Biochemistry Team 435

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# CELL SIGNALLING

**“HAPPINESS IS FORMED WHEN YOU STOP COMPARING YOURSELF TO OTHER PEOPLE”**

# OBJECTIVES:

- Different steps in signalling pathways
- The second messenger system
- Function of signalling pathways for:
  - Signalling transmission
  - Amplification
- The role of signalling pathways in regulation and integration of metabolism

# Extra information that might help you

- **Glucagon** is a peptide hormone, produced by alpha cells of the pancreas, that raises the concentration of glucose in the bloodstream
- **Glycogen** is a multi-branched polysaccharide of glucose that serves as a form of energy storage
- **Glycogenolysis** is the breakdown of glycogen (n) to glucose-6-phosphate and glycogen

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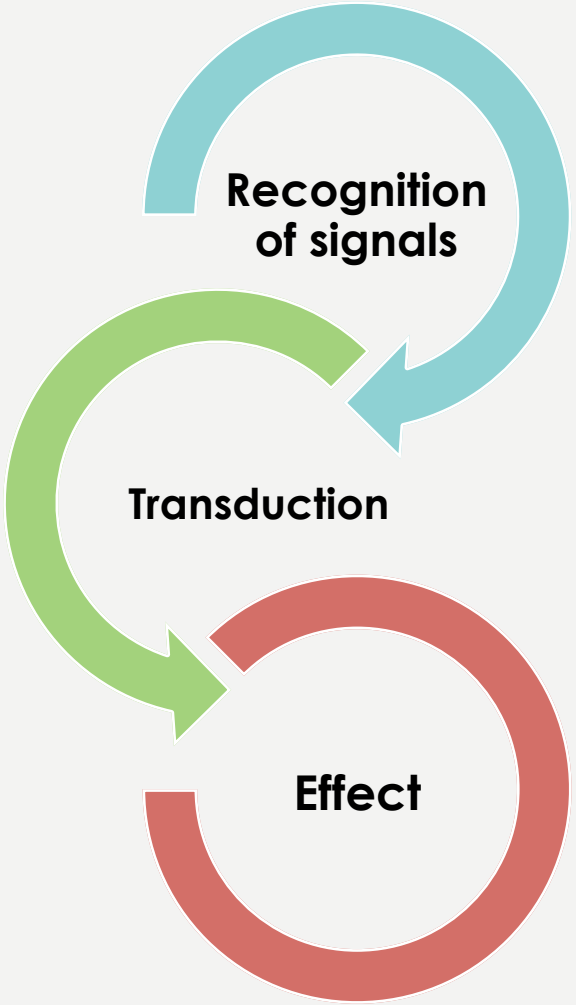
# Signalling Process

**Cells must**

- communicate with each other
- send and receive information (signals)
- Produce the response

- **stimulated by** the ligand (hormone, growth factor, neurotransmitter).




- By Receptors (could be on the cell surface or inside the cell).
- Ligand will produce response only in cells that have receptors for this particular ligand.
- Each cell has a specific set of receptors.

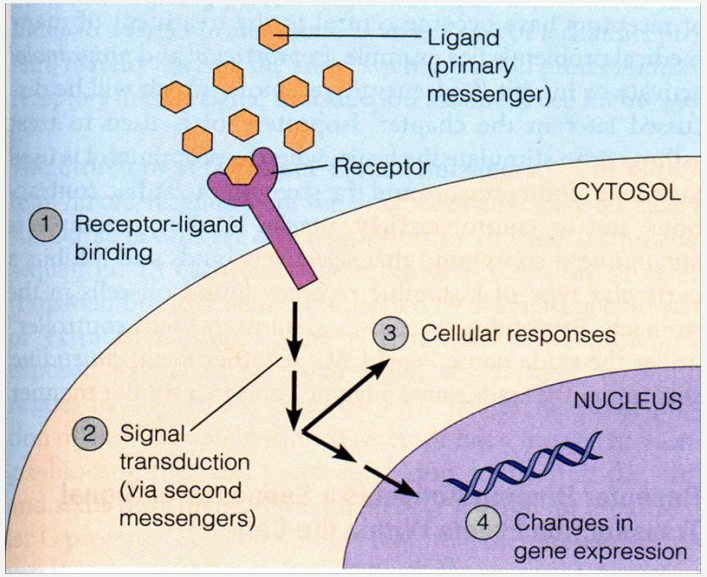
- Change of external signal into intracellular message with amplification and formation of 2nd messenger .

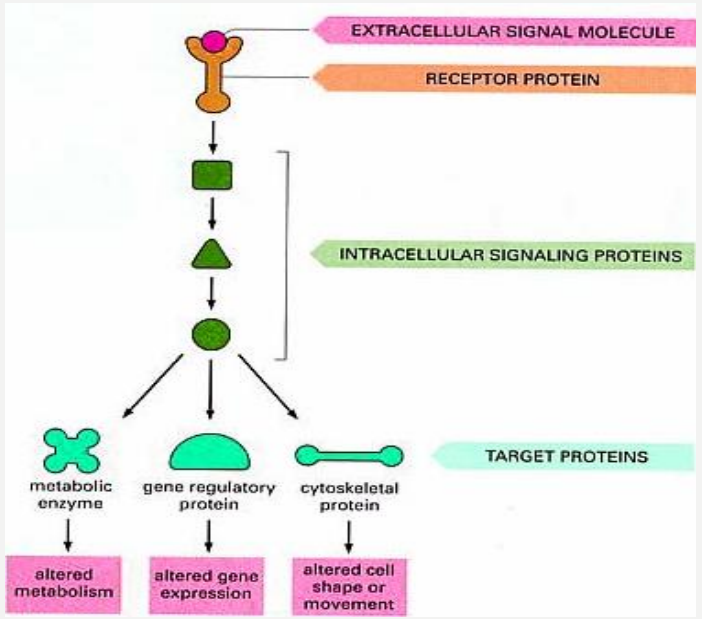
- Modification of cell metabolism and function .

# General signaling pathway and cascade

- The ligand (primary messenger) binds to the receptor, then the receptor recognizes the ligand.

- Once the ligand binds, it stimulates cascade of events end up with:
  - Transmission of signals to inside of the cell.
  - Amplification.
  - Formation of second messenger and mediate of the ligand.




Note: the ligand is still outside of the cell because it is hydrophilic (cannot cross the lipid bilayer). However, there are few lipid soluble hormones that can cross the lipid bilayer, but bind to a receptor inside the cell.

# Recognition

- **Performed by** receptors
- **Receptors are** highly sensitive structures
- Ligand will produce response only in cells that have receptors for this particular ligand
  - e.g. Glucagon is secreted by the pancreas, and it doesn't make any effect except on the liver cells. So it doesn't make an effect on the muscle cells because it doesn't have a receptor in the muscles.
- Each cell has a specific set of receptors
  - e.g. A cell could have a receptor for glucagon, a receptor for insulin, and one for epinephrine.. etc.

# Different response to the same molecule

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

### 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 in same cell , but different pathways.

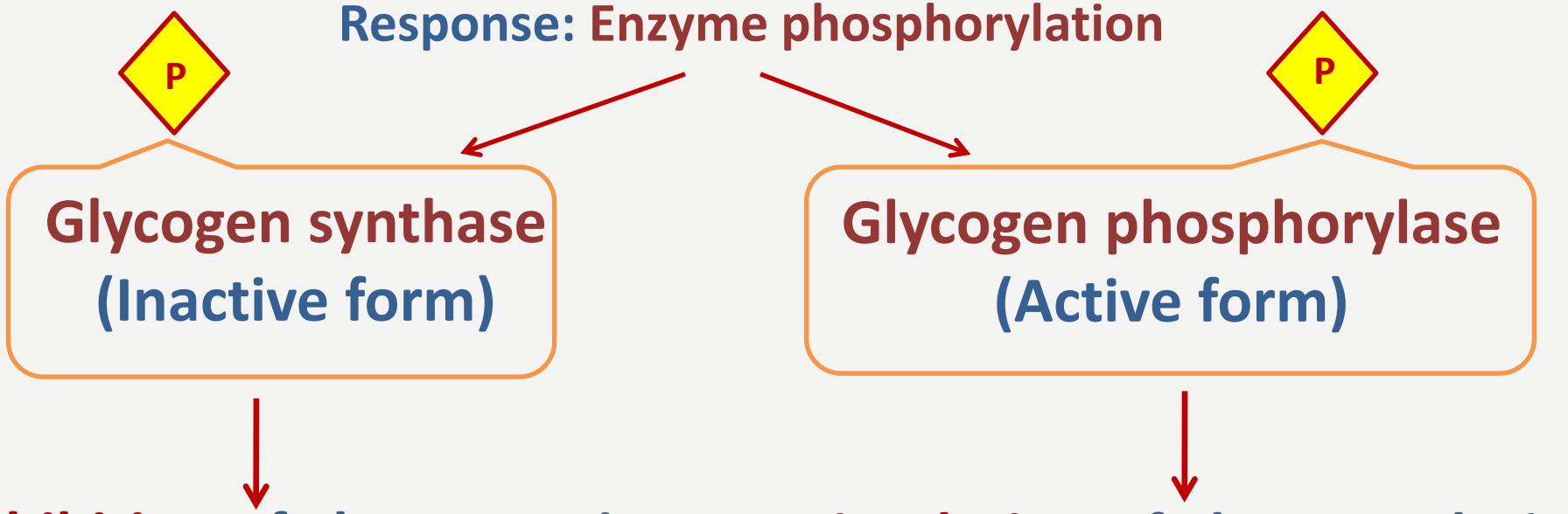
Hypoglycemia*

Glucagon secretion

Hepatocyte: Glucagon/receptor binding

Second messenger: cAMP

Response: Enzyme phosphorylation




* Low blood sugar

# GTP-Dependant Regulatory Proteins (G-Proteins)

- **G-Proteins:** *Trimeric* (has 3 subunits) membrane proteins **(αβγ subunits)**
- **Types according to its function:** G-stimulatory ($G_s$) and G-inhibitory ($G_i$)

Binds to GTP/GDP

- الجي بروتينز هي عبارة عن بروتينات مكونة من ٣ وحدات .. الفا ، بيتا ، غاما .
- لديها ٢ فورمز : النشط وهو يكون عندما تكون الالفا مرتبطة بالGTP والغير نشط عندما تكون الالفا مرتبطة بالGDP.
- الالفا لديها intrinsic GTPase activity هذه الخاصية ستؤدي الى تحول ال GTP الى GDP أو بمعنى آخر تحولها من الفورم النشط الى الفورم الغير نشط!!

**Forms of G-Proteins**

Inactive form
Trimeric –bound GDP
**(αβγ/GDP)**

Active form
Only α -bound GTP
**(α/GTP)**

- The α-subunit has intrinsic GTPase activity, resulting in hydrolysis of GTP into GDP and inactivation of G-proteins

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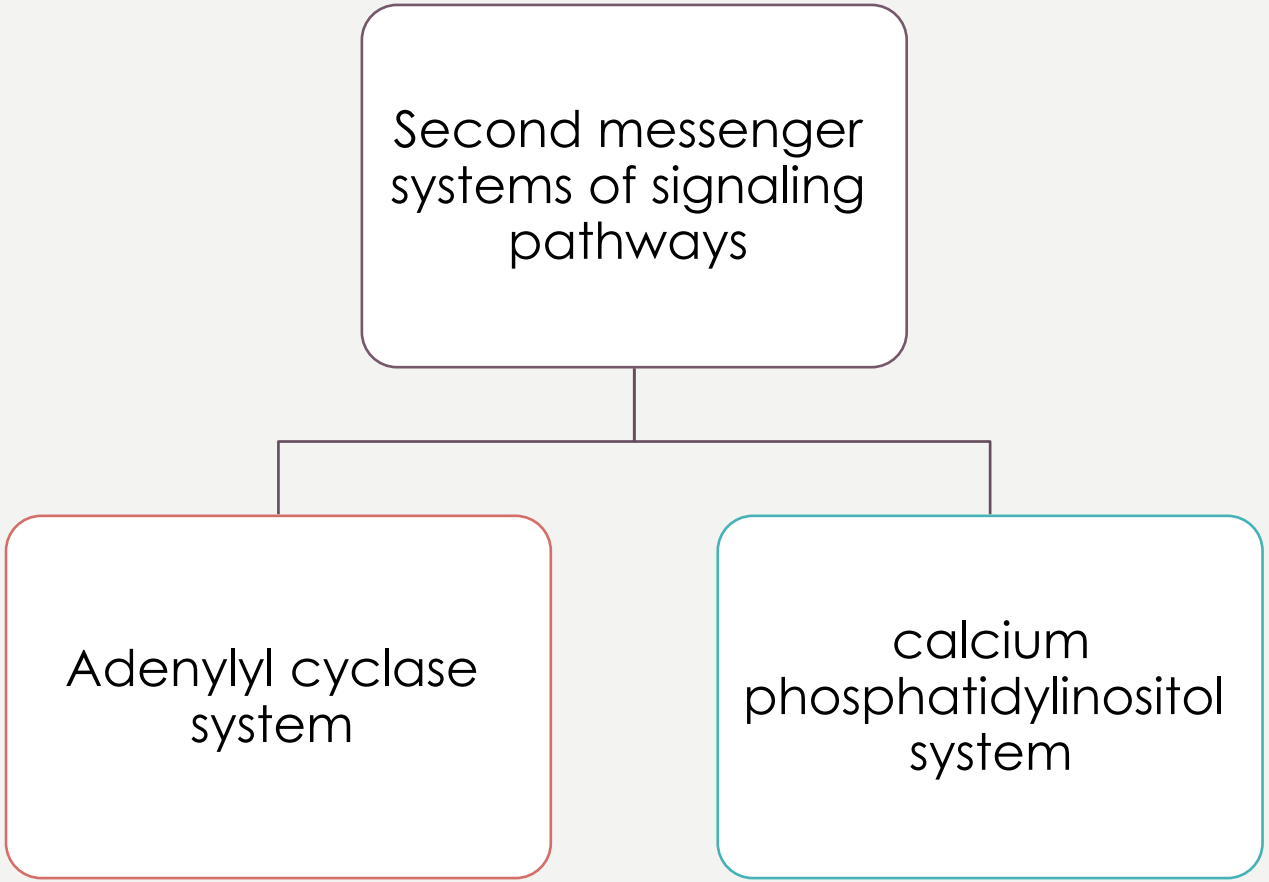
# Second messenger systems



# Adenylyle cyclase system

**Adenylyle cyclase :** a membrane bound enzyme
**Function :** It converts ATP to cAMP (cyclic AMP)
**Second messenger** : cAMP
**Receptor:** G-protein coupled receptor

**Signal:** Hormones or neurotransmitters are primary messengers

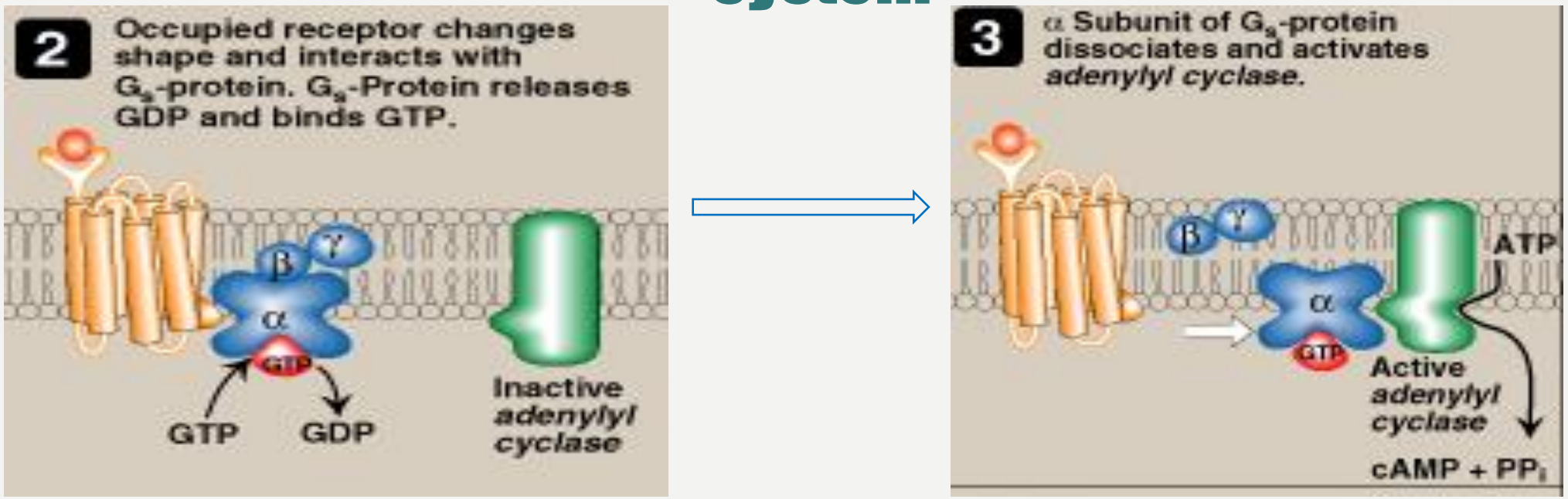
- Hormones or neurotransmitters such as :Glucagon & Epinephrine
- Toxins such as :Cholera & pertussis toxins

According to G-protein`s function
The resulting response will be

Inhibition of
protein kinase A
**(cAMP-dependent protein kinase)**

Activation of
protein kinase A
**(cAMP-dependent protein kinase)**

# Signal transduction of Adenylyle cyclase system

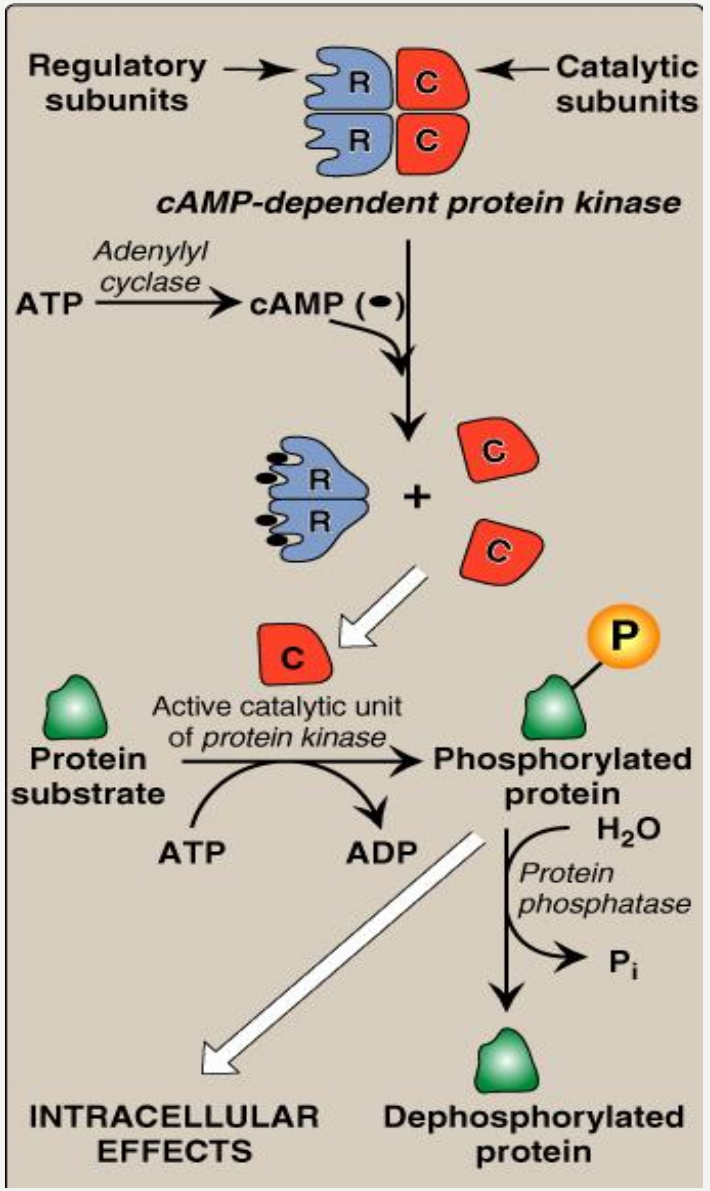



- Binding of ligand ( primary messenger ) to the receptor activates G-protein.
- **GDP is replaced by GTP** which is bound to **α- subunit**, then **α-** subunit dissociates from **β&γ** subunits.
- **α-** subunit binds to adenylyl cyclase and make it active.
- Adenylyl cyclase converts ATP to cAMP .
- cAMP is the second messenger.

# Signal transduction of Adenylyle cyclase system

- cAMP binds to cAMP-dependent protein kinase at regulatory subunits.
- Then the catalytic subunits of cAMP-dependent protein kinase will be released.
- Catalytic subunits catalyze the transferring of phosphate group from ATP to the specific amino acids of protein such as : serine & threonine.
- When the phosphate group is bounded to the protein, it becomes phosphorylated . 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

**Degradation of phosphorylated protein**

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

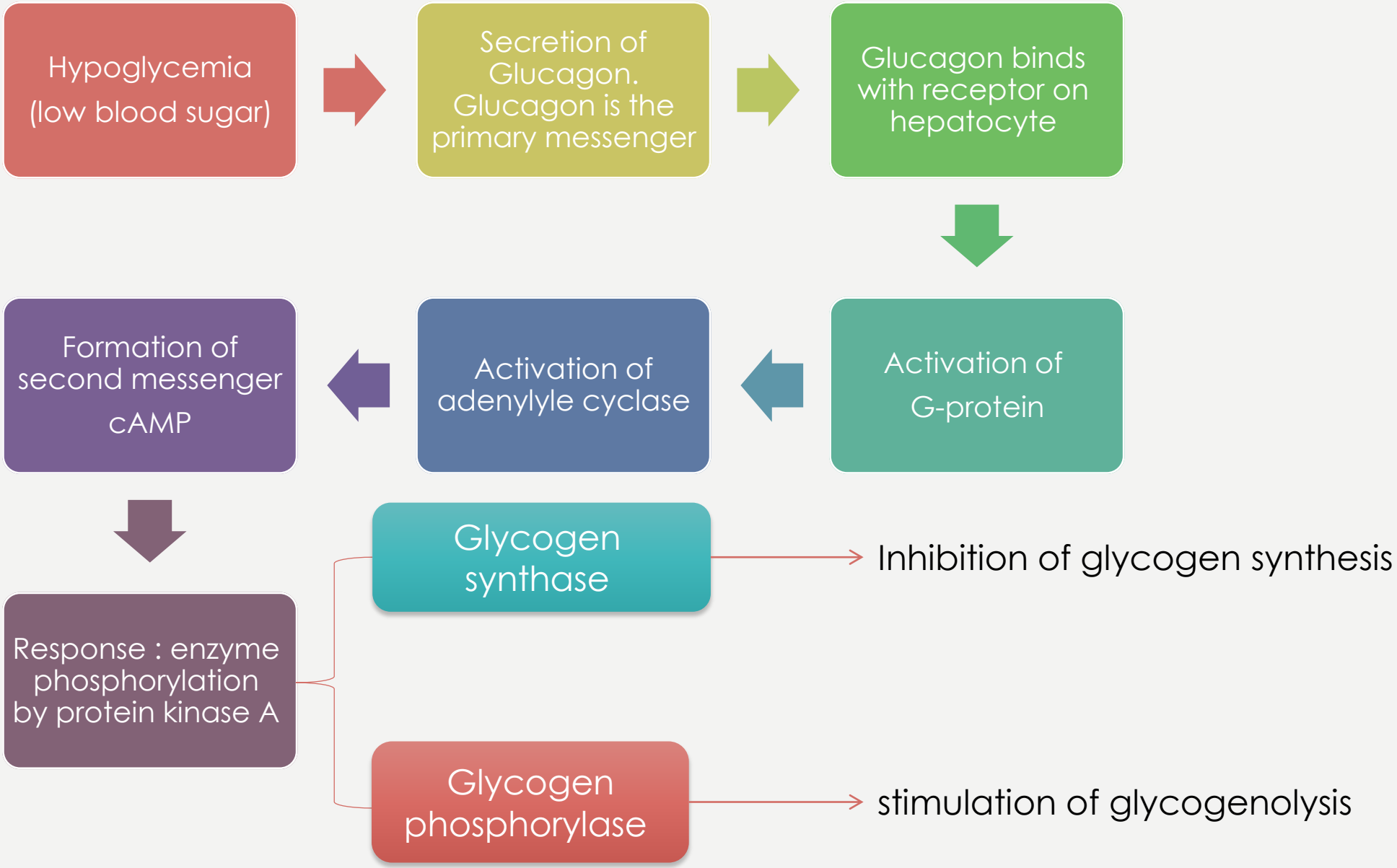
**Inhibition of protein kinase A**

- 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

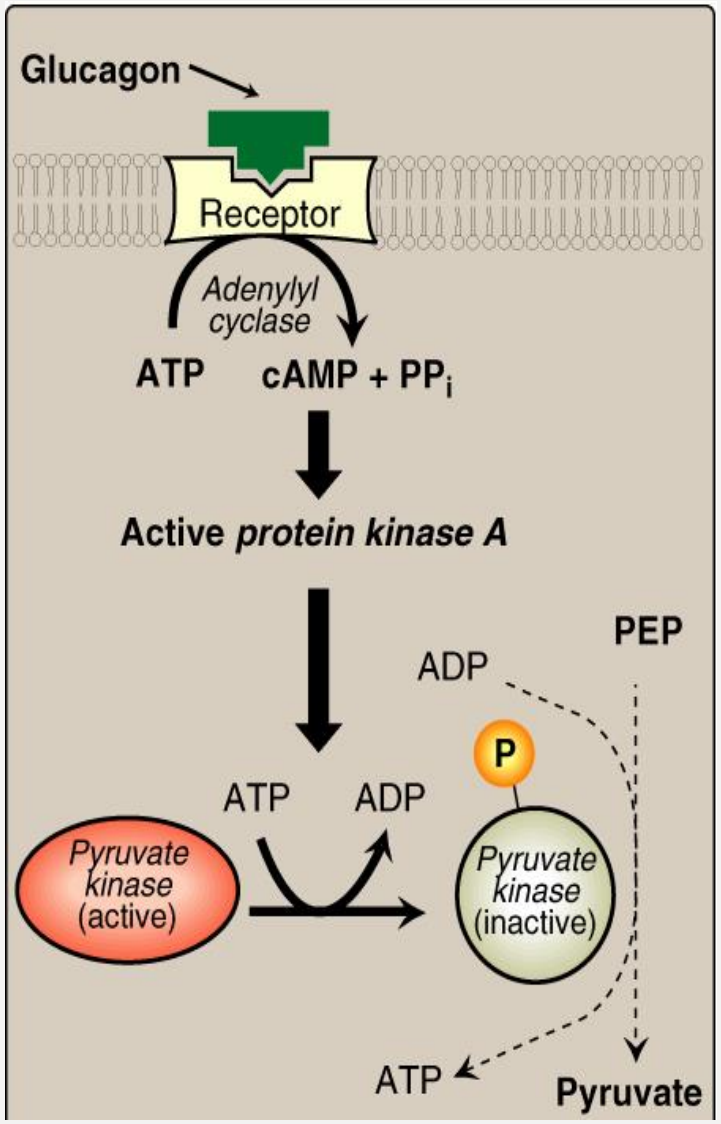
# summary


Hypoglycemia (low blood sugar)
Secretion of Glucagon. Glucagon is the primary messenger
Glucagon binds with receptor on hepatocyte
Activation of G-protein
Activation of adenylyle cyclase
Formation of second messenger cAMP
Response : enzyme phosphorylation by protein kinase A
Glycogen synthase
Inhibition of glycogen synthesis
Glycogen phosphorylase
stimulation of glycogenolysis

# Pyruvate Kinase Regulation: Covalent Modification

- 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
- Phosphorylating Pyruvate kinase making it Inactive
- This blocks glucose catabolism.
- Remember: glucagon secreted during tendency of

Hypoglycemia to increase glucose levels.




خطوط منقطة معناها أن التفاعل لا يتم في الصورة هذه

الصورة هذه نفس العملية السابقة هي مثال لها .

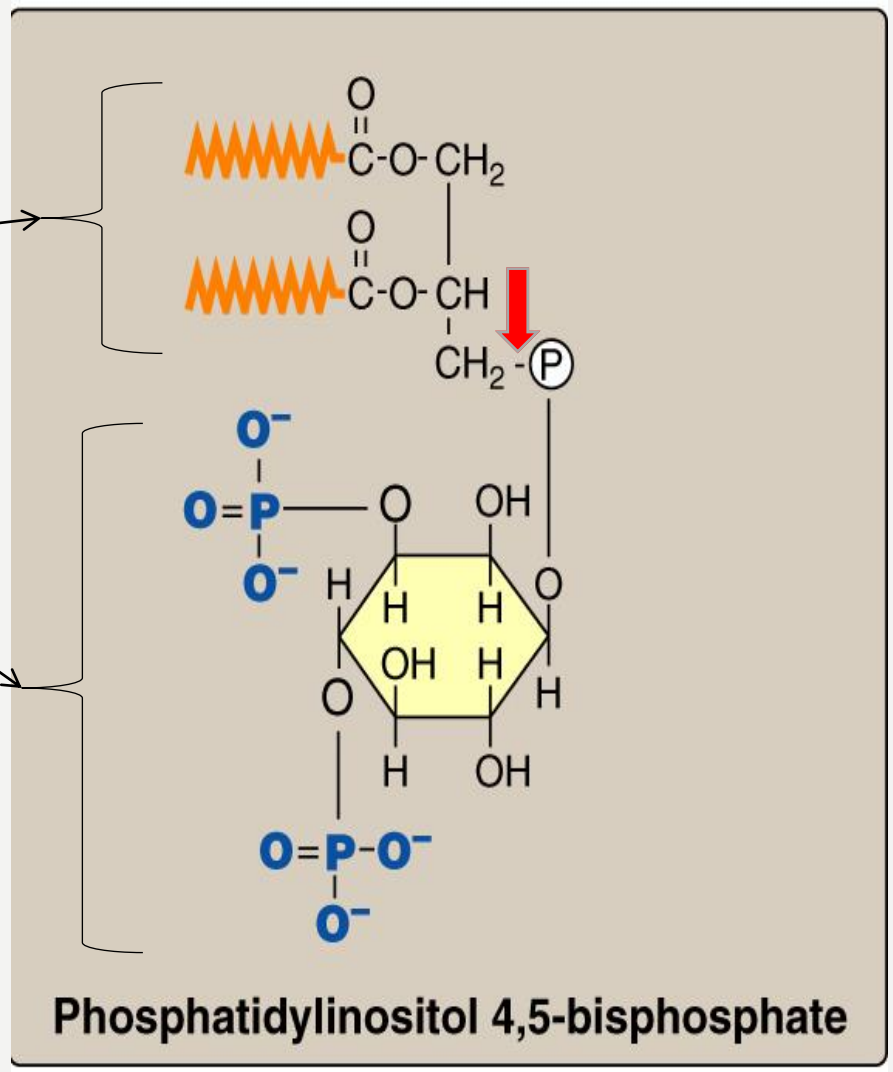
# CALCIUM/PHOSPHATIDYLINOSITOL SYSTEM

**Structure of Phosphatidylinositol :**

Diacylglycerol (DAG)

+

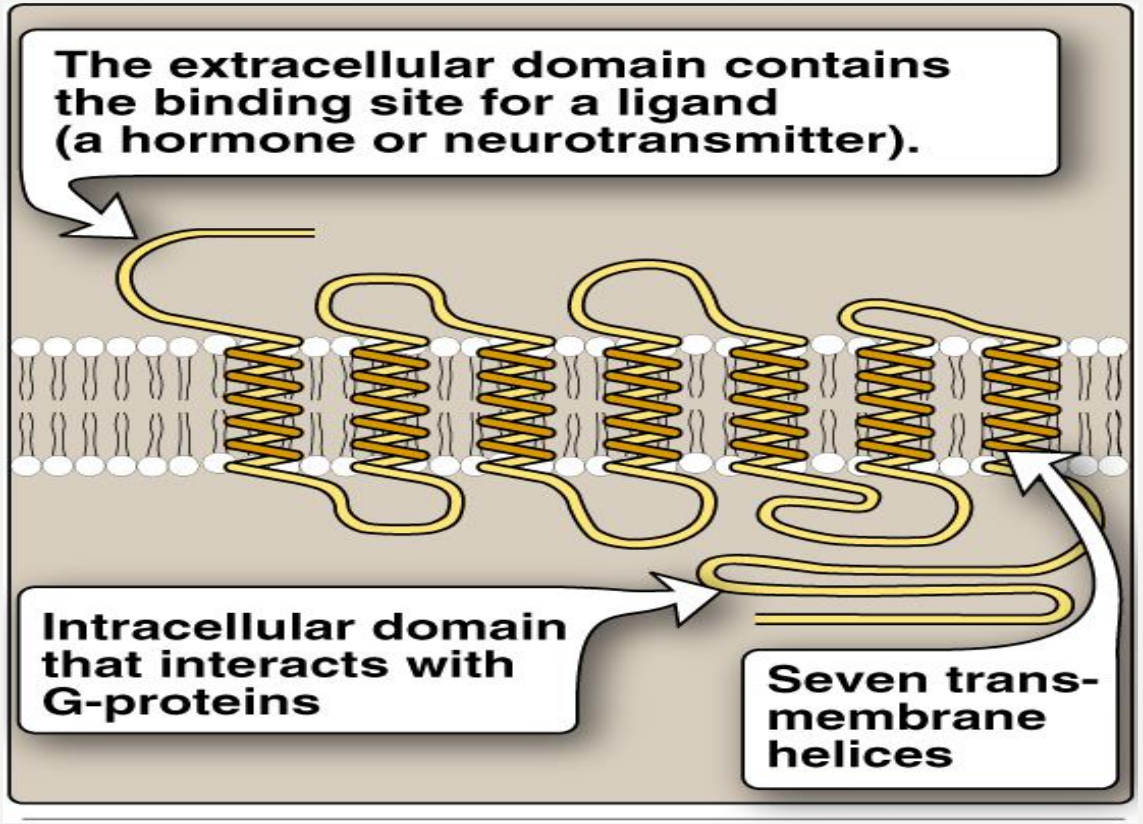
inositol 4-5bisphosphate




- Phospholipase C breaks the bond with red arrow.
- After breakdown, inositol 4-5bisphosphate

Takes phosphate group (PO4) with red arrow becoming Inositol 1,4,5 triphosphate.

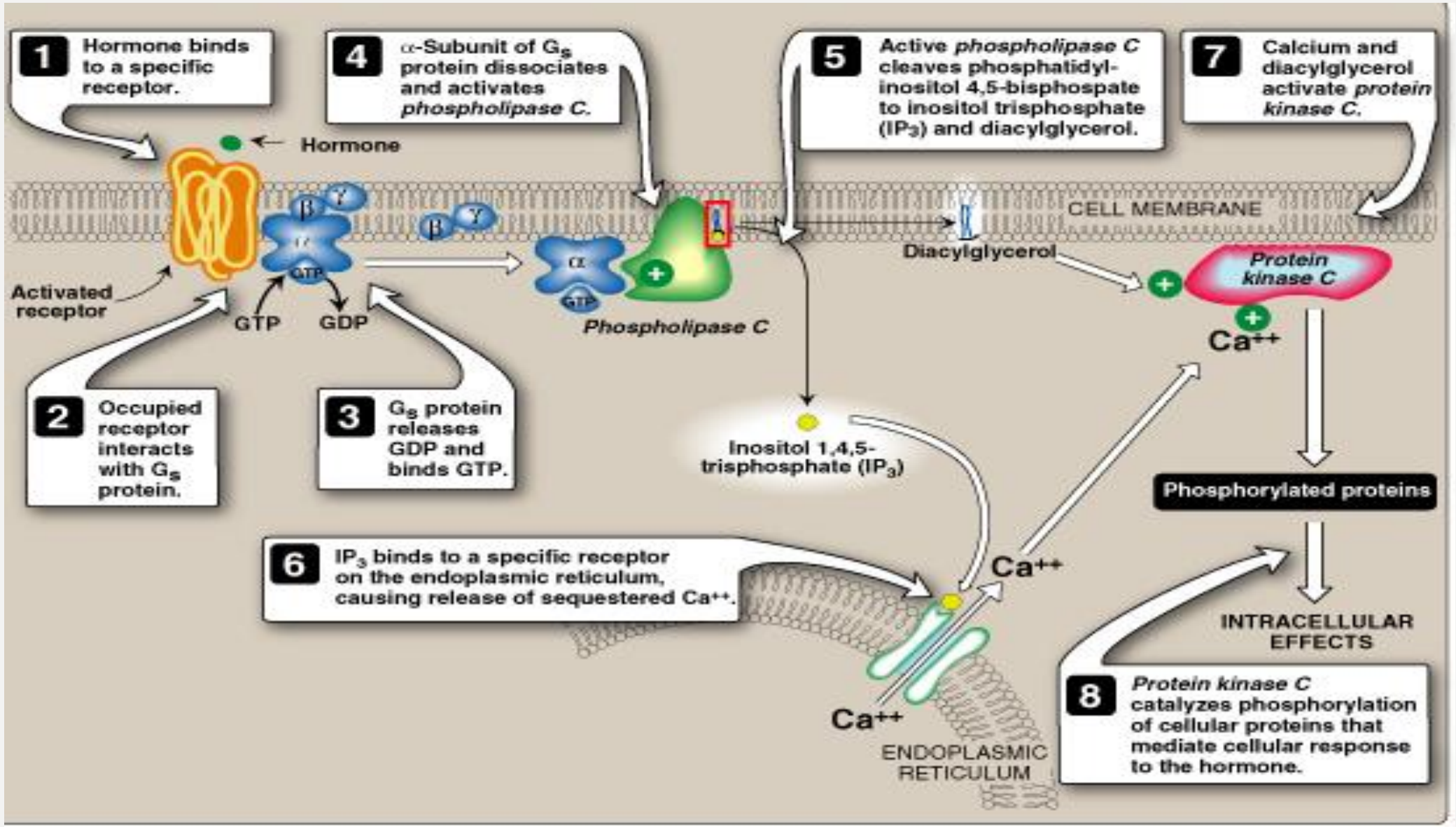
# G-PROTEIN COUPLED RECEPTOR




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

# CALCIUM/PHOSPHATIDYLINOSITOL SYSTEM



# CALCIUM/PHOSPHATIDYLINOSITOL SYSTEM

1. Hormone or neurotransmitter (acetylcholine and anti-diuretic hormone) binds to g-protein coupled receptor.

2&3. Receptor Interacts with G-protein Which releases GDP and binds with GTP.

4. Alpha subunit dissociates (تفصل) from beta and gamma subunits, and activates Phospholipase C.

5. Phospholipase C break phosphatidyl inositol 4-5bisphosphate into Diacylglycerol and Inositol 1,4,5 triphosphate (تذكر من صورة شرح السابقة وين الانفصال)

6. Inositol 1,4,5 triphosphate (IP3) has Receptors on ER. ER stores Calcium Which released to the cytoplasm when IP3 binds.

7. Calcium and Diacylglycerol activate protein kinase C (C because needs calcium)

8. Protein kinase C catalyze protein phosphorylation. These proteins will give the response of the hormone or neurotransmitter. (hormone or neurotransmitter يخلي الخلية تسوي شغلة)

الخطوات مرقمة نفس الصورة اقرأ الخطوة بعدين ارجع عليها في الصورة

- Diacylglycerol and Inositol 1,4,5 triphosphate are secondary messengers.

# ADENYLYLE CYCLASE VS CALCIUM/PHOSPHATIDYLINOSITOL

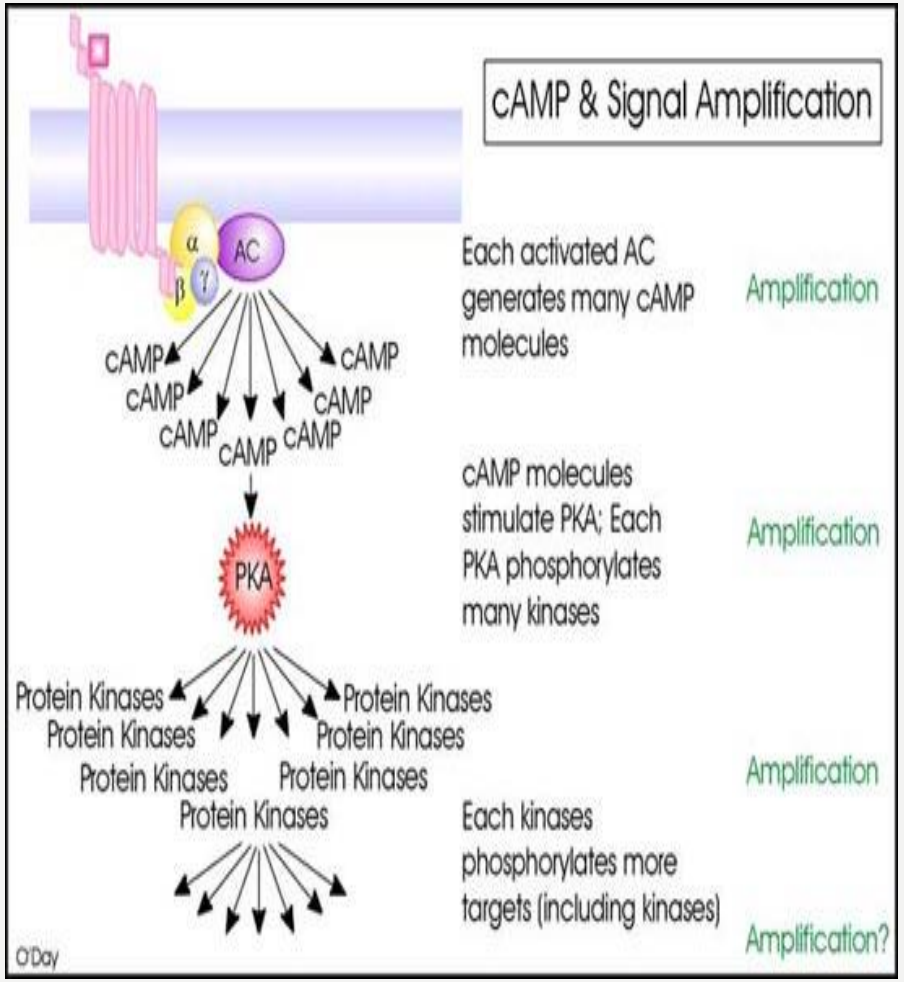
| | Adenylyle cyclase system | Calcium/Phosphatidylinositol System |
|---|---|---|
| **Enzyme** | Adenylyle cyclase | Phospholipase C |
| **Secondary messenger** | cAMP | Diacylglycerol (DAG) & Inositol 1,4,5 triphosphate (IP3) |
| **Protein** | Protein kinase A | Protein kinase C |
| **signal** | -hormones or neurotransmitters ( e.g. Glucagon & Epinephrine)<br>- 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.

يعني يتضاعف التفاعل بدل ما واحد يشغل واحد

واحد يشغل ١٠٠و ١٠٠ تشغل ١٠٠٠ و تستمر.



# TAKE HOME MESSAGE

**Cell signaling allows**

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

Important 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 (very recommended video)**
https://www.youtube.com/watch?v=ZBSo_GFN3qI

**- Signal Transduction Pathways:**
https://www.youtube.com/watch?v=qOVkedxDqQo

**- Cell Signaling Pathways part 1:**
https://www.youtube.com/watch?v=U8j6rveCCvo

**- Cell Signaling Pathways part 2:**
https://www.youtube.com/watch?v=ft0YpIpqx2c

**Q1. The functions of signaling process is : recognition of signal and transduction only:**

1) True
2) False

**Q2. Change of external signal into intracellular message with amplification and formation of :**

1) Fires messenger
2) Second messenger
3) Third messenger
4) Fourth messenger

**Q3. Ligand will produce response with any receptor :**

1) True
2) False

**Q4. Different Responses to the Same Signaling Molecule occur only different cells :**

1) True
2) False

**Q5. The Second messenger is :**

1) ATP
2) GTP
3) cAMP
4) GDP

**Q6. The function of Glycogen phosphorylase is :**

1) Stimulation of glycogenolysis
2) Inhibition of glycogenesis
3) Stimulation of glycogenesis
4) Formation of first messenger

**Q7. which one of the following is the inactive form of G-protein?**

1) G-protein bound with GTP
2) G-protein bound with GDP

**Q8. When the blood glucose in our body is low, the condition is named :**

1) Hepatocyte
2) glycogenolysis
3) Hyperglycemia
4) Hypoglycemia

**Q9. When glycogen synthase is phosphorylated the glycogenesis is inhibited?**

1) True
2) False

**Q10. Adenylyl cyclase convert :**

1) ATP to cAMP
2) cAMP to ATP

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# Answers

Q1-2
Q2-2
Q3-2
Q4-2
Q5-3
Q6-1
Q7-2
Q8-4
Q9-1
Q10-1

## :Boys Team

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- أحمد الرويلي .
- محمد الصهيل .
- خالد النعيم .
- إبراهيم الشايع.
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- نوره الرميح .
- بدور جليدان.
- علا النهير.
- أفنان المالكي.
- ساره الحسين.
- دلال الحزيمي.
- فاطمه الدين.
- جواهر الحربي.
- جوهره المالكي.
- خوله العريني.
- لجين السواط.
- منيال باوزير.
- نوره القحطاني.
- رزان السبتي .
- رهف العباد .
- وضحى العتيبي.
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