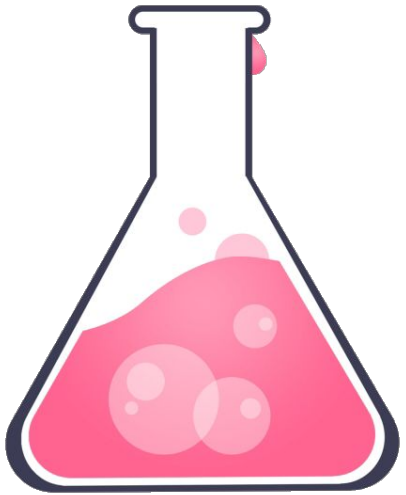
MED439
KING SAUD UNIVERSITY

Revised & Approved by: Shayma Abdullah Alfaraidan, Yusuf Mohammad Alhablani

14

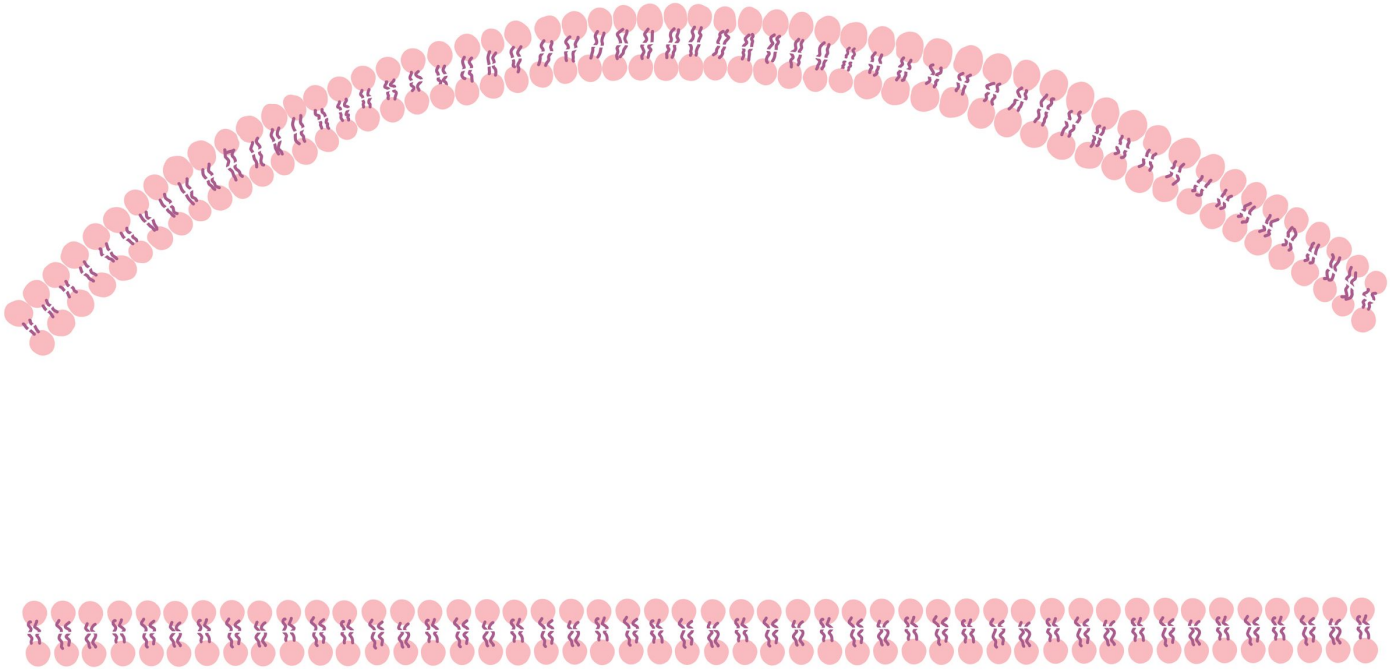
Cell Signaling and Regulation of Metabolism

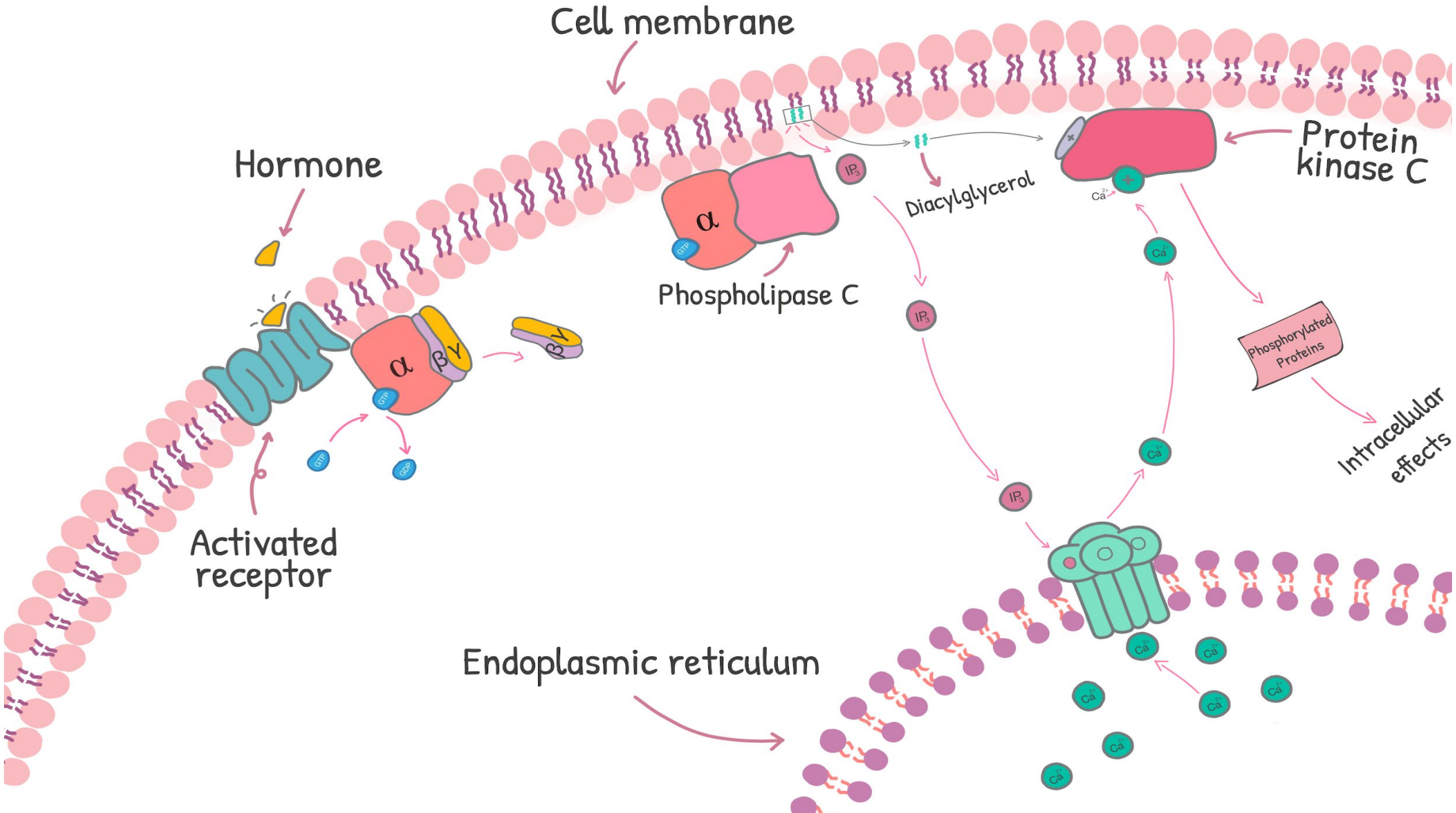


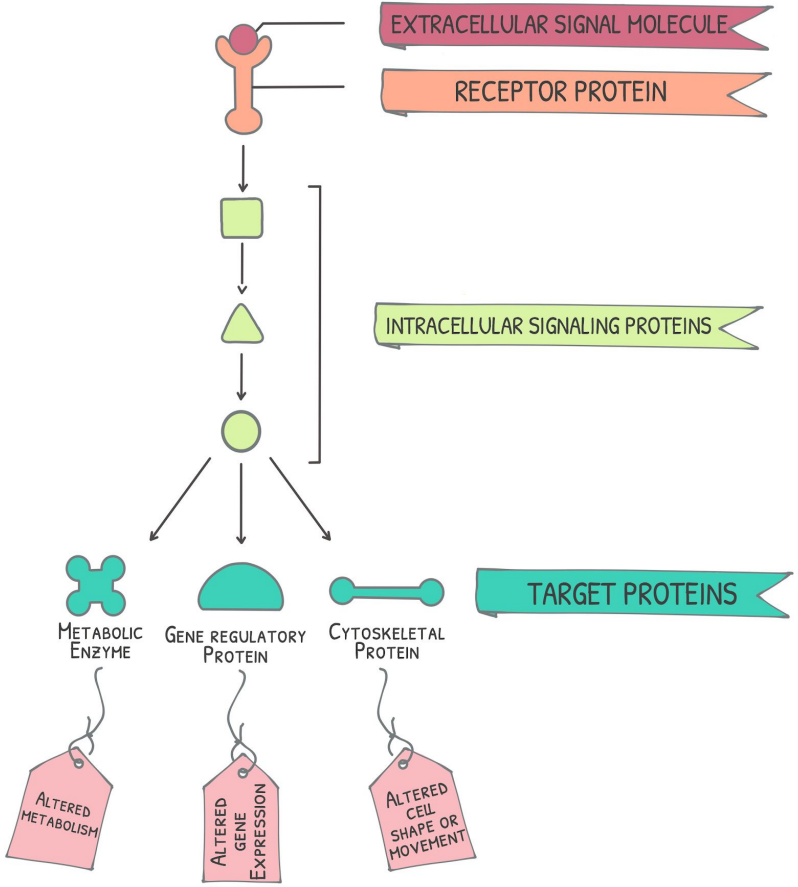
Color Index :

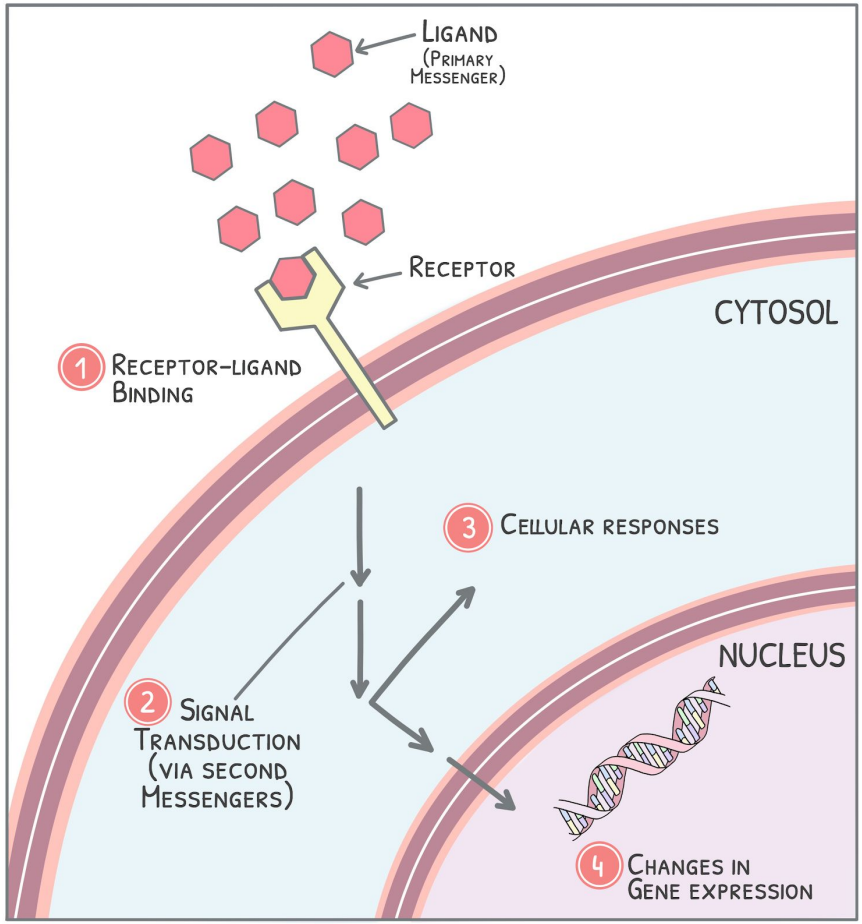
- original content
- Important
- Notes
- Extra information

Editing file

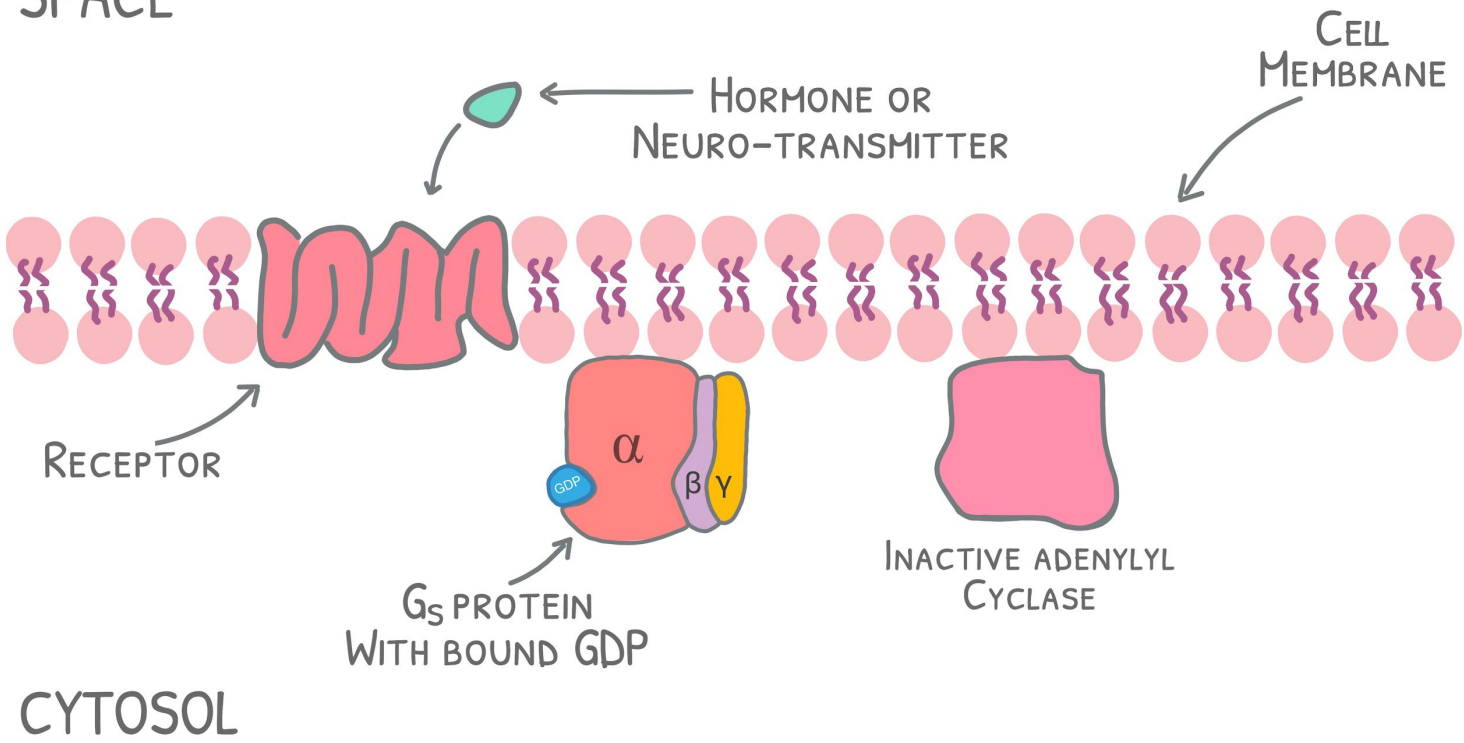



Cell membrane
Hormone
Activated receptor
α
β
γ
GTP
GDP
Phospholipase C
IP3
Diacylglycerol
Protein kinase C
Ca2+
Ca
Phosphorylated Proteins
Intracellular effects
Endoplasmic reticulum

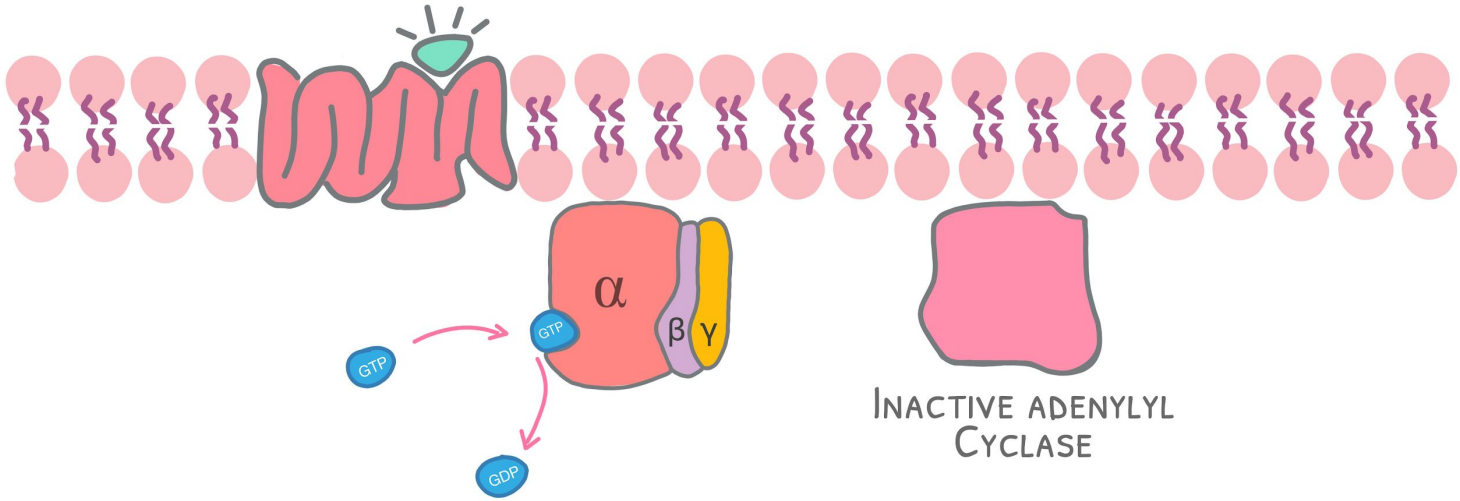

EXTRACELLULAR SIGNAL MOLECULE
RECEPTOR PROTEIN
INTRACELLULAR SIGNALING PROTEINS
TARGET PROTEINS
METABOLIC ENZYME
GENE REGULATORY PROTEIN
CYTOSKELETAL PROTEIN
ALTERED METABOLISM
ALTERED GENE EXPRESSION
ALTERED CELL SHAPE OR MOVEMENT


LIGAND
(PRIMARY MESSENGER)
RECEPTOR
CYTOSOL
1 RECEPTOR-LIGAND BINDING
3 CELLULAR RESPONSES
NUCLEUS
2 SIGNAL TRANSDUCTION (VIA SECOND MESSENGERS)
4 CHANGES IN GENE EXPRESSION

1


EXTRACELLULAR SPACE
HORMONE OR NEURO-TRANSMITTER
CELL MEMBRANE
RECEPTOR
α
β
γ
GDP
INACTIVE ADENYLYL CYCLASE
GS PROTEIN WITH BOUND GDP
CYTOSOL

2



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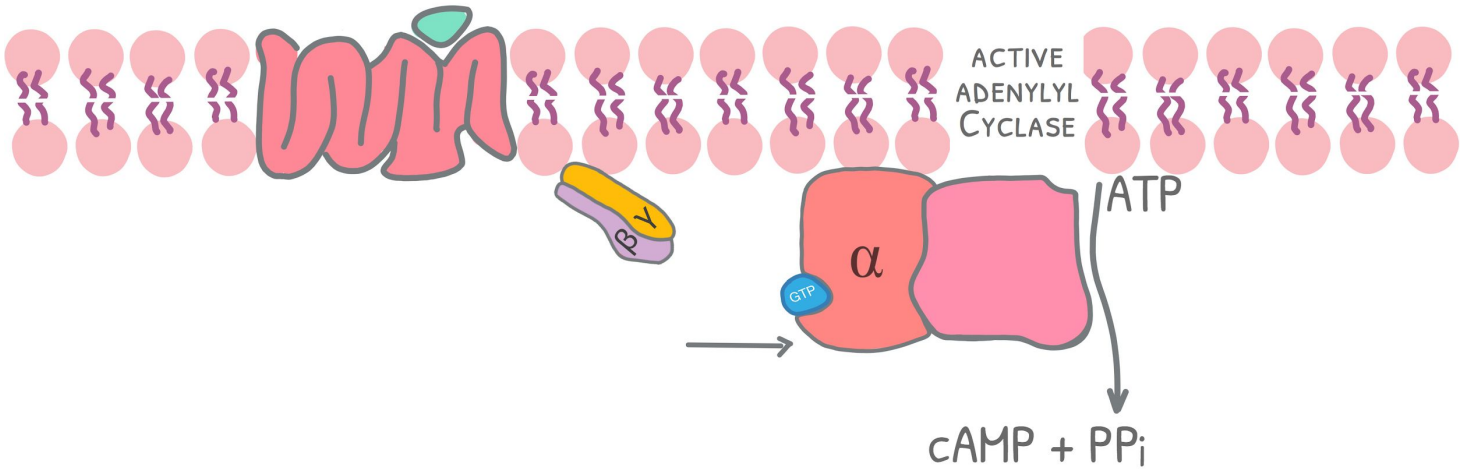

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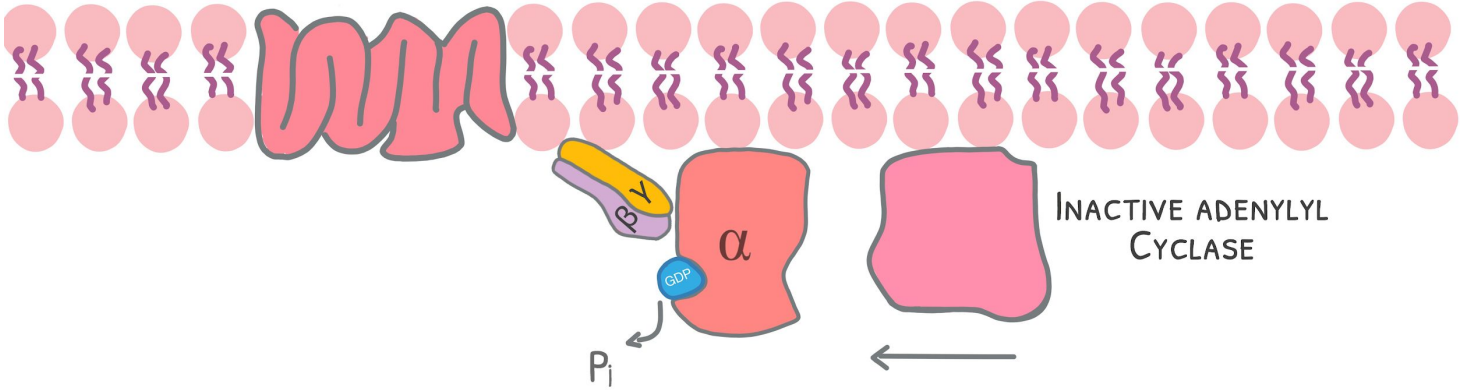

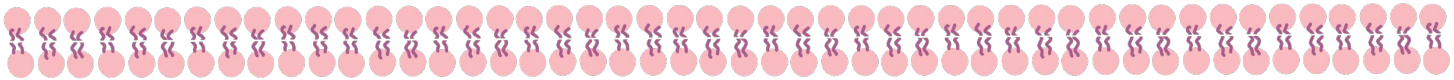

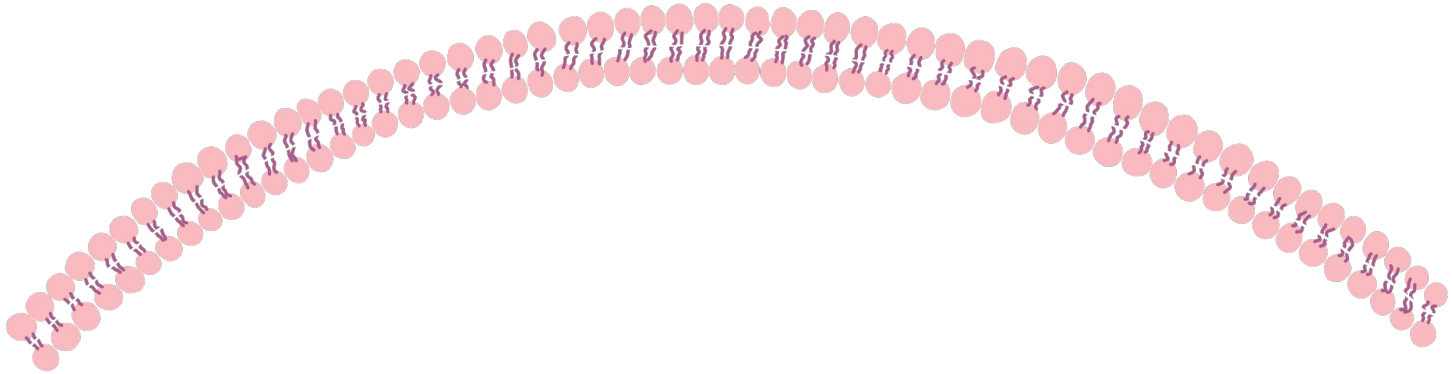

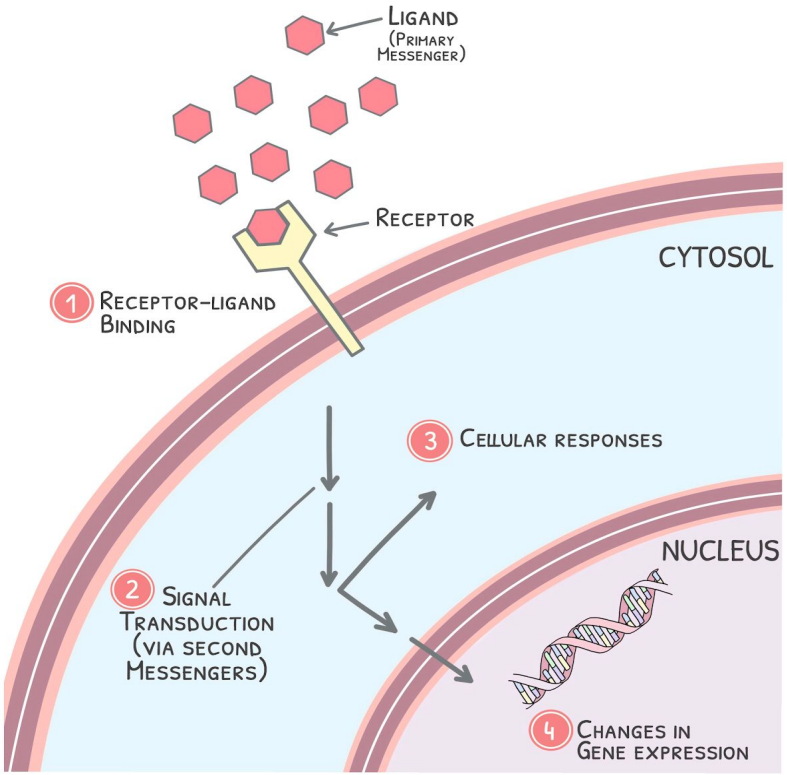
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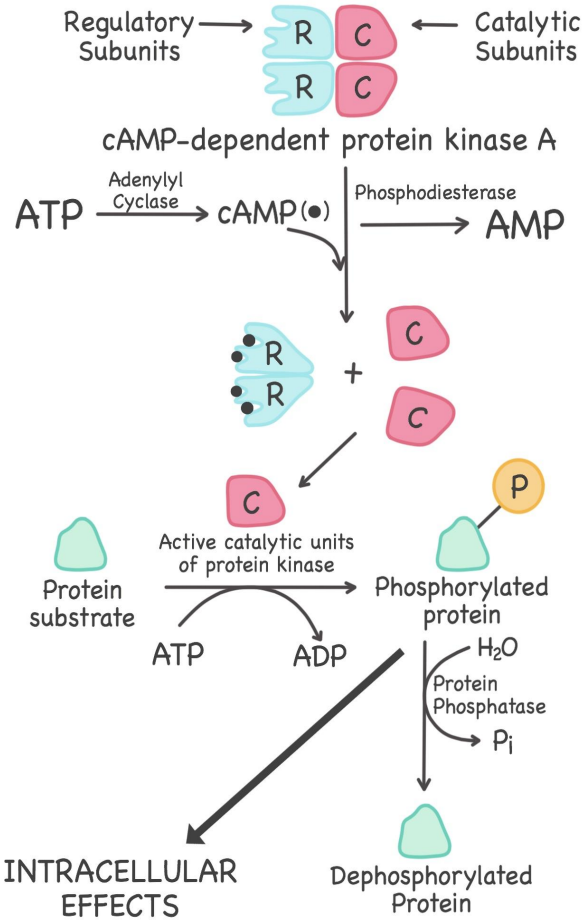
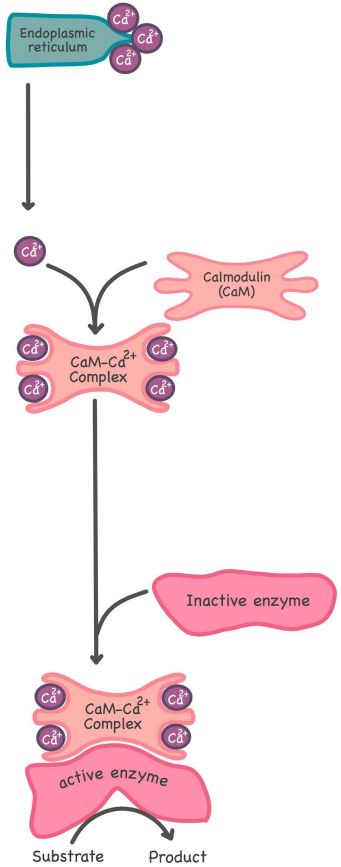

Regulatory Subunits
R
C
R
C
Catalytic Subunits
cAMP-dependent protein kinase A
ATP
Adenylyl Cyclase
cAMP (•)
Phosphodiesterase
AMP
R
R
+
C
C
C
Active catalytic units of protein kinase
Protein substrate
ATP
ADP
P
Phosphorylated protein
H2O
Protein Phosphatase
Pi
INTRACELLULAR EFFECTS
Dephosphorylated Protein


Endoplasmic reticulum
Ca2+
Ca2+
Ca2+
Ca2+
Calmodulin (CaM)
CaM–Ca2+ Complex
Inactive enzyme
active enzyme
Substrate
Product

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

Before you start studying this lecture we recommend you to watch this **video**

Introduction

438 notes

- "Cell signaling is a process by which hormones or neurotransmitters (also called Ligands) interact with a receptor" and transmit their signals into a living cell.

- The receptor 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."

No cell live alone

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

The process of signaling

Recognition of signal

- Receptors

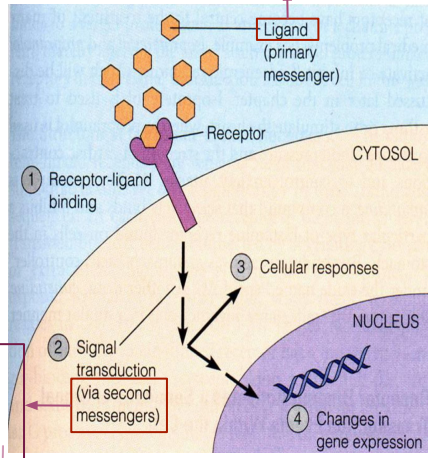
Transduction

- Change of external signal into intracellular message with amplification and formation of second messenger

Effect

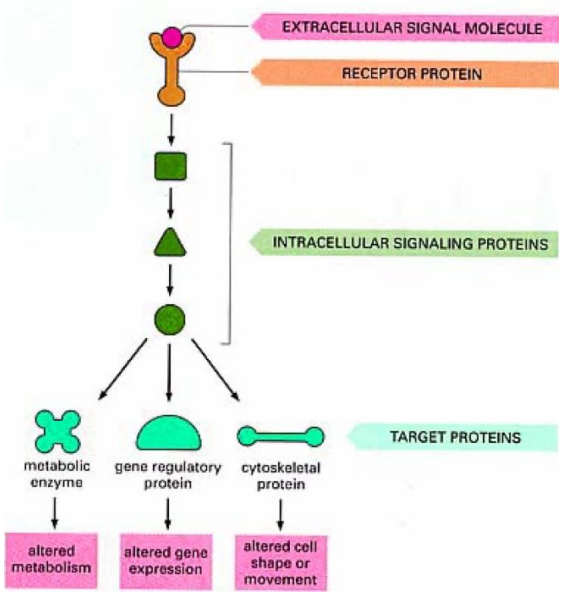
- Modification of cell metabolism and function

Ligands (anything that will bind to a receptor we call it a LIGAND) (e.g. hormones and neurotransmitters) are the primary messengers, secondary messengers are intracellular and differ in chemical structure. *438 notes



the second messenger modifies and stimulates the function of cell metabolism. *438 notes

Signaling Cascades



Note:
1-First the signaling molecule (a transmitter) attach to an extracellular receptor.
2-Then the receptor activate intracellular signaling proteins.
3-which effect the target cell.
And produce the desired outcome

Note : cAMP = cyclic Adenosine Monophosphate

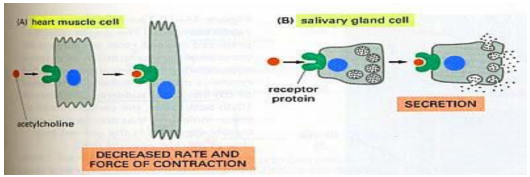
Recognition

Different response to the same signaling molecule

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

Different cells

* Same signal but different cells



Acetylcholine can decrease the rate and the force of contraction of heart muscle cell also stimulate the secretion of salivary gland cell
SAME SIGNAL , DIFFERENT CELLS
(because it's **parasympathetic** neurotransmitter, remember?)

Med428 example:
Norepinephrine can stimulate the increase of heart rate and activity of cardiac cells. Norepinephrine also decreases saliva production of salivary glands.

(because it's a **sympathetic** neurotransmitter)

One cell but, Different Pathways

*Low blood sugar

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

P

Glycogen synthase (Inactive form)
The enzyme's function will be inhibited

Inhibition of glycogenesis

* Add phosphate

P

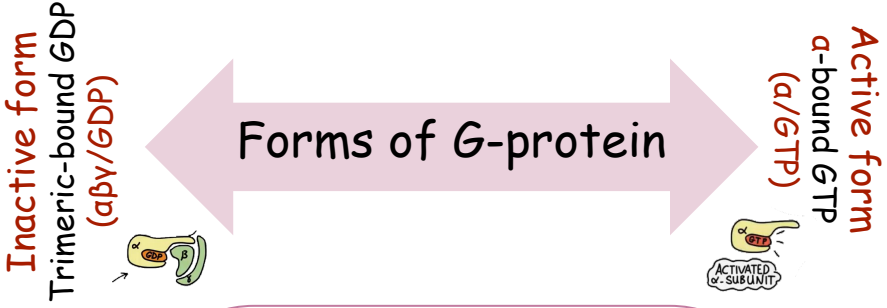
Glycogen phosphorylase (Active form)
The enzyme's function will be activated

Stimulation of glycogenolysis

GTP-Dependant Regulatory Proteins (G-Proteins)

Before starting this part, we **HIGHLY** suggest you to watch the video Click here

G-Proteins: Trimeric (3 subunits) membrane proteins: (αβγ) G-stimulatory (G_s) and G-inhibitory (G_i) binds to GTP/GDP



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

438 note : 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:

- Adenylyl cyclase system (AC)
- Calcium/phosphatidylinositol system (PLC)

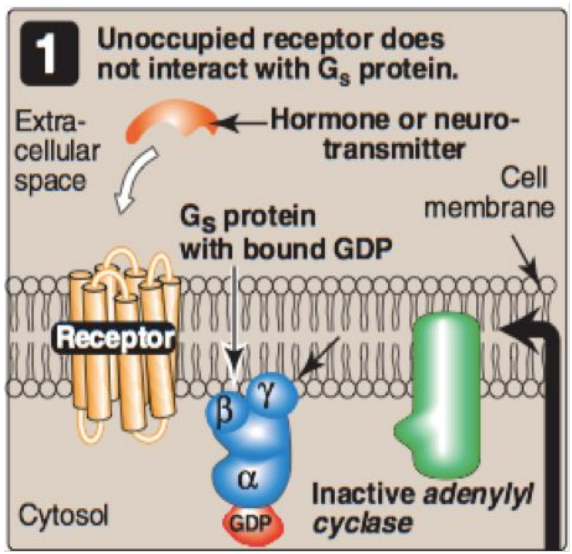
Adenylyl Cyclase System

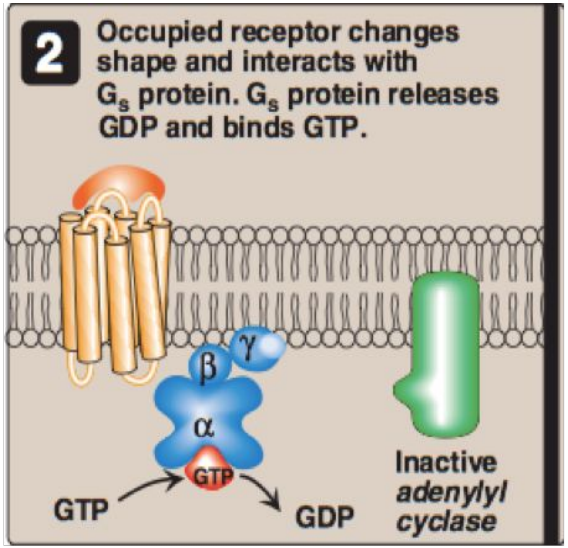
Adenylyl cyclase: Membrane-bound enzyme, Converts ATP to cAMP

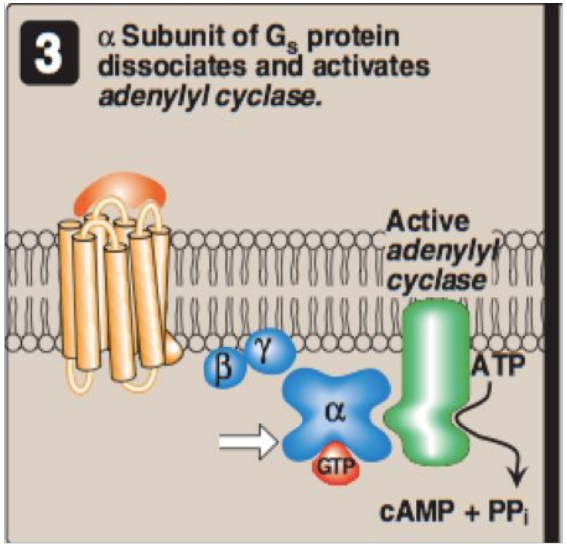
Activation/Inhibition:

- **Signal**: Hormones or neurotransmitters (e.g., Glucagon and epinephrine) or Toxins (e.g., Cholera and pertussis toxins)
- **Receptor**: G-protein coupled receptor
  *what kind of receptor is responsible for cyclase system?
- **Response**: Activation/inhibition of protein kinase **A** (cAMP-dependent protein kinase)

Signal Transduction: Adenylyl Cyclase System







Resting state: No Signal

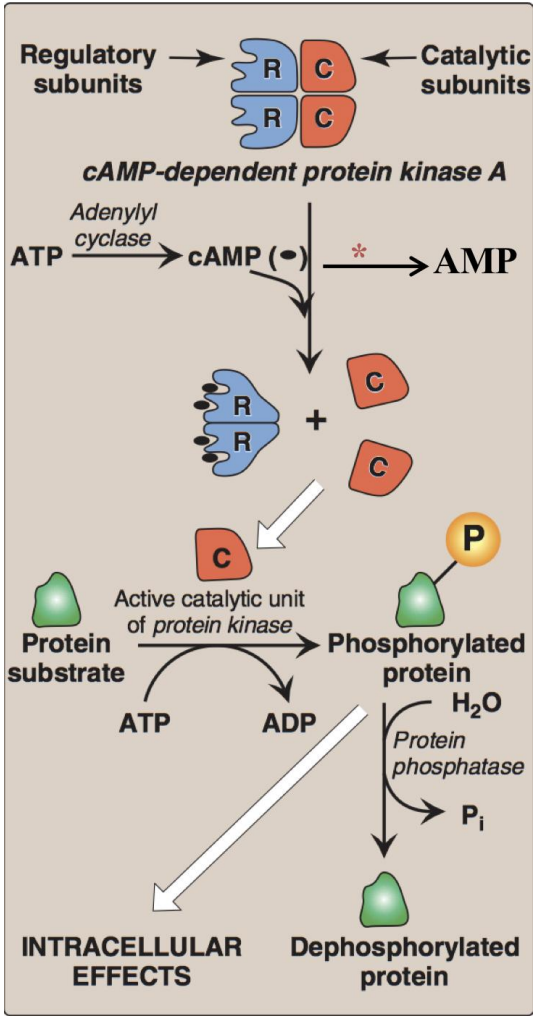
Ligand/Receptor Binding Activation of adenylyl cyclase
Activation of G_s-protein

438 notes
Adenylyl cyclase: is the enzyme ***Gs***: stimulation of adenylyl cyclase which synthesizes cyclic adenosine, ***Gi***: Inhibition of adenylyl cyclase. Monophosphate or cyclic AMP from adenosine triphosphate (ATP).

ACTIONS OF cAMP

dependent means that the enzyme can't work without cAMP

1. cAMP binds to cAMP-dependent protein kinase at its regulatory subunits part in the presence of Adenylyl cyclase enzyme
2. When it binds to regulatory subunits catalytic subunits will be released to be active
3. Active catalytic unit adds phosphate to protein substrate and make phosphorylated protein
4. Phosphorylated protein produces intracellular effects



Signal Termination

Dephosphorylation *

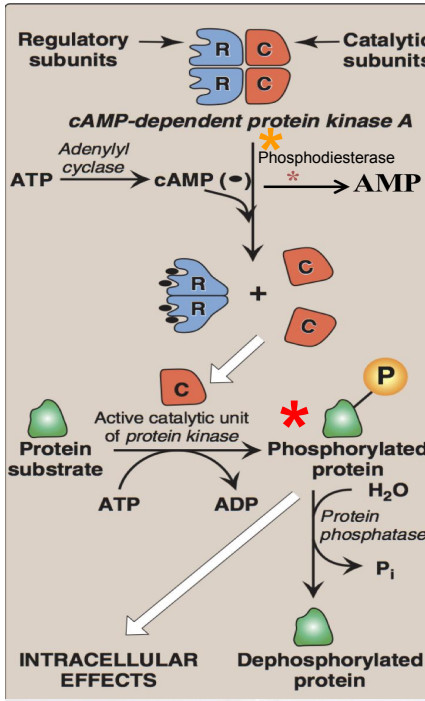
The phosphate of phosphorylated protein is removed and becomes dephosphorylated protein in the presence of Protein phosphatase enzyme

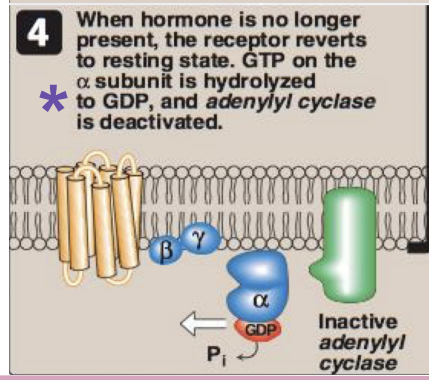
Protein kinase A inhibition *

Converting cAMP to AMP in the presence of Phosphodiesterase enzyme decreases the number of cAMP which leads to inactivation of protein kinase

Adenylyl cyclase inhibition *

When hormone is no longer present, the receptor reverts to resting state. GTP on the **α** subunit is hydrolysed to GDP, and adenylyl cyclase is deactivated



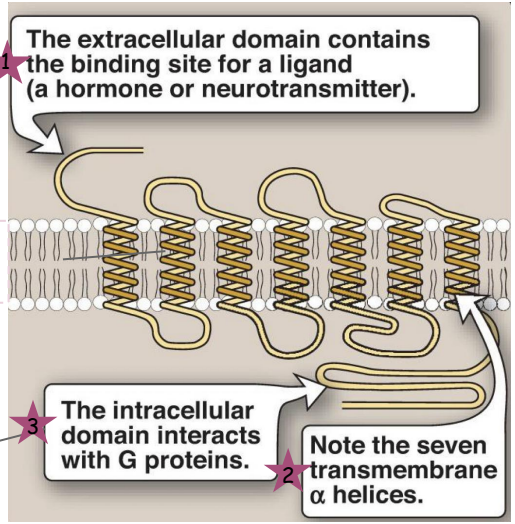


G-protein Coupled Membrane receptor

Have 3 domains

Transduction of signal

Activates G protein

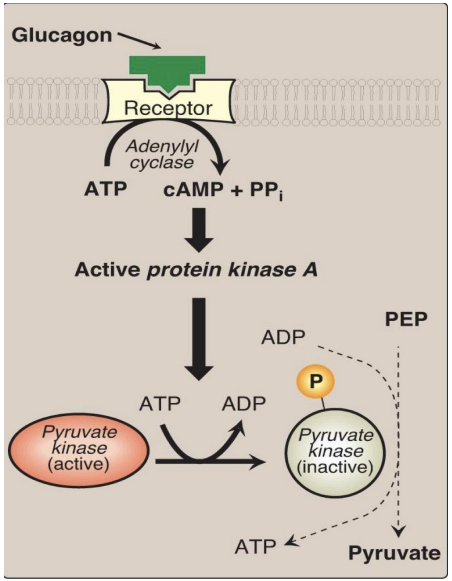


What is the function of G-protein coupled receptor?
Activation of G-protein

436 note:
-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

Pyruvate Kinase Regulation: Covalent Modification

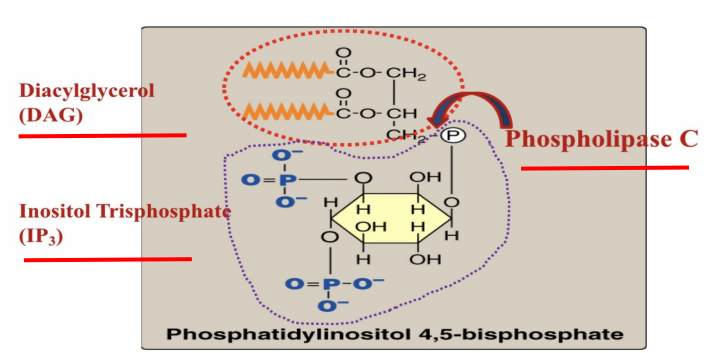
Covalent modifications: are alterations to the chemical structure of an enzyme by the addition or removal of chemical groups.
In this case, the addition of Phosphate group which deactivated the enzyme. (remember that phosphorylating can activate or deactivate enzymes).
This figure represents the last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



436 note:
1- Glucagon is released then binds with the receptor
2- It activates the Adenylyl Cyclase which will convert ATP to cAMP
3- cAMP activates the Protein Kinase A
4- This protein Kinase A can phosphorylate (Add phosphate group) the pyruvate kinase and become inactive

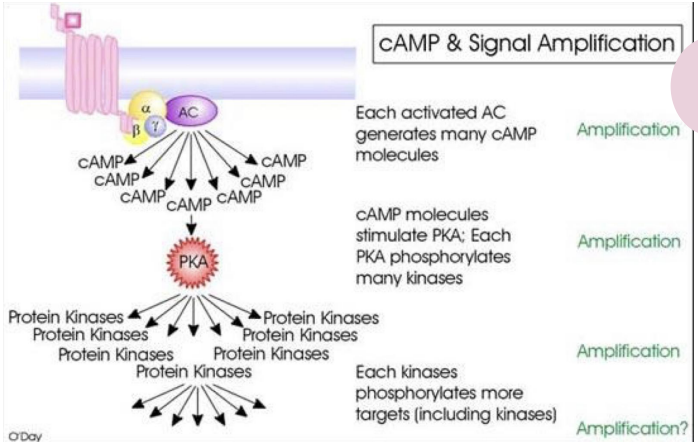
Calcium/Phosphatidylinositol System

1



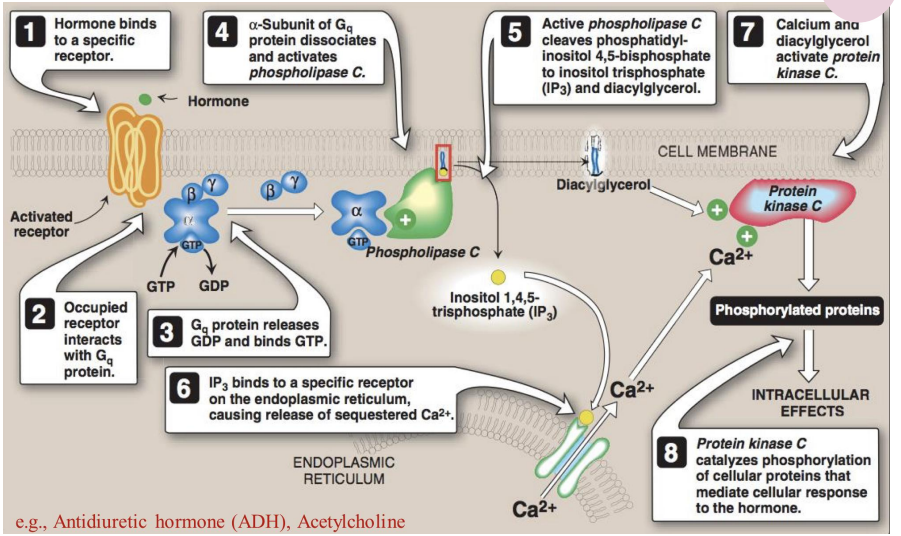
Signal Amplification

3



Intracellular Signaling by Inositol Trisphosphate

2



we recommend you to watch this to understand this slide **video**

If you want to read the explanation click here

Take home messages

Cell signaling allows :

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

To wrap it up:
Collagen is a polypeptide chain
Made of 3 Amino acids
Glycine and proline are found in it , third amino acid differs can ve variable
Seen as a triple helix structure
They are held together by hydrogen bonds

QUIZ ♥

MCQs

Q1: The signaling cascade begins from?

A) The signal of extracellular molecule
B) Receptor
C) Intracellular signals
D) A & B

Q2:What is the function of G-Protein coupled receptors?

A) Inhibition of G-Protein
B) Activation of G-Protein
C) Binding with extracellular ligands
D) Transduction of signals

Q3: Cell signaling allows

A) Signal transmission and amplification
B) Intracellular communication
C) Regulation of metabolism
D) All of them

Q4: Which of these substrates make the intracellular effect?

A) cAMP
B) Protein Kinase
C) Phosphorylated protein
D) All of them

SAQ

Q1 : Main function of Adenylyl cyclase

MCQs answers

1) A
2) B
3) D
4) C

SAQ answer:

~~Converts ATP into cAMP~~

Team members

Girls Team :

- Alia Zawawi
- Nada Babilli
- Rania Aqil
- Reem alamri
- Reema Alomar
- Reem Alqahtani
- Renad Alhumaidi
- Samar Almohammedi
- Shaden Alobaid
- Budoor Almubarak
- Somow Abdulrahman
- Noura Alsalem
- Lama Alahmadi
- Sadem Alhazmi
- Nuha Alkudsi
- Norah Alsheikh
- Muneerah Alssdhan
- Mayasem Alhazmi

Special thanks to Noura Alshathri #Med439

Boys Team :

- Mansour albawardy
- Hassan alshurafa
- Abdulrahman almebki
- Mohammed alsayyari
- Abdullaziz alomar
- Ahmed Alkhayat
- Abdulaziz alrabiah
- Saud alrasheed
- abdullah almazroo
- Hamad almousa

Special thanks to Hamad Almousa #Med439

Team leaders

- Shatha Aldhohair
- Mishal Althunayan

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