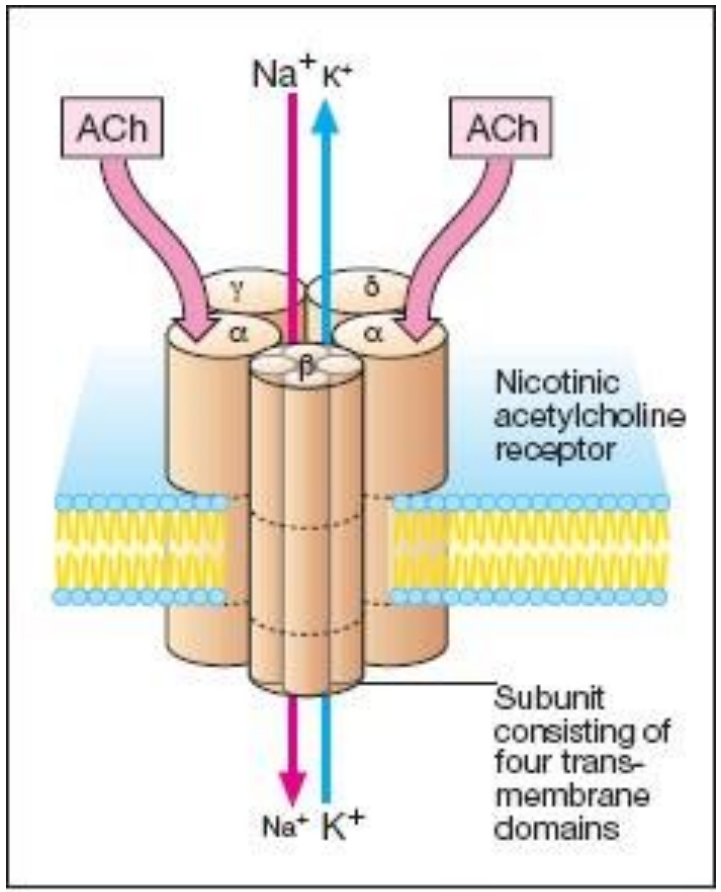
Ligand-gated ion channels

- Responsible for regulation of the flow of ions channels across cell membranes.
- Regulated by binding of a 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 in skeletal muscle



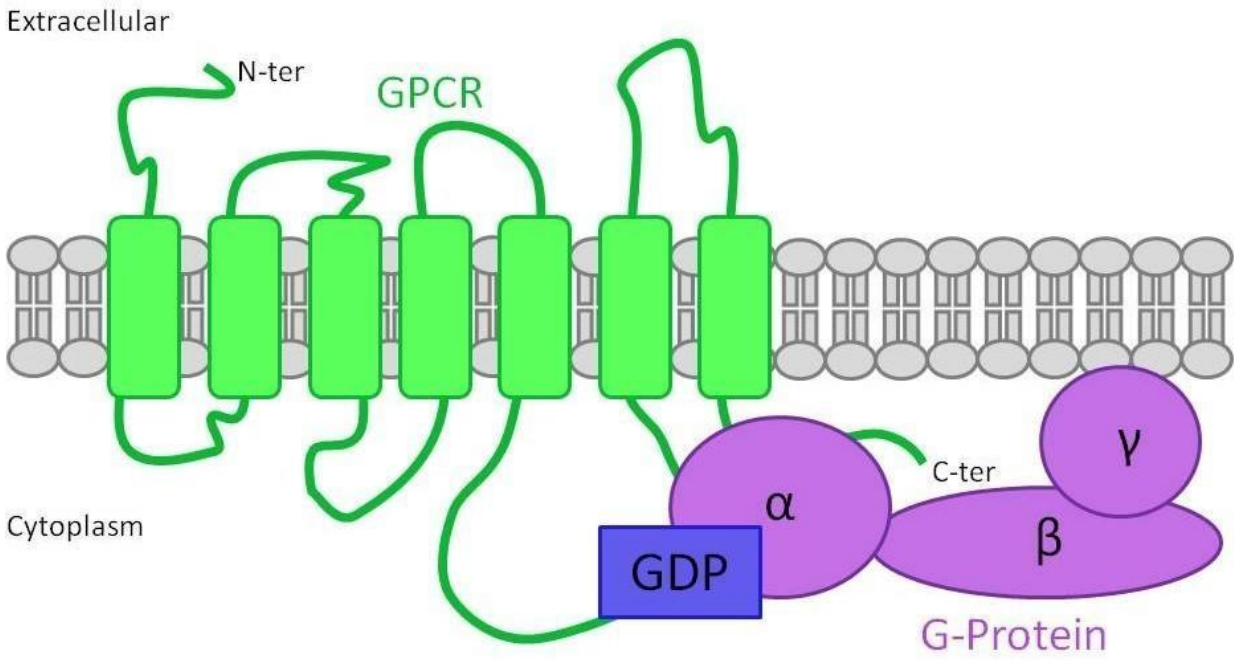


B. Ligand-gated ion channel

It is the biggest family in receptors

GPCR and G PROTEINs

- GPCR are so called because they are bound to an intracellular G protein
- **Guanine nucleotide-binding proteins (G proteins)** act as molecular switches inside cells, and are involved in transmitting signals from a variety of stimuli.



GPCR (G protein-coupled receptor) is an integral membrane protein that crosses the membrane seven times. The G protein is located on the inner surface of the plasma membrane and is attached to the receptor.

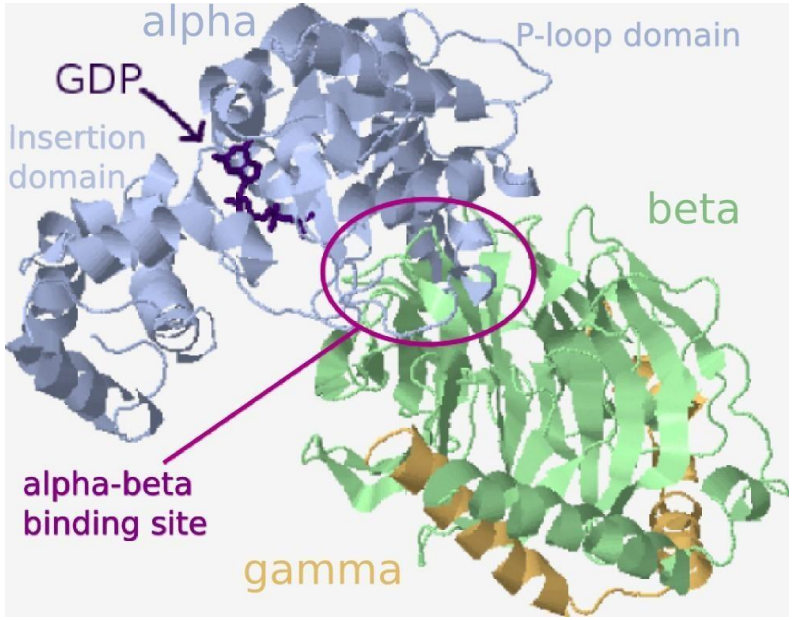
Explanation for the previous picture :

We have three types of subunits in the G protein: alpha (α), beta (β), and gamma (γ). The alpha subunit has four main types: Gs, Gi, Gq, and Go. These different types of α subunits are coupled to different signal transduction pathways, and this is what gives the receptors their selectivity in response to various signals. For example, the Gs subunit causes an increase in cyclic AMP, while Gi causes inhibition of(decrease)cyclic AMP production. That's why in some muscles we observe either contraction or relaxation depending on which G protein is activated.

G PROTEIN

There are two classes of G proteins: the **monomeric small GTPases**, and the **heterotrimeric G protein complexes**.

That's why they are called molecular switches, because they switch between two forms: the active GTP-bound form and the inactive GDP-bound form.



- The heterotrimeric G protein is made up of ***alpha*** (α), ***beta*** (β) and ***gamma*** (γ) subunits.
- The ***alpha*** (α) subunit holds the catalytic GTPase activity.
- The ***beta*** (β) and ***gamma*** (γ) subunits can form a stable dimeric complex referred to as the beta-gamma complex with regulatory activity.

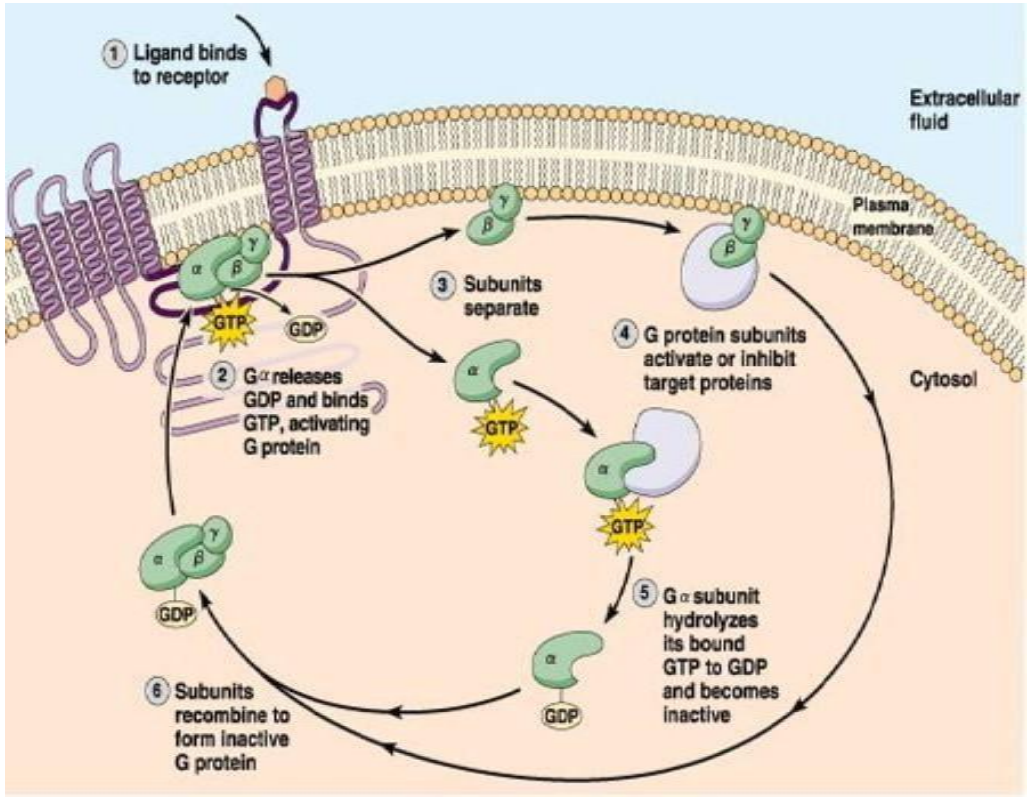
That hydrolyzes GTP to GDP

A stable dimeric complex means that the β and γ subunits always stay together, forming a stable structure that regulates several intracellular signal transduction pathways.

Their activity is regulated by factors that control their ability to bind to and hydrolyze guanosine triphosphate (GTP) to guanosine diphosphate (GDP.(

ACTIVATION/INACTIVATION CYCLE OF GPCR

ACTIVATION: ligand binding results in G-protein exchange of GTP for GDP. The activated G-protein then dissociates into an **alpha (G-alpha)** and a **beta-gamma** complex.



- G-alpha bound to GTP is active, and diffuses along the membrane surface to activate target proteins, (often that generate **second messengers.(**

Like adenylate cyclase for example

- The beta-gamma complex is also able to diffuse and activate proteins, typically affecting ion channels

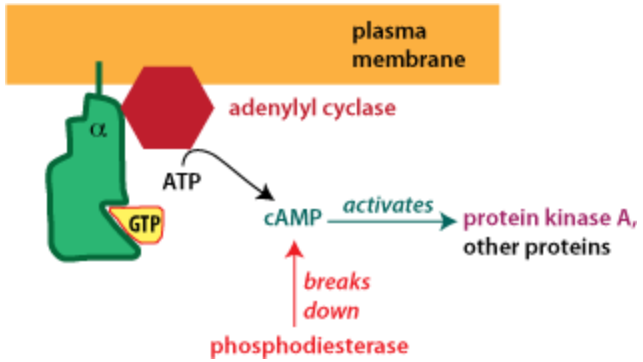
Like calcium channel

INACTIVATION: it occurs because G-alpha has intrinsic **GTPase activity**. After GTP hydrolysis, G-alpha bound to GDP will reassociate with a beta-gamma complex to form an inactive G-protein that can again associate with a receptor

DISTINCT Gα subunits

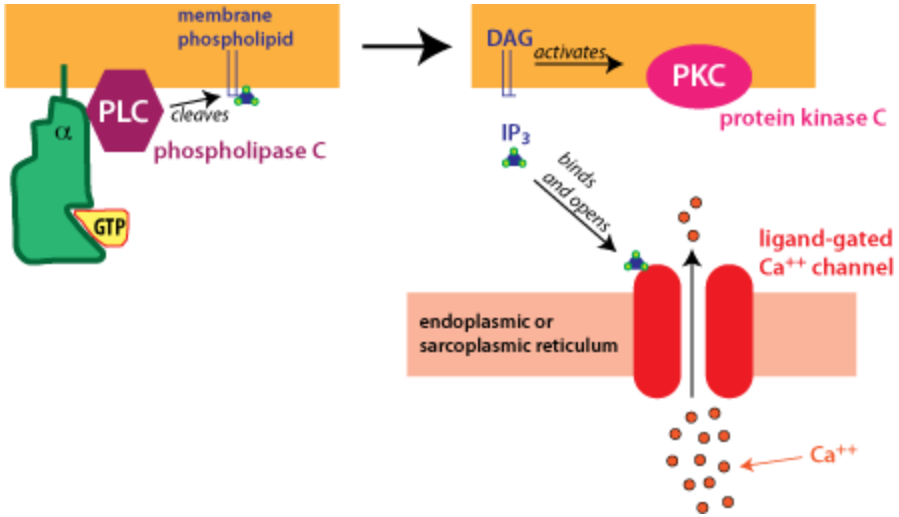
The many classes of G_α subunits behave differently in the recognition of the effector molecule, but share similar activation mechanisms.

differ in the molecules they affect. The difference lies in the signal transduction that comes after them, not in the part that comes up from them that All G-alpha subunits can recognize adrenaline, but they differ in the downstream molecule they act upon



- **G_i/G_o inhibit adenylyl cyclase (AC),** activate K^+ channels or inhibit Ca^{2+} channels

- **Gs activates adenylyl cyclase (AC),** and increase intracellular cAMP levels. cAMP major effect is to bind to and activate **cAMP-dependent kinase (PKA)**



- **G_q activates phospholipase C (PLC),** which transforms PIP_2 into $InsP_3$ and DAG.

In turn, DAG activates protein C kinase (PKC) while InsP3 increases intracellular [Ca.] $^{+2}$

Note: Any kinase causes phosphorylation that usually leads to activation, but sometimes it can be inhibitory depending on the target protein. So it's better to say that it modulates the effect>> change the activity (to become more or less active.

In addition to what mentioned in the previous slide :

- Gi/Go decrease cAMP levels, which can lead to muscle relaxation. They also activate K^+ channels or inhibit Ca^{2+} channels, and this inhibition of Ca^{2+} channels further contributes to the relaxation of muscles.

- Gs activates protein kinase A (PKA), which phosphorylates and mostly activates target proteins; however, in some cases, it can also cause inhibition.

Remember:

- Gi → relaxation.
- Gs → most of the time cause increase in cAMP and more contraction .

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.

- Some hormones peptide receptors and neurotransmitter receptors (e.g., adrenergic and muscarinic receptors depend n the G proteins) mediate their action on cells.

Muscarinic receptors exist on the effector sites of the parasympathetic nervous system.

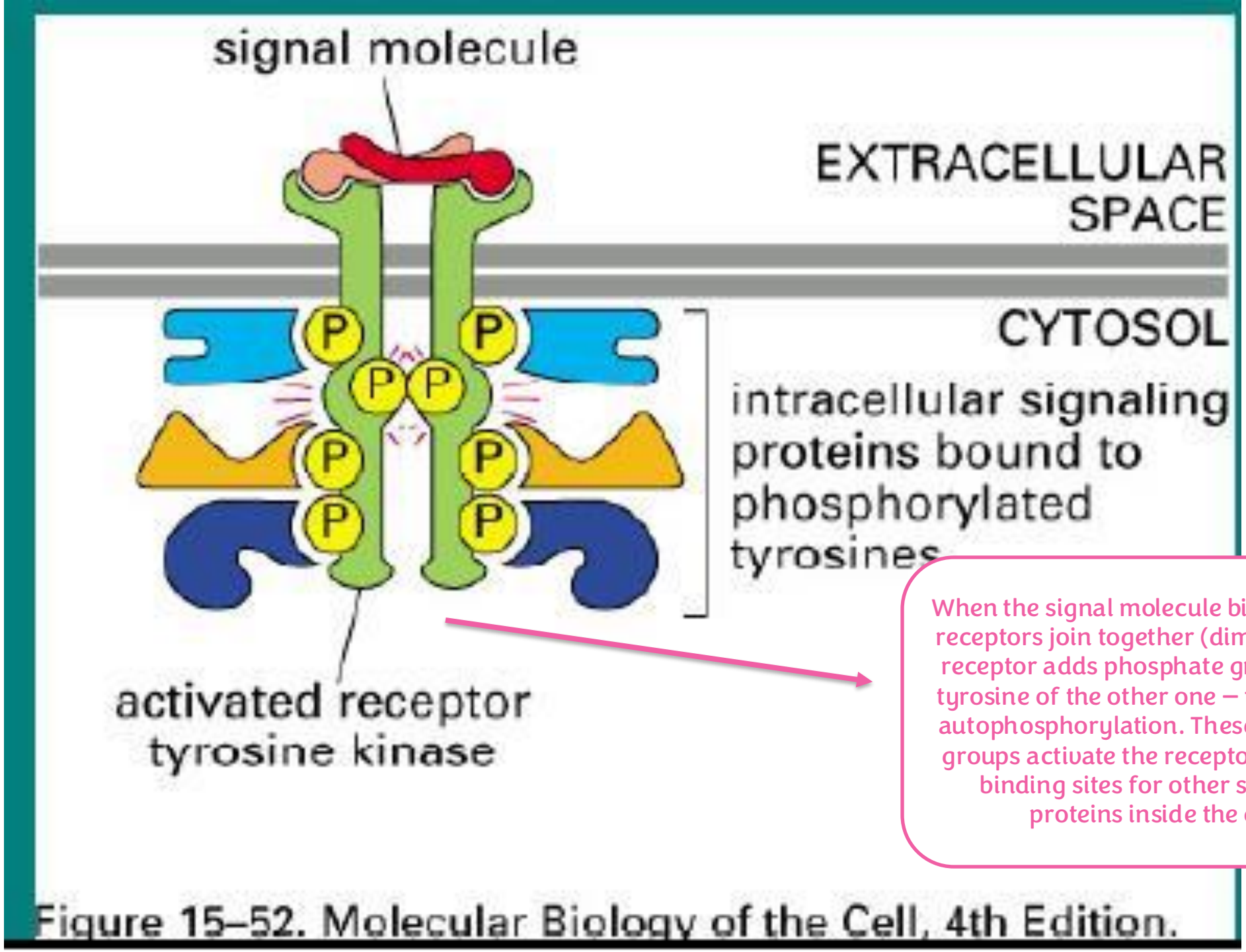
Enzyme-linked receptors

- Binding of the ligand to the extra cellular domain activates or inhibits the related cytosolic enzyme .
- The most common are the receptors that have a tyrosine kinase activity as part of their 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 .

More explanation :

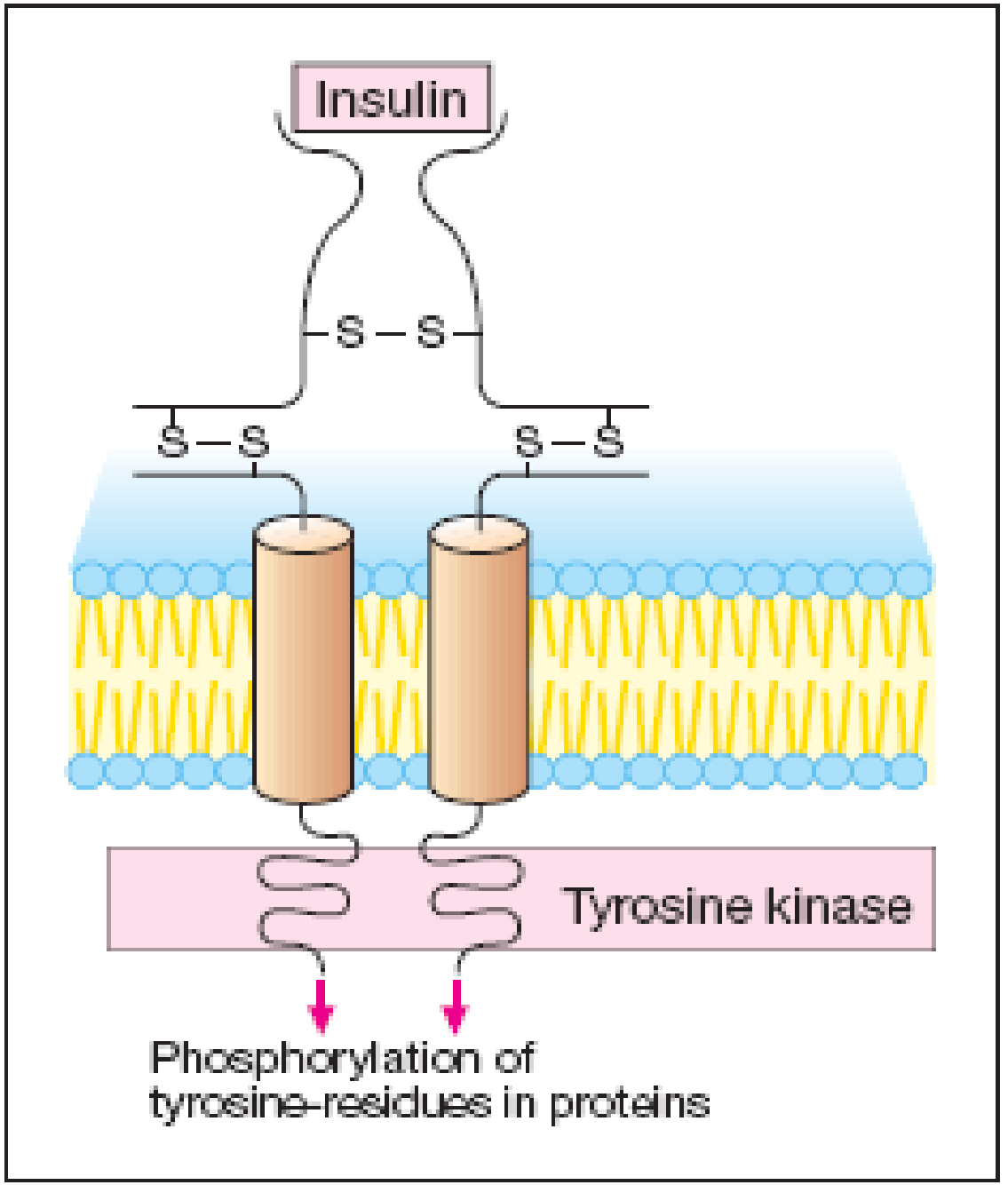
The receptor itself has an intrinsic tyrosine kinase activity, meaning the enzyme is a built-in part of the receptor and not a separate one. When a ligand binds to the extracellular domain of the receptor, it activates this tyrosine kinase activity in the cytosolic domain, leading to phosphorylation of specific target proteins. This phosphorylation works like a molecular switch – it changes the activity of the target protein and starts a signaling cascade inside the cell. These signaling pathways, such as JAK-STAT and Ras-Raf, operate in the cytoplasm to regulate cell functions. If these receptors become overactive or malfunction, they can cause uncontrolled cell growth, leading to cancer. This concept formed the basis for targeted cancer therapies, which specifically inhibit the overactive tyrosine kinase and produce fewer side effects than traditional chemotherapy .

I recommend you listen to this explanation from the doctor as provided in the QR code.



When the signal molecule binds, the two receptors join together (dimerize). Each receptor adds phosphate groups to the tyrosine of the other one – this is called autophosphorylation. These phosphate groups activate the receptor and make binding sites for other signaling proteins inside the cell.

Figure 15–52. Molecular Biology of the Cell, 4th Edition.



C. Ligand-regulated enzyme

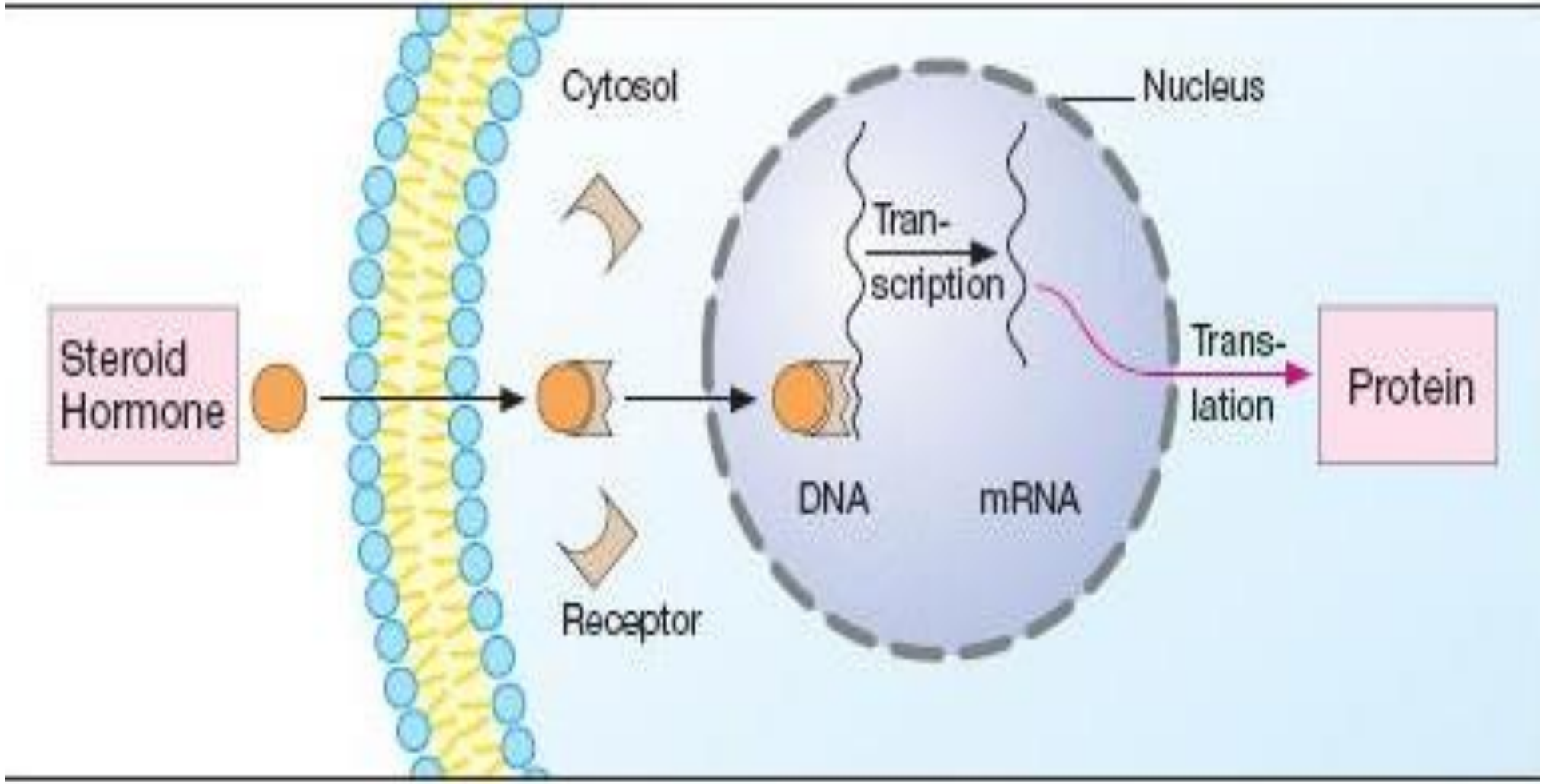
Intercellular receptors

These receptors, also known as nuclear receptors,because they affect the DNA

- In this family the ligand must diffuse into the cell to interact with the receptors .
- Therefore the ligand must have sufficient lipid solubilities to be able to move across the target cell membranes .
- The best example being the steroids hormones. In which the activated ligand-receptor complex migrate to the nucleus, where it bind to a specific DNA sequences, resulting in regulation of the gene expression .

These receptors, also known as nuclear receptors, are located inside the cell, usually in the cytosol.

Their ligands can be drugs or natural molecules (such as steroid hormones like cortisol). To activate the receptor, the ligand must enter the cell – it usually does this by diffusing through the plasma membrane because it is lipid-soluble. Once inside, the ligand binds to its receptor in the cytosol, causing the receptor to become active. After activation, the ligand-receptor complex moves from the cytosol to the nucleus, where it binds to DNA and affects gene expression. This interaction can increase or decrease the production of specific proteins by stimulating or inhibiting transcription. However, not all intracellular ligands can diffuse freely. For example, thyroid hormones (T3 and T4) require special transporters to cross the plasma membrane and reach their receptors inside the cell.



D. Protein synthesis-regulating receptor

HOW DO DRUGS WORK?

Most work by interacting with endogenous proteins:

- Some *antagonize, block or inhibit endogenous proteins*
- Some *activate endogenous proteins*
- A few have *unconventional mechanisms of action*

HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

- Antagonists of Cell Surface Receptors
- Antagonists of Nuclear Receptors
- Enzyme Inhibitors
- Ion Channel Blockers
- Transport Inhibitors
- Inhibitors of Signal Transduction Proteins

Definition of *CELL SURFACE RECEPTOR*:

A receptor that is embedded in the cell membrane and functions to receive chemical information from the extracellular compartment and to transmit that information to the intracellular compartment .

HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS? KEY CONCEPTS:

- **Cell surface receptors exist to transmit chemical signals from the outside to the inside of the cell.**

- **Some compounds bind to cell surface receptors, yet do not activate the receptors to trigger a response.**

- **When cell surface receptors bind the molecule, the endogenous chemical cannot bind to the receptor and cannot trigger a response.**

- **The compound is said to "antagonize" or "block" the receptor and is referred to as a receptor antagonist.**

Neutral antagonist : a compound that binds to the binding sites in a receptor and takes place of the endogenous ligand without giving me an effect

Beta adrenergic receptor in the heart increases heart rate.
Adrenaline or noradrenaline binds to the beta receptor and activate the G-protein molecule and increase cAMP to increase heart rate

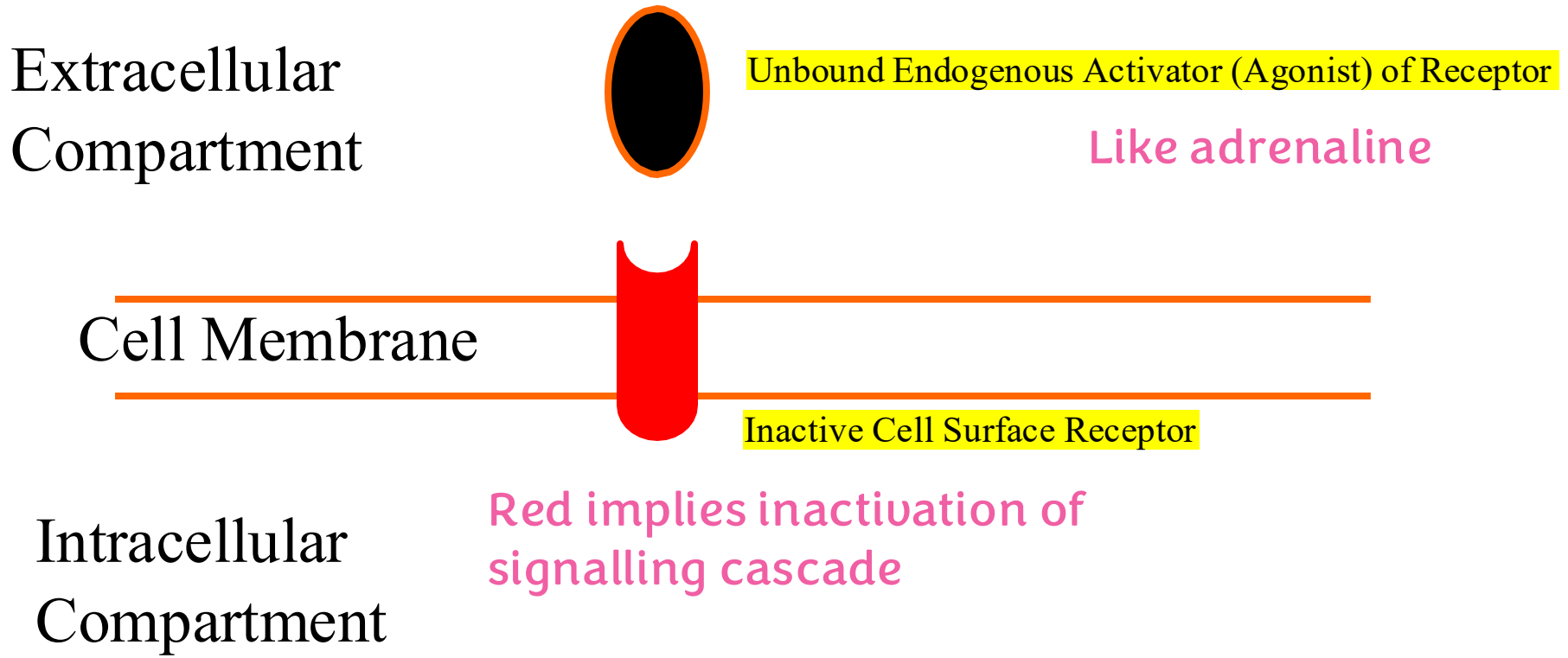
Let's talk about propranolol (a beta blocker) , it is bound to beta1 receptor, it prevents the signaling by taking the place of adrenaline>>> which will decrease heart rate . This is what antagonist do , they take the place of the endogenous ligand.
The beta blocker here will bind only for milliseconds and then it gets removed and another drug molecule or adrenaline or noradrenaline will bind instead (because of the reversible binding those ligands make) ; this is called the competitive effect.
If the endogenous ligand's concentration (adrenaline/noradrenaline) = beta blocker (drug) concentration and they both have equal affinity to the target. ,, they both will bind to the receptor for the same amount of time
يعني وحدة بتفك و وبتربط محلها التانية و هكذا

Some compounds bind to cell surface receptors, yet do not activate the receptors to trigger a response

This means that the antagonist doesn't do anything inside the cell like the normal ligand , it just occupied the space intended for the ligand (adrenaline/ noradrenaline) . And it prevent the activation of the receptor so automatically this will create an "inhibition" but it doesNOT activate the Gi subunit, but only stopped the Ga subunit.

IT DOES NOT HAVE A RESPONSE BUT ONLY PREVENTS THE ORIGINAL RESPONSE

HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?



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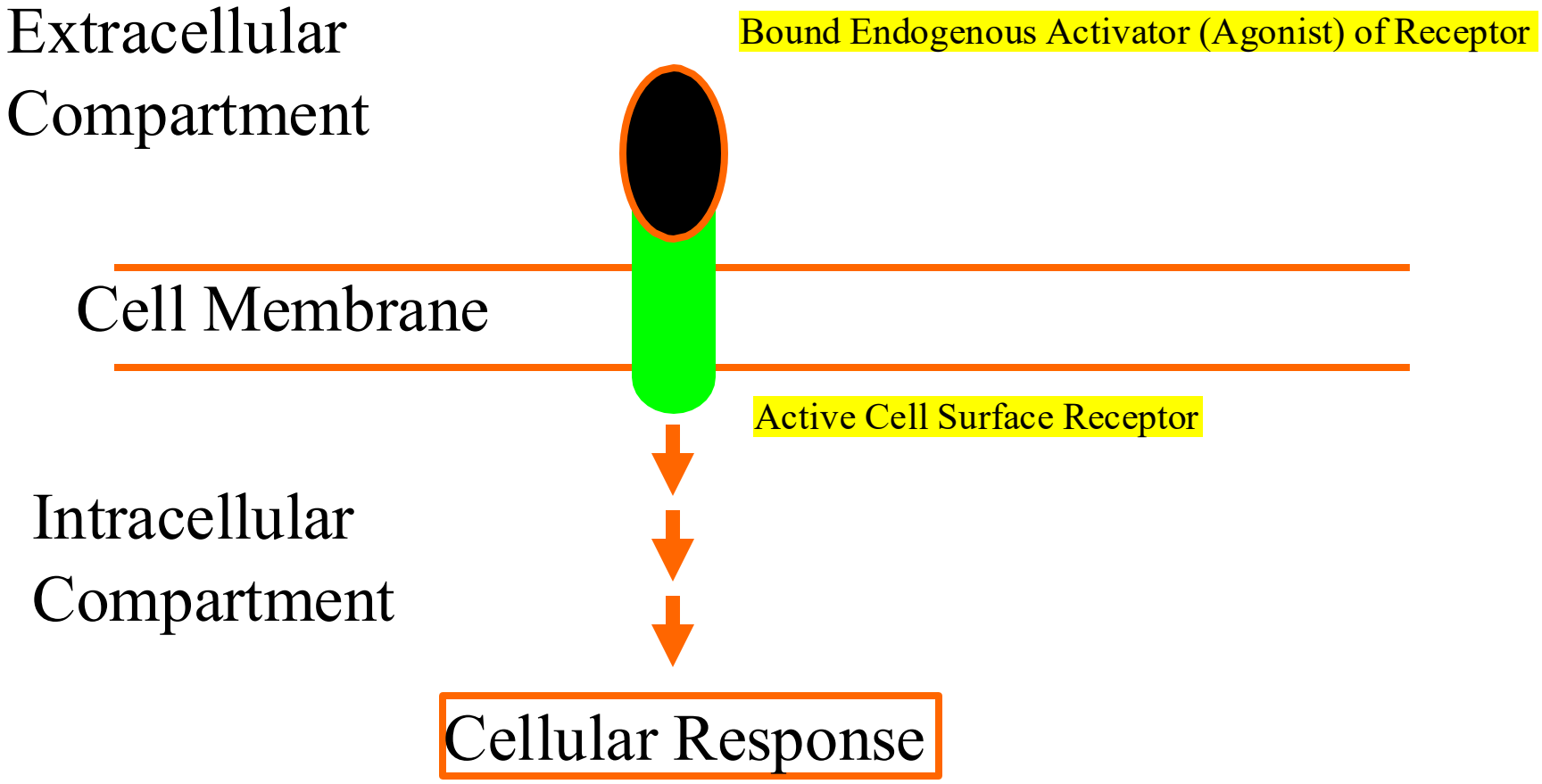

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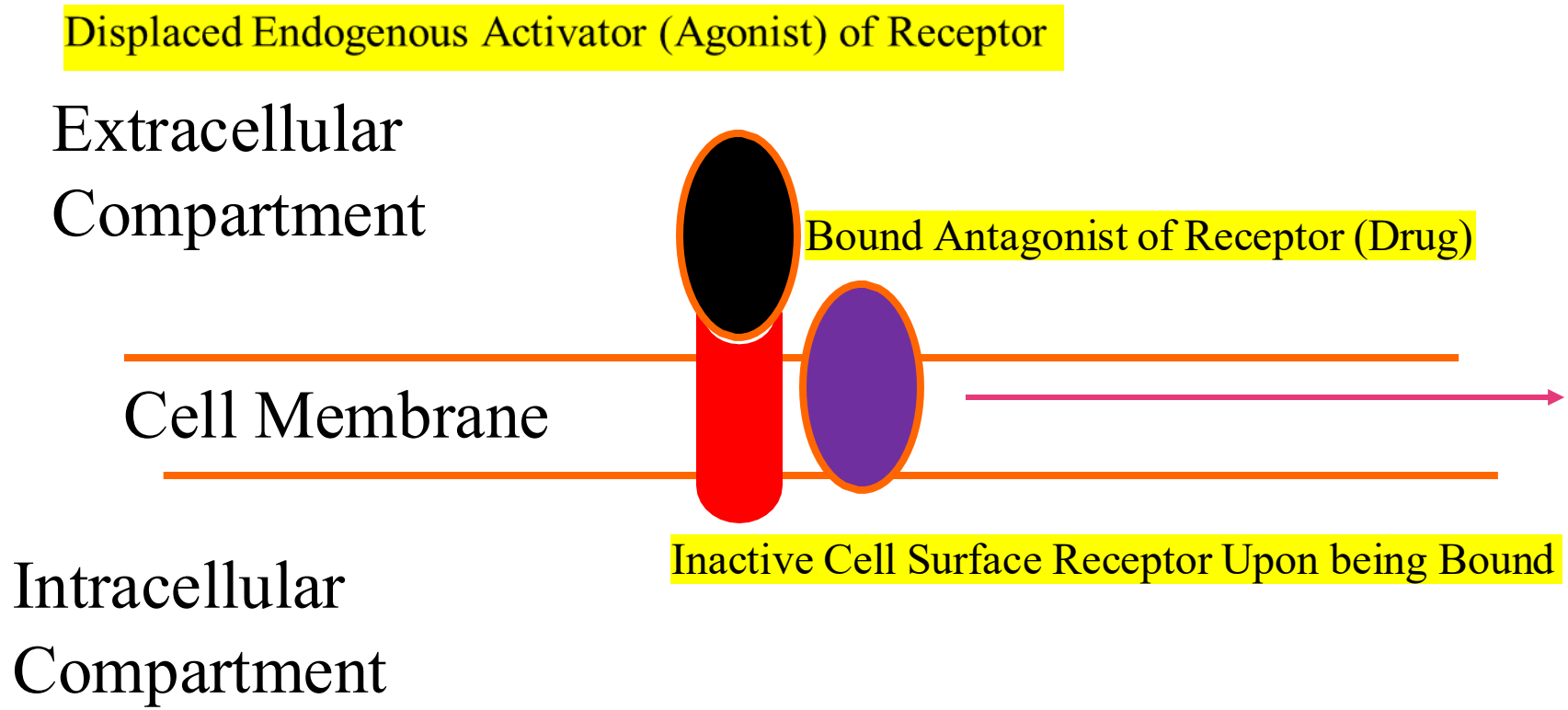


Looks exactly like the endogenous ligand , it will occupy its place but will not have any activation response.

If we said that the endogenous ligand gives me a positive response, then the neutral antagonist gives zero response. (But prevents the positive response that's why I am getting a decrease in response)

I prefer my drug to be noncovalent so it binds reversibly so there will be times that ligands bind...the endogenous ligand and drug compete to bind to the receptor's same binding site : this is called competitive antagonism.
If the bond is irreversible, there will be no competition

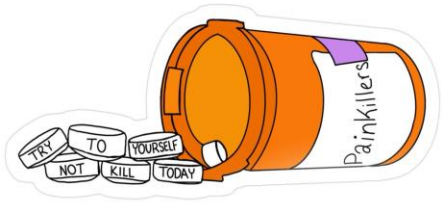
If we change the concentration of any of the two , the effect will prevail to the higher in concentration. So will be the effect if we increase one's affinity over the other.
This is the reason why when we have different drugs and all of them target the same receptor we will have different responses for each one; because they differ in their affinity for it

HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?

Footnote:

Most antagonists attach to binding site on receptor for endogenous agonist and sterically prevent endogenous agonist from binding.
If binding is reversible - Competitive antagonists
If binding is irreversible - Noncompetitive antagonists

The drug will have a longer effect.
There are ways to get rid of the binding, but definitely not through concentration

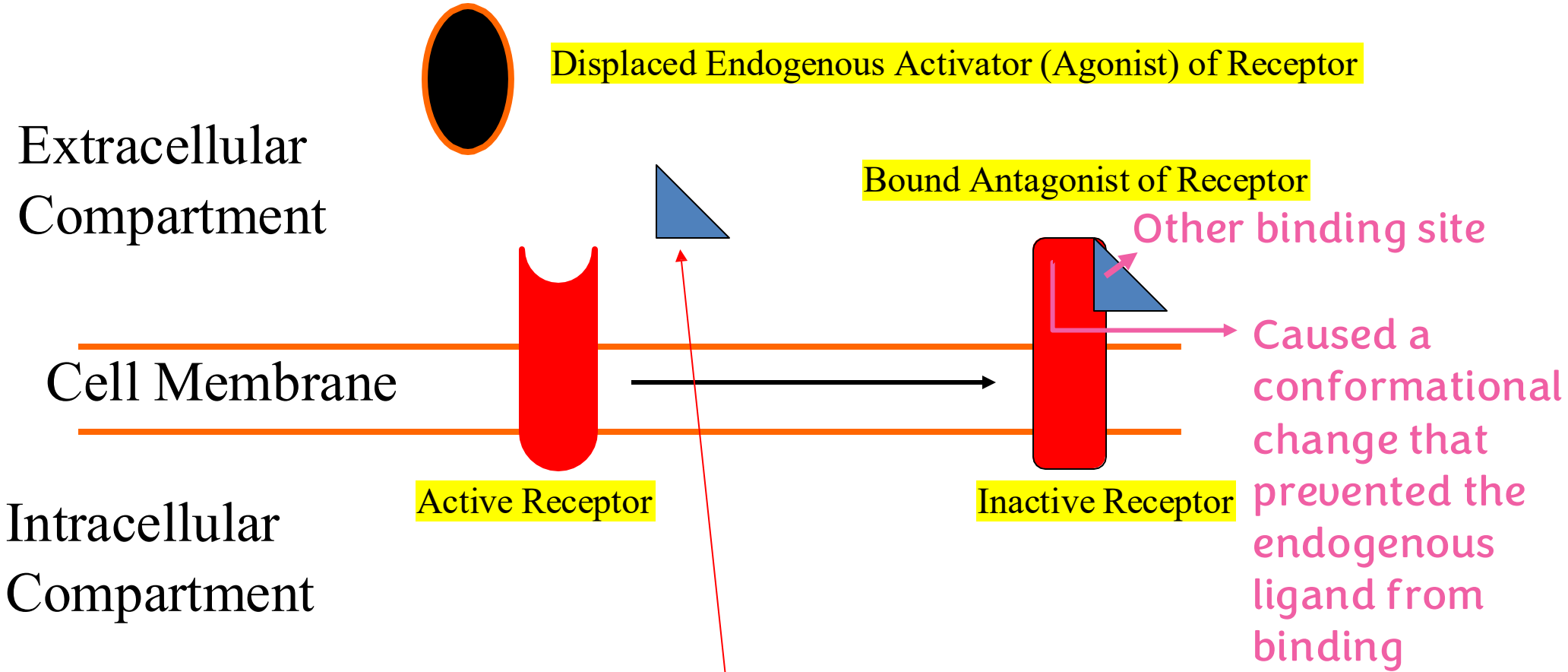


Displace : طرد

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

Allo : using a different place other than the one meant for the endogenous

HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?



Not competitive but it gave me an antagonistic effect by causing a conformational change that prevented the endogenous ligand from binding

ARE DRUGS THAT ANTAGONIZE CELL SURFACE RECEPTORS CLINICALLY USEFUL?

Some important examples:

Angiotensin Receptor Blockers (ARBs) for high blood pressure , heart failure, chronic renal insufficiency)losartan [Cozaar®]; valsartan [Diovan(]®

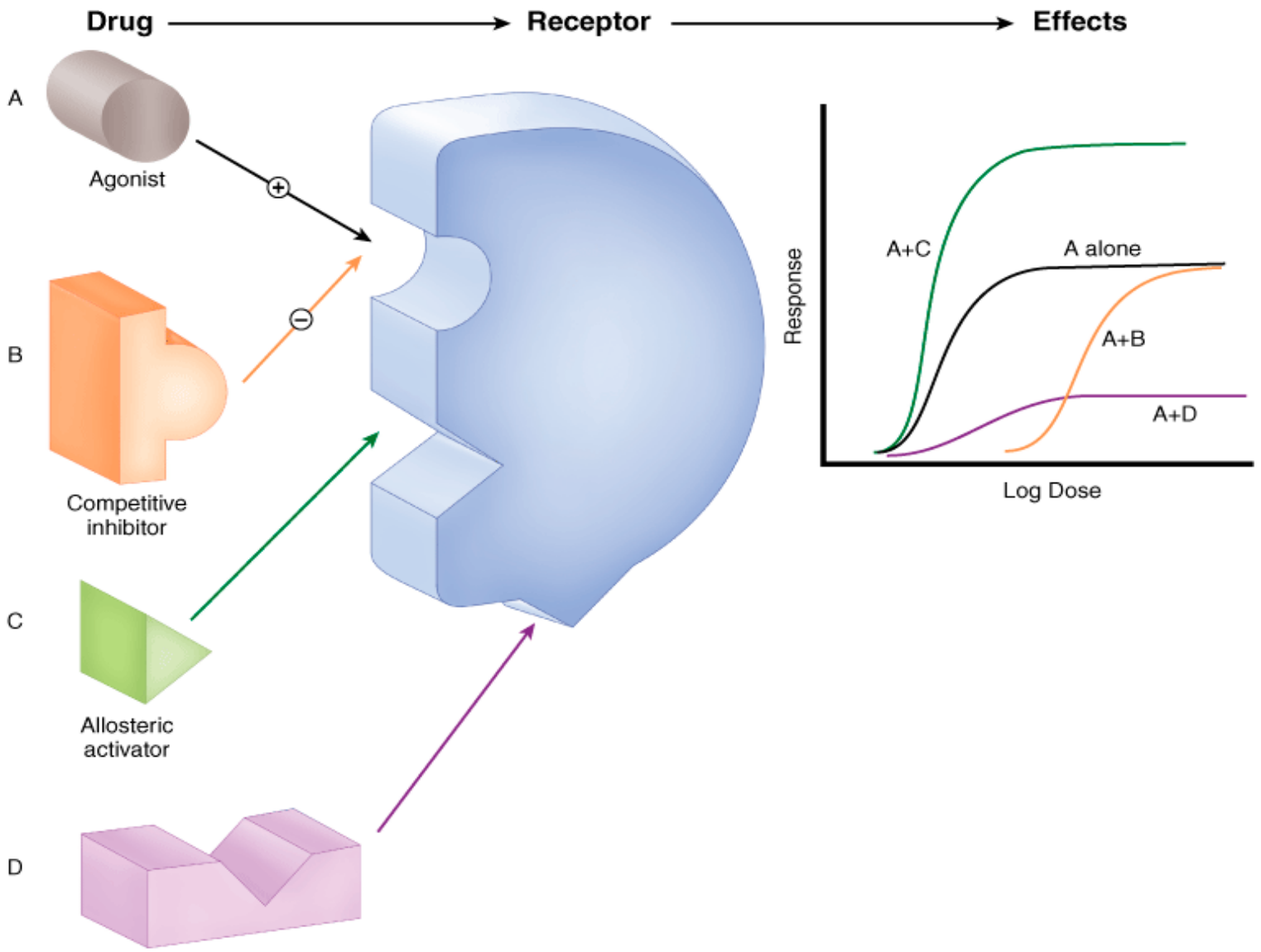
Block angiotensin (endogenous) from binding to its receptor and stop it from doing its function in rising blood pressure-> blood pressure will decrease

Beta-Adrenoceptor Blockers for angina, myocardial infarction , heart failure, high blood pressure, performance anxiety)propranolol [Inderal®]; atenolol [Tenormin(]®

Not selective

Selective

Drug Receptor Interactions



HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

Antagonists of Cell Surface Receptors

- Antagonists of Nuclear Receptors

- Enzyme Inhibitors

- Ion Channel Blockers

- Transport Inhibitors

The drug here also needs to be able to diffuse through plasma membrane to interact with intracellular receptors and bind to prevent endogenous ligand binding and effect

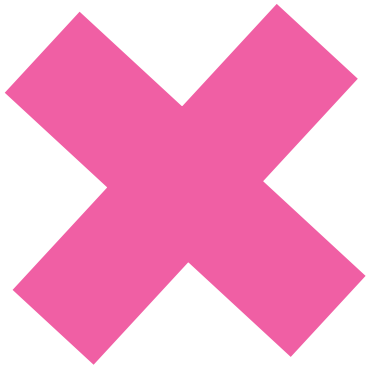
- Inhibitors of Signal Transduction Proteins

ARE DRUGS THAT ANTAGONIZE NUCLEAR RECEPTORS CLINICALLY USEFUL?

Some important examples:

- Mineralocorticoid Receptor Antagonists for edema due to liver cirrhosis and for heart failure (spironolactone [Aldactone®])

- Estrogen Receptor Antagonists for the prevention and treatment of breast cancer (tamoxifen [Nolvadex®])



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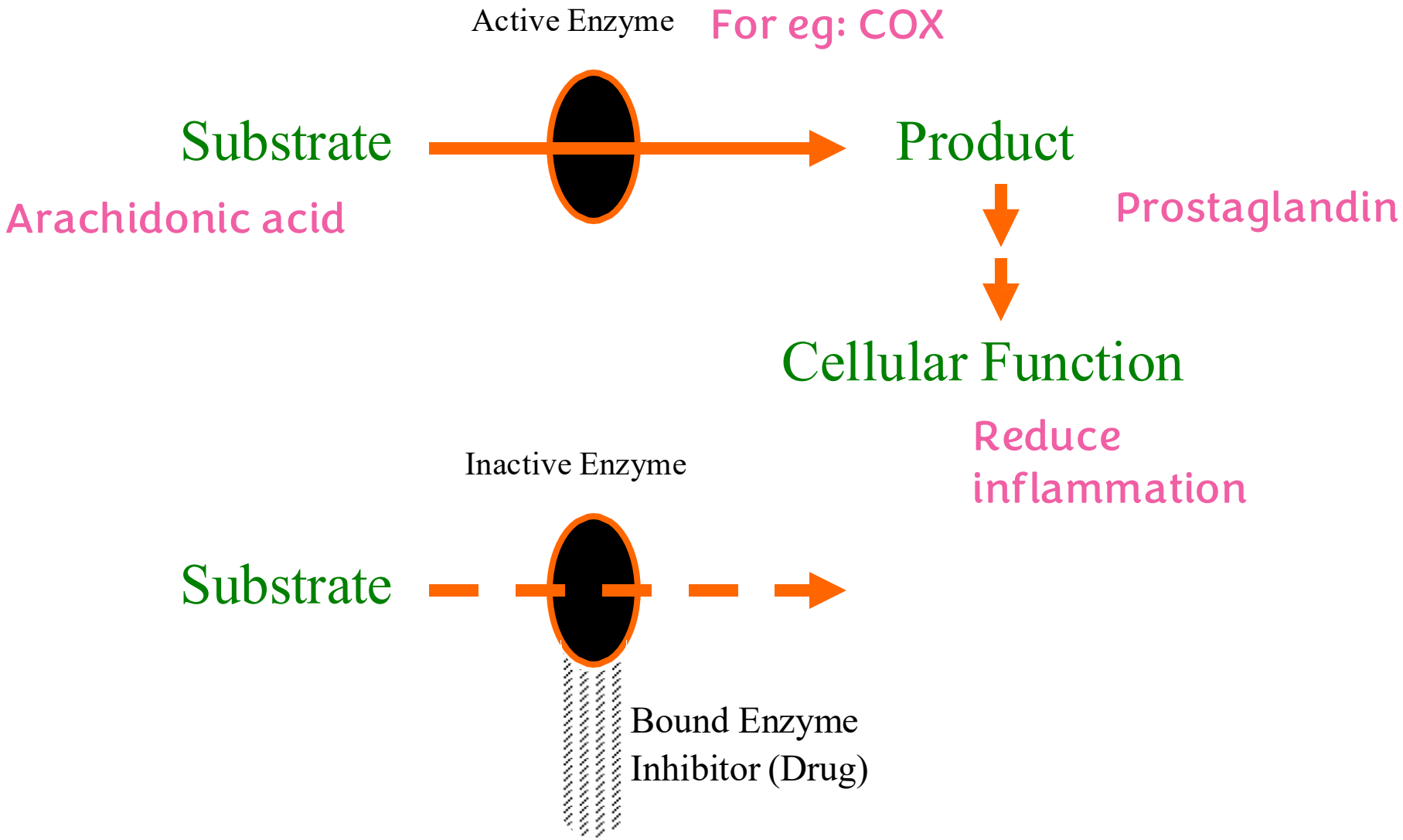
HOW DO DRUGS WORK BY INHIBITING ENZYMES?



HOW DO DRUGS WORK BY INHIBITING ENZYMES? KEY CONCEPTS:

Enzymes catalyze the biosynthesis of products from substrates.

- Some drugs bind to enzymes and inhibit enzymatic activity.

- Loss of product due to enzyme inhibition mediates the effects of enzyme inhibitors.

ARE DRUGS THAT INHIBIT ENZYMES CLINICALLY USEFUL?

Some important examples:

• Cyclooxygenase Inhibitors for pain relief, particularly due to arthritis (aspirin; ibuprofen [Motrin(]®

not required

HMG-CoA Reductase Inhibitors for hypercholesterolemia)atorvastatin [Lipitor®]; pravastatin [Pravachol(]®

Angiotensin Converting Enzyme (ACE) Inhibitors for high blood pressure, heart failure, and chronic renal insufficiency)captopril [Capoten®]; ramipril [Altace(]®

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ARE DRUGS THAT BLOCK ION CHANNELS CLINICALLY USEFUL?

Some important examples:

Calcium Channel Blockers (CCBs) for angina and high blood pressure
)amlodipine [Norvasc®]; diltiazem [Cardizem(]®

• Sodium Channel Blockers to suppress cardiac arrhythmias
)lidocaine [Xylocaine®]; amiodarone [Cordarone(]®

Heart and vascular diseases : When Ca+ enters the cell it leads to contraction of the muscle (smooth muscles in blood vessels here)>which will lead to vasoconstriction and hypertension > using this drug in hypertension cases will led to vasodilation-> decreasing hypertension.

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ARE DRUGS THAT INHIBIT TRANSPORTERS CLINICALLY USEFUL?

Some important examples:

Selective Serotonin Reuptake Inhibitors (SSRIs) for the treatment of depression

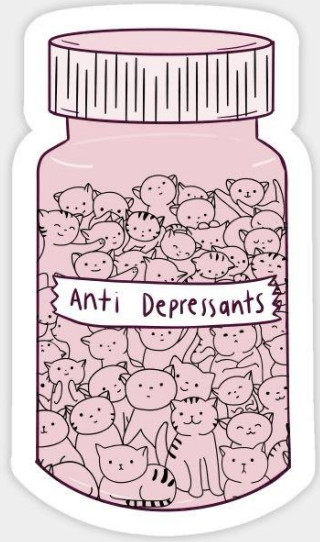
)fluoxetine [Prozac®]; fluvoxamine [Luvox(]®

Inhibitors of Na-2Cl-K Symporter (Loop Diuretics) in renal epithelial cells to increase urine and sodium output for the treatment of edema

)furosemide [Lasix®]; bumetanide [Bumex(]®

SSRIs:

Serotonin will be released to the synaptic cleft (this is the hormone of happiness) and it will bind to its receptors but the body are not going to leave it released for so long , there transporters that take it back to the nerve endings . SSRI prevents this re-uptake and the hormone will stay longer in the cleft. -> this increases the chances of activating the receptors and your mood will be raised (this is why we use it as an antidepressant)



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ARE DRUGS THAT INHIBIT SIGNAL TRANSDUCTION PROTEINS CLINICALLY USEFUL?

Some important examples:

Tyrosine Kinase Inhibitors for chronic myelocytic leukemia

)imatinib [Gleevec(]®

It has been found that some types of cancer are due to tyrosine kinase being overactive, so drugs were developed to inhibit it

For blood cancer only

Type 5 Phosphodiesterase Inhibitors for erectile dysfunction

)sildenafil [Viagra(]®

- This is a major focus of drug development

Additional Resources:

رسالة من الفريق العلمي:

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			