بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

PHYSIOLOGY

وَلَقَدْ خَلَقْنَا الْإِنسَانَ وَنَعْلَمُ مَا تُوَسْوِسُ بِهِ نَفْسُهُ ۖ وَنَحْنُ أَقْرَبُ إِلَيْهِ مِنْ حَبْلِ الْوَرِيدِ

Final | Lecture 5

Receptors Functions and Signal Transduction Pt.3

Written by : Amal Al-khatib
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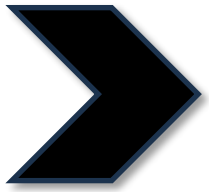
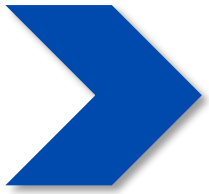
Color coding used in the modified:

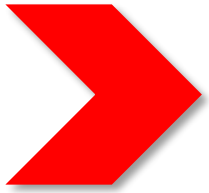


Black: the original slides



Blue: the doctor's explanation/words

Gray: additional information and explanation



Red: important information

Receptors Functions and Signal Transduction- L3

Faisal I. Mohammed, MD, PhD

Second Messenger Targets

- Enzymes
  - Modulate phosphorylation
  - Phosphorylation ⇨ **activation or inactivation**
- Protein Kinases
  - Increase phosphorylation of proteins or substrate like enzymes
- Protein Phosphatases decrease phosphorylation
  - Activated by Ca2+/calmodulin
  - Decrease phosphorylation ~

Second Messengers

- Calcium (Ca^{2+})
- Target: calmodulin
- Calmodulin ⇨ protein kinases B (calcium calmodulin dependent protein kinase)
- Cyclic nucleotides
- cAMP & cGMP
- Target: protein kinases ~

Second Messengers

- Diacylglycerol (DAG) & IP3
- From membrane lipids
- DAG ⇨ Protein Kinase C (membrane)
- IP3 ⇨ Ca2+ (endoplasmic reticulum) ~

To sum up :
Protein kinase A = cAMP dependent protein kinase .
Protein kinase C = DAG or Phospholipid-calcium dependent protein kinase .
Protein kinase B = Calcium-Calmodulin-dependent Protein Kinase.

So basically

When the ligand binds to the receptor, it activates **phospholipase c**. This enzyme acts on the membrane phospholipids and splits them into two things: **diacylglycerol (DAG) and IP3**, which comes from **inositol bisphosphate**. **DAG** stays in the membrane, while **IP3** moves down into the cytoplasm. **IP3** then goes and stimulates the release of calcium from the endoplasmic reticulum, so now you have an increase in intracellular calcium. At this point, **calcium** works together with **DAG**, and both of them activate a **protein kinase called protein kinase C (PKC)**. Now for the calcium side on its own—when calcium increases inside the cell, it binds to an intracellular protein called **calmodulin** (intracellular protein which calcium binding protein). **Calmodulin** is **inactive** at first, but once it binds **calcium**, it becomes **active**. After activation, this calcium-calmodulin complex goes and activates **protein kinase B**, which is called a **calcium-calmodulin dependent protein kinase**.

Hormones That Use 2nd Messengers

- Hormones cannot pass through plasma membrane (water soluble) use 2nd messengers.
- Catecholamine, polypeptide, and glycoprotein hormones bind to receptor proteins on the target plasma membrane.
- Actions are mediated by 2nd messengers (signal-transduction mechanisms).
- Extracellular hormones are transduced into intracellular 2nd messengers.

Function of the second messenger is the amplification of response

Water-soluble hormones cannot pass through the plasma membrane, so instead of entering the cell, **they bind to receptor proteins located on the cell's surface**. These hormones include **catecholamines** such as **epinephrine, norepinephrine, and dopamine,** as well as **polypeptide** and **glycoprotein** hormones. Because they **stay outside** the cell, their effects are carried out **through second messenger systems** inside the cell. When the hormone binds to its membrane receptor, it **activates a signal-transduction pathway**, for example by stimulating **adenylyl cyclase to produce cyclic AMP (cAMP).** This cAMP then **activates protein kinases**, which go on to **phosphorylate many different proteins** within the cell. The reason this process is called amplification is that **a single hormone binding event** leads to the **production** of **many cAMP molecules**, which activate multiple protein kinases, which then affect a large number of proteins, resulting in a strong and widespread cellular response.

Adenylate Cyclase-cAMP

- Polypeptide or glycoprotein hormone binds to receptor protein causing dissociation of α subunit of G-protein. G-proteins subunits : Alpha,beta and gamma subunits
- G-protein subunit binds to and activates adenylate cyclase.
- ATP → cAMP + PPi
- cAMP attaches to inhibitory subunit of protein kinase.
- Inhibitory subunit dissociates and activates protein kinase.

Adenylyl Cyclase–cAMP Second Messenger System

- Stimulation of adenylyl cyclase, by the Gs protein
- Catalyzes the conversion of a small amount of cytoplasmic *Adenosine triphosphate ATP* into cAMP inside the cell.
- Then activates *cAMP-dependent protein kinase.* Protein kinase A
- Phosphorylates specific cell proteins, triggering biochemical reactions that ultimately lead to the cell's response to the hormone.

Not all cells that have cyclic AMP have the same action (each cell response depends on the specifity)

Gs protein is the stimulus part of the G-protein

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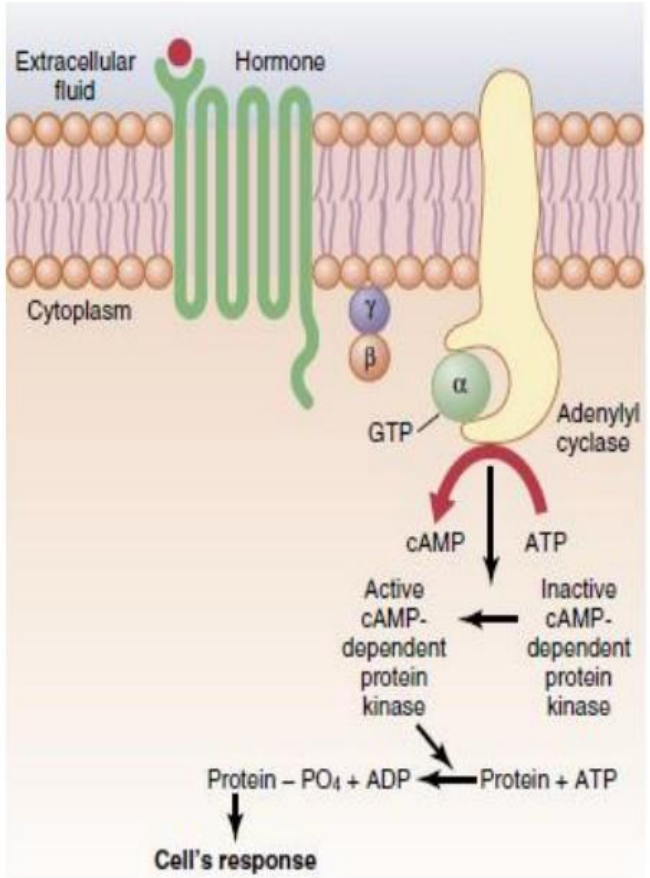


Make sure that you understand this image

It binds to a specific area in the DNA, why specific so that it can form a specific protein (transcription)

CREB : cAMP Response element Binding protein) which is specific protein acts as receptor

A. cAMP:

❖ Regulation of adenylate cyclase:

Receptors that cause increase in cAMP do so by activating G_s, a stimulatory protein that activates adenylyl cylcase

Adenylyl cyclase is turned off by G_i, an inhibitory protein.

PKA enters the nucleus and phosphorylates CREB (CRE binding protein), which binds to the cAMP response element (CRE), a regulatory DNA sequence associated with specific genes. This results in activation of transcription of those genes.

B. cGMP:

1. produced from GTP by guanylyl cyclase;
2. activates cGMP-dependent kinases or other targets
3. example: G-prot. Coupled rhodopsin photoreceptor in rod cells of retina

So second messenger can act on the gene system

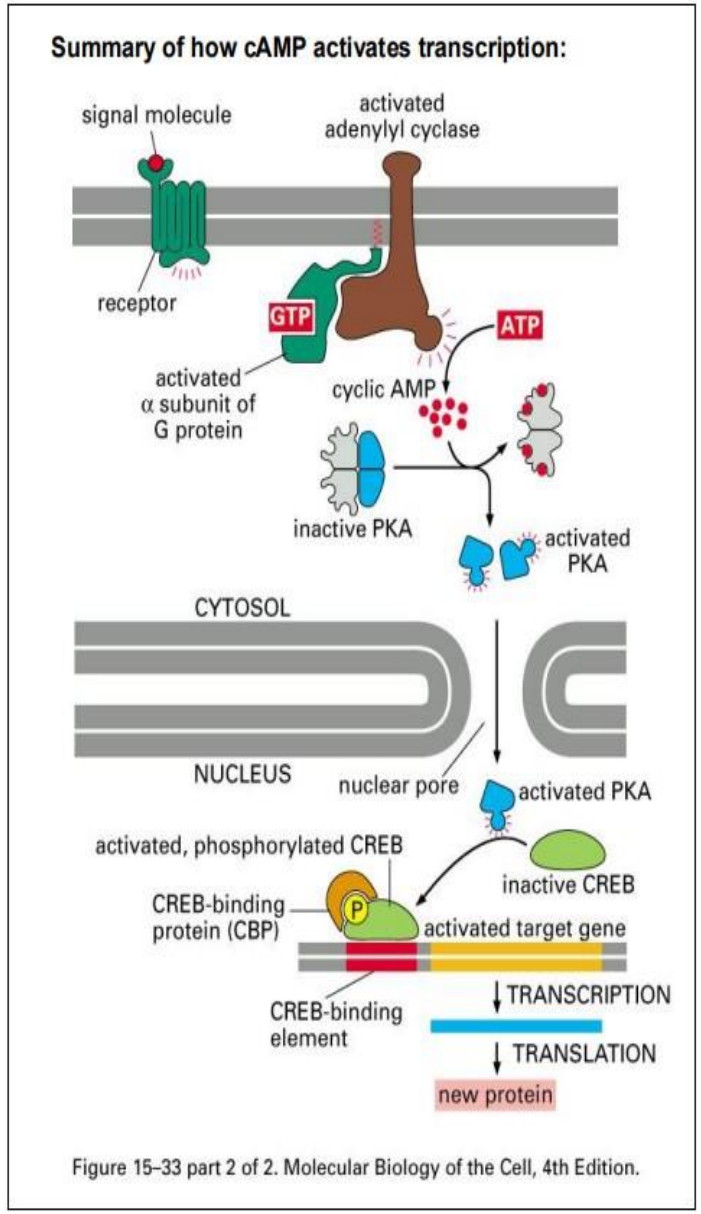
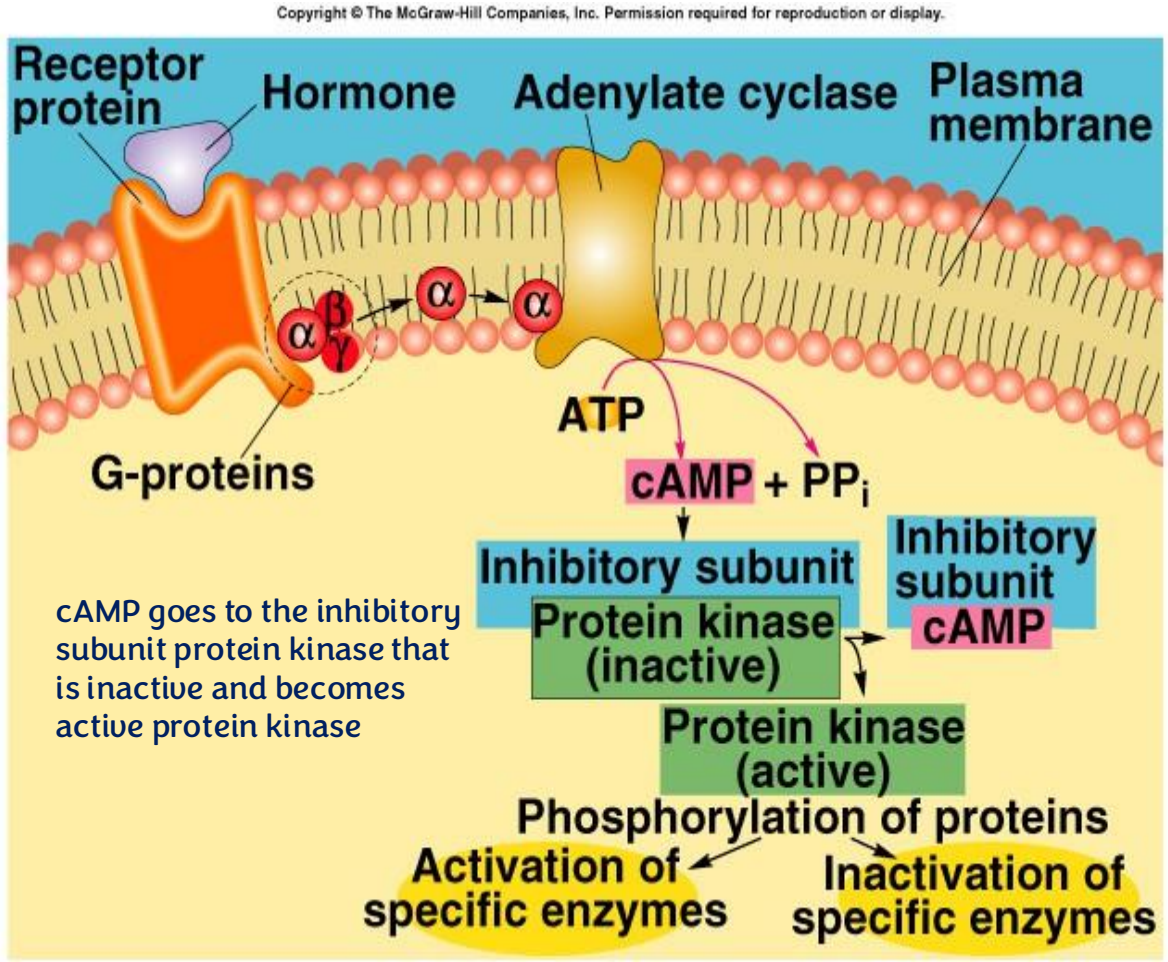


Figure 15–33 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

Adenylate Cyclase-cAMP (continued)

- Phosphorylates enzymes within the cell to produce hormone's effects.
- Modulates activity of enzymes present in the cell.
- Alters metabolism of the cell.
- cAMP **inactivated by phosphodiesterase.**
- Hydrolyzes cAMP to inactive fragments.



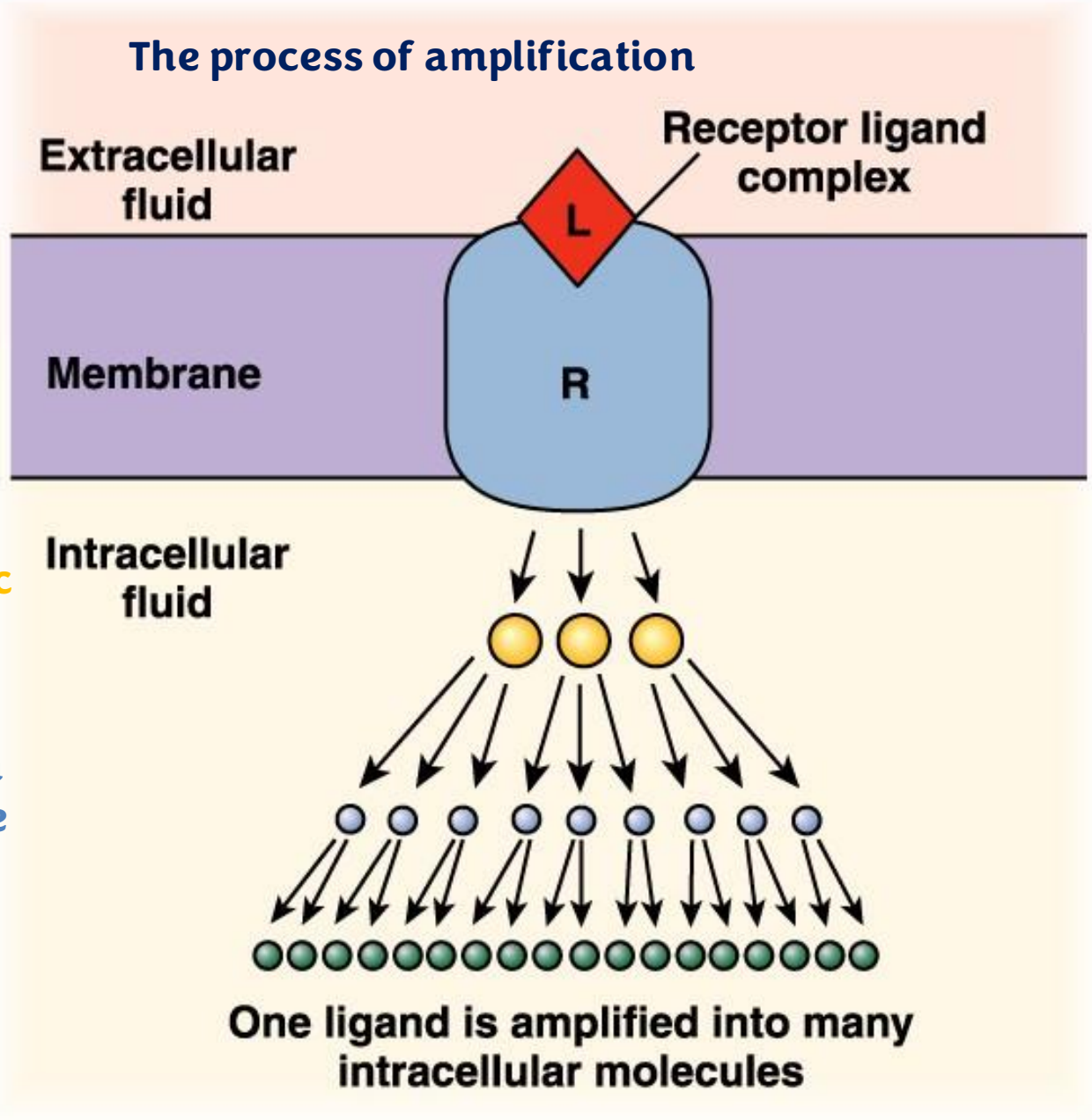
3 Cyclic AMP, each cyclic AMP activates

⇩

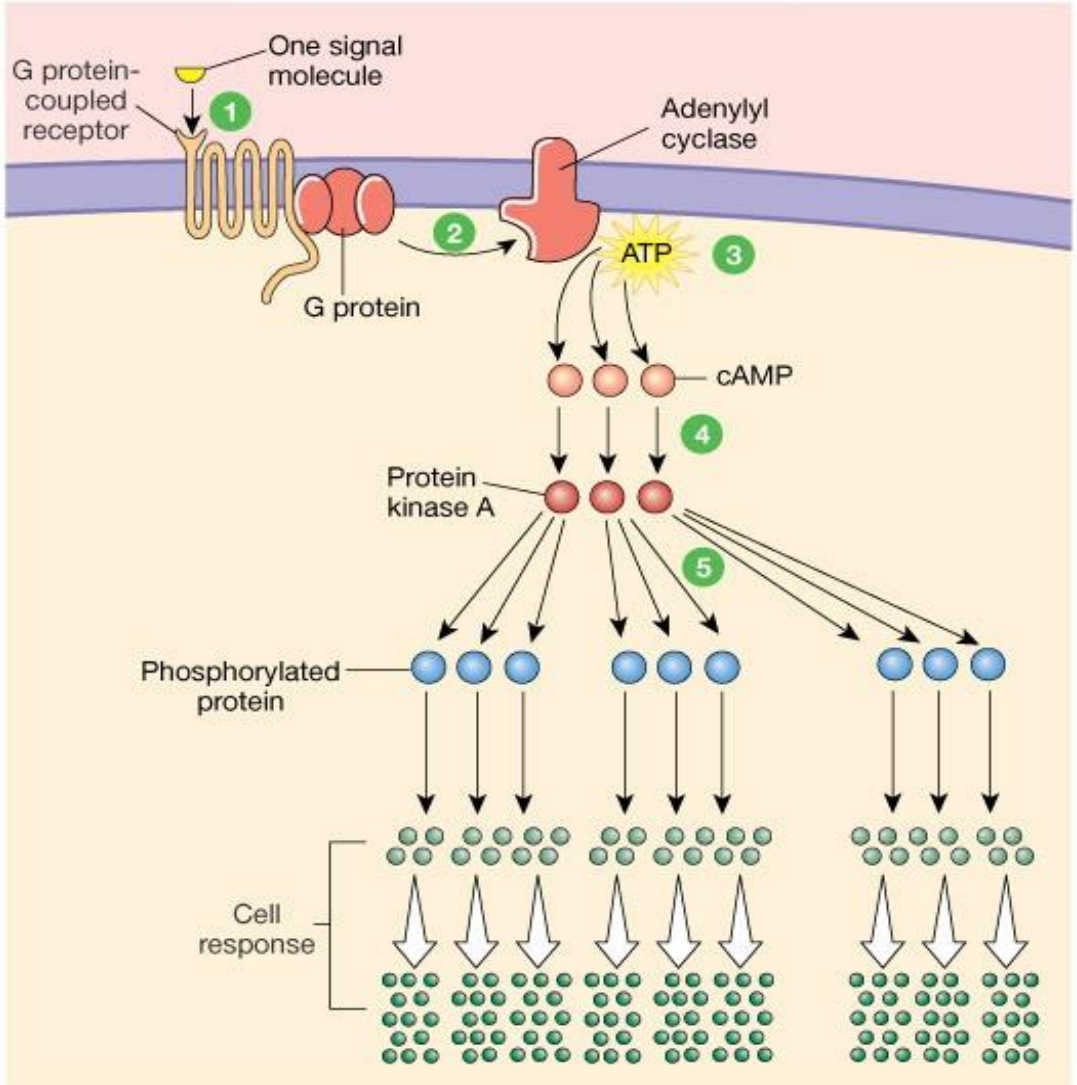
Activates too many protein kinase, each protein kinase phosphorylates

⇩

Too many hormones



G-Protein-coupled Receptors



1. Signal molecule binds to G protein-linked receptor, which activates the G protein.
2. G protein turns on adenylyl cyclase, an amplifier enzyme.
3. Adenylyl cyclase converts ATP to cyclic AMP.
4. cAMP activates protein kinase A.
5. Protein kinase A phosphorylates other proteins, leading ultimately to a cellular response.

Phospholipase-C-Ca^{2+}

- Binding of Epinephrine to α - adrenergic receptor in plasma membrane activates a G-protein intermediate, phospholipase C.
- Phospholipase C splits phospholipid into inositol triphosphate (IP3) and diacyglycerol (DAG).
- Both derivatives serve as 2^{nd} messengers.
- IP3 diffuses through cytoplasm to endoplasmic reticulum (ER).
- Binding of IP3 to receptor protein in ER causes Ca^{2+} channels to open- releases calcium into the cytosol.

Epinephrine and norepinephrine can bind to **two types** of receptors on the cell, each receptor has a **different action** , as there as alpha receptor and beta receptor , even beta receptors has **subunits** and **sub types** like there is alpha 1 and alpha 2 , beta 1**(in the heart)** and beta 2 **(in the lungs)**

Considering the last 4 slides so that you don't mix up

Alright, think of all these slides as one continuous story about how a signal from outside the cell turns into a big internal response. It starts when a ligand (like a hormone) **binds** to a receptor on the cell membrane—**this forms a receptor-ligand complex.** That binding **activates a G-protein sitting** on the inside of the membrane, and the G-protein then **switches on an enzyme** called **adenylate (adenylyl) cyclase**. This enzyme **takes ATP** and **converts it into cAMP**, which is the **"second messenger."** Now here's where things start to scale up: **one** activated receptor can lead to the production of **many** cAMP molecules, which is what the amplification slide is showing—one signal outside becomes a whole cascade inside the cell. cAMP then activates protein kinase A (PKA) by **removing its inhibitory subunits**, turning it from **inactive** to **active**. Once active, **PKA phosphorylates different proteins** (adds phosphate groups), and this can either **activate** or **inactivate** specific enzymes, which is how the cell actually produces the hormone's effects, modulates enzyme activity, and alters its metabolism.

BUUUT

this signal **isn't supposed to last forever (recall acetylcholine in the brain and epilepsy)** so cAMP gets broken down by **phosphodiesterase** into **inactive fragments**—basically **shutting the signal off** so things don't go out of control. In a parallel pathway , **phospholipase C-Ca^{2+}** , a ligand like epinephrine, **binds to an α-adrenergic receptor,** activates a **G-protein**, and **instead** of adenylate cyclase, **it activates phospholipase C.** This enzyme **splits** a membrane phospholipid into **two second messengers: IP_3** and **DAG. IP_3 diffuses** through the **cytoplasm** to the **endoplasmic reticulum (ER)**, binds to its receptor there, **and opens Ca^{2+} channels**, **releasing calcium** into the cytosol. So overall, whether it's cAMP or IP_3/DAG, the idea is the **SAME** : a **small** signal outside gets **massively amplified** inside, leading to **protein phosphorylation** and a **big** cellular response, then gets shut down to keep everything controlled.

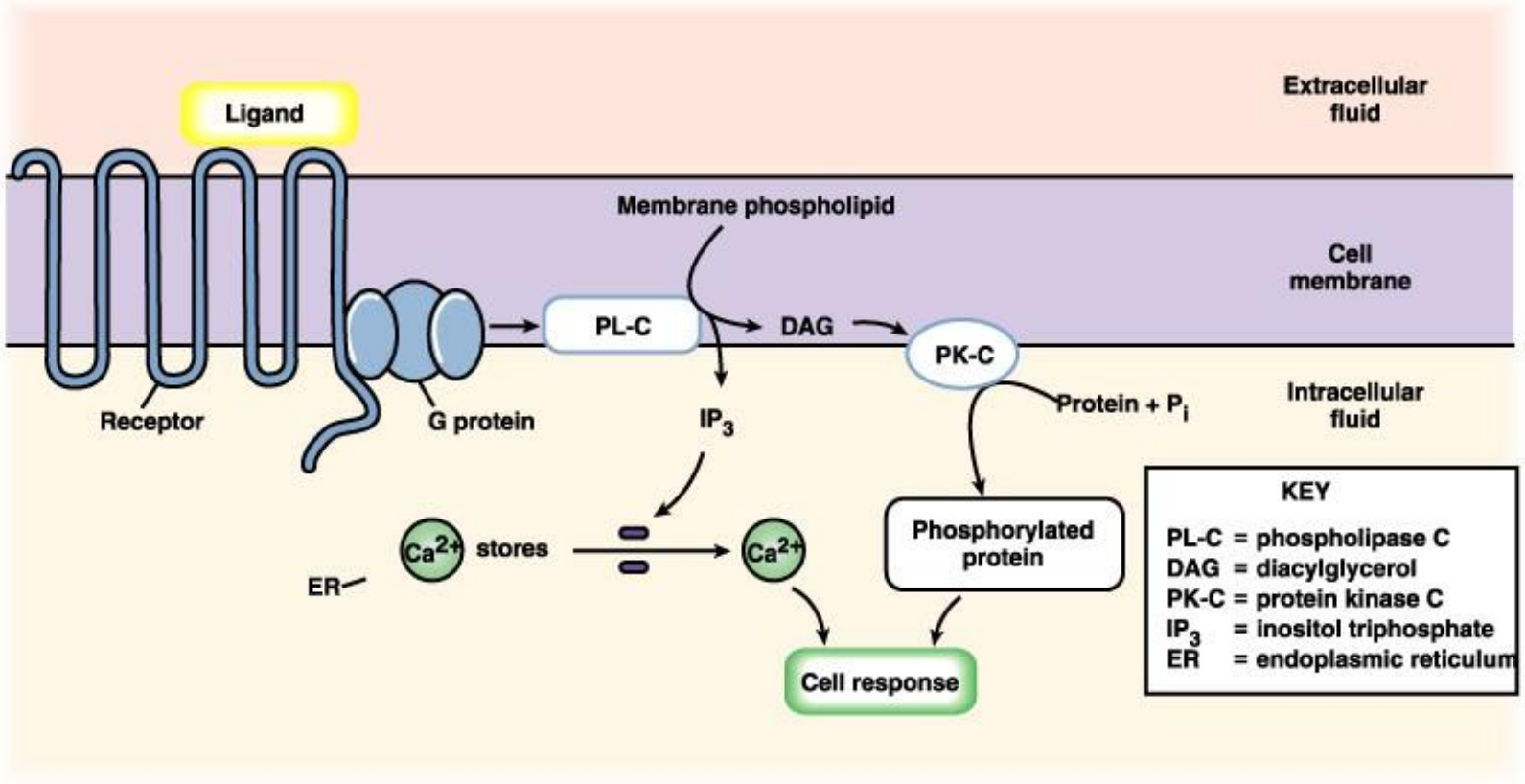
Phospholipase-C-Ca^{2+}

Protein kinase A or B or C ,they might phosphorylate the **same protein** especially if it was on the same cell. So this means that the action of this protein kinase could be the same if they phosphorylate the same protein

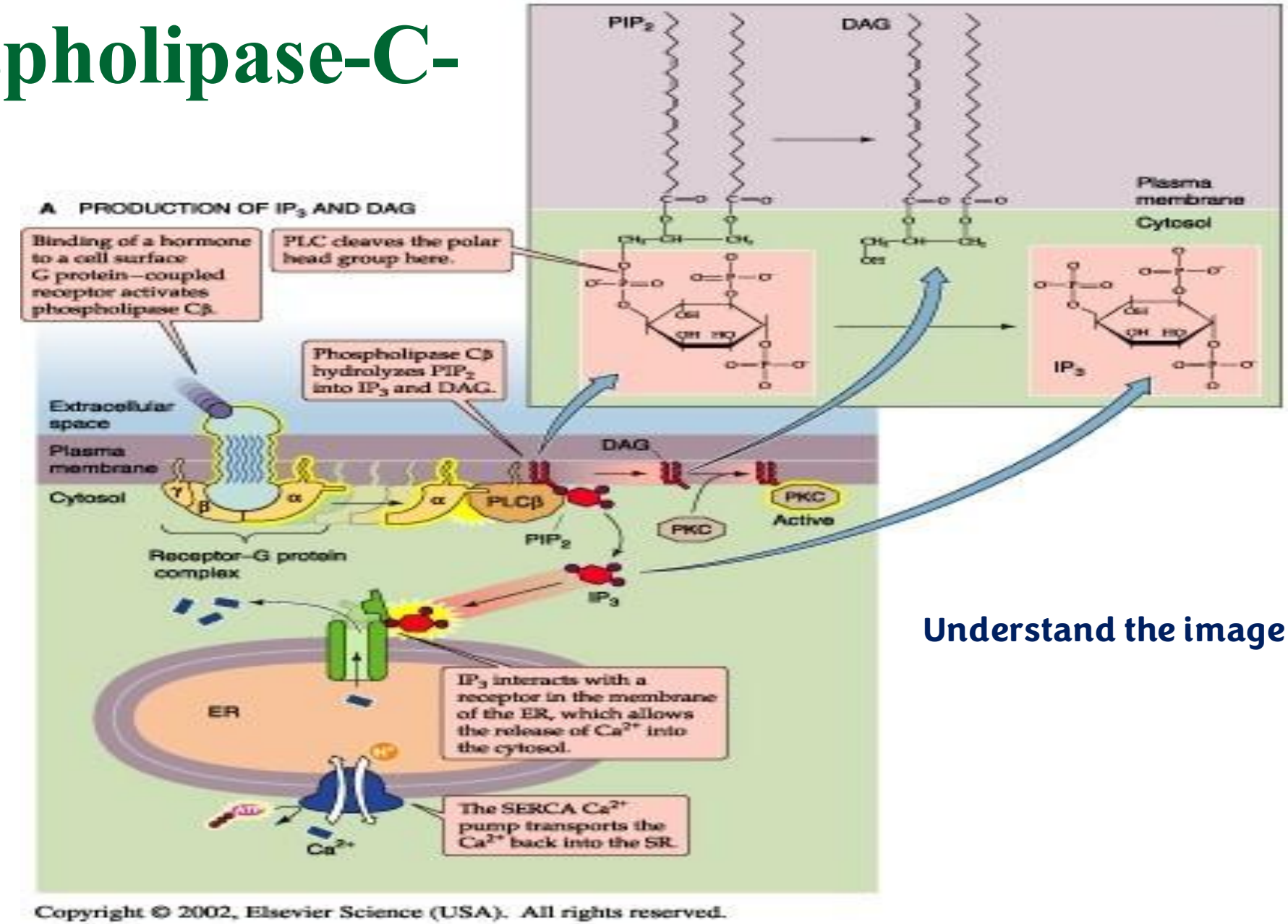
One of the proteins in endoplasmic reticulum is

called **phospholamban** (it activates calcium pump in the

sacroplasmic reticulum) and its **activated** by protein kinase A and B and C



Phospholipase-C-Ca^{2+}



Understand the image

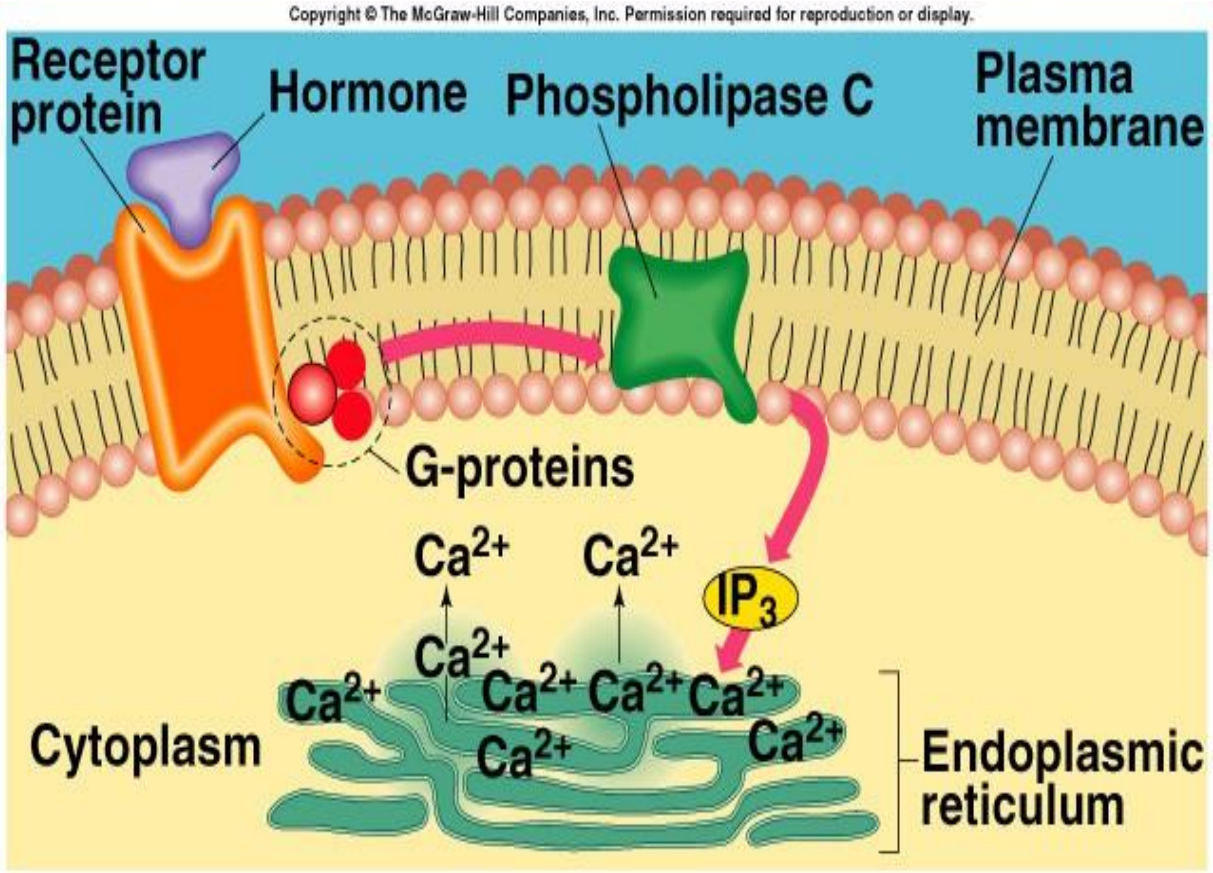
Ca^{2+}- Calmodulin (continued)

Ca2+ diffuses into the cytoplasm.

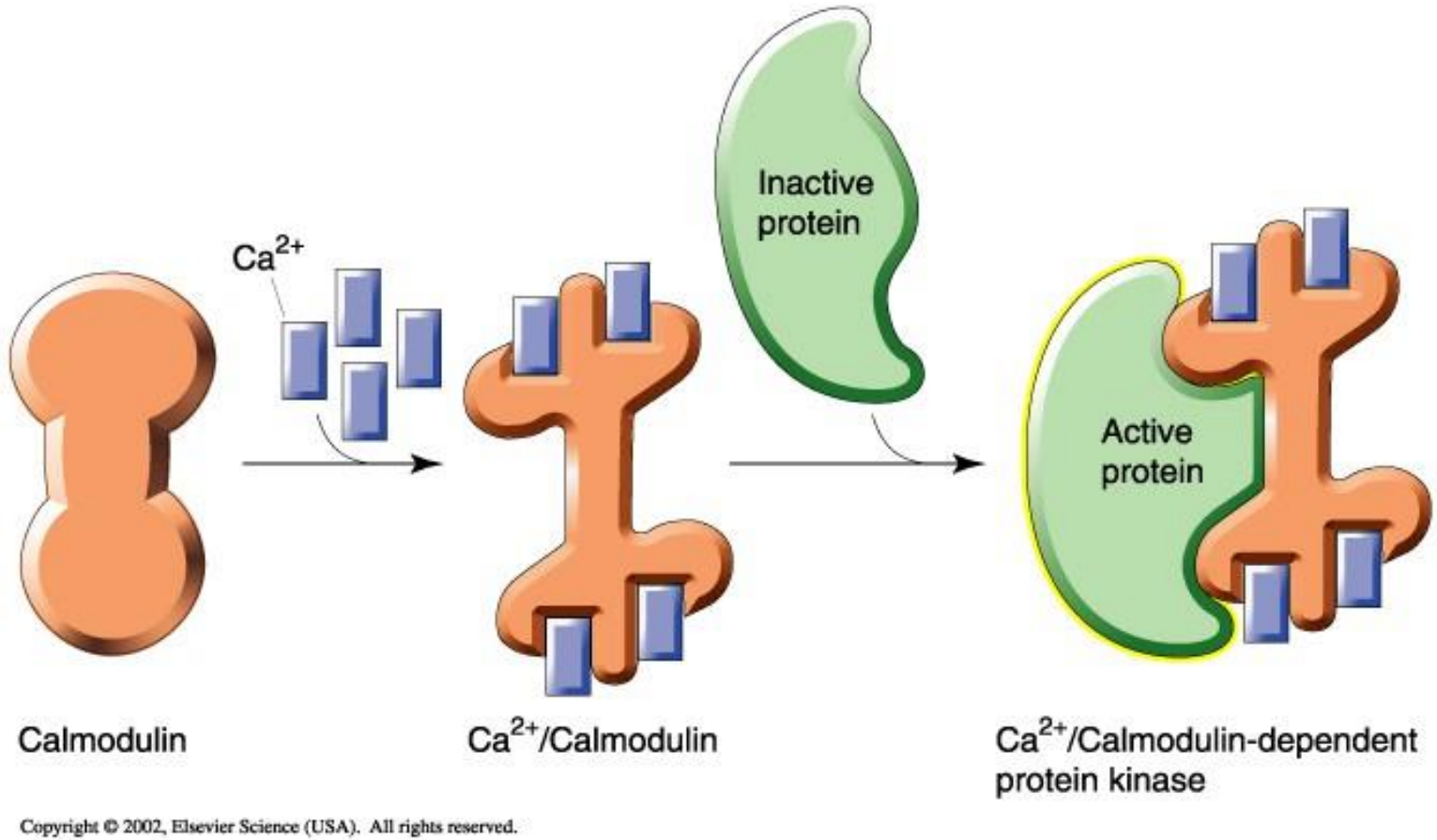
Ca2+ binds to calmodulin.

Calmodulin activates specific protein kinase enzymes.

Alters the metabolism of the cell, producing the hormone's effects.

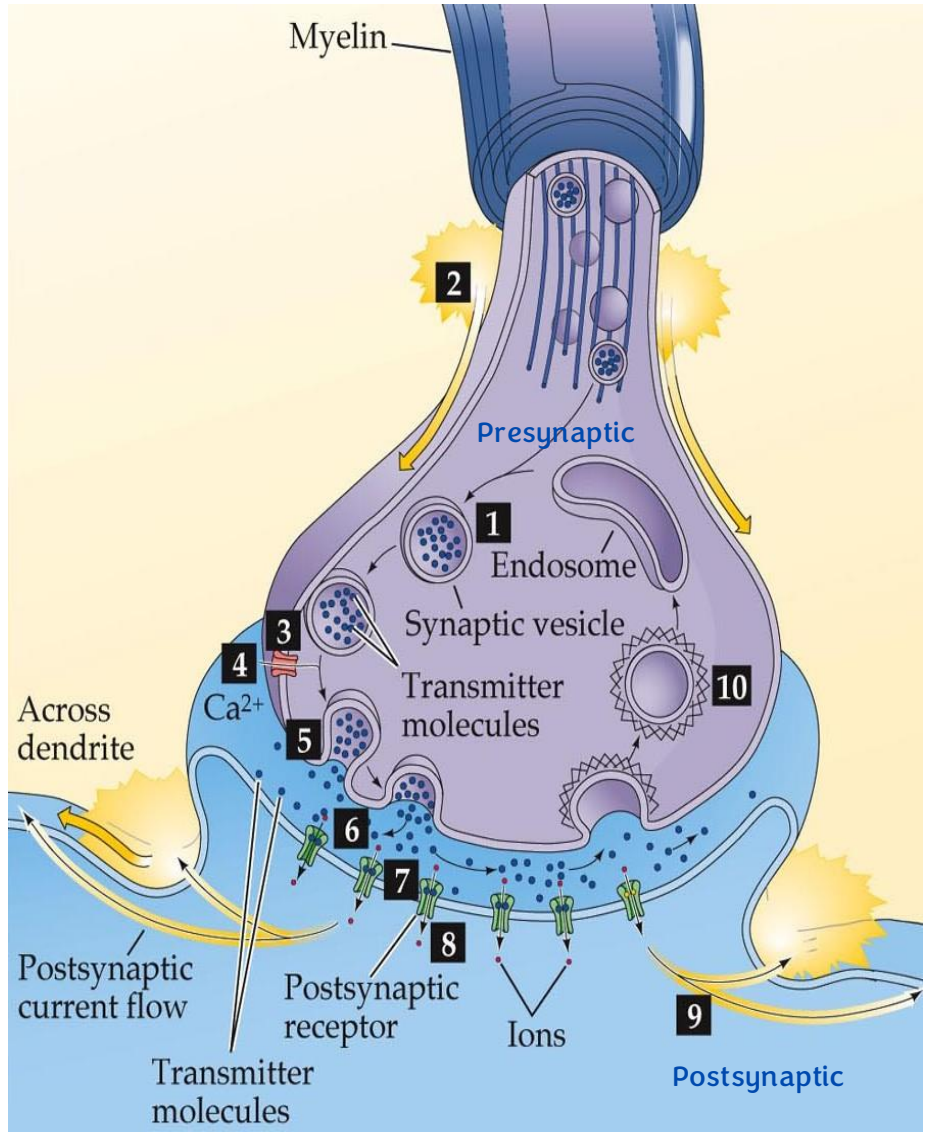


Ca^{2+}- Calmodulin (continued)

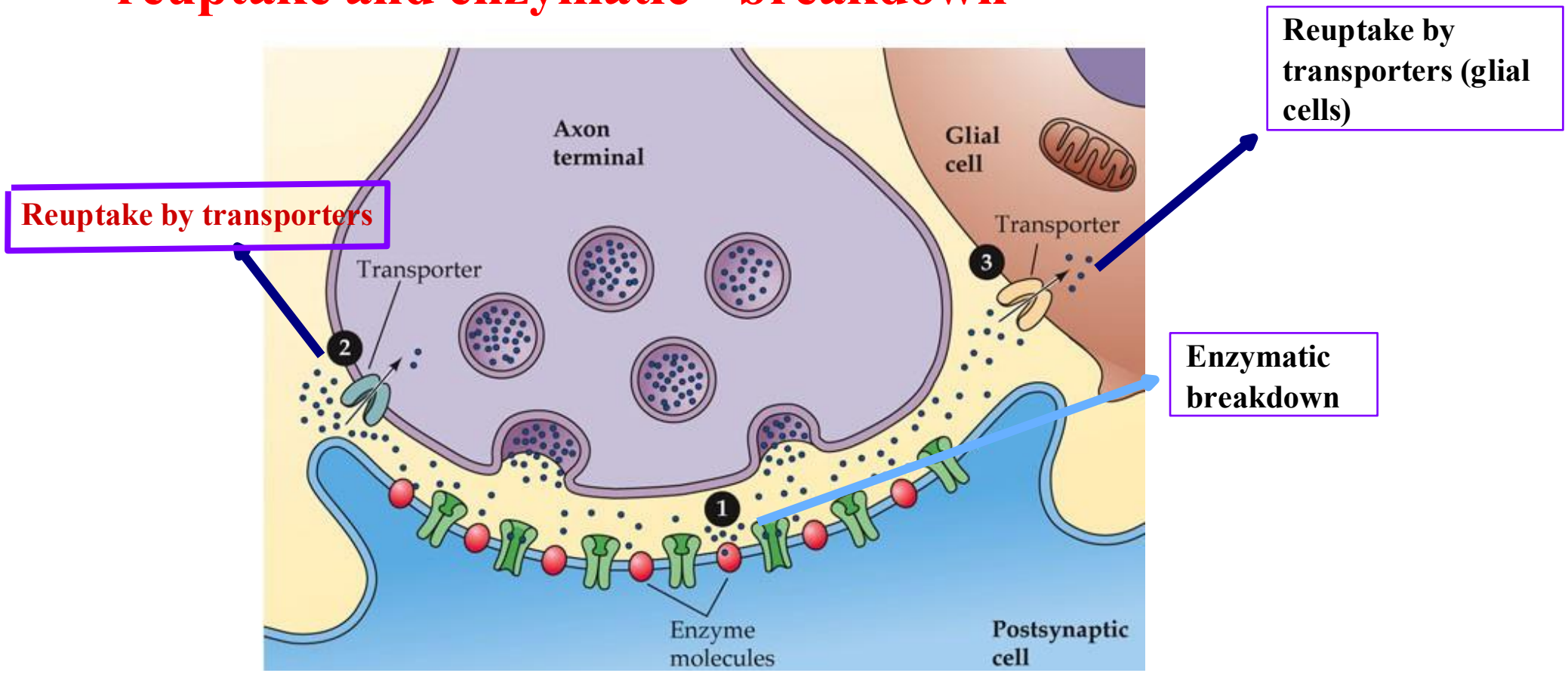


● Neurotransmitter Release: exocytosis and endocytosis

1. Transmitter synthesized and stored
2. Action Potential
3. Depolarization: open voltage-gated Ca2+ channels
4. Ca^{2+} enter cell
5. Ca^{2+} causes vesicles to fuse with membrane
6. Neurotransmitter released (exocytosis)
7. Neurotransmitter binds to postsynaptic receptors (receptors : ionotropic –fast because it is an ion channel- and metabotropic)
8. Opening or closing of postsynaptic channels (change in the permeability of the channel), if sodium channels opened => Depolarization which is EPSP and might lead to an action potential if it reach the threshold, Potassium channels opened => hyperpolarization which is IPSP make the potential away from the threshold and can't lead to an action potential.
9. Postsynaptic current excites or inhibits postsynaptic Potential to change excitability of cell
10. Retrieval of vesicles from plasma membrane (endocytosis)



- **Transmitter Inactivation: reuptake and enzymatic breakdown**



Neurotransmitter can be <u>recycled</u> (small molecules not neuropeptides because neuropeptides formed in the soma then transported to the presynaptic terminal by axonal transport which is very slow) **in presynaptic terminal or can be <u>broken down</u> by enzymes within the cell**

NT – Receptor Binding

Receptors are large, dynamic proteins that exist along and within the cell membrane.

Dynamic – they can increase in number (up regulation) which can be externalization or synthesis, synthesis means stimulation in gene system **and avidity for their neurotransmitter according to circumstances** or decrease in number (down regulation)

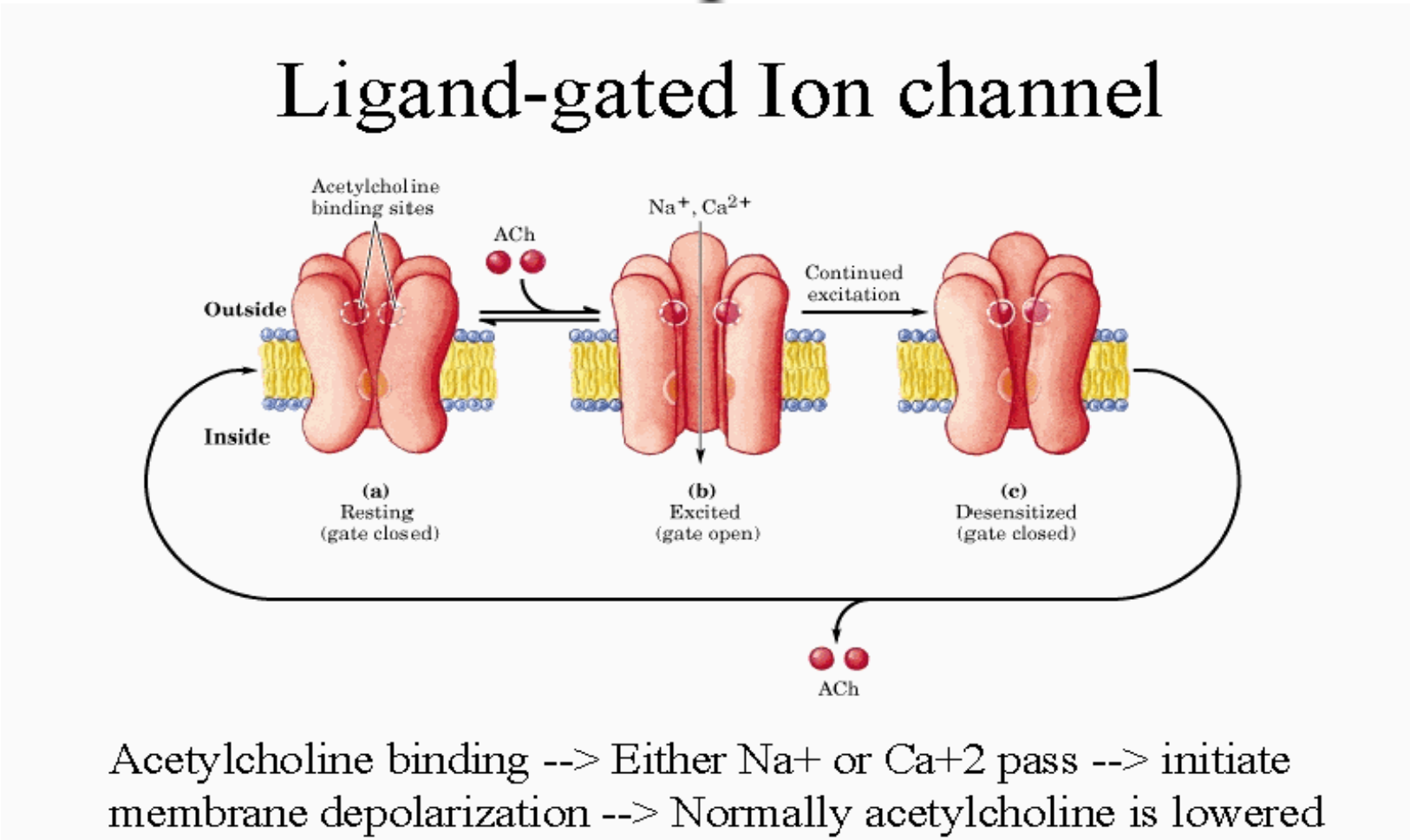
Two Types of Post synaptic Receptors:

Ionotropic receptors: NT binding results in direct opening or closure of specific ion channels

Metabotropic receptors: binding of NT initiates a sequence of internal molecular events which in turn open specific ion channels

NT binding -> Membrane Potential Response

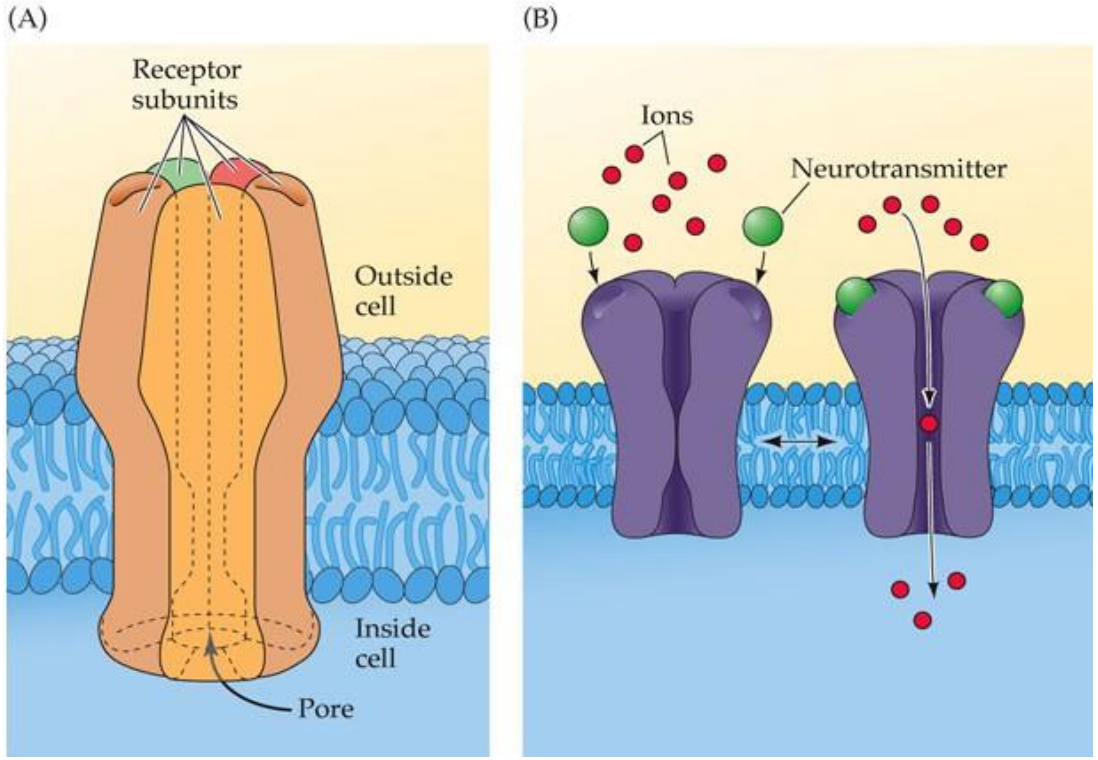
Acetylcholine receptor is a penta-subunit (contains 5 subunit)



Ionotropic Receptors

Work very fast; important role in fast neurotransmission

1. Each is made of several subunits (together form the complete receptor)
2. At center of receptors is channel or pore to allow flow of ions
3. At rest – receptor channels are closed
4. When neurotransmitter binds – channel **immediately** opens
5. When ligand leaves binding site – channel quickly closes

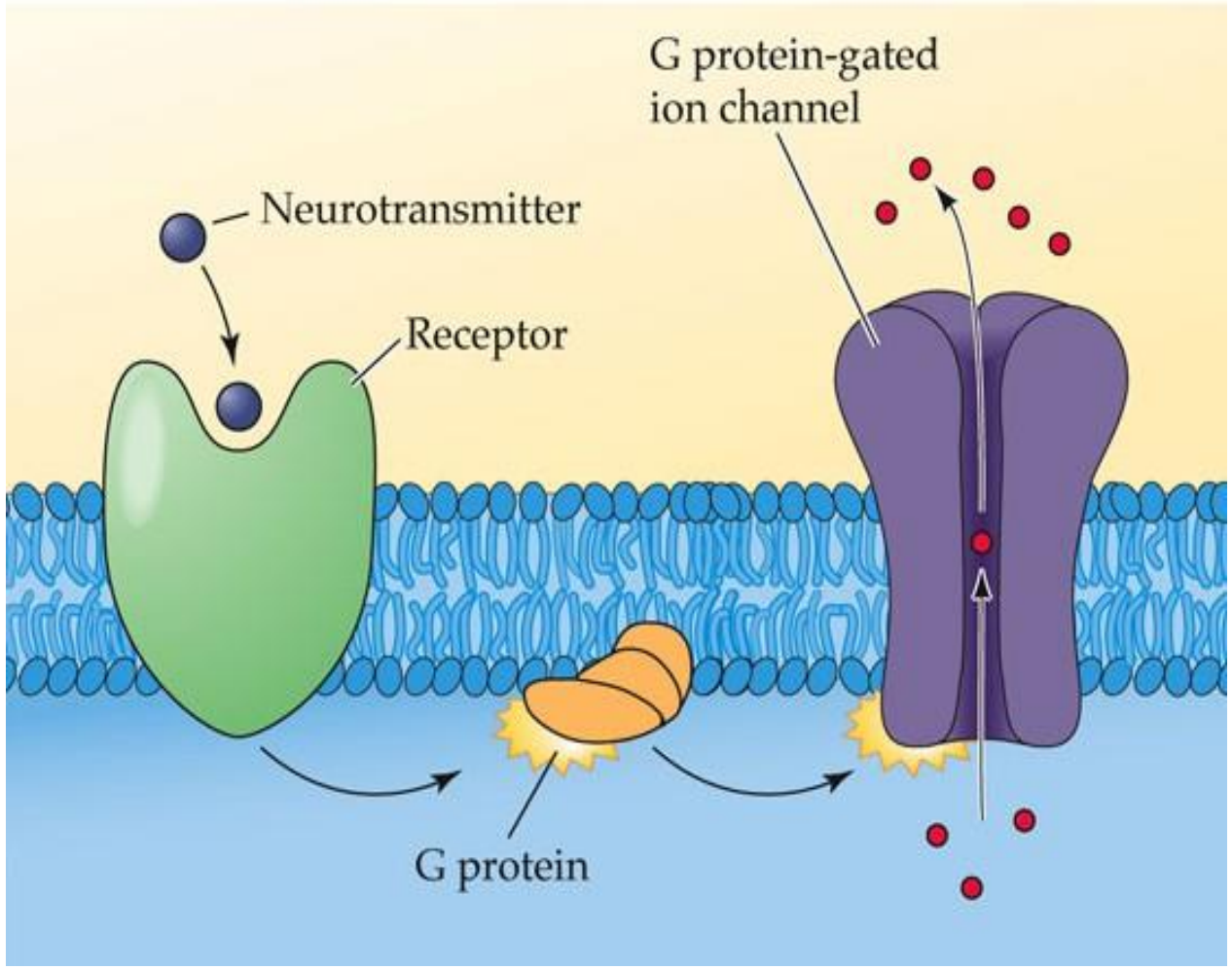


Metabotropic Receptors…

G protein: made of several subunits : Alpha, Beta and Gamma

Work by activating other proteins called **G proteins**

1. Each is made of several transmembrane regions
2. Stimulate or inhibit the opening of ion channels in the cell membrane (change in permeability)
3. Work **more slowly** than ionotrophic receptors but **lasts longer** , it still attached little bit fast but slower than ionotropic .

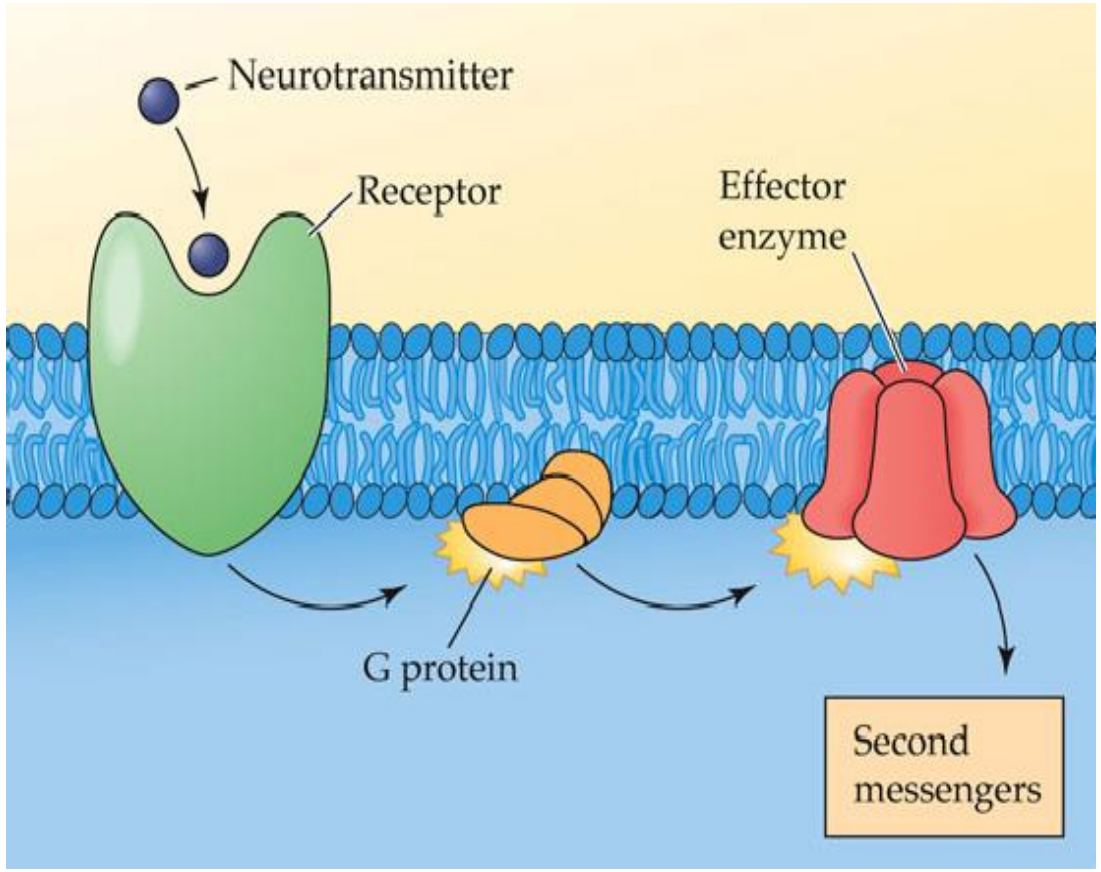


Metabotropic Receptors…

1. Stimulate or inhibit certain **effector enzymes**
2. Most **effector** enzymes controlled by G proteins are involved in synthesis of second messengers.

*First messenger: ligand.

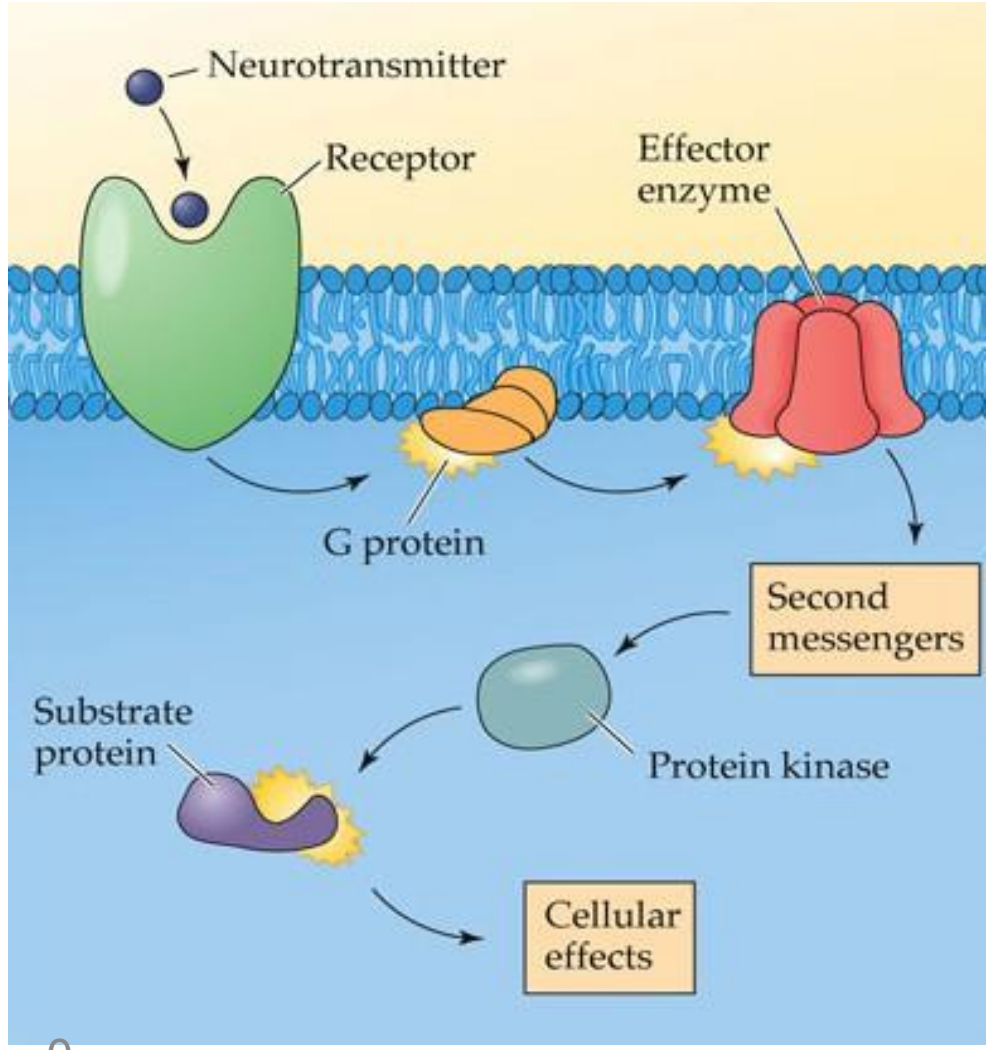
*Second messenger: effector enzyme



This is slower which is going to stimulate the effector and the slowest that goes to the gene system (stimulate the information of protein)

Second messengers: Activate Protein Kinases

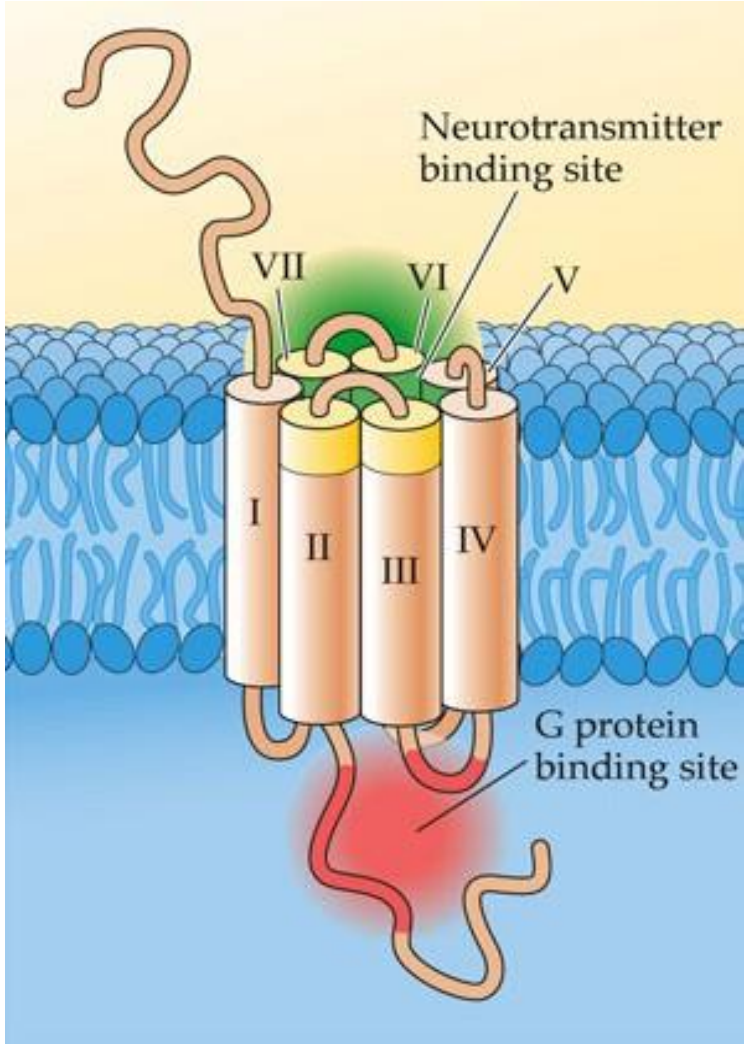
Can work by affecting:
NT production, no. synapses formed, sensitivity of receptors, or expression of genes (long term effects).
Can result in **amplification** - interconnections.



Other Metabotropic Receptors

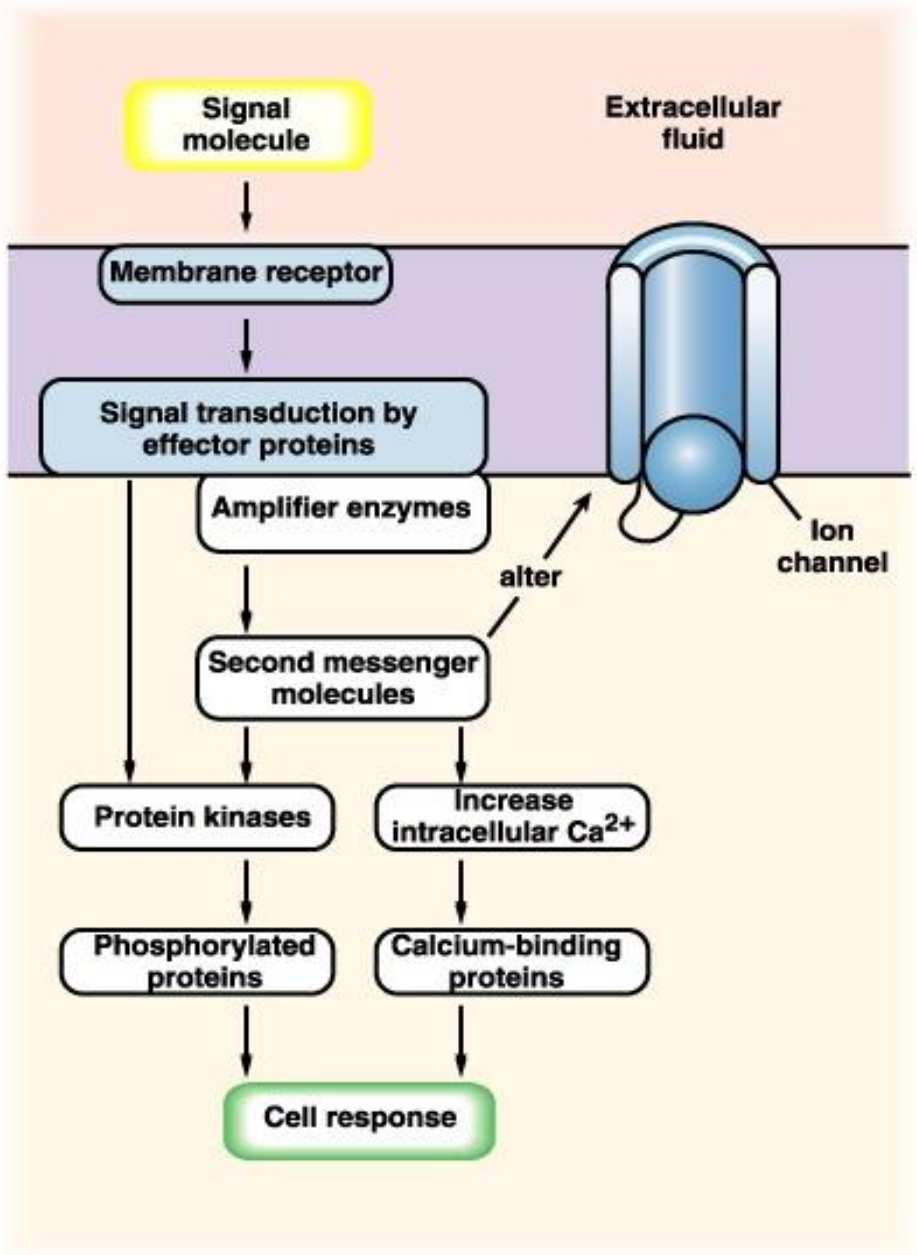
Work **more slowly** than ionotropic receptors and even slower than the metabotropic that connected to stimulation to ion channels.

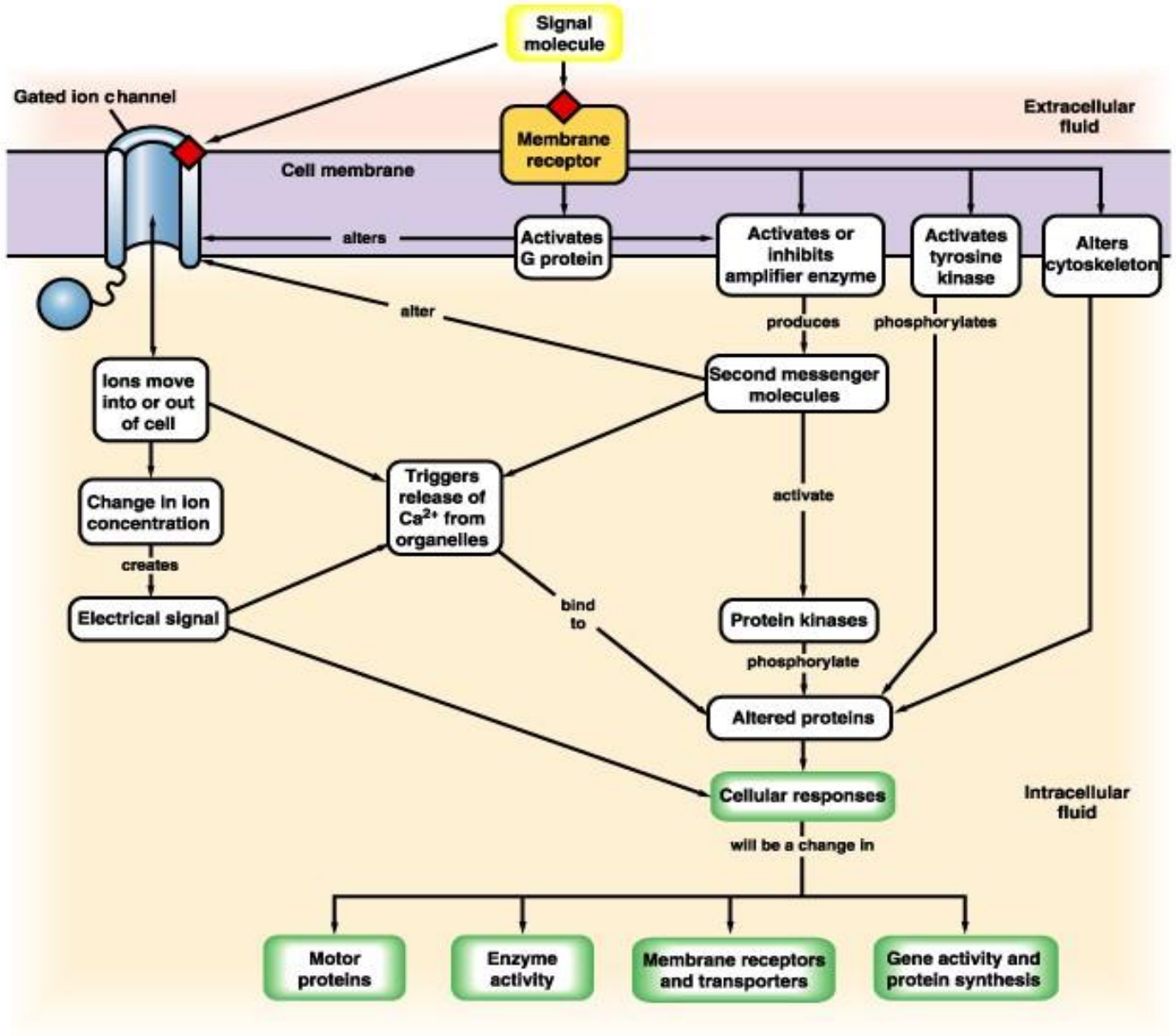
- Though it takes **longer** for postsynapic cell to respond, response is somewhat longer- lasting
- Comprise a **single protein subunit**, winding back-and-forth through cell membrane **seven** times (**transmembrane domains**)
- They do not possess a channel or pore



Hepta-subunits

When a signaling molecule binds to a membrane receptor, the signal is transduced inside the cell through different mechanisms.
If the receptor is associated with an amplifier enzyme, such as adenylate cyclase or guanylate cyclase, this leads to the production of a second messenger inside the cell.
The second messenger can then act in multiple ways:
It may activate protein kinases, leading to phosphorylation of target proteins, which produces a cellular response.
Alternatively, the second messenger can directly affect ion channels, causing them to either open or close .




Signal molecule
Gated ion channel
Extracellular fluid
Membrane receptor
Cell membrane
alters
Activates G protein
Activates or inhibits amplifier enzyme
Activates tyrosine kinase
Alters cytoskeleton
alter
produces
phosphorylates
Second messenger molecules
Ions move into or out of cell
Triggers release of Ca^{2+} from organelles
activate
Change in ion concentration
creates
Electrical signal
bind to
Protein kinases
phosphorylate
Altered proteins
Cellular responses
Intracellular fluid
will be a change in
Motor proteins
Enzyme activity
Membrane receptors and transporters
Gene activity and protein synthesis

Explanation for the previous slide :

Ion channels are selective, meaning they may allow the passage of specific ions such as sodium (Na^+), potassium (K^+), or calcium (Ca^{2+}).

If sodium permeability increases, this leads to a change in the membrane potential (depolarization). Such changes in membrane potential can produce a cellular response.

In some cases, the change in membrane potential can trigger the **opening of voltage-gated calcium channels**. Calcium then acts as an **second messenger**.

Calcium can:

Activate calmodulin, which becomes **calmodulin dependent protein kinase**.

Stimulate **protein phosphorylation** through **calmodulin-dependent protein kinase**.

Additionally, receptor activation can stimulate **G-proteins**, which may:

Activate nearby amplifier enzymes such as **adenylyl cyclase or guanylyl cyclase,** leading to the formation of **second messengers** like cAMP.

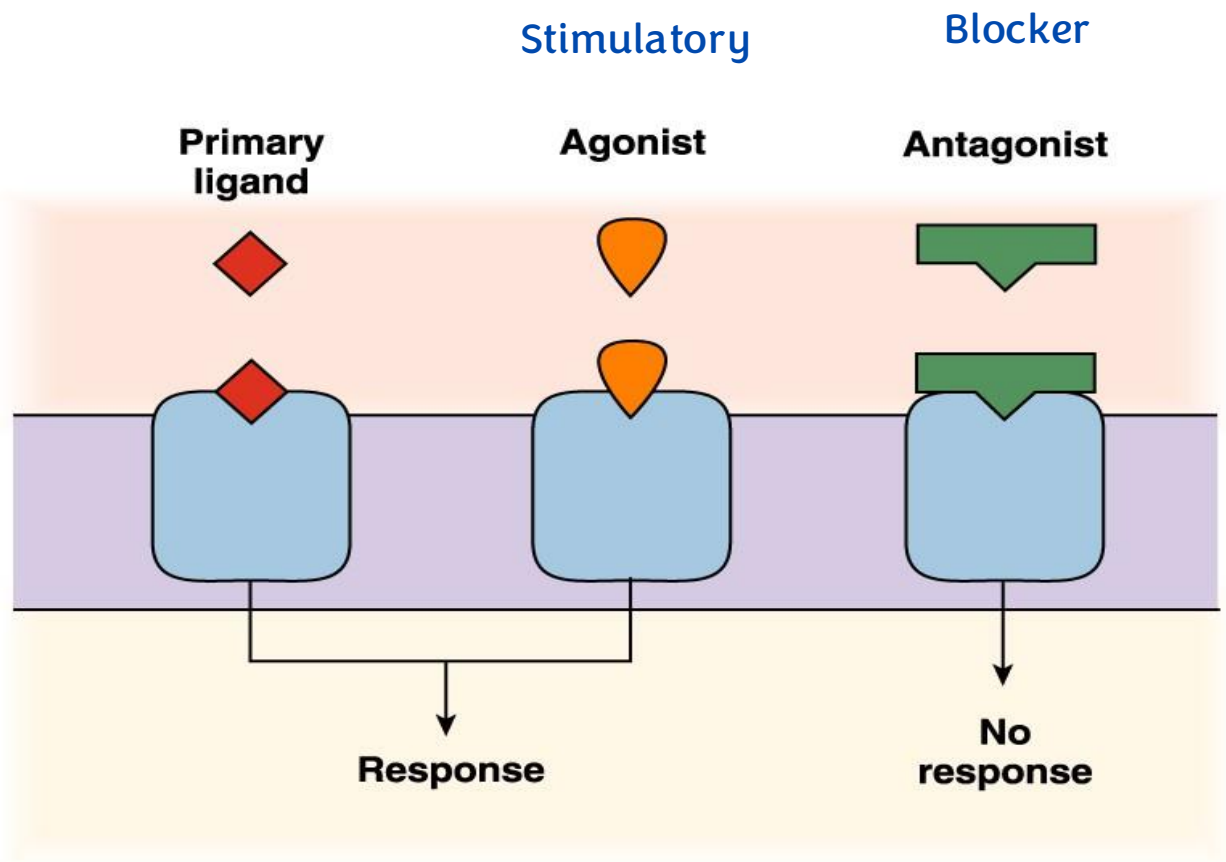
Activate other pathways such as phospholipase C.

Another important mechanism involves **enzyme-linked receptors**, such as **tyrosine kinase receptors**.

A key example is the insulin receptor, which is a membrane receptor.

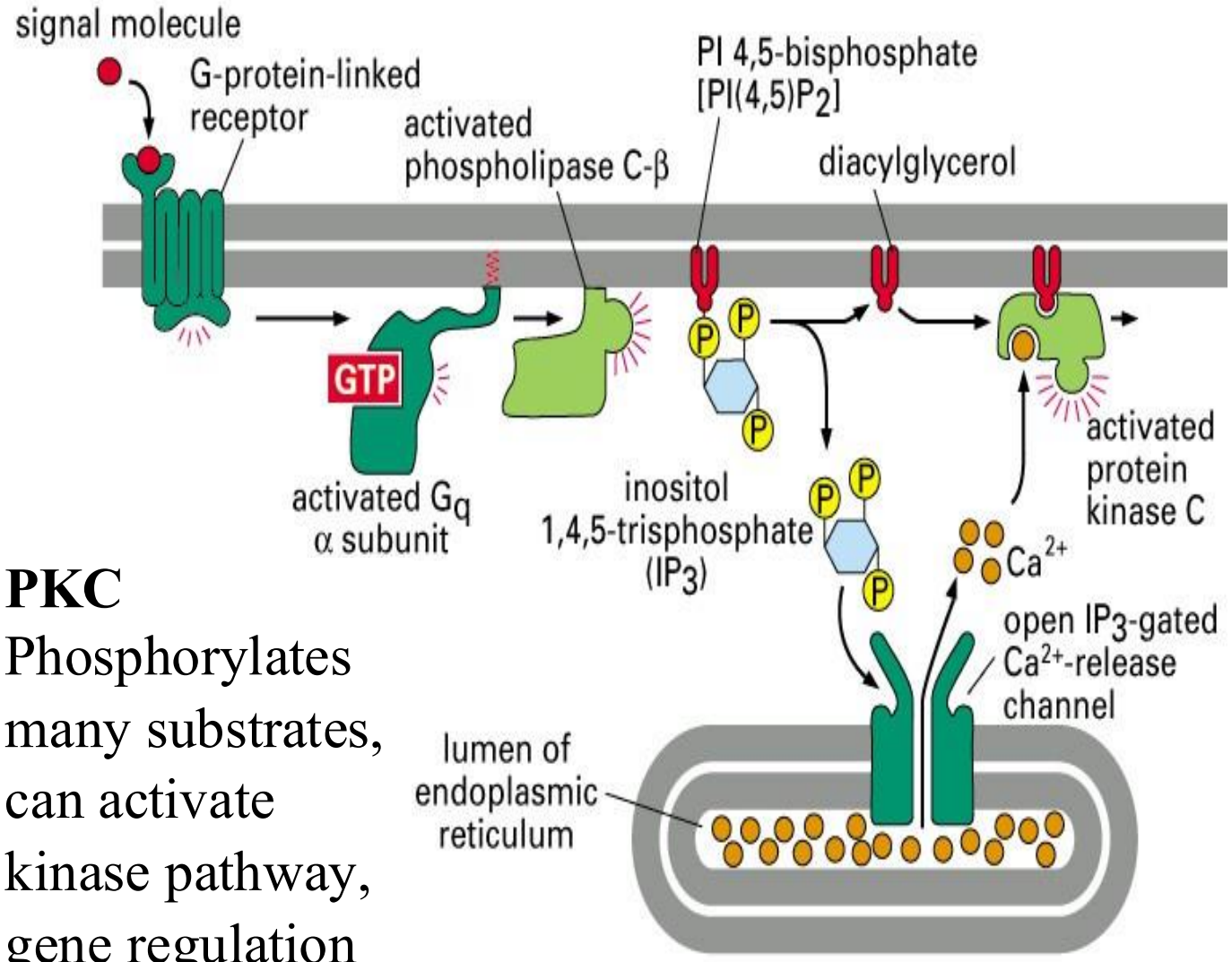
When insulin binds to its receptor ,it **autophospholarate** tyrosine kinase, which is a membranous protein and when it is autophospholarated , it will be activated to be an protein kinase and phosphorylation of intracellular proteins .

We use the terms agonist and antagonist to describe how different molecules interact with receptors.
A **ligand** is any molecule that binds to a receptor. This can be a natural substance (like a hormone) or a drug.
An **agonist** is a molecule that binds to a receptor and produces the same effect as the ligand.
For example, a drug that mimics the action of epinephrine and activates its receptor is called an agonist.
→ **Agonists** stimulate the receptor and trigger a physiological response.
An **antagonist** is a molecule that binds to the receptor but does not activate it. Instead, it blocks the action of the ligand.
→ **Antagonists** act as blockers, preventing the normal response.
Both agonists and antagonists:
Bind to the **same receptor**
But have **opposite effects**:
Agonist → activates (stimulates)
Antagonist → blocks (inhibits)



For example:
If a patient has an increased heart rate, we may use a **beta-blocker (beta antagonist)** to reduce heart rate by **blocking β-receptors**.
In contrast, if a patient has bronchoconstriction (such as in asthma) and needs help breathing, we use a **beta agonist** to **stimulate β-receptors** and cause bronchodilation.

PLC- signaling pathway



PKC
Phosphorylates many substrates, can activate kinase pathway, gene regulation

A signaling molecule can bind to a G protein–coupled receptor (GPCR).
The **alpha (α)** subunit of the G-protein exchanges **GDP for GTP**, becoming active.
The activated α-subunit then **stimulates phospholipase C (PLC).**
Phospholipase C acts on membrane phospholipids to produce two important second messengers:
IP3 (inositol trisphosphate) → moves to the endoplasmic reticulum and causes the release of calcium (Ca^{2+})
DAG (diacylglycerol) → remains in the membrane
Then:
Calcium + DAG together activate Protein Kinase C (PKC)
Activated Protein Kinase C leads to **phosphorylation of intracellular proteins**, resulting in specific cellular responses.


THANK YOU

Receptors Functions and Signal Transduction- L4- L5

Faisal I. Mohammed, MD, PhD

- **Receptors superfamilies:**
- Ionotropic receptors (ligand-gated channels)
- Metabotropic receptors (G protein-coupled receptors)
- Tyrosine Kinase

Comparison of Ionotropic and Metabotropic Receptors

Characteristics	Ionotropic receptors	Metabotropic receptors
Structure	4 or 5 subunits that assemble in the cell membrane	1 subunit
Mechanism of action	Contain an intrinsic ion channel that opens in response to neuro-transmitter or drug binding	Activate G proteins in response to neurotrans-mitter or drug binding
Coupled to second messengers?	No	Yes
Speed of action	Fast	Slower

Ion channels

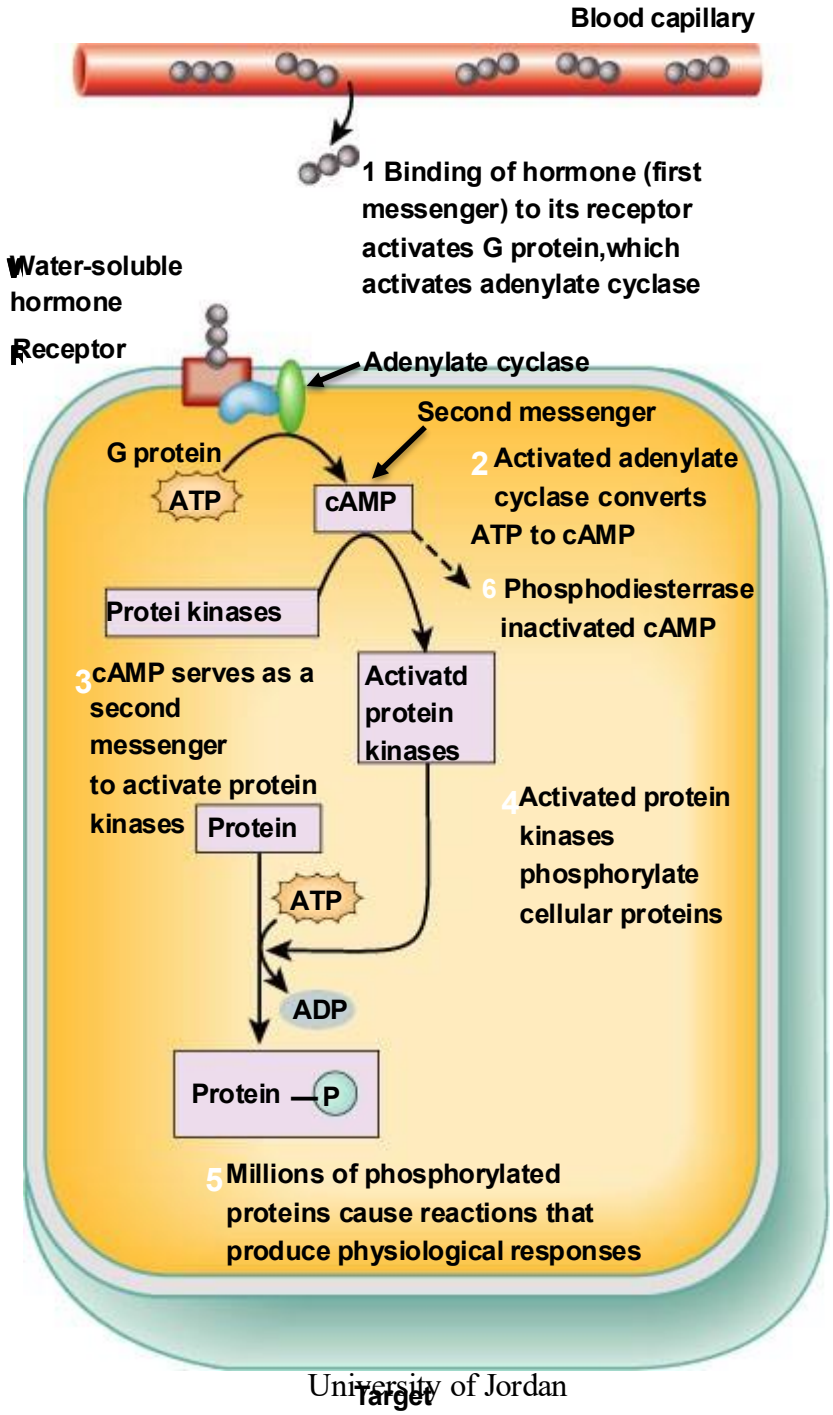
G- protein coupled receptor

The channel opens or close

Almost all neurotransmitters discovered so far have more than one kind of receptor -- called **receptor subtypes.**

For example: Epinephrine has alpha 1 and beta 1

Water-soluble Hormones



Explanation for the previous slide :

Regulation of cAMP and cGMP Signaling :

Second messengers such as cyclic AMP (cAMP) and cyclic GMP (cGMP) must be tightly regulated inside the cell.If they remain active for too long, they will continuously stimulate signaling pathways, which can lead to abnormal or excessive cellular responses.

cAMP Pathway :

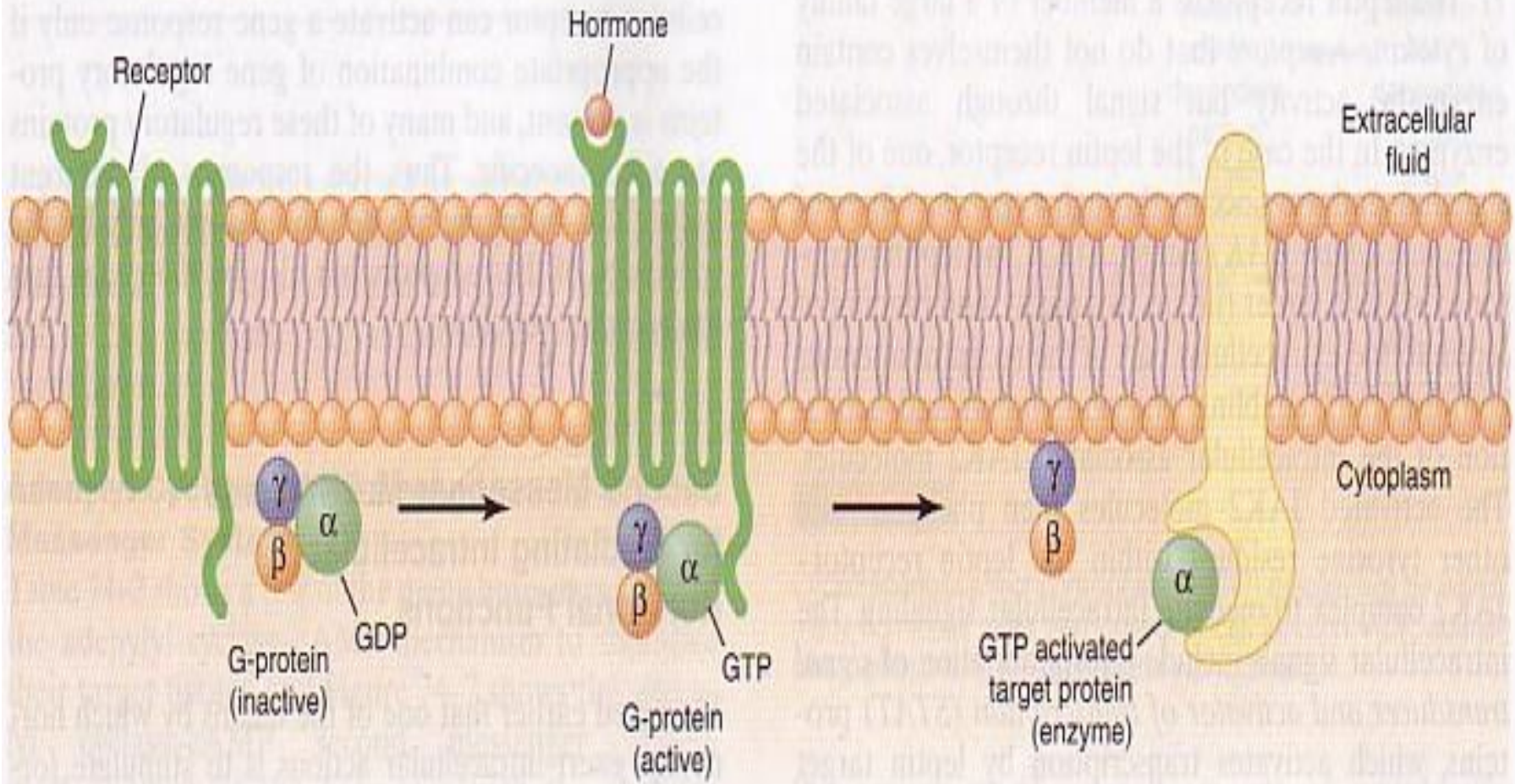
A water-soluble ligand binds to a membrane receptor (usually a G protein-coupled receptor).
This activates adenylyl cyclase, which converts ATP into cyclic AMP (cAMP).
cAMP then Activates protein kinase A (PKA) (also called cAMP-dependent protein kinase). PKA phosphorylates many intracellular proteins. This phosphorylation leads to the cellular response.

Termination of cAMP Signal =>To stop the signal:

cAMP must be broken down into AMP (adenosine monophosphate). This is done by the enzyme phosphodiesterase (PDE). Specifically: cAMP-dependent phosphodiesterase breaks down cAMP.

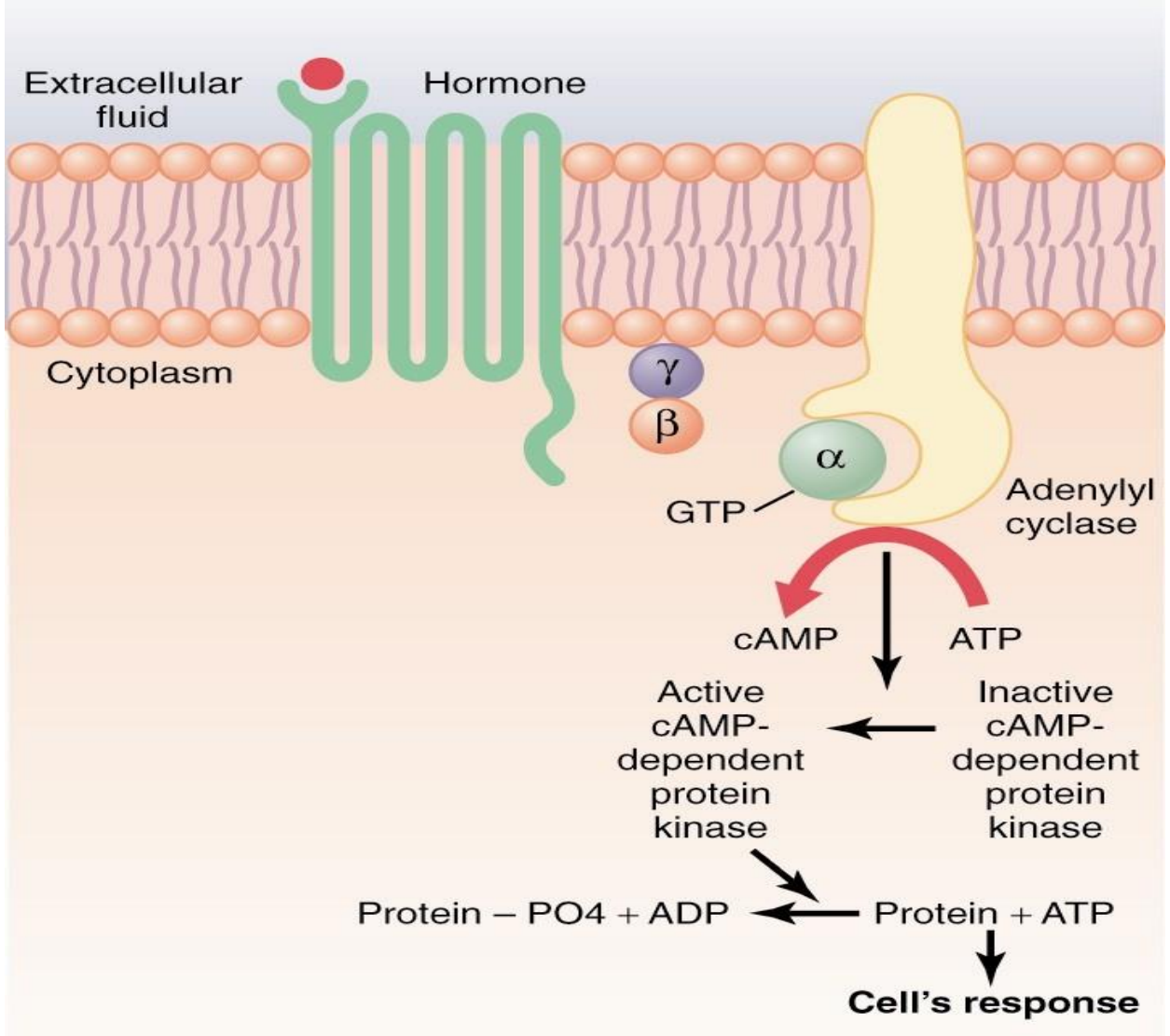
cGMP Pathway :

cGMP is also degraded by a specific enzyme called cGMP-dependent phosphodiesterase.
Each type of cyclic nucleotide usually has its own specific phosphodiesterase enzyme.
Some drugs work by **inhibiting** phosphodiesterase enzymes, which prevents the breakdown of cyclic nucleotides and **prolongs** their action.
An example is sildenafil (Viagra):
It **inhibits cGMP-specific phosphodiesterase** .This increases cGMP levels and enhances its physiological effects

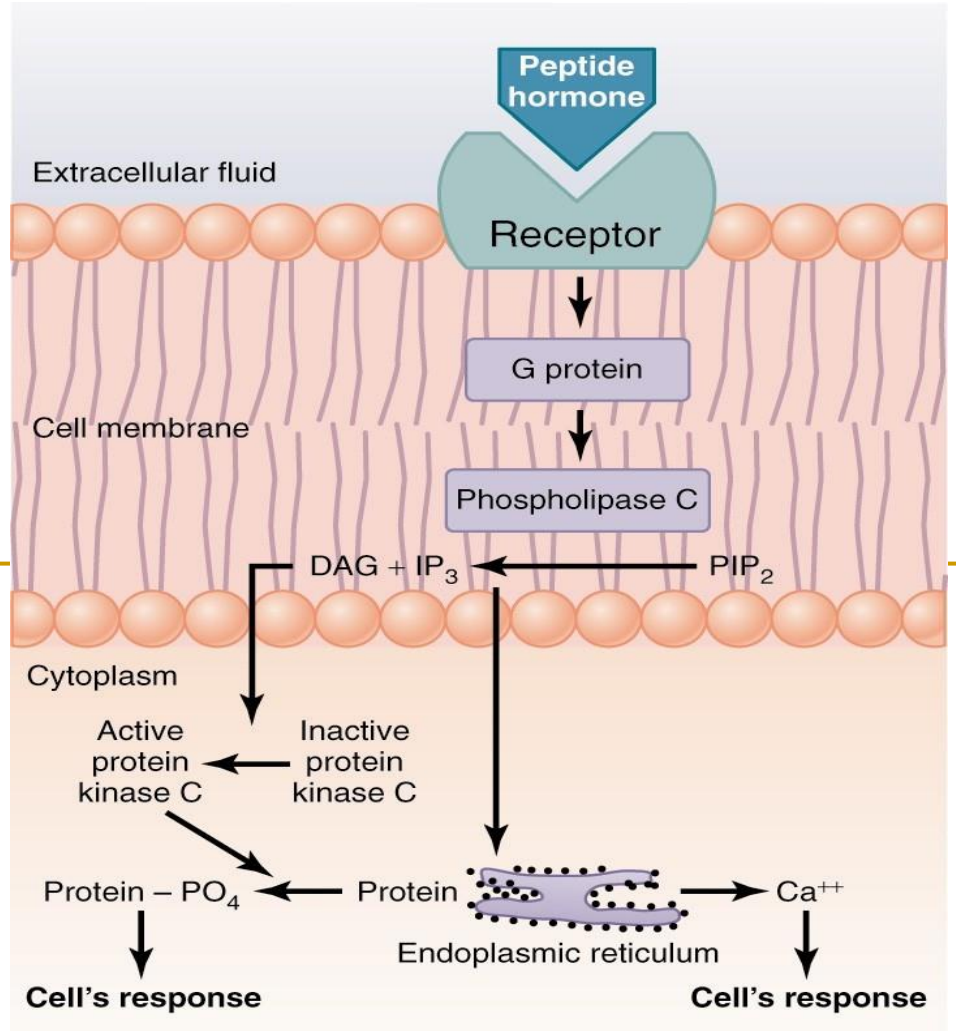


Mechanism of activation of a G protein-coupled receptor. When the hormone activates the receptor, the inactive α, β, and γ G protein complex associates with the receptor and is activated, with an exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP). This causes the α subunit (to which the GTP is bound) to dissociate from the β and γ subunits of the G protein and to interact with membrane-bound target proteins (enzymes) that initiate intracellular signals.

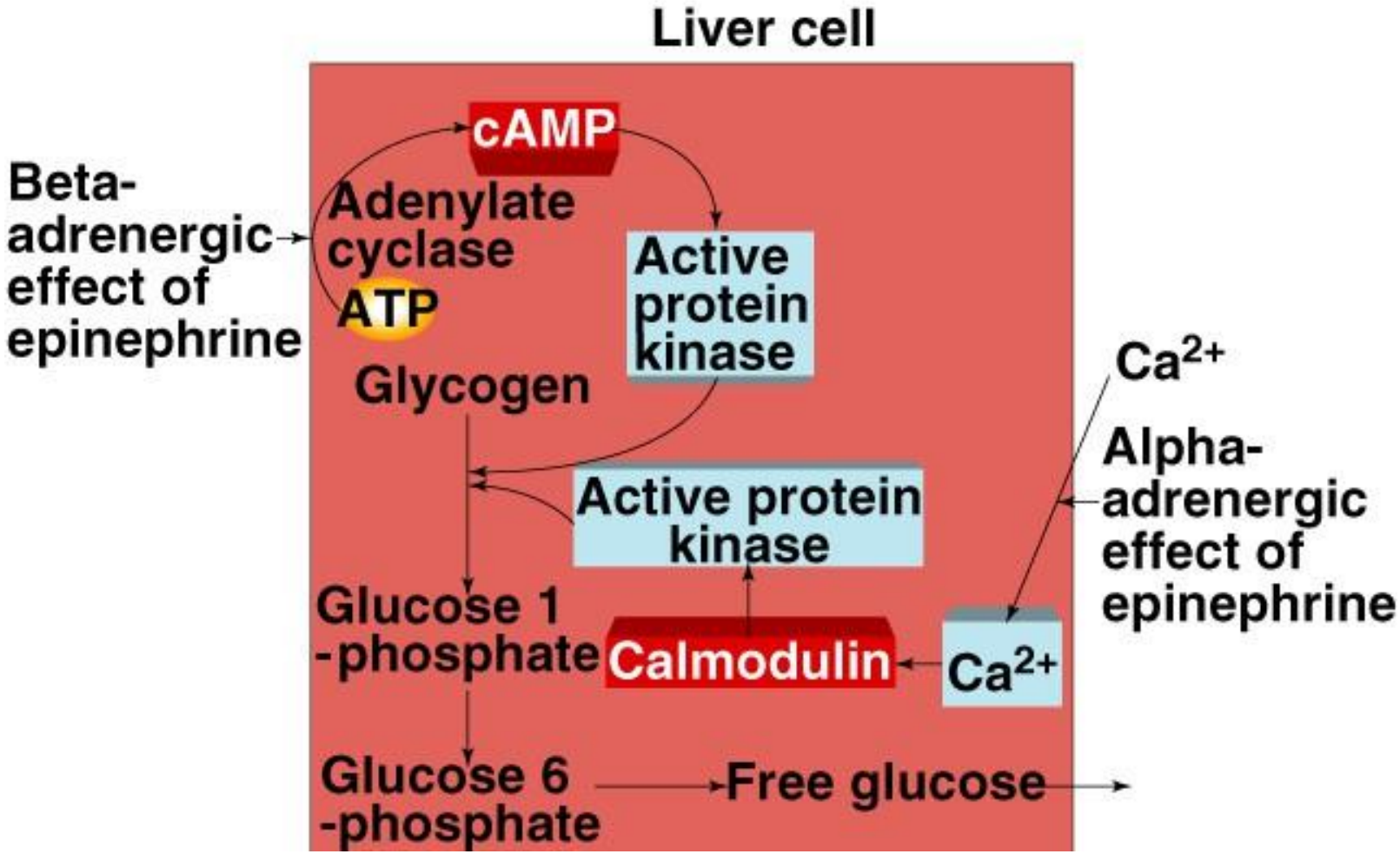
Cyclic Monophasphate (cAMP) Second Messenger Mechanism



Cell Membrane Phospholipid Second Messenger System



Epinephrine Can Act Through Two 2nd Messenger Systems



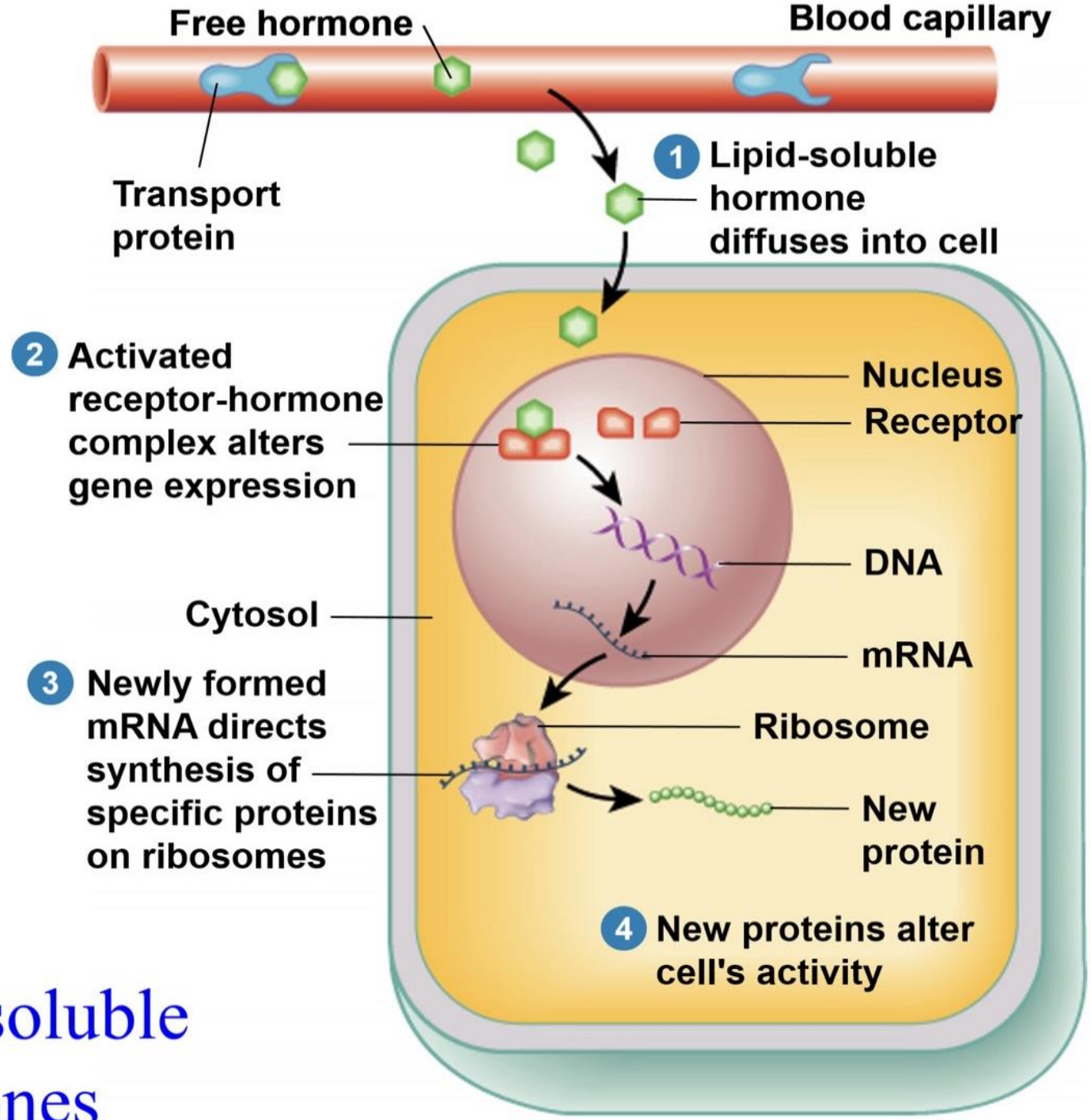
Explanation for the previous slide :
Epinephrine and norepinephrine can act on two main types of receptors: alpha (α) and beta (β) receptors.

Alpha (α) Receptors :
Work mainly through **intracellular calcium** (Ca^{2+}). Activation of α-receptors stimulates pathways that increase Ca^{2+} inside the cell. Calcium and calmodulin activate protein kinases B .
This leads to phosphorylation of intracellular proteins and produces a cellular response.

Beta (β) Receptors :
Work through the **cyclic AMP (cAMP)** pathway.Activation of β-receptors stimulates adenylyl cyclase, increasing cAMP. cAMP activates protein kinase A (PKA).
PKA causes phosphorylation of proteins.
✨Both work on glycogen as an example in the liver and make phosphorylation to break down the glycogen into free glucose.

We can found them in the same cell as in the liver cell or different cell. **Beta** receptors locates in the **heart** and **lungs** and **alpha** receptors locates in the **blood vessels**.

Lipid-soluble Hormones



Lipid-soluble hormones cannot dissolve in plasma, so they cannot travel freely in the bloodstream. Instead, they must be transported by carrier proteins.

Carrier proteins can be:

Specific carriers:

Testosterone-binding globulin → specific carriers for testosterone

Steroid-binding globulin → specific carriers for steroid hormones

Thyroxine-binding globulin (TBG) → specific carriers for thyroxine

Non-specific carriers:

Albumin → can carry any hormones

📍 In circulation, the hormone is bound to a carrier protein. When it reaches the target cell, the hormone is released from the carrier. Because it is lipid-soluble, the hormone diffuses across the cell membrane. The hormone binds to its intracellular receptor, which may be in the **cytoplasm**, or in **the nucleus**. If the receptor is in the cytoplasm: The hormone-receptor complex translocates to the nucleus and in the nucleus the complex binds to specific regions on DNA called **Hormone Response Elements (HREs)** as in cAMP

This leads to transcription of genes (mRNA formation) and translation of proteins

Final Result

➡️ **New protein synthesis .**

Lipid-soluble hormones → intracellular receptors → DNA → gene expression → new proteins

Now , test yourself by this quiz:

https://forms.gle/qSN9piGcRVQd2H2s8

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

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

Additional Resources:

Reference Used:
(numbered in order as cited in the text)

1. Dr. Faisal’s lecture

Extra References for the Reader to Use:

1. Video : G protein
2. Video : Signal transduction

"لا حول ولا قوة إلا بالله"

كلمة عظيمة تهز كيان المسلم، وتملأ قلبه ثقة بالله وتوكلاً عليه

لا حول: لا أملك من أمري شيئاً

لا تخطيط ولا ترتيب ولا إدارة

لا قوة ولا دهاء ولا سياسة

لا حول: لا أملك شيئاً من أمري

أي: أنا الضعيف

أنا الذي ملأ الضعف كل حياتي، فظهر في قولي وفكري

وظهر في تدبيري وفعلي

"ولا قوة" لا أملك قوة مستقلة أعتمد عليها

"إلا بالله"

إلا بالكامل العظيم

إلا بالصمد، الذي نحتاجه ولا يحتاجنا

إلا بمن ملك السماوات والأرض، وأمره للشيء: كن، فيكون

مهما مكر الأعداء بأهل الدين فإن الله يمد عباده بالقوة ويمكر بأعداء الملة

مهما طغى أهل الباطل وتجبروا فإن الله هو جابر ضعف المؤمنين، وهو وحده القادر على المبطلين

مهما دبرت وخططت وأردت فإن تدبيرك وتخطيطك لا يساوي شيئاً دون أمر الله وإذنه

يا رب دبر لي فإني لا أحسن التدبير