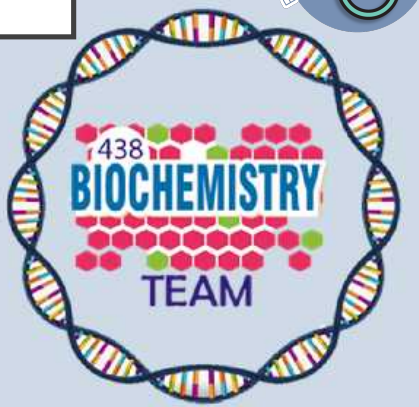
# Cell Signaling
# and
# Regulation of Metabolism

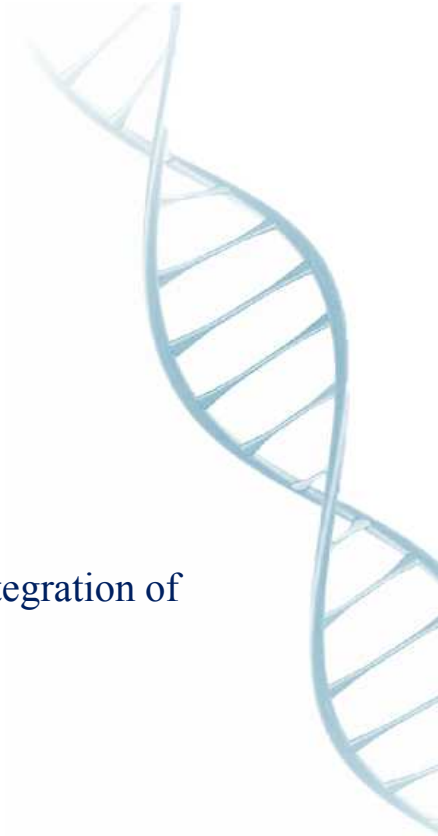

Biochemistry team 438

- **Color Index:**
  - **Original slides.**
  - Important.
  - 436 Notes
  - **438 notes**
  - **Extra information**

رابط التعديل:
https://docs.google.com/document/d/1WvdeC1atp7J-ZKWOUSukSLsEcosjZ0AqV4z2VcH2TA0/edit?usp=sharing

# Objectives:

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



DON'T SKIP

# Introduction

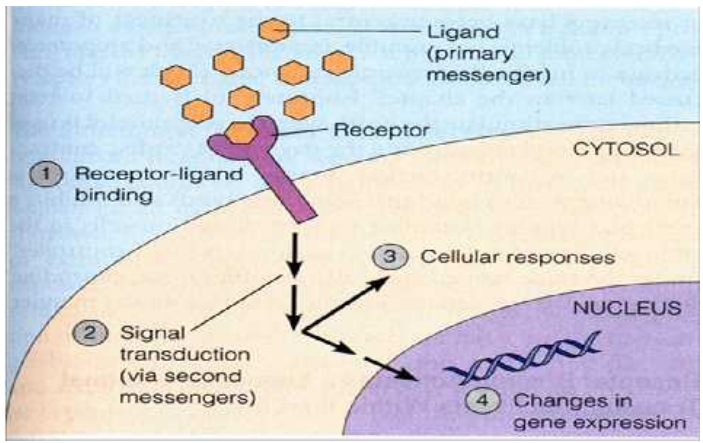
*"Cell signaling is a process by which hormones or neurotransmitters "also called Ligands when they're interacting with a receptor" transmit their signals into a living cell. The receptor for the signal for the signal is a protein. After the ligands bind to a receptor, this initiates a series of intracellular mechanisms that might include altered gene expression, conformational changes of proteins and other biochemical reactions. These mechanisms are the basis of cell growth, metabolism, proliferation and many other biochemical processes. Many drugs act as interceptors or activators of these series of signals, hence the importance of learning about them."*

**- Team Note.**

this video will explain almost all of this lecture: https://youtu.be/GskbODSxAU8 Time: 4:16
Another video that explain the other pathway in this lecture & a lecture in pharma https://youtu.be/erHdQ6cCu_s Time: 5:41

# No cell lives in isolation

Cells communicate with each other.
Cells send and receive information (signals).
Information is relayed (transmitted and reinforced) within cell to produce a response.
(this response is necessary to maintain the homeostasis)



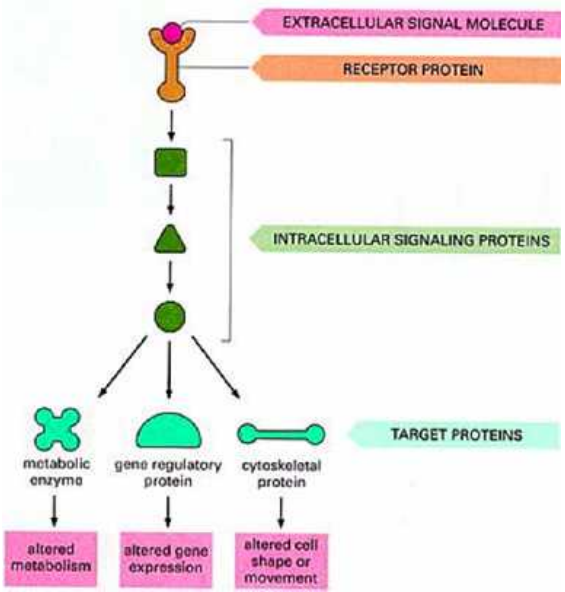

# Signaling Process

Recognition of signal
– Receptors
Transduction
– Change of external signal into intracellular message with amplification and formation of second messenger
Effect
– Modification of cell metabolism and function

## general signaling pathway

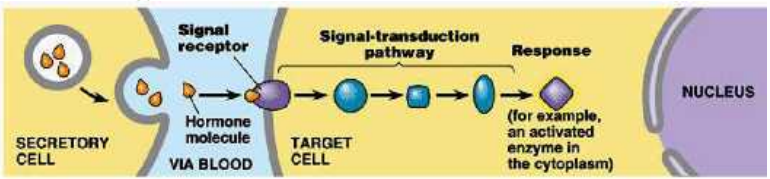
- Ligands (e.g. hormones and neurotransmitters) are the primary messengers, secondary messengers are intracellular and differ in chemical structure.
- Lipid soluble molecule (e.g. steroids) have receptors which are intracellular, they can diffuse right through the plasma membrane but they're not discussed throughout this lecture and are irrelevant to its understanding.
- Doctor's note: the second messenger modifies and stimulates the function of cell metabolism.

# Signaling Cascades




A signaling cascade or a biochemical cascade is a series of biochemical reactions initiated by a stimuli, in this case an extracellular signal molecule, resulting in a cell response.

From Zoology 109:

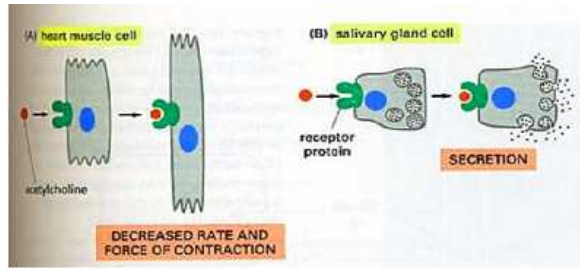


Cells may react differently for the same signal

(B) One Cell but, Different Pathways

Will be discussed in the next slide.

(A) Different Cells




For example: Norepinephrine can stimulate the increase of heart rate and activity of cardiac cells.
Norepinephrine also decreases saliva production of salivary glands.
SAME SIGNAL, DIFFERENT CELLS

# Recognition

- Performed by receptors
- Ligand will produce response only in cells that have receptors for this particular ligand
- Each cell has a specific set of receptors

**Ligand:** If a molecule binds to a receptor then it's a ligand for that specific receptor. A ligand can be a hormone or a neurotransmitter as an example.

Ligand e.g. a hormone will go to the blood stream and will be transmitted everywhere BUT it'll produce a response only when binding with a specific receptor

# (B) One Cell but, Different Pathways

**Stimulus: Hypoglycemia**

**Outcome**: Glucagon secretion

**(Targeted cells) Hepatocyte:** Glucagon/receptor binding

**Second messenger:** cAMP (short for cyclic Adenosine Monophosphate)

(act on the targeted protein)

**Response:** Enzyme phosphorylation

**Enzyme phosphorylation is a kind of enzyme regulation.**

**Enzyme 1 : Glycogen synthase**

**After phosphorylation it will become inactive**

**(Inactive form)**

**Therefore the enzyme's function will be inhibited**

**Inhibition of glycogenesis**

**Glycogenesis:** Is the formation of glycogen from glucose.

**Enzyme 2: Glycogen phosphorylase**

**After phosphorylation it will be activated**

**(Active form)**

**Therefore the enzyme's function will be stimulated.**

**Stimulation of glycogenolysis**

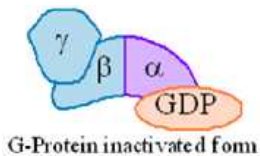
**Glycogenolysis:** Is the biochemical breakdown of glycogen to glucose.

Phosphorylation can either activate or deactivate an enzyme, some enzymes are activated when they are dephosphorylated, and some are activated when they are phosphorylated.

# GTP-Dependant Regulatory Proteins (G-Proteins)

**G-Proteins:** Trimeric (consist of 3 subunits) membrane proteins (αβγ) G-stimulatory ($G_S$) and G-inhibitory ($G_I$) binds to GTP/GDP.

**Forms of G-Proteins**



G-Protein inactivated form

Inactive form
Trimeric –bound GDP
(αβγ/GDP)

Active form
α-bound GTP
(α/GTP)

G-Protein activated form

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

**GTPase activity:** **GTPases** (singular GTPase) are a large family of hydrolase enzymes that can bind and hydrolyze guanosine triphosphate (GTP).

# Signaling Pathways for Regulation of Metabolism

**Two important second messenger systems:**

**1-Adenylyl cyclase system**

**2-Calcium/phosphatidylinositol system**

## 1-Adenylyl Cyclase System.

**Adenylyl cyclase:** Membrane-bound enzyme, Converts ATP to cAMP.

**Activation/Inhibition:**

Memorize them

- **Received signal:** Hormones or neurotransmitters (e.g., Glucagon and epinephrine) or Toxins (e.g., Cholera and pertussis toxins).

- **Signal Receptor:** G-protein coupled receptor.

(not the G-protein but it's coupled receptor).

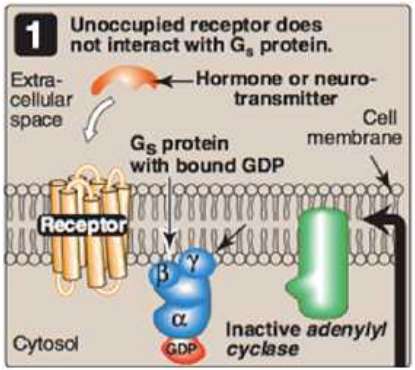
- **Response:** Activation/inhibition of protein kinase A (cAMP-dependent protein kinase).

Notes

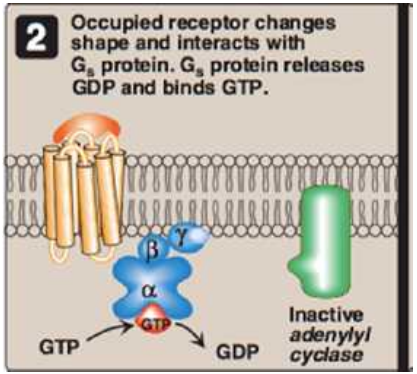
**cAMP(Cyclic adenosine monophosphate)**:
is a second messenger important in many biological processes. cAMP is a derivative of adenosine triphosphate (ATP)

**Phosphatidylinositol is a phospholipid**

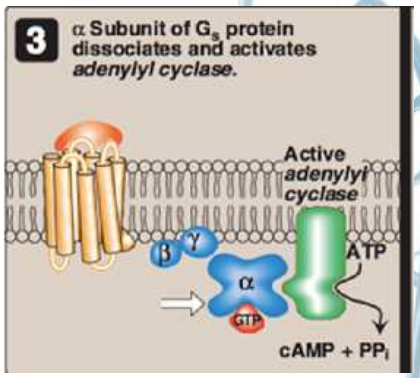
# Signal Transduction: Adenylyl Cyclase System




Resting state: No Signal




Ligand/Receptor Binding
Activation of $G_s$-protein




Activation of adenylyl cyclase

Note

**Keep in mind the different G-protein types:**
**Gs:stimulation of adenylyl cyclase.**
**Gi:Inhibition of adenylyl cyclase.**

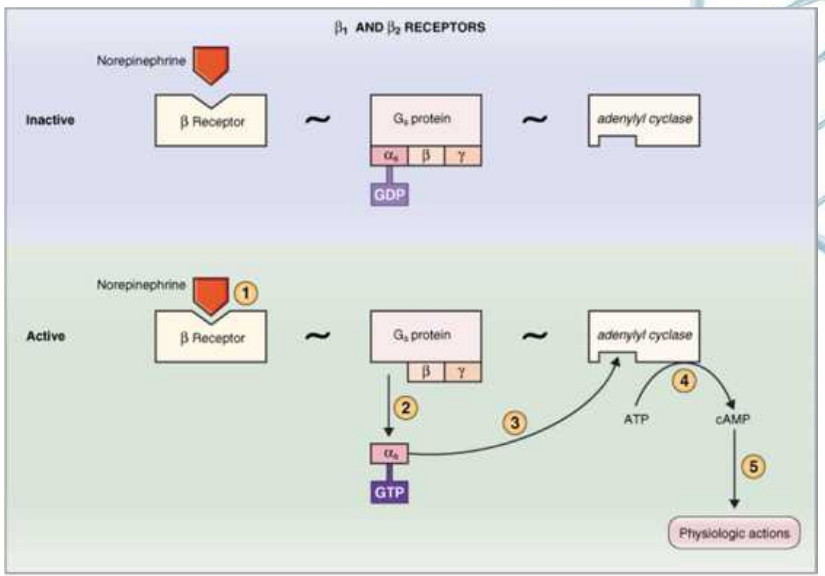
Note

**Adenylyl cyclase:** is the enzyme that synthesizes cyclic adenosine monophosphate or cyclic AMP from adenosine triphosphate (ATP).

# Signal Transduction: Adenylyl Cyclase System

Note

**Extra example from Physiology lectures for deeper understanding:**



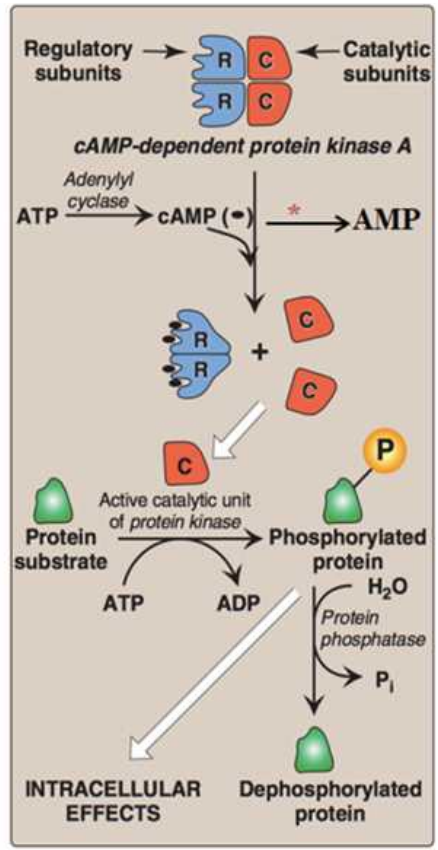
# Actions of cAMP

" Team 436's notes.

*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."*

***- Protein kinases function is mainly phosphorylating proteins "enzymes" so they can either activate them or deactivate them, they're important chemical regulators.***

*Phosphodiesterase



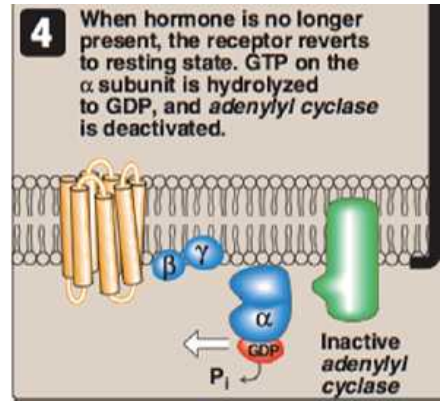
# Termination of Signal:

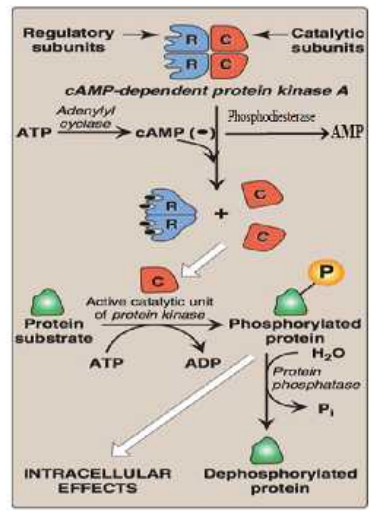
By 3 ways:

1- **GTPase activity:** the alpha subunit of G-protein hydrolyzes GTP turning it into GDP resulting in deactivation of G-protein and G-protein will return to its resting state.

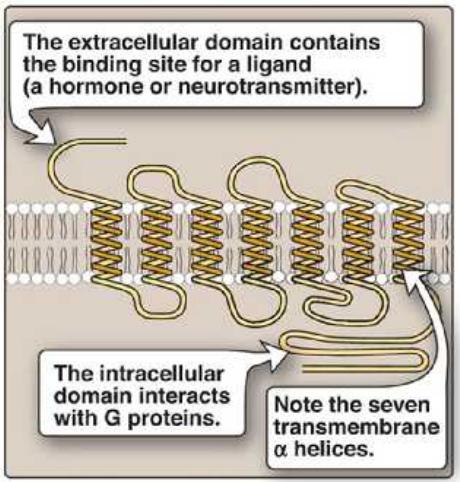
2- **Phosphodiesterase activity:** breakage of the cyclic form of cAMP turning it into AMP, resulting in fewer amount of cAMP which is the secondary messenger required to interact with Protein Kinase A.

3- **Protein phosphatase activity**: removal of phosphate group from the phosphorylated protein that was initially phosphorylated by Protein Kinase A.



# G-Protein Coupled Receptor:




Note

The important thing to know is that G-protein coupled receptors (GPCR) cross the plasma membrane seven times, this is an essential feature of the structure.

This coiled transmembrane structure allows it to smoothly interact with G-protein.

The extracellular part interacts with the ligand (primary messenger), and the intracellular part interacts with G-protein which initiates the process of forming the second messenger (e.g. cAMP).

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

**Stimulus: Hypoglycemia**

**Outcome**: Glucagon secretion

**(Targeted cells) Hepatocyte:** Glucagon/receptor binding

**Second messenger:** cAMP (short for cyclic Adenosine Monophosphate) (act on the targeted protein)

**Response:** Enzyme phosphorylation

**Enzyme phosphorylation is a kind of enzyme regulation.**

## Enzyme 1 : Glycogen synthase

**After phosphorylation it will become inactive (Inactive form)**

**Therefor the enzyme's function will be inhibited.**

**Inhibition of glycogenesis**

**Glycogenesis:** Is the formation of glycogen from glucose.

## Enzyme 2: Glycogen phosphorylase

**After phosphorylation it will be activated (Active form)**

**Therefor the enzyme's function will be stimulated.**

**Stimulation of glycogenolysis**

**Glycogenolysis:** Is the biochemical breakdown of glycogen to glucose.

Note

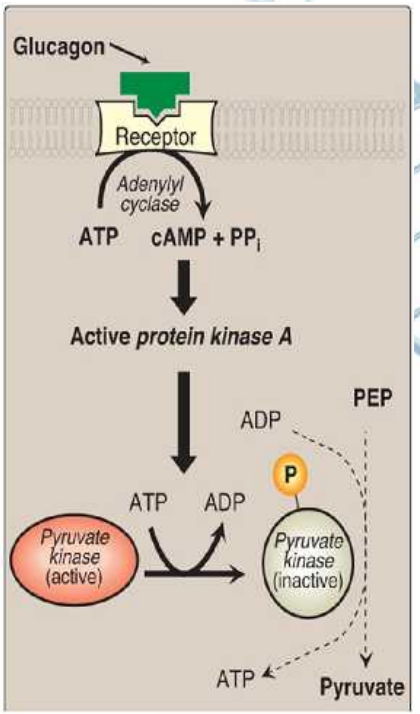
**In low blood sugar levels, the pancreas gland secretes the hormone Glucagon, which initiates the breakdown of Glycogen in muscles and the liver, resulting in molecules of Glucose which get released into the bloodstream.**

# Pyruvate Kinase Regulation: Covalent Modification

Notes:

**Covalent modifications**: are alterations to the chemical structure of an enzyme by the addition or removal of chemical groups. In this case, the addition of Phosphate group which deactivated the enzyme.
(remember that phosphorylating can activate or deactivate enzymes).

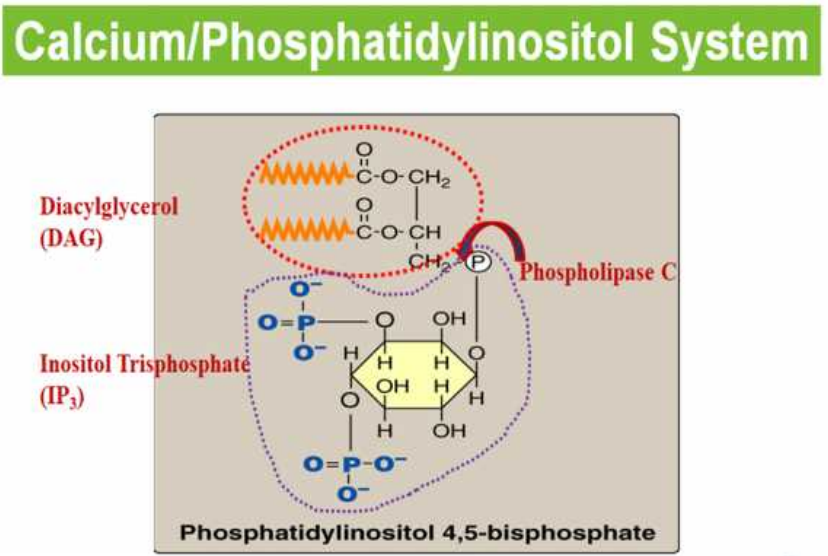
This figure represents the last step of Glycolysis.
**Pyruvate Kinase:** converts PEP (Phosphenolpyruvate) to Pyruvate, producing one ATP in the progress. If active, the pyruvate proceeds to pre-krebs cycle and krebs cycle if Oxygen and mitochondria are present.
If inactive, **glycolysis is inhibited.**



## Second: Calcium/Phosphatidylnositol System

Note

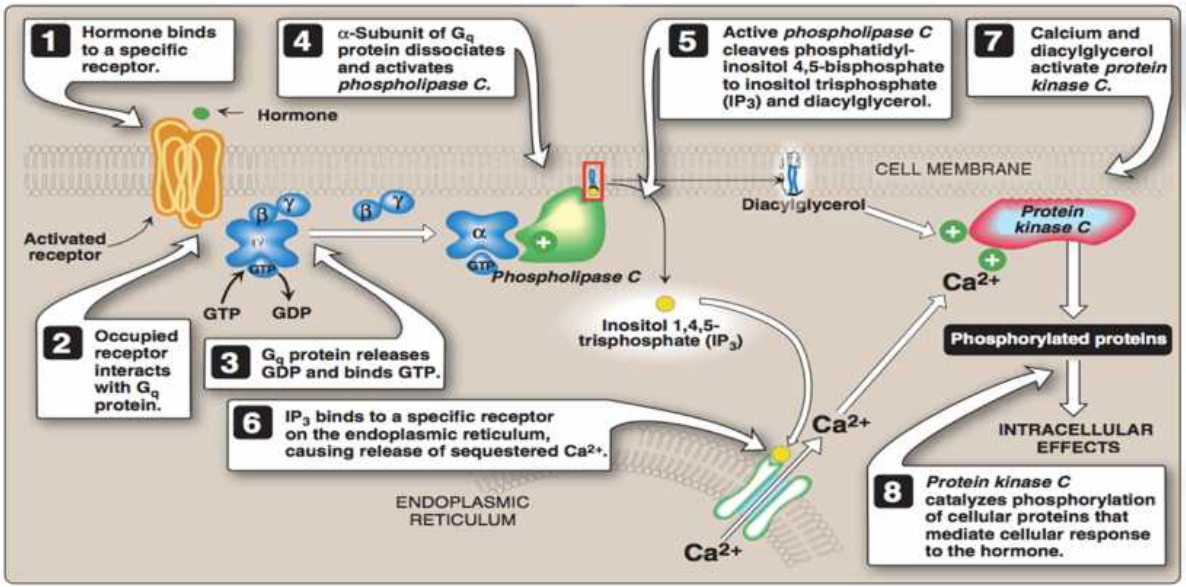
This is a minor phospholipid, and is a component of the cell membrane.
After the breakage of the bond by Phospholipase C. The product formed will be Inositol 1,4,5-triphosphate (IP3) along with a remnant byproduct, more on this will come in the next slides.




You don't have to memorize the structure

# Intracellular Signaling by Inositol Triphosphate:

More details in the next slide.



# Intracellular Signaling by Inositol Triphosphate:

Notes:

1- A specific Ligand "first messenger" (hormone or neurotransmitter), binds to G-protein coupled receptors.

2- Receptor interacts with G-protein, stimulates its release of GDP and replaces it with GTP, therefore activating it.

3- Alpha subunit disassociate from G-protein, alpha subunit binds to Phospholipase C activating it in the process.

4- Phospholipase C breaks phosphatidylinositol 4,5-biphosphate into IP3 and DAG.

5- IP3 "second messenger" binds to Endoplasmic Reticulum (ER), a major store of Calcium ions, causing the release of Calcium ions.

6- Protein Kinase C responds to second messengers, in this case they're Calcium from ER and signals from DAG.

7- Protein Kinase C phosphorylates proteins in response to the signals from DAG and IP3 (remember that kinase proteins function in phosphorylating proteins).

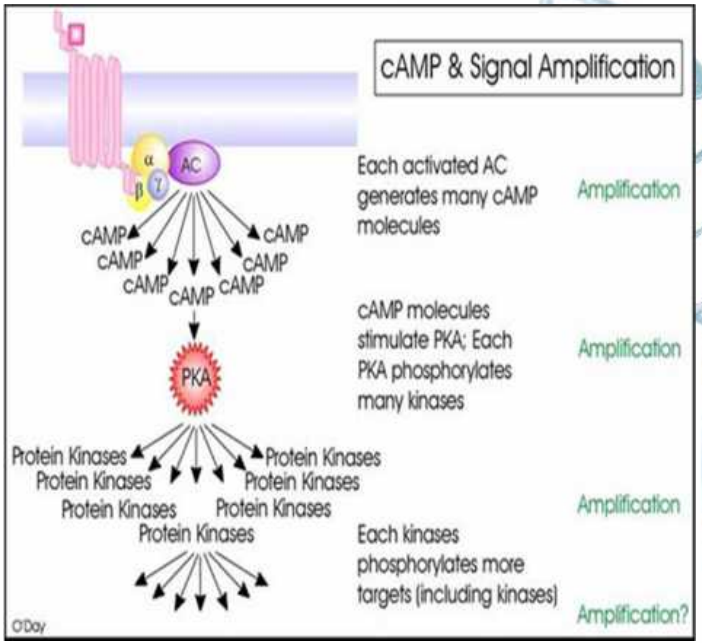
8- Intracellular effect and response.

# Signal Amplification:

Notes:

From a primary messenger, an activated Adenylyl Cyclase (AC)
converts a large number of ATP molecules into cAMP molecules, forming a large amount of secondary messengers.

Secondary messengers (cAMP) stimulate Protein Kinase A (PKA),
PKA's then go on to phosphorylase more and more proteins leading
to a further amplification of the initial signal.

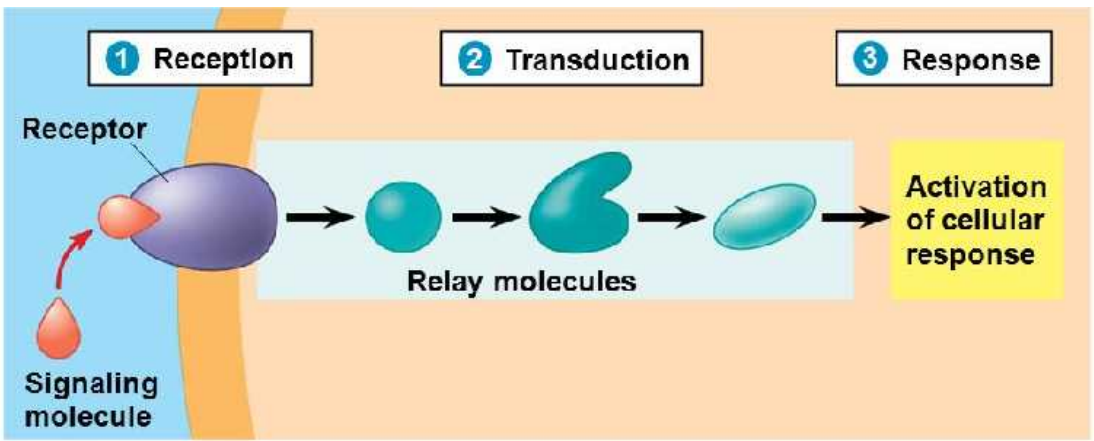


# Take home massages

Cell signaling allows

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

## Review



# MCQs

**Q1; What do you expect protein kinase primary function to be?**

A- Converting ATP to cAMP
B- Adding a phosphate group to its protein target.
C- Calcium pump

**Q2; G-proteins are:**

A- Tetrameric
B- Trimeric
C- Dimeric

**Q3; Which of the following best describes a ligand?**

A- A primary messenger that binds to a specific protein receptor.

B- A secondary messenger to amplify intracellular signals.

C- A membrane bound protein helps maintaining metabolism.

**Q4; Which of the following is accurate about G-protein coupled receptors?**

A- The extracellular domain contains binding site for secondary messengers.

B- The extracellular domain contain binding sites for primary messengers.

C- It is formed of 7 transmembrane beta pleated sheets.

**Answer key:**

1) B
2) B
3) A
4) B

# SAQs

**Q1: The main function of adenylyl cyclase enzyme is?**

Converting ATP to cAMP

**Q2: Provide two examples of important second messenger systems that produce biochemical effects within cells.**

1- Adenylyl cyclase system
2- Calcium/phosphatidylinositol system

## Girls team:

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- غيداء البريثن
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