جامعة الملك سعود
King Saud University

Biochemistry team 436

Cell signaling

- Color Index:

- Important.
- Extra Information.
- **Doctors slides.**

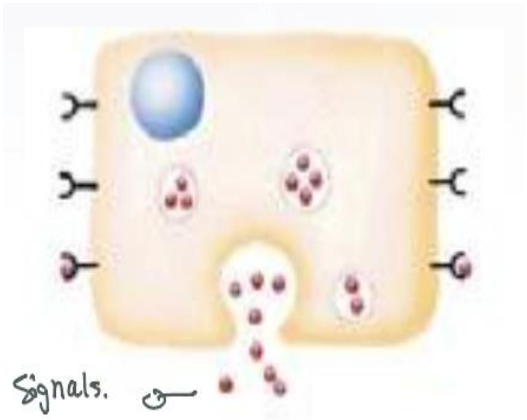
436 Biochemistry team

Objectives:

- Differentiate different steps in signaling pathways
- Describe the second messenger systems
- Recognize the function of signaling pathways for
  - Signal transmission
  - Amplification
- Discuss the role of signaling pathways in regulation and integration of metabolism

NO CELL LIVES IN ISOLATION*

- **Cells communicate with each other.**
- **Cells send & receive information (signals)****
- **Information is relayed** (received) **within cell to produce a response.**



Signalling Process

Recognition of signal*

By receptors

Transduction

Change of external signal into intracellular message with amplification & formation of **second messenger****

General concept ☺
Cell signaling is part of a complex system of communication that governs basic activities of cells and coordinates cell actions. The ability of cells to understand correctly respond to their microenvironment is the basis of development, tissue repair, and immunity as well as normal tissue homeostasis.

#للربط
Transduction= transformation= change

Effect

Modification of cell **metabolism** & **function*****

Notes:
*Because cell survival depends on communication.
**Dr's note:
If cells are adjacent to each other, they can communicate without signals

Dr's notes :
*Signals which are lipid soluble can go directly to the cell without the recognition by a receptors. (No recognition step)
**The first messenger is called (Signals) while the second messenger is called (intracellular signals)
***The modification of cell metabolism & function is done by the second messenger (Intracellular signals)

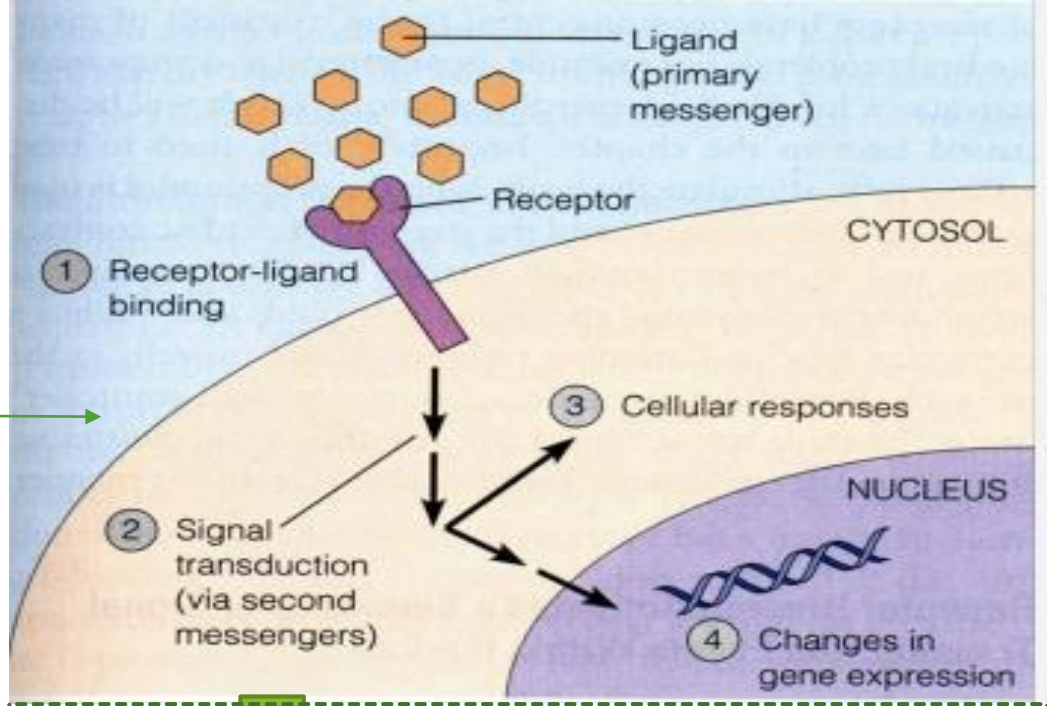
General signaling pathway (cascade)

1- The **ligand** (signal or primary messenger) will bind to the receptor

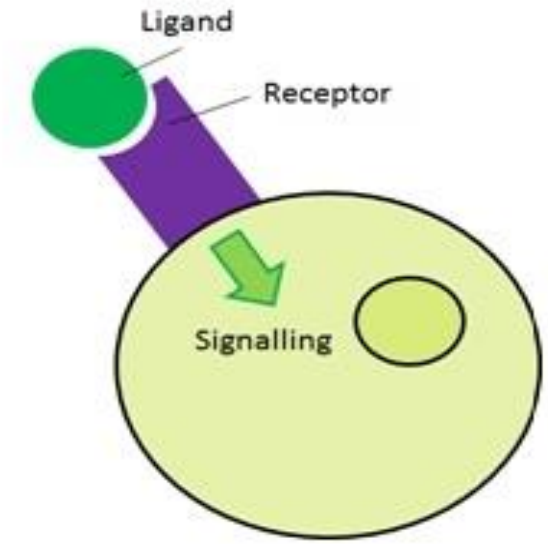
2- the receptor will recognize this signal.

3- This binding will stimulates the transduction by the second messenger, and this transduction includes:

- Cellular responses
- Changes in gene expression.



Biochemical cascade: a series of biochemical reactions, in which a product of the previous step is the substrate of the next.

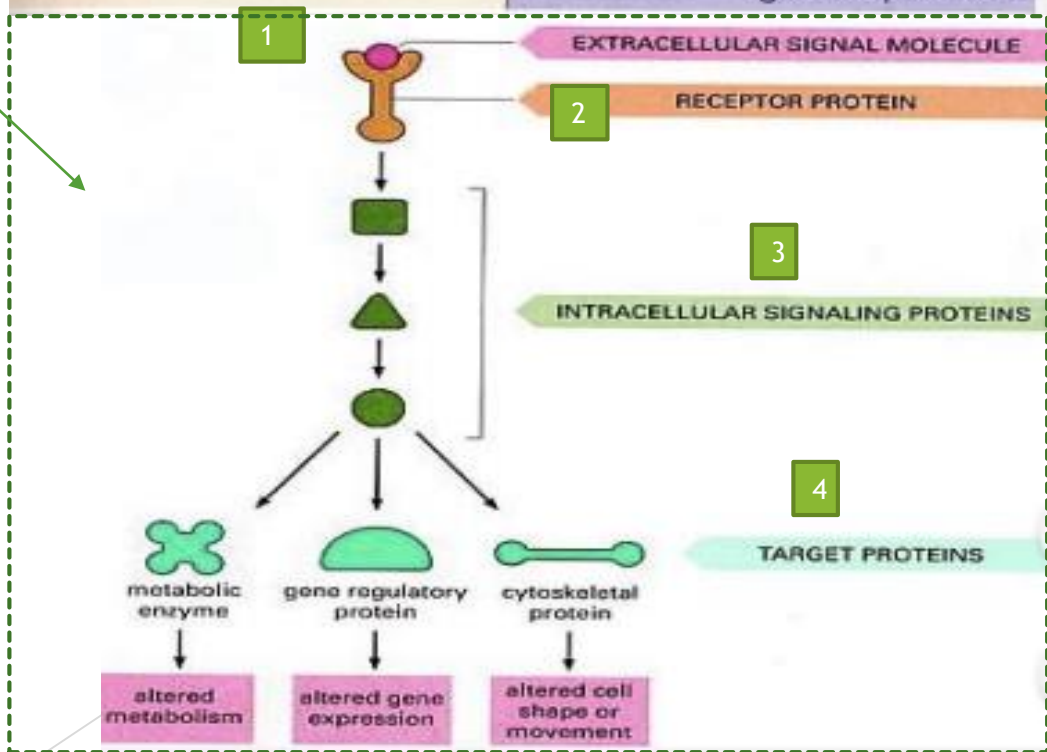


Recognition

More in Next slide

Performed by **receptors**
Ligand (hormone or neurotransmitter) will produce response only in cells that have receptors for this particular ligand.

Each cell has a specific set of receptors



Different response to the same molecule

الفكرة هنا :
- لدينا مركب يؤثر على خليتين ، ويكون تأثيره عليهم مختلف.
- مثلا: الاسيتايل كولاين .. عند إفرازه على خلايا العضلات القلبية فإنه سيتسبب بتقليل نبضات القلب وعند إفرازه على خلايا الغدد اللعابية سيتسبب بإفراز اللعاب.

Different cells

Acetylcholine

- Heart cells → Causes decreasing of contraction force which decreases heat rate
- Salivary cells → Causes stimulation of saliva secretion

Same cell but different pathways

More in next slide

Glucagon

Glucagon is a peptide hormone, produced by alpha cells of the pancreas, that raises the concentration of glucose in the bloodstream

In hepatocytes (liver cells)

- Causes stimulation of **Glycogenolysis**
- Causes inhibition of **Glyconeogenesis**

الفكرة هنا :
- لدينا هرمون واحد يأثر على نفس نوع الخلية ولكن تأثيره على هذه الخلية ينتج باثوايز مختلفة .. فمثلا الجلوكاجون الذي هو هرمون يعمل على زيادة تركيز نسبة سكر الجلوكوز بالدم .
- عند افرازه يقوم بتثبيط عملية تكوين الجلايكوجين *الجلوكوز يخزن بصوره جلايكوجين* ويحفز عملية glycogenolysis حتى نحصل على نسبة جلوكوز أكبر في الدم.

Different Responses to the Same Signaling Molecule:
(B) Same Cell but, Different Pathways (continued)

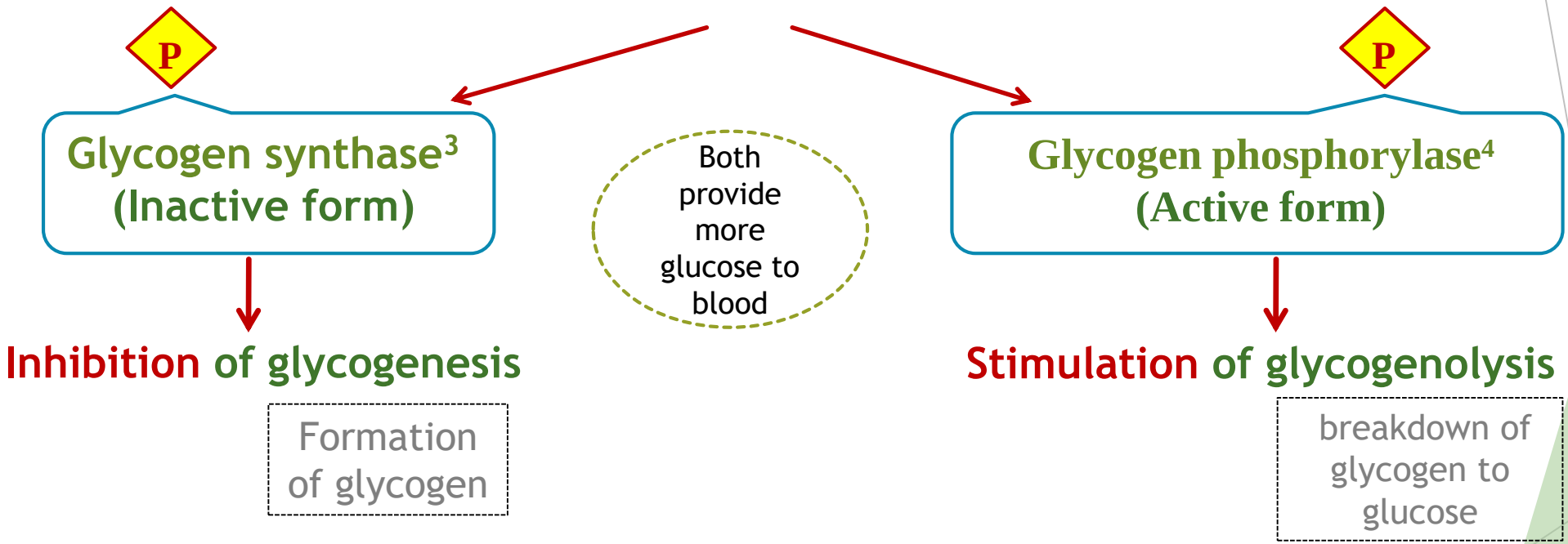
Glucagon (hormone) secretion[1]

Its secretion is stimulated by:
Hypoglycemia
(deficiency of glucose in the bloodstream)

Hepatocyte (liver cells) **:** They have glucagon receptor [2]

Second messenger: cAMP (cyclic Adenosine Monophosphate)

Response: Enzyme phosphorylation (add P group)



1. Glucagon is a peptide hormone, produced by alpha cells of the pancreas. The effect of glucagon is to make the liver release the glucose it has stored in its cells into the bloodstream, with the net effect of increasing blood glucose.
2. A receptor coupled with G-protein *more in next slide*
3. Is an enzyme involved in converting glucose to glycogen → therefore glucagon makes it INACTIVE.
4. Glycogen phosphorylase is one of the phosphorylase enzymes. It breaks up glycogen into glucose subunits.

(G-Proteins)
GTP-Dependant Regulatory Proteins

- come in between the **receptor & 2nd messenger .**
- **Regulate** the formation of synthesis of 2nd messenger

G-Proteins : Trimeric (3 subunits α,β,γ **)** membrane proteins.
Types according to its function :
G-stimulatory (G_s) and G-inhibitory (G_i) binds to GTP/GDP

Forms of G-Proteins

Inactive form
Trimeric –bound GDP
(αβγ/GDP)

Active form
ONLY α-bound GTP
(α/GTP)

(β , γ separate from α)

- The α-subunit has intrinsic GTPase activity (act as an Enzyme), resulting in hydrolysis of GTP into GDP and inactivation of G-proteins

Note: GTP: Guanosine triphosphate. GTP is essential to signal transduction, in particular with G-proteins, in second-messenger mechanisms where it is converted to guanosine diphosphate (GDP) through the action of GTPases.

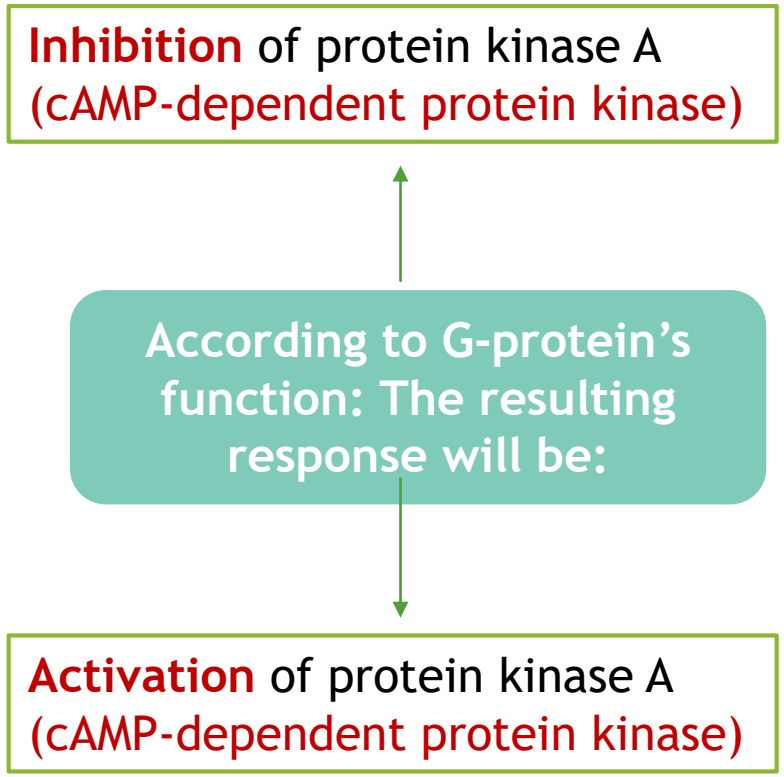
Two important second messenger systems:

- Adenylyl cyclase system.
- Calcium phosphatidylinositol system.

Remember ☺
Second messenger:
(intracellular signal
Formed during transduction)
intracellular signaling molecules released **within the cell** in response to a hormone to trigger physiological changes.

First: Adenylyl cyclase system

- **Signal**: Hormones or neurotransmitters are **primary messengers**
  - Hormones or neurotransmitters such as : Glucagon & Epinephrine
  - Or toxins such as : Cholera & pertussis toxins
- **Receptor**: G-protein-coupled receptor
  - **Adenylyle cyclase :** a membrane bound enzyme
  - **Function :** It converts ATP to cAMP (cyclic AMP)
- **Second messenger** : cAMP
- **Response**: Activation/inhibition of protein kinase A



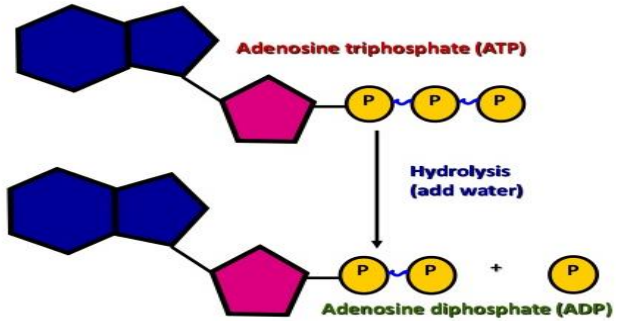
Note: For example: The effect of adrenaline is via a G protein signaling cascade, which transmits chemical signals from outside the cell across the membrane to the inside of the cell (cytoplasm). The outside signal (in this case, adrenaline) binds to a receptor, which transmits a signal to the G protein, which transmits a signal to adenylyl cyclase, which transmits a signal by converting ATP to cAMP (2nd messenger)

Note: protein kinase A is a family of enzymes whose activity is dependent on cellular levels of cyclic AMP (cAMP).
It is activated by cAMP.

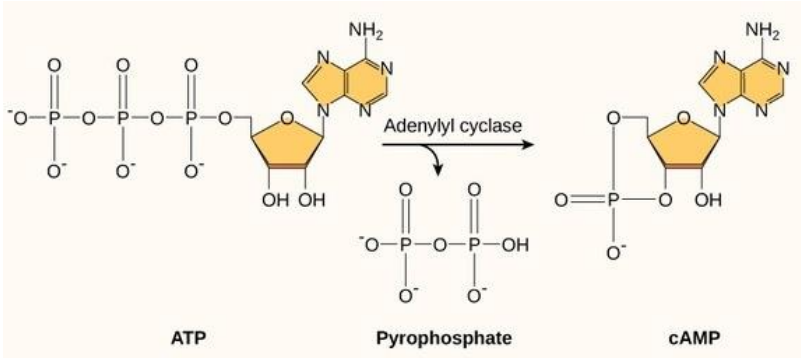
Extra information that might help you:

What is AMP & CAMP ?

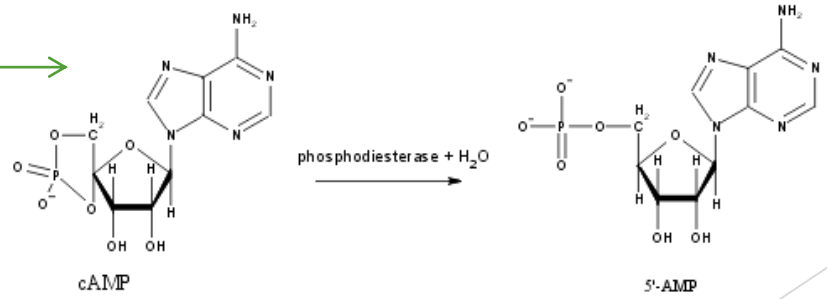
- We know that When the third phosphate is removed from **ATP**, we get **ADP**, which stands for Adenosine Di Phosphate.



- BUT when **two** phosphates are removed from **ATP**, we get **AMP**.



- **cAMP** is the **cyclic** structure of **AMP**, AMP is converted to cAMP by a specific Enzyme.

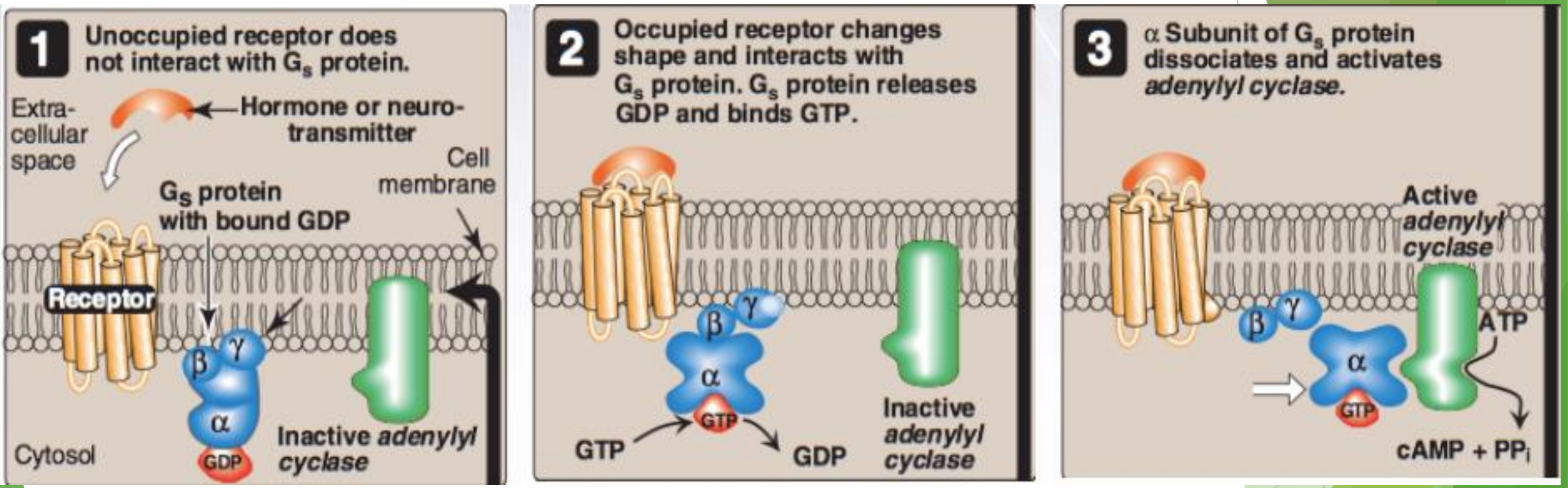


Signal Transduction: Adenylyl Cyclase System

Resting state: No Signal

Ligand/Receptor Binding Activation of Gs-protein

Activation of adenylyl cyclase



Binding of ligand (primary messenger) to the receptor activates G-protein.

→

GDP is replaced by GTP which is bound to α- subunit, then α-subunit dissociates from **β&γ** subunits.

→

α- subunit binds to adenylyl cyclase and makes it active.

→

Adenylyl cyclase converts ATP to cAMP . **cAMP is the second messenger.**

#NOTE: This information isn't mentioned on the slides, but it's already mentioned on the objective, so you should know it .

Actions of cAMP

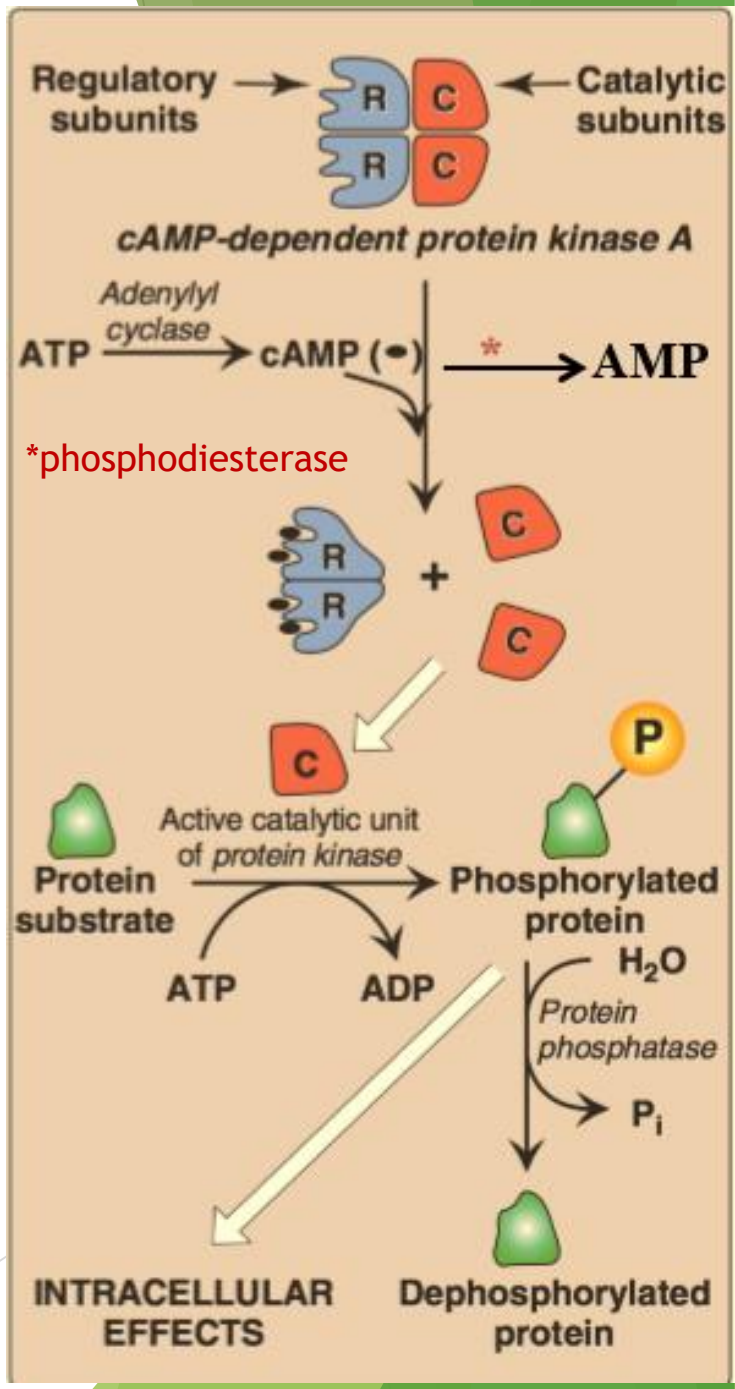
1-cAMP binds to cAMP-dependent protein kinase at its **regulatory subunits**.

2- then the catalytic subunits of cAMP-dependent protein kinase will be **released.**

3-Catalytic subunits catalyze the **transferring of phosphate** group from ATP to the specific amino acids of protein such as : **serine & threonine**.

4-When the **phosphate group** is bounded to the protein, it becomes **phosphorylated**

5-The **resulting protein** could be either **active or inactive**



e.g. phosphorylated form of **glycogen synthase** is **inactive** while The Phosphorylated form of **glycogen phosphorylase** is **active**

Termination of signal: *3 ways*

Degradation of Phosphorylated protein

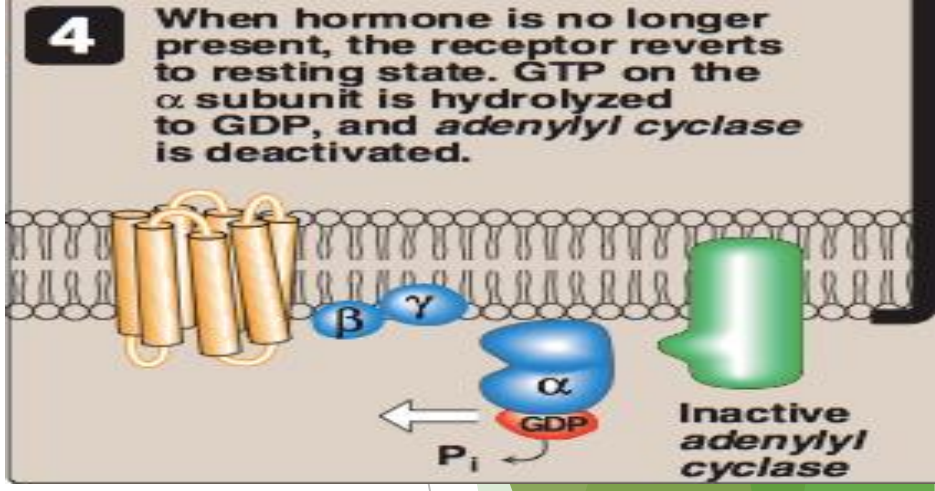
Removing phosphate group (PO4) from protein by enzyme called **protein phosphatase**

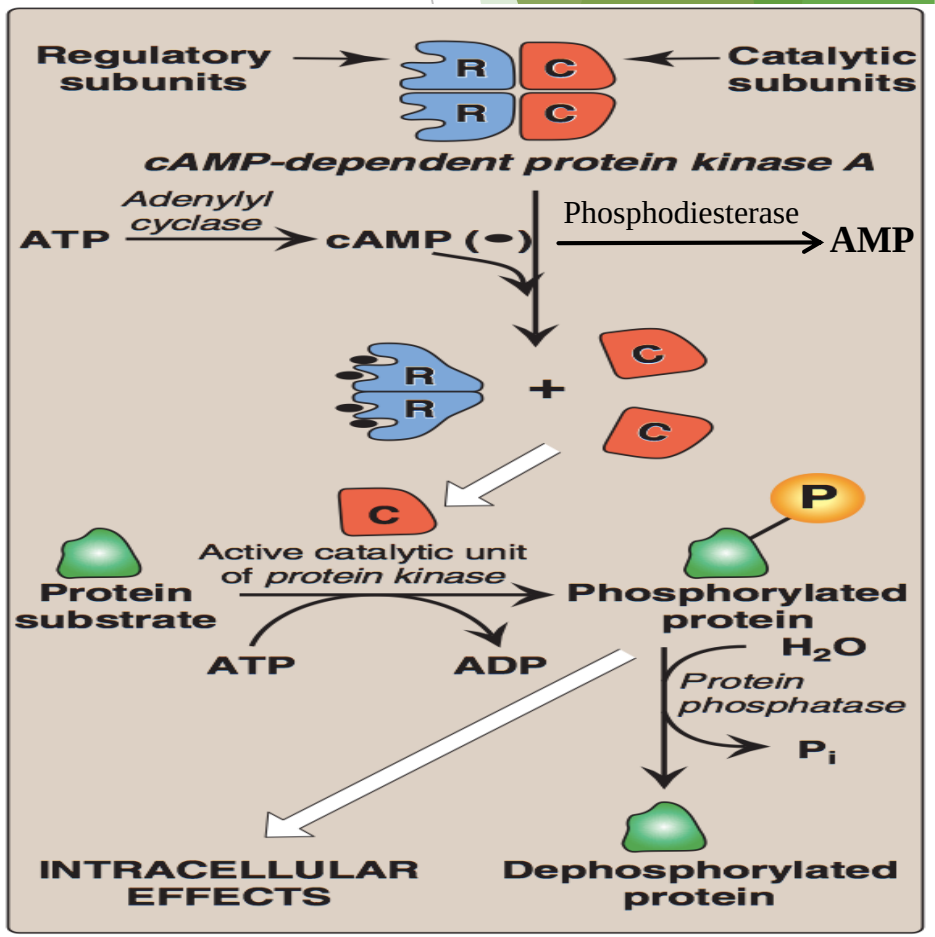
Inhibition of protein kinase A

Decreasing the amount of cAMP by enzyme called **phosphodiesterase** which converts **cAMP to AMP**

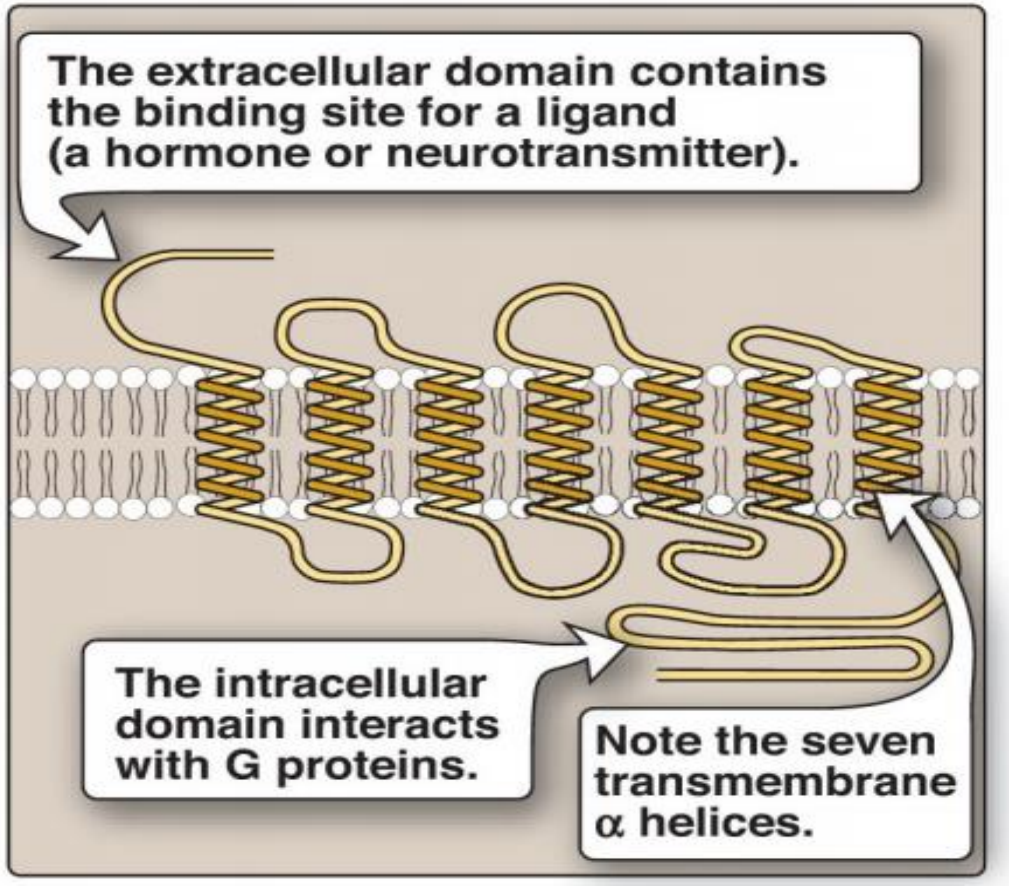
Inhibition of adenylyl cyclase

By hydrolyzing GTP to GDP in G-protein which leads to inactive form of G protein then **α-subunit** will bind to **β &γ subunits**





G-PROTEIN COUPLED RECEPTOR



-This is called seven pass receptor because it crosses cell membrane seven times.

-It has an extracellular domain receives signals and intracellular domain which holds G-PROTEIN

Regulation of Glycogen Metabolism by Glucagon:
Effects on Glycogen Synthase and Phosphorylase

لما يقل مستوى السكر أو الجلكوز بالدم ، يبدأ البنكرياس يفرز هرمون الجلوكاجون اللي بدوره يزيد مستوى الجلوكوز ، كيف؟ يروح هالهرمون للهدف اللي هي خلايا الكبد ويسوي شيئين، ليش الكبد بالذات؟ عشان فيه يتخزن الجلايكوجين وش هو هالجلايكوجين؟ هذا بوليمر (بولي سكرايت) متكون أساسا من مونومر (الجلكوز) ، طيب وش الفايدة؟ عشان احنا نبغى نزيد كمية الجلكوز بالدم، من وين نجيب هالجلوكوز ؟ من تكسير الجلايكوجين اللي متخزن من قبل بالكبد إلى جلوكوز وننزله على الدم، بالمقابل نبغى نقتصد أو نقلل استهلاك الجلوكوز إلا للضرورة فنروح نثبط عملية تكوين الجلايكوجين، وهالشيئين طبعًا نحتاج فيها إنزيمات.

The Action (stimuli)
Hypoglycemia

↓

The Hormone
Glucagon secretion

↓

The Target
Hepatocyte: Glucagon/receptor binding

↓

Second messenger
cAMP

↓

Response
Enzyme phosphorylation

- ✓ ***Glycogen*** : *polysaccharide form with glucose is stored in animal tissues like liver .*
- ✓ ***Glucagon*** : *protein hormone produced by pancreas .*

- ✓ ***Insulin*** : *Decreased the level of glucose in the blood .*
- ✓ ***Glucagon*** : *Increased the level of glucose in the blood.*

- ✓ ***Glycogenesis*** : *The formation and storage of glycogen .*
- ✓ ***Glycogenolysis*** : *the breakdown of glycogen .*

Glycogen phosphorylase (the enzyme)	(Active form)	*Stimulation of glycogenolysis*
Glycogen synthase(the enzyme)	(Inactive form)	*Inhibition of glycogenesis*

Pyruvate Kinase Regulation: Covalent Modification

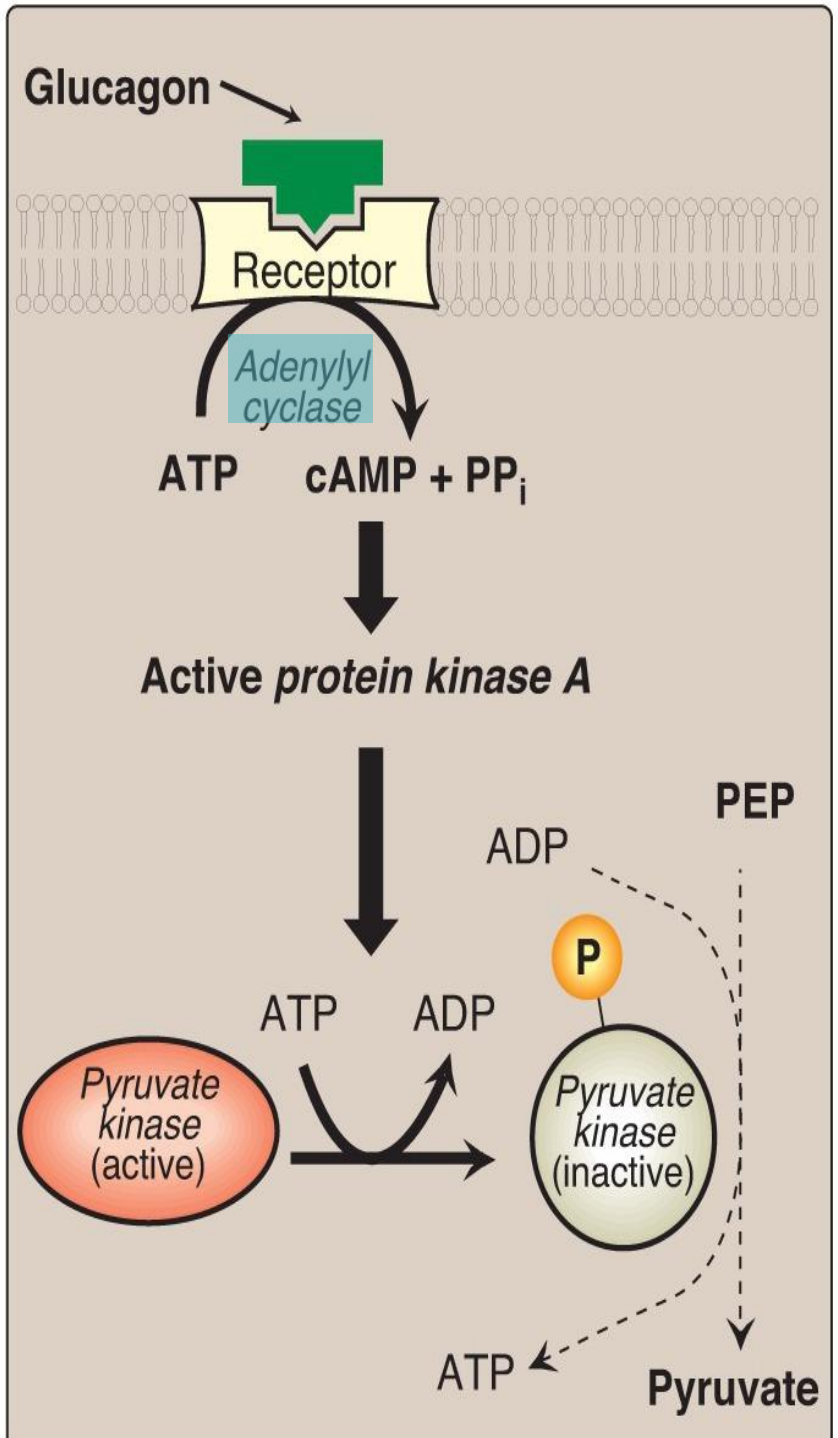
➢ **In Hypoglycemia :**
- ✓ *Stop Glycolysis .*
- ✓ *Stop Glycogenesis.*
- ✓ *Start Glycogenolysis .*

تكمله لأحداث السلايد اللي قبل ، هرمون الجلوكاجون ممكن يستهدف شيء ثاني غير خلايا الكبد مثلا خلايا الجسم العادية ،ايش يبغى منها ؟ طبعا إنها توفر أو تقلل من استهلاك الجلوكوز ، ليش ؟ لأنها بشكل طبيعي تستخدم الجلوكوز في عملية التنفس الخلوي عشان تنتج طاقة، فيروح للخلايا هذي ويثبط شوي عملية تكسير الجلوكوز إلا للضرورة .

- **Pyruvate kinase** is regulated by covalent modification
- **Covalent modification** are alterations of proteins by enzymes. It includes addition and removal of chemical groups (phosphate in this case).
- **This is an example of pathways with adenylyl Cyclase.**

- It is the last step in Glycolysis.
- Glucagon is released then binds with the receptor .
- It activates the Adenylyl Cyclase which will convert ATP to cAMP .
- cAMP activates the Protein Kinase A .
- This protein Kinase A can phosphorylate (Add phosphate group) the pyruvate kinase .
- After that it becomes Inactive
- **So the Glycolysis is stopped .**

Remember:
Protein Kinase A has several functions in the cell, including regulation of glycogen, sugar & lipid metabolism



Second: Calcium/Phosphatidylinositol System

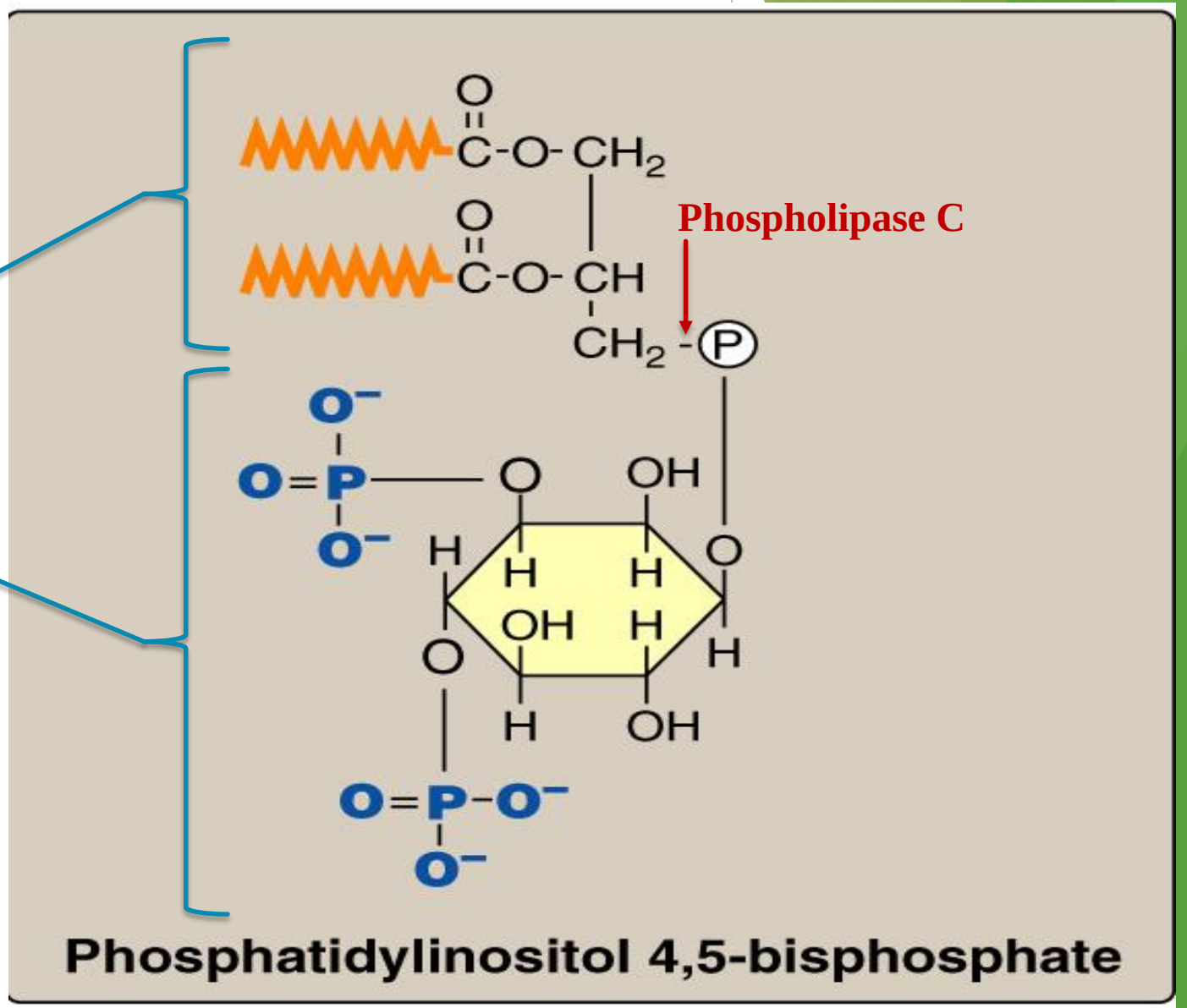
We can find it in the cell membrane , it plays an important role in cell signaling by Calcium/Phosphatidylinositol System .

Structure of Phosphatidylinositol :

Di-acyl-glycerol (DAG)

+

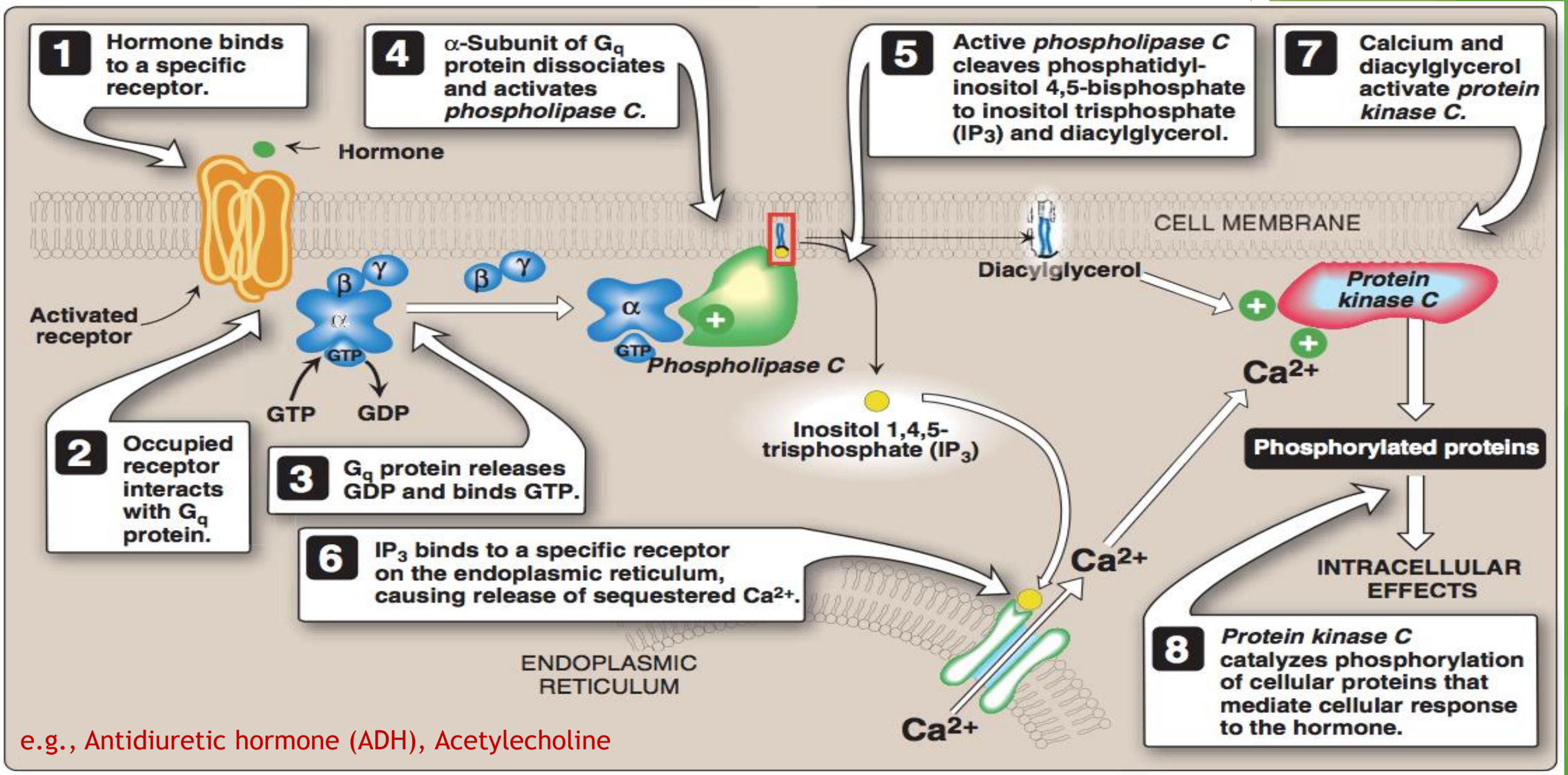
inositol 4-5 bisphosphate



Phospholipase C breaks the bond with red arrow.

After breakdown, inositol 4-5bisphosphate Takes the phosphate group (PO4) with red arrow becoming Inositol 1,4,5 triphosphate.

Intracellular Signaling by Inositol trisphosphate



e.g., Antidiuretic hormone (ADH), Acetylecholine

1. Binding

- Hormone/neurotransmitter binds to G-protein coupled receptor.
- e.g. “Antidiuretic hormone (ADH), Acetylecholine”

2,3. Receptor Interaction

- Receptor will Interact with G-protein Which will lead to replacing GDP with GTP.

4. Dissociation

- α-subunit dissociates from β & γ subunits, and activates Phospholipase C.

5. Breaking Down

- Phospholipase C break phosphatidylinositol 4-5bisphosphate into DAG + inositol 4-5 bisphosphate

6. Ca Releasing

- ER stores Calcium Which released to the cytoplasm when IP3 binds. (IP3: Inositol 1,4,5 triphosphate)

7. Kinase C Activation

- Calcium and DAG activate protein kinase C

8. Responding to Action

- Protein kinase C catalyze protein phosphorylation. These proteins will give the response of the hormone or neurotransmitter.

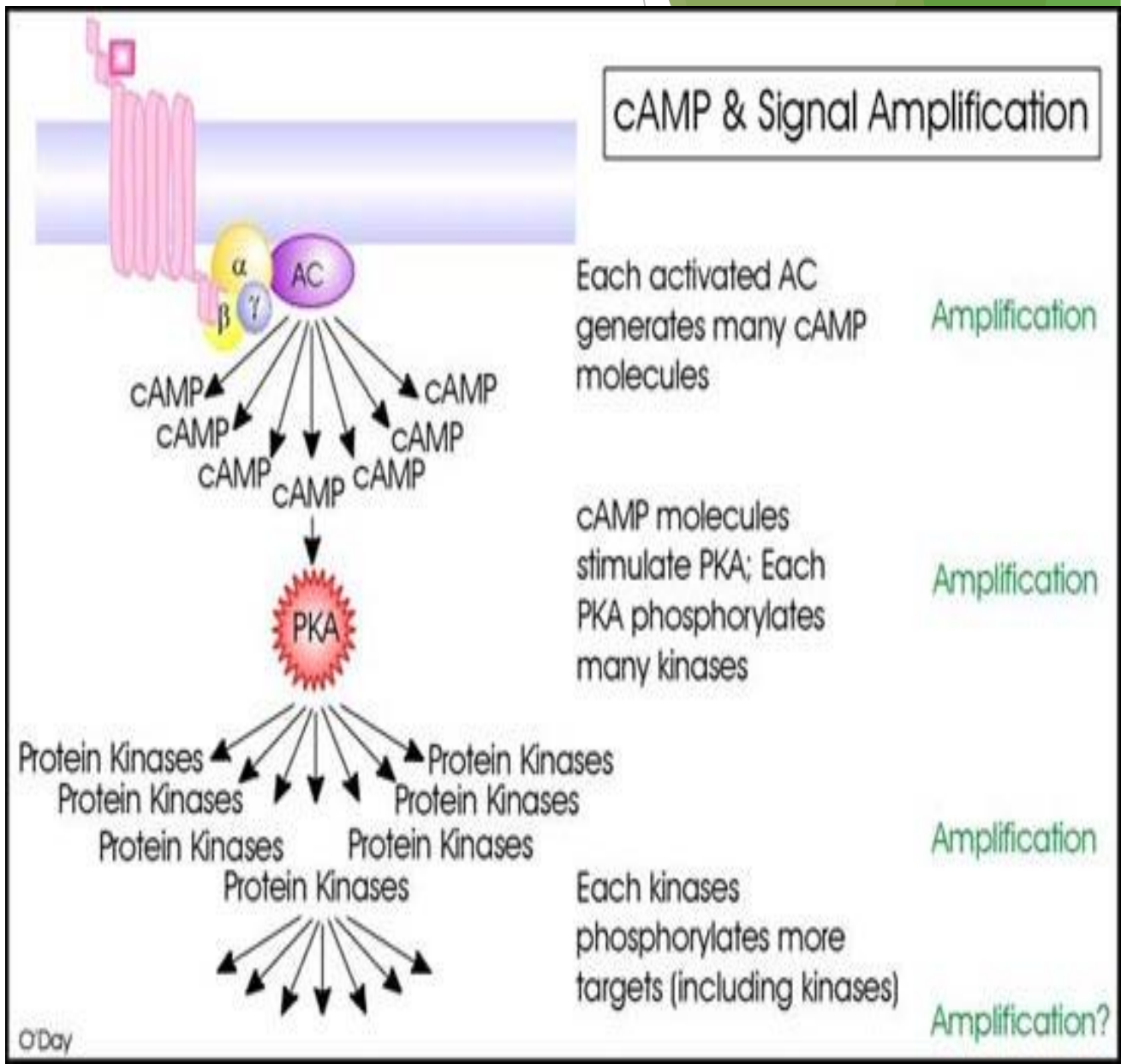
The system	Adenylyle cyclase	Calcium/Phosphatidylinositol
Enzyme	Adenylyle cyclase	Phospholipase C
Secondary messenger	cAMP	Diacylglycerol (DAG) & Inositol 1,4,5 triphosphate (IP3)
Protein	Protein kinase A (A stand for cAMP)	Protein kinase C (C stand for Ca++)
signal	-hormones or neurotransmitters (e.g. Glucagon & Epinephrine) - Toxins (e.g. cholera and pertussis toxins)	Acetylcholine & Anti-diuretic Hormone

Signal Amplification

- *Signal amplification means that the process*

doesn't occur in 1:1 ratio for example:

- *1 adenylyl cyclase generates 10 or 100 cAMP*
- *cAMP activates 1000 protein kinases*
- *Protein Kinase phosphorylates a lot of targets.*



كل شي أخذناه إلى الآن أكيد ما يصير بشكل بسيط أو حبة حبة ، كل خطوة فيها تتضاعف مرات ومرات وتعطي انتشار للإشارة ، بمعنى إذا وصل الهرمون للمستقبل بعد ما ينشط البروتين ، البروتين بدل ما ينتج cAMP واحد لا ينتج عشر ، و هالعشر كل واحد فيها يستهدف ميه وكل واحد من هالمية يستهدف ألف ، وبكذا يكون الإشارة تضاعفت عشر آضعافها أو حتى ألف ضعف .

TAKE HOME MESSAGE

Cell signaling allows:

- Signal transmission and amplification.
- Regulation of metabolism.
- Intercellular communications & coordination of complex biologic functions.

#NOTES:

- Phosphorylation doesn't mean activation, certain enzymes are activated by dephosphorylation.
- Enzymes stimulated by insulin activated by dephosphorylation while enzymes stimulated by glucagon are activated by Phosphorylation.

videos

- G-Protein Coupled Receptors| Khan Academy
- Signal Transduction Pathways
- Signal Amplification
- Calcium/phosphatidylinositol system
- cAMP+G-Protein (highly recommended)
- Calcium/Phosphatidylinositol System (highly recommended)

MCQs

TEAM 436

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5- سارة الشمراني.
6- روان سعد.
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