Cell signaling & regulation of metabolism

Editing File

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- Main Text (black)
- Female Slides (Pink)
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- Important (Red)
- Dr's Notes (Green)
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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.

Introduction

•**Cell signaling:** the fundamental process by which specific information is transferred from the cell surface to the cytosol and ultimately to the nucleus, leading to changes in gene expression.

Cells interact with the receptors of other cells by a ligand

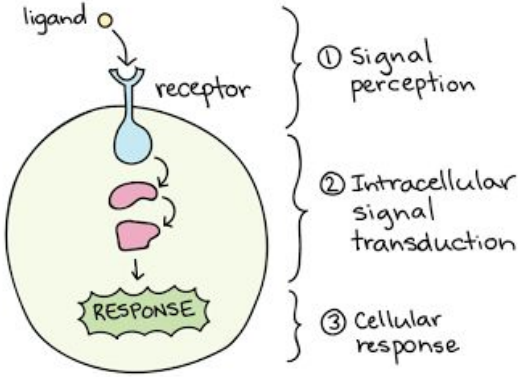
hormones or) .(neurotransmitter

The receptor for the signal is a .protein

After interacting, the signal is transmitted into the living cell by .transduction

Cell signaling is important for the extracellular environment to allow development, growth and .immunity

This is an extra slide just to help you to understand the lecture .



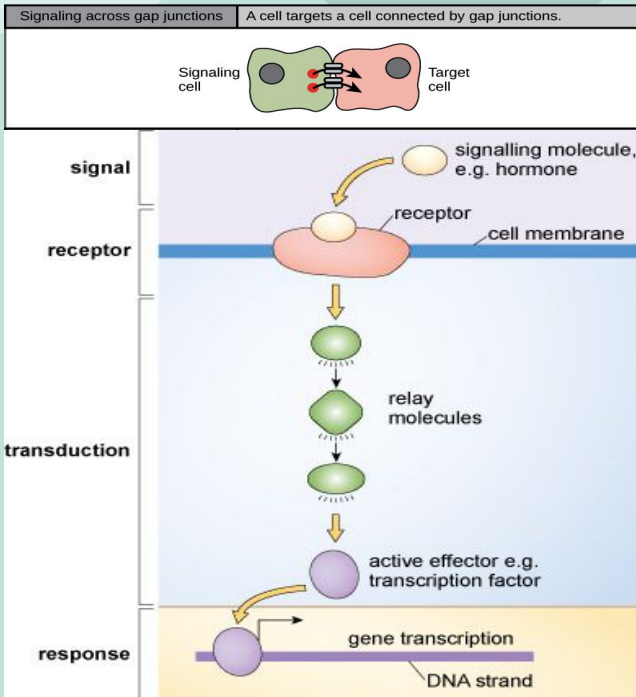
Cell Signaling

No cell lives in isolation

- ✔ Cells communicate with each other
- ✔ Cells send and receive information (Signals).
- ✔ Information is relayed within cell to produce a response.
- ✔ (The response is necessary in maintain homeostasis)

signaling Process:

1. **Recognition of signal:** Receptors
   (always on the cell's surface) , (It's primary messenger)
2. **Transduction:** Change of external signal into intracellular message with amplification and formation of second messenger.
   (تحويل الغير مفهوم الى مفهوم)
3. **Effect:** Modification of cell metabolism and function

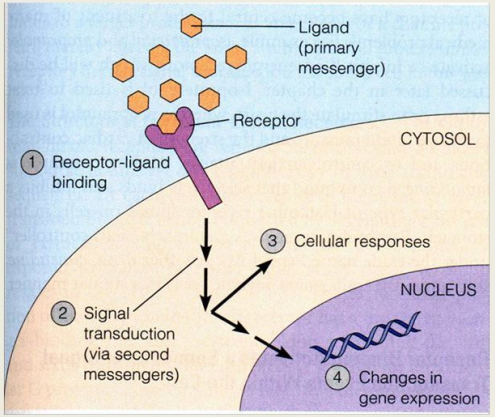


General Signaling Pathway

- any disruption or error found in this process gives rise to various diseases and cancers.

The ligand binds to the receptor	The ligand is the primary messenger and it could be hormones or neurotransmitters
Signal transduction	The change of the primary messenger into an intracellular second messenger
Cellular response or changes in gene expression	The second messenger modifies the .cell's function and metabolism

General Signaling Pathway

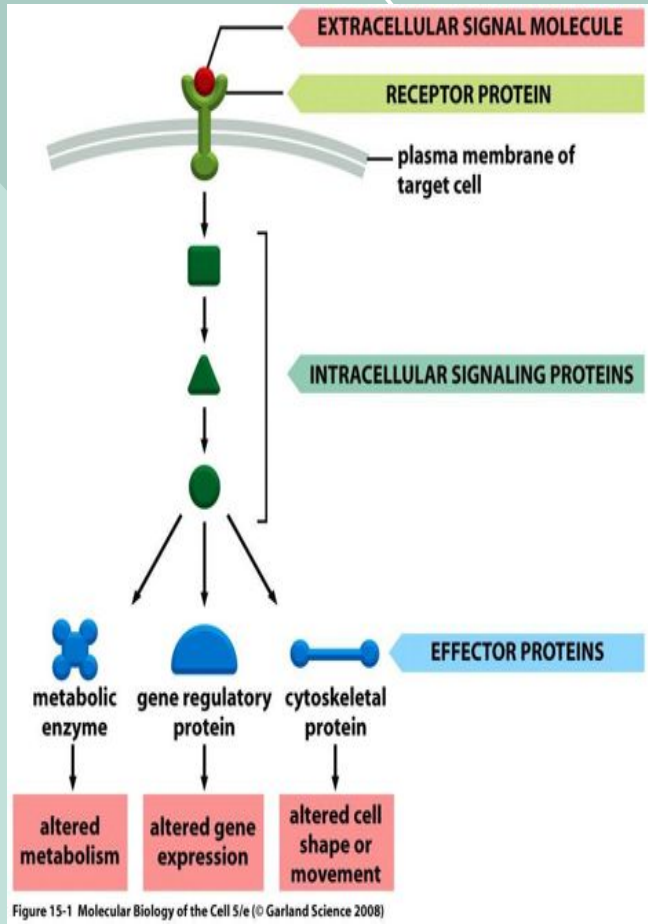


Signaling Cascades

The Ligand will bind to the receptor in the extracellular .environment

The receptor will activate the intracellular signaling protein . forming a second messenger

The second messenger will affect the target cell and producing the required .outcome

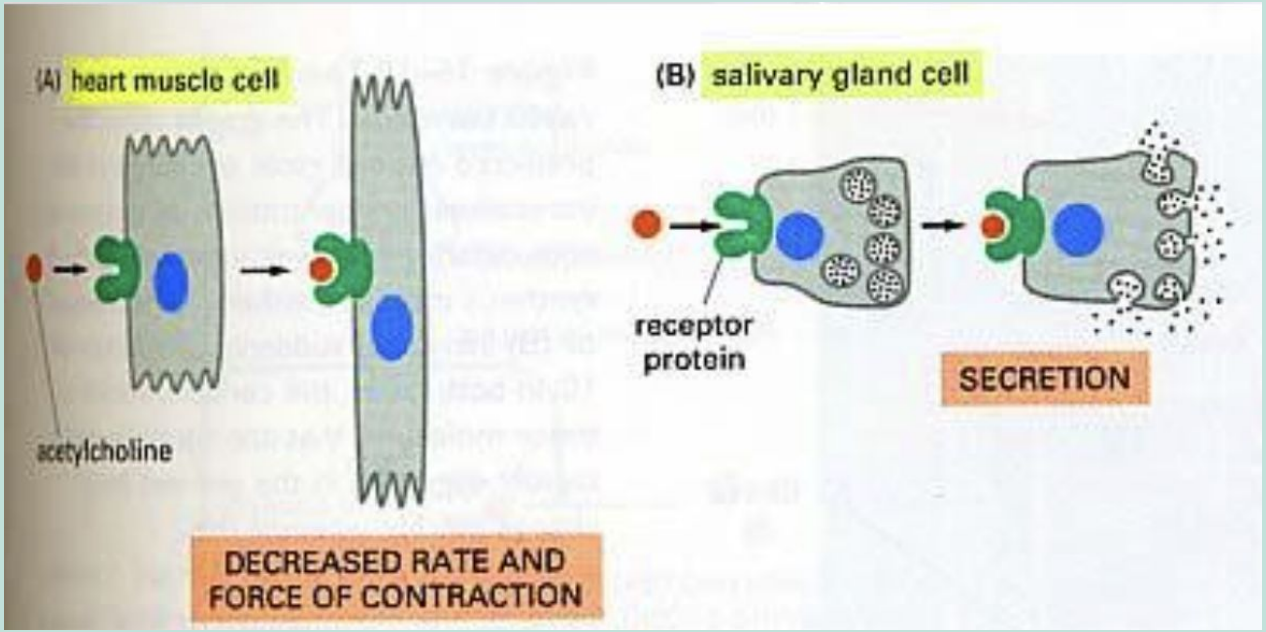


Recognition

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

Different Responses to the Same Signaling Molecule. (A) Different Cells



- ردة الفعل قد تختلف بناءً على الخلية المستقبلة لنفس المؤثر

Different Responses to the Same Signaling Molecule.

(B) One Cell but Different Pathways

You must understand the example

Glycogen phosphorylase
It breaks glycogen and helps in glucose synthesis

Hypoglycemia
Glucagon secretion
Hepatocyte: Glucagon/receptor binding
Second messenger: cAMP
Response: Enzyme phosphorylation

- Glycogen synthesis (inactive form) → Inhibition of glycogenesis
- Glycogen phosphorylase (Active form) → Stimulation of glycogenolysis

GTP- Dependant Regulatory Proteins (G-Proteins)

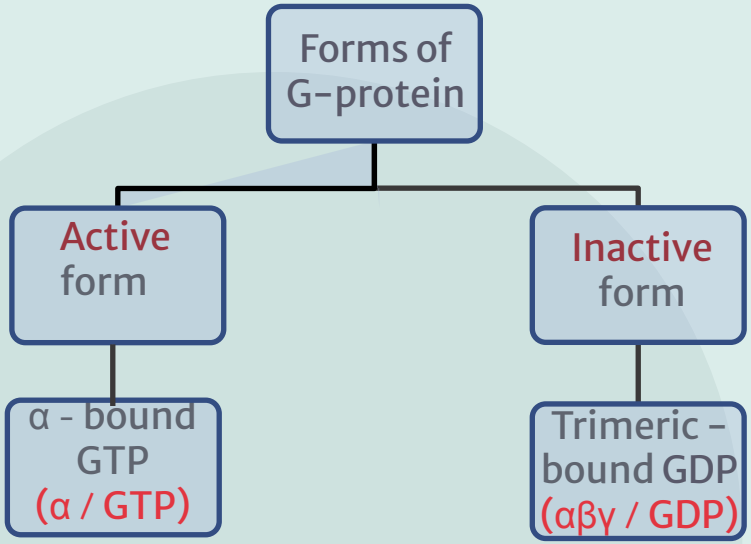
Important slide

G-Proteins : trimeric membrane proteins (αβγ) :

- G-stimulatory (G_s)
- G-inhibitory (G_i)

binds to GTP/GDP.

- G-proteins have three subunits: α, β, and γ.
- G-proteins bind to guanosine nucleotides: GTP or GDP.



β & γ: they are closer to membrane than α

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

Signaling Pathways for Regulation of Metabolism:

The important of second messenger system:

Adenylyl cyclase system

Calcium/ phosphatidylinositol system

Example of second messenger system is adenylyl cyclase system example of second messenger is cAMP

1- Adenylyl cyclase system

- Adenylyl cyclase : Membrane-bound enzyme, converts ATP to cAMP. (second messenger)
- Activation/Inhibition:

Signal

01

- Hormones or neurotransmitters (e.g. glucagon and epinephrine)
- Toxins (e.g. cholera and pertussis toxins)

Receptor

02

G-protein coupled receptor

The receptor starts coupling with G-protein only when there is signal

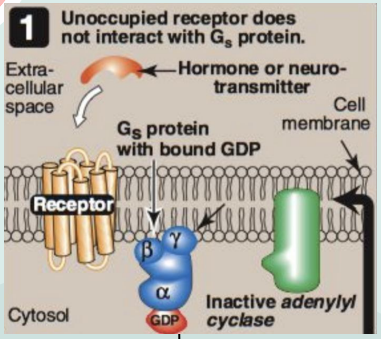
Response

03

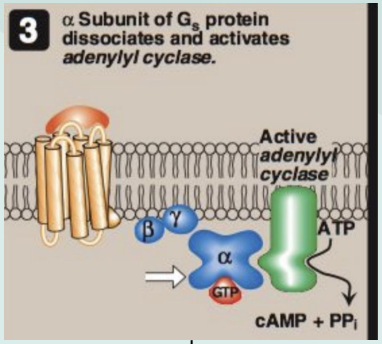
- Activation/inhibition of protein kinase A (cAMP-dependent protein kinase)
- Kinase A cause phosphorylation

- The signal won't affect the enzyme (adenylyl cyclase) directly. It will affect the receptor (G-protein coupled receptor) first.
- Then the receptor will activate G-protein which will activate the system.

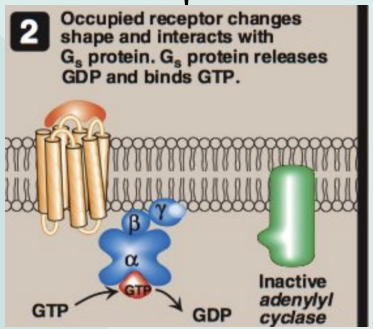
Signal transduction: adenylyl cyclase system



Ligand/Receptor Binding Activation of Gs-protein



Resting state: No Signal

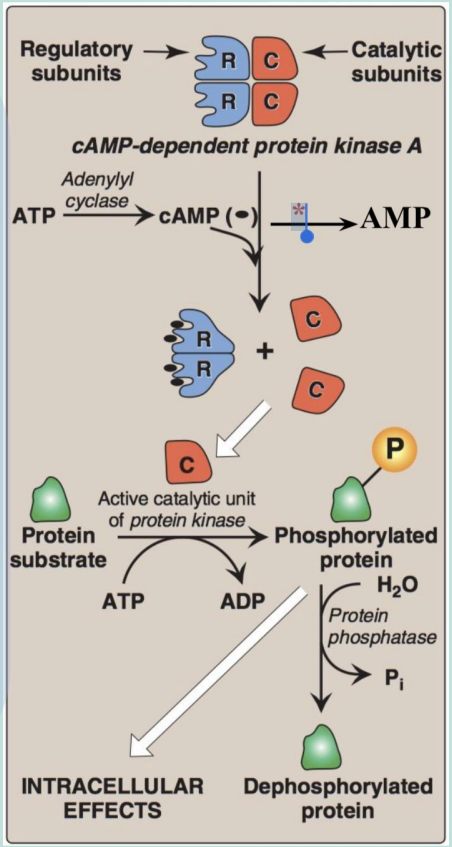


Activation of adenylyl cyclase

Helpful video

Actions of cAMP

Adenylyl cyclase is responsible for (ATP cAMP)



Med441:

1) CAMP binds with the regulatory subunits of kinase A leading to activation of the catalytic unit of protein kinase.
2) Activated catalytic unit will phosphorylate a protein giving us a phosphorylated protein.
3) The phosphorylated protein will do its intra-Cellular effect.

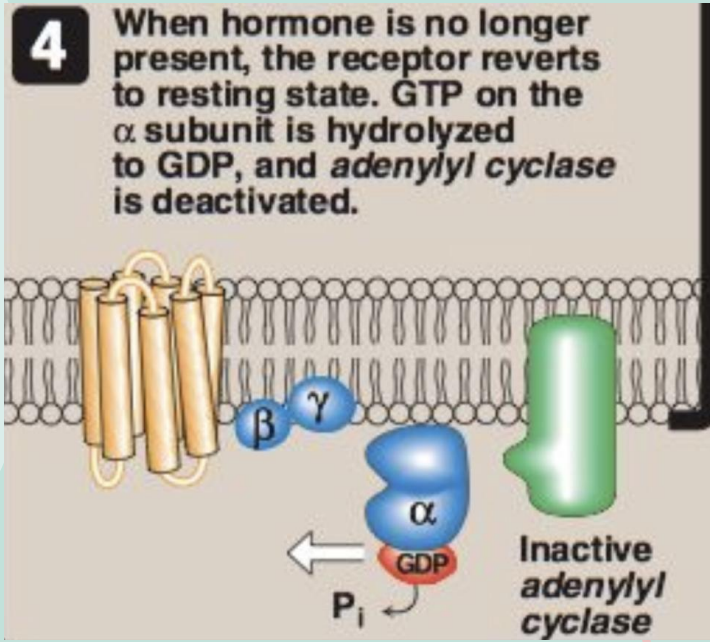
phosphodiesterase

Signal termination

There is 3 ways for signal termination:

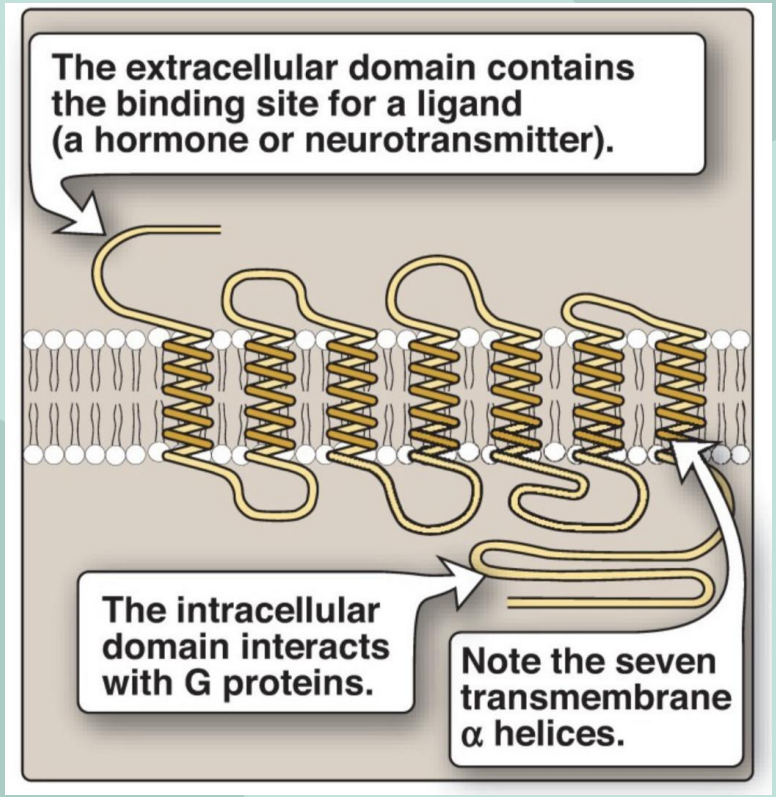
1- protein phosphatase	Protein phosphatase removes the phosphate group from the phosphorylated protein which gives us dephosphorylated protein.
2- phosphodiesterase	Using phosphodiesterase to decrease cAMP which give us an inactive protein kinase.
3-hormon is no longer present	- receptor back to resting state - GTP on alpha subunits is hydrolyzed into GDP - Adenylyl cyclase is deactivated.

GTPase is responsible for
(GTP⟶GDP)



G-Protein Coupled Membrane Receptor

Must know those 3 features of G-coupled receptor

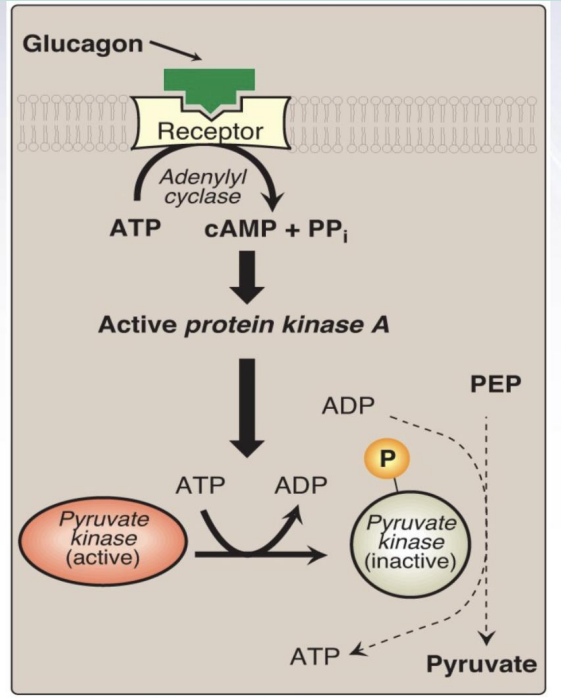


Pyruvate Kinase Regulation

Covalent Modification

- This is an example of adenylyl cyclase system

Covalent Modification:
It's a name for any substance addition



Here, it is the same as the previous

- Target : pyruvate kinase
- This occurs due to hypoglycemia

2- Calcium/Phosphatidylinositol System

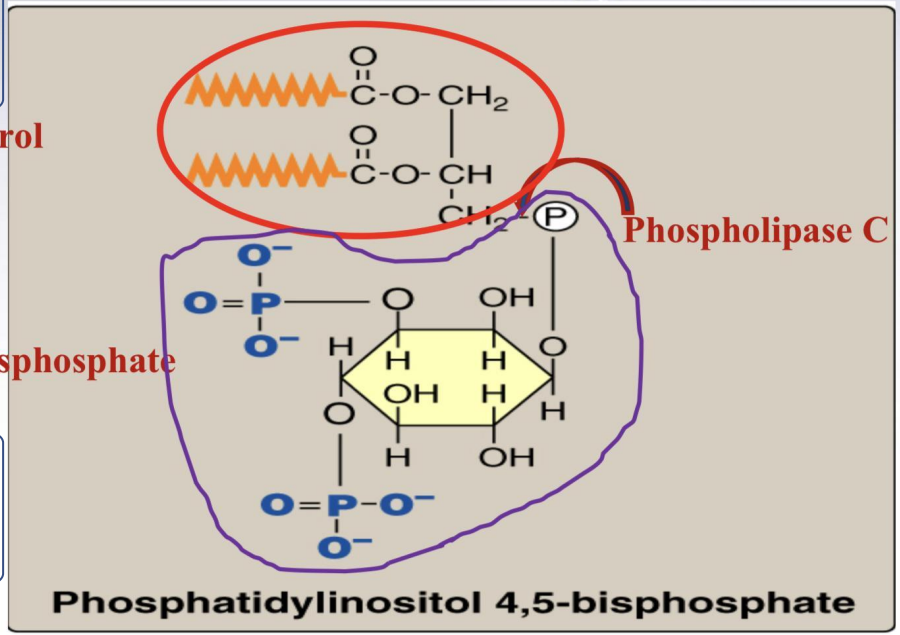
Inside the cell membrane

Diacylglycerol (DAG)

Outside the cell membrane

Inositol Trisphosphate (IP_3)

Act as second messenger



There are Different type of phospholipase .

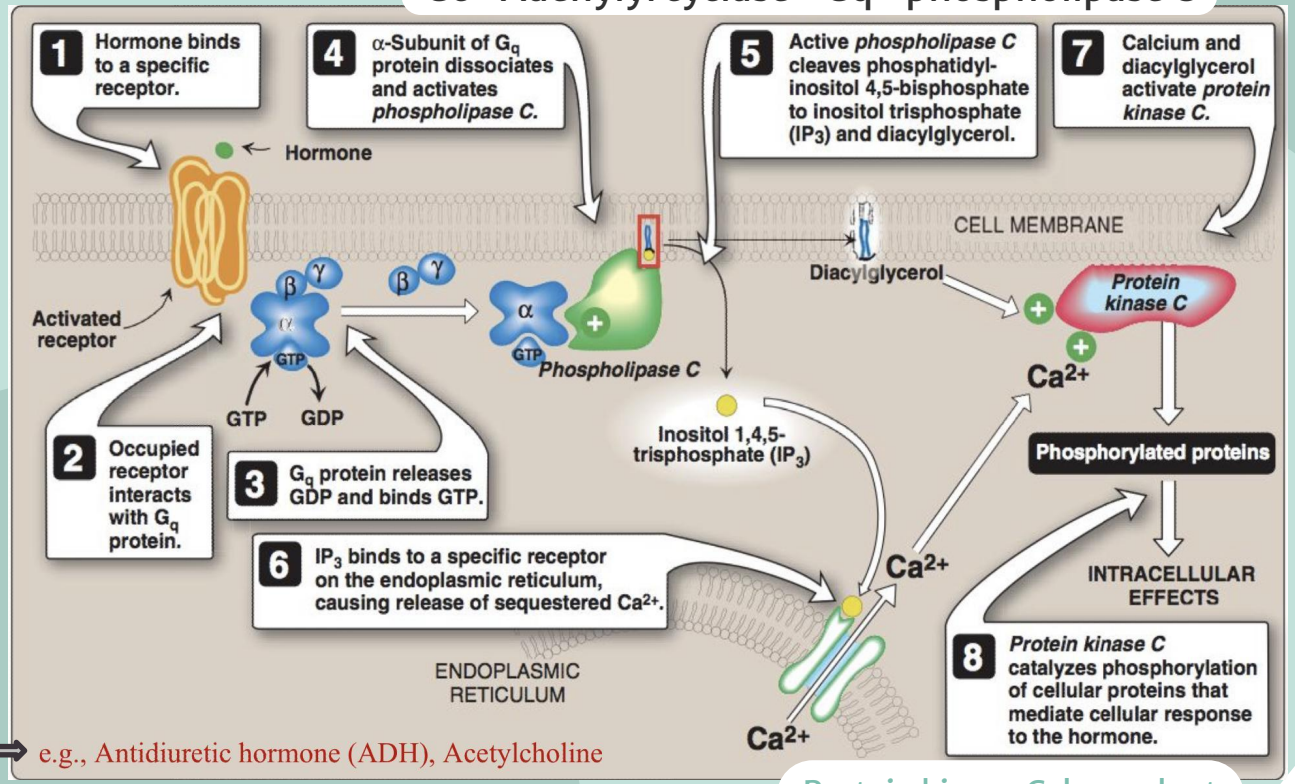
The difference between them is the target bond they are going to break.

Di=bis= two.
Tri=tris=three
Correct terminology : bis& tris

Phospholipase C : It's important to move to next step

Intracellular Signaling by Inositol trisphosphate

Gc= Adenylyl cyclase Gq= phospholipase C

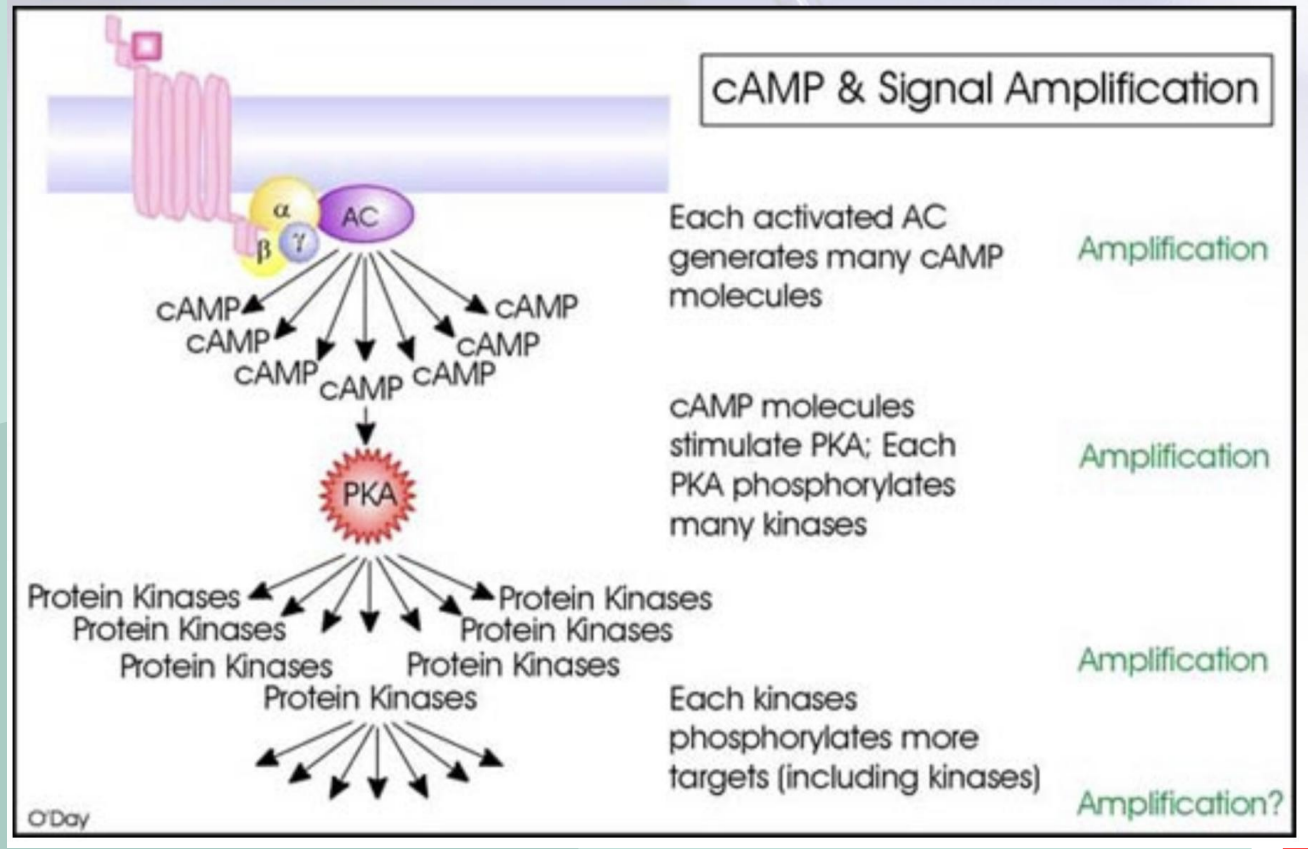


Examples of ligands that can bind To the receptor:

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

Protein kinase C dependent on Ca for activation

Signal Amplification



Take Home Messages

Cell signaling allows

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

MCQs

1. Change of external signal into intracellular message with amplification and formation of second messenger is called?			
A) Recognition	B) Effect	C) None	D) Transduction
2. The recognition process is done by?			
A) Receptors	B) Neurotransmitter	C) Hormones	D) DNA
3. The inactive form of G-protein is ?			
A) αβγ/GTP	B) αβγ/GDP	C) α/GTP	D) α/GDP
4. cAMP activates ?			
A) Kinase B	B) Kinase A	C) Kinase C	D) Both C&B
5. An enzyme that can terminate signal?			
A) Phospholipase C	B) Kinase A	C) Phosphatase	D) cAMP

Answer key: 1)D 2)A 3)B 4)B 5)C

Biochemistry Team

Yasser Almutairi

- Ahmad Addas
- Faisal Alomran
- Abdulrahman Almalki
- Ziyad Bukhari
- Talal Alrobaian
- Essam Nawaf

Alanoud Alnajawi

- Hossam Alhussain
- Abdullah Alzoom
- Ziyad Alenazi
- Tariq Alshumrani
- Mohammed Almurshid
- Abdullah Almutlaq

Lura Almusaeeb

- Ghala Alyousef
- Huda Bassam
- Manar Alqahtani
- Marwa Fal
- Jenan Al-Sayari
- Rahaf Aldawood
- Mays Altokhais

- Shaden Alotaibi
- Aljawharah Alyahya
- Norah Albahdal
- Ghaida Alotaibi
- Ghida Alkahtani
- Lama Alhayan
- Shaden Alshammari

Team Med444