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14

Cell signaling and regulation of metabolism

Color index :

Main text

IMPORTANT

Extra Info

Drs Notes

Foundation Block - Biochemistry Team

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MED439

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 (Extra explanation)

A helpful video

- 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.

Thanks to #Med438

No cell lives in isolation

Because cell survival depends on communication

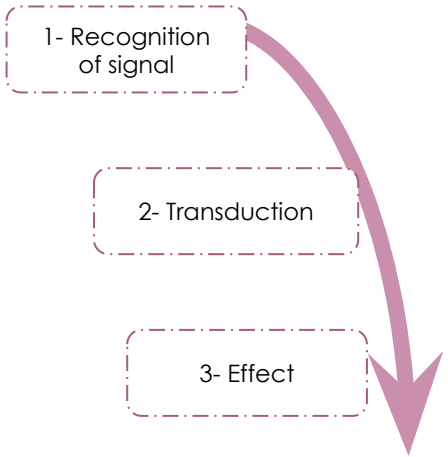
- Cells communicate with each other.
- Cells send and receive information (signals)."If cells are adjacent to each other, they can communicate without signals"
- Information is relayed (received) within a cell to produce a response.this response is necessary to maintain the homeostasis

Signaling process

1. Recognition of signal
- Performed by receptors. Ligand will produce response only in cells that have receptors for this particular ligand and each cell has a specific set of receptors "Signals which are lipid soluble can go directly to the cell without the recognition by a receptors. (No recognition step)"

2. Transduction
- Change of external signal into intracellular message with amplification and formation of second messenger."The first messenger is called (Signals) while the second messenger is called (intracellular signals)"

3. Effect
- Modification of cell metabolism and function."The modification of cell metabolism and function is done by the second messenger (Intracellular signals)"



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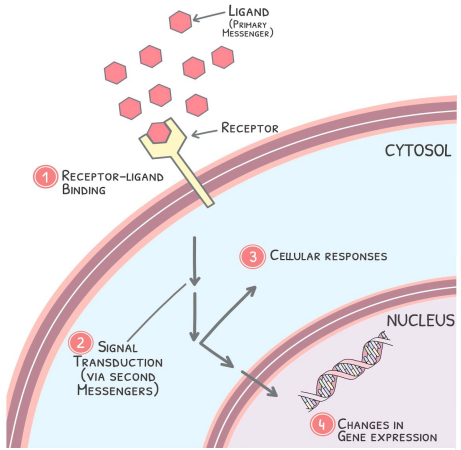
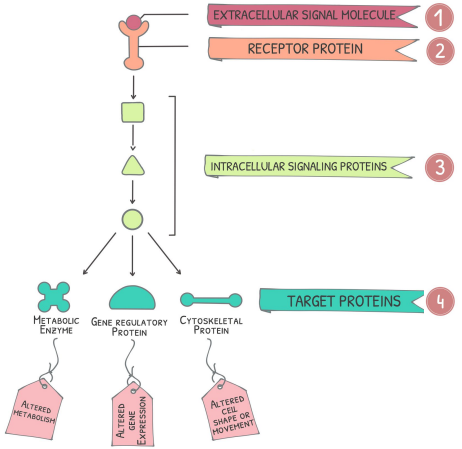
General Signaling Pathway (Cascade)

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





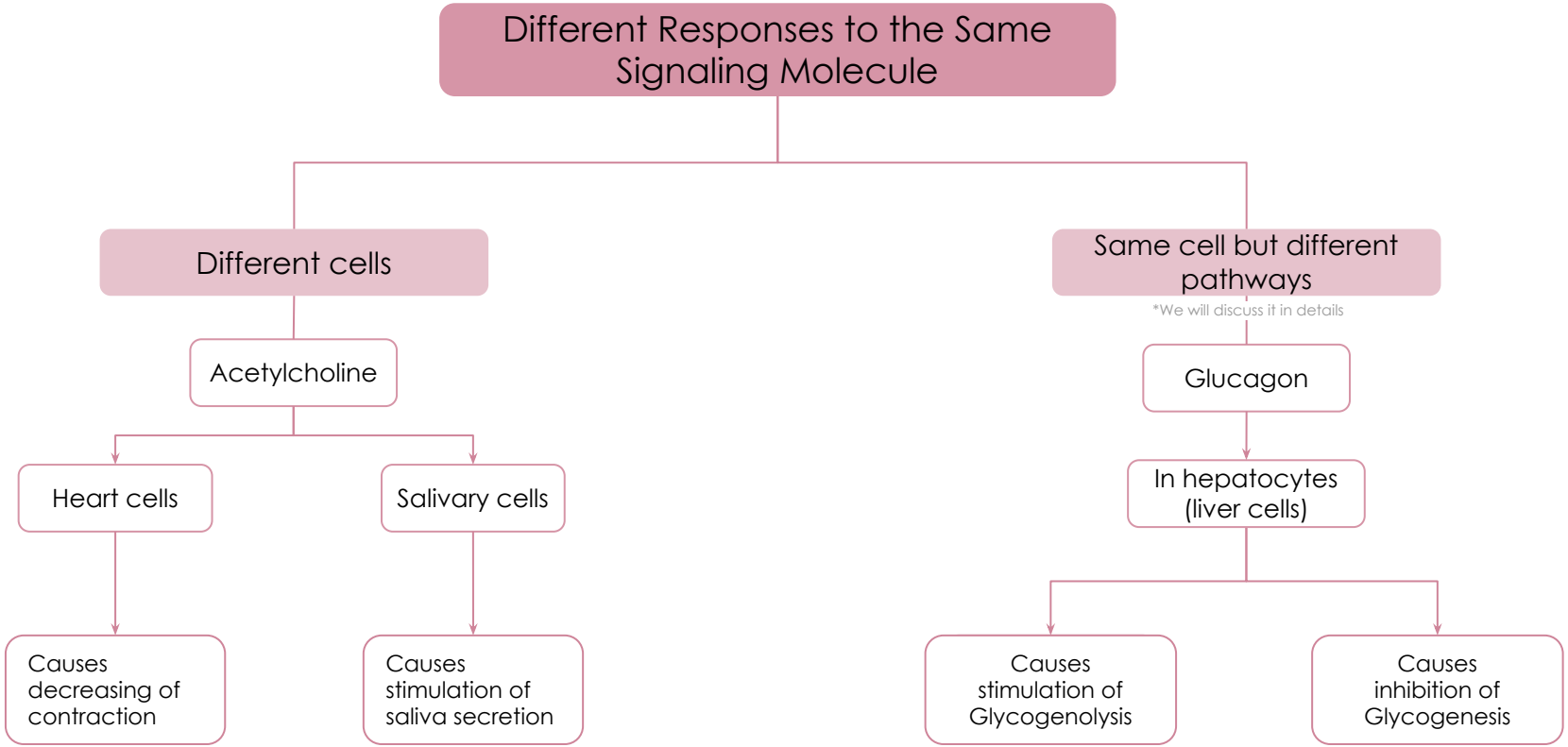
1 The ligand (signal or primary messenger) will bind to the extracellular receptor.

- Ligands (anything that will bind to a receptor we call it a ligand) (e.g. hormones and neurotransmitters) are the **primary messengers** whereas **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.

2 The receptor will recognize this signal.

3+4 This binding will stimulates the transduction by the second messenger, and (activating intracellular signaling proteins)this transduction includes:

- Cellular responses.
- Changes in gene expression.



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

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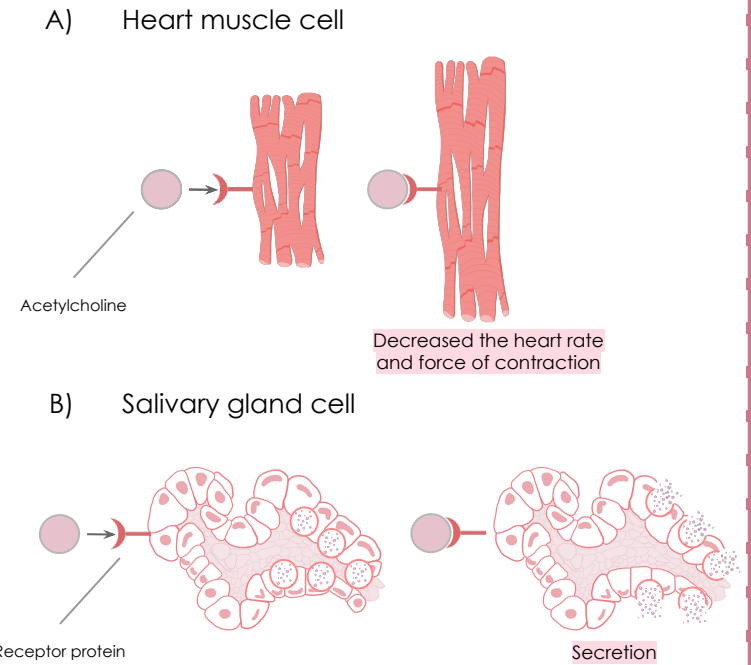
Different Responses to the Same Signaling Molecule

1. Same signal but different cells

- We have a molecule that can affect two cells, but each cell has a different response.
  e.g. Ach when it's secreted to the heart cells it will decrease the contraction and that will decrease the heart rates and when it secreted ro the salivary glands it will cause saliva secretion.
- Acetylcholine can decrease the rate and the force of contraction of heart muscle cell and also stimulate the secretion of salivary gland cell.
- Same signal but different cell (because it's **parasympathetic** neurotransmitter, remember?)
- #Med428 example:
  - Norepinephrine can increase the heart rates and the activity of cardiac cells.
  - Norepinephrine also decreases saliva production of salivary glands.
    (because it's a **sympathetic** neurotransmitter)



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Different Responses to the Same Signaling Molecule

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

2. Same cell but different pathways

A. Stimulus: Hypoglycemia
B. Outcome: Glucagon hormone secretion.
C. (Targeted cells) Hepatocyte "liver cells": have Glucagon/receptor binding
D. Second messenger: cAMP (cyclic Adenosine Monophosphate)
E. Response: Enzyme phosphorylation (adds a phosphate group)

When the blood glucose level is low, the pancreas will secrete glucagon which can rise blood glucose levels, How?
the hormone will go to the hepatocytes "cuz the liver store glycogen" and do two things:
1. Stimulate the degradation of glycogen which was stored in the liver and convert it to glucose to be released to the blood
2. inhibit the synthesis of glycogen

P Glycogen synthase
Inactive

- Is an enzyme involved in converting glucose to glycogen, therefore glucagon hormone makes it **inactive**

⊖ **Inhibition** of glycogenesis "formation of glycogen"

P Glycogen phosphorylase
Active

- Is one of the phosphorylase enzymes. It breaks up glycogen into glucose subunits.

⊕ **stimulation** of glycogenolysis "breakdown of glycogen to glucose"

GTP-Dependant Regulatory Proteins (G-Proteins)

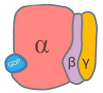
A helpful video

- **G-Proteins**: Trimeric (consists of 3 subunits) membrane proteins (αβγ).
  - Come in between the receptor and 2nd messenger .
  - Regulate the formation and synthesis of 2nd messenger
- Types according to the function:

1. G-stimulatory (G_s)
2. G-inhibitory (G_i)

} binds to GTP/GDP

- Forms of G protein:



Inactive form
Trimeric-bound GDP (αβγ/GDP)

Active form
a-bound GTP (a/GTP)
- (β and γ separate from a)

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

GTPase activity: GTPases (singular GTPase) are a large family of hydrolase enzymes that can bind and hydrolyze guanosine triphosphate (GTP). #Med438

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.

Signaling Pathways for Regulation of Metabolism

Two important second messenger systems"

1. Adenylyl cyclase system (AC)

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- Adenylyl cyclase: Membrane-bound enzyme, converts ATP to cAMP (cyclic AMP).
- 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?
- **Second messenger:** cAMP
- **Response:** Activation/inhibition of protein kinase **A** (cAMP-dependent protein kinase).
- According to G-protein's function: The resulting response will be:

1. Activation of protein kinase **A** (cAMP-dependent protein kinase).
2. Inhibition of protein kinase **A** (cAMP-dependent protein kinase).

- Protein kinase A is a family of enzymes whose activity is dependent on cellular levels of cyclic AMP (cAMP). It is **activated** by cAMP.
- 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).Thanks to #Med436

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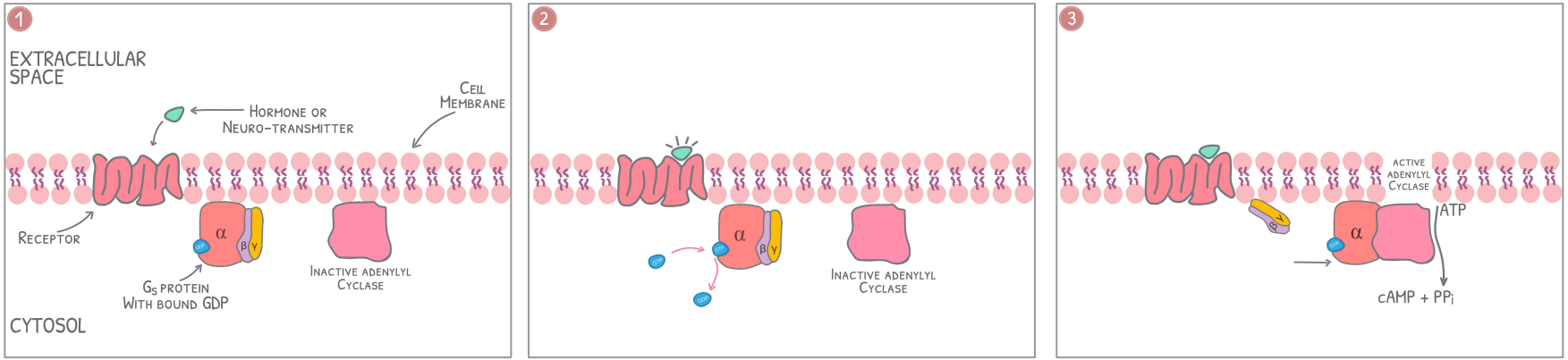
1. Adenylyl cyclase system (AC), Contd...

Signal Transduction: Adenylyl Cyclase System



1

- Unoccupied receptor does not interact with G_s protein. "**G_s**: causes stimulation of adenylyl cyclase which synthesizes cyclic adenosine whereas **G_i**: causes Inhibition of adenylyl cyclase".
- **Resting state: No signal**

2

- Occupied receptor changes shape and interacts with G_s protein. G_s protein releases GDP and binds GTP
- **Ligand/Receptor binding → activation of G_s protein.**
- Binding of ligand (primary messenger) to the receptor activates G-protein and GDP is replaced by GTP which is bound to a-subunit.

3

- a Subunit of G_s protein dissociates and activates adenylyl cyclase.
- **Activation of adenylyl cyclase.**
- a-subunit dissociates from β and γ subunits then a-subunit binds to adenylyl cyclase and makes it active. Now,Adenylyl cyclase converts ATP to cAMP "cAMP is the second messenger".

original pic

1. Adenylyl cyclase system (AC), Contd...

Actions of cAMP

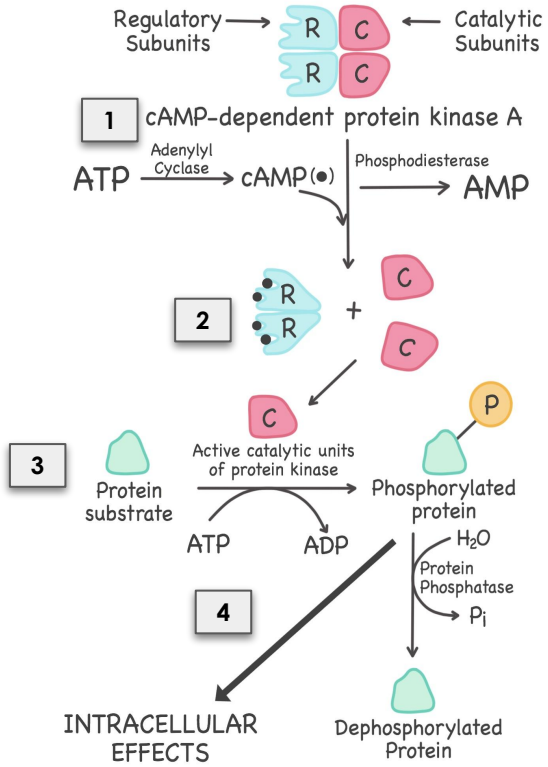
- What is AMP and cAMP?
  - We know that when the third phosphate is removed from ATP, we get ADP, which stands for Adenosine Diphosphate.
  - BUT when two phosphates are removed from ATP, we get AMP.
  - cAMP is the cyclic structure of AMP, AMP is converted to cAMP by a specific Enzyme.

1 cAMP binds to cAMP-dependent protein kinase **at its regulatory subunits** part in the presence of Adenylyl cyclase enzyme.
- dependent means that the enzyme can't work without cAMP

2 When it binds to regulatory subunits catalytic subunits will be **released** to be active

3 Active catalytic unit catalyze the **transferring of phosphate group** from ATP to the specific amino acids of protein such as: **serine and threonine**.
"adds phosphate to protein substrate and make phosphorylated protein"
and 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.

4 Phosphorylated protein produces intracellular effects



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1. Adenylyl cyclase system (AC), Contd...

Signal termination in 3 ways

A(1) Degradation of Phosphorylated protein:

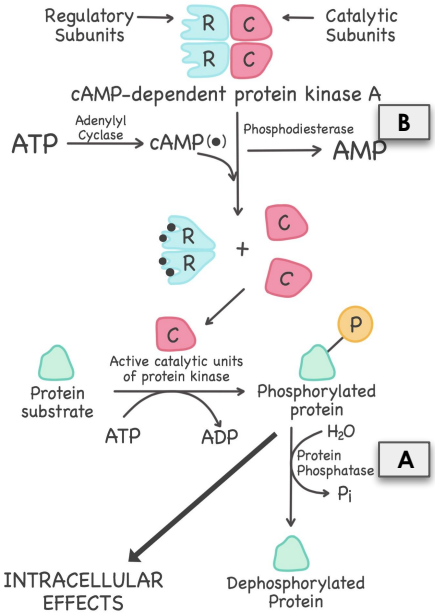
- Removing phosphate group (PO_4) from protein and becomes dephosphorylated protein by enzyme called **protein phosphatase**.

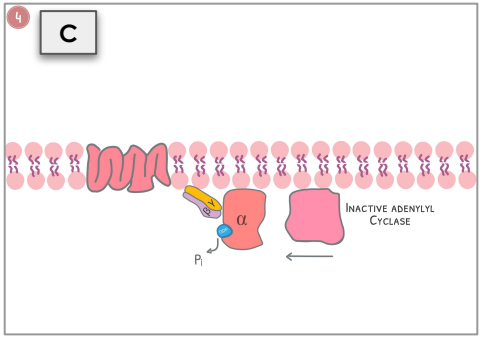
B(2) Inhibition of protein kinase A:

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

C(3) Inhibition of adenylyl cyclase:

- When hormone is no longer present, the receptor reverts to resting state. GTP on the **a** subunit is hydrolysed to GDP, and adenylyl cyclase is deactivated "By hydrolyzing GTP to GDP in G-protein which leads to inactive form of G protein then a-subunit will bind to β and γ subunits".





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1. Adenylyl cyclase system (AC), Contd...

G-Protein Coupled Membrane Receptor

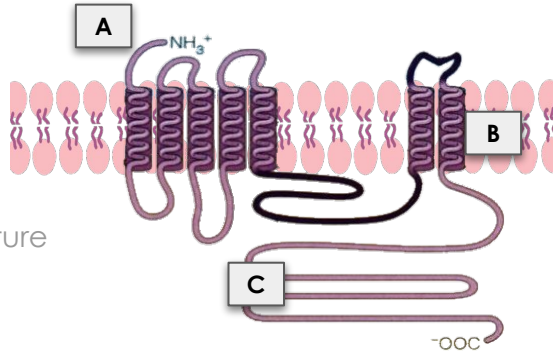
A The extracellular domain contains the binding site for a ligand (a hormone or neurotransmitter)"have 3 domains"

B Note the seven transmembrane a-helices. "Here will be transduction of signal"

C The intracellular domain interacts with G proteins and activates G protein.

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

- The important thing to know is that G-protein coupled receptors (GPCRs)cross the plasma membrane **seven times**, this is the essential feature of the structure. And that's why it's called seven pass receptor.
- This called transmembrane structure allows it to smoothly interact with G-protein.
- The extracellular part interacts with ligand (primary messengers, and the intracellular part interacts with G-protein which initiates the process of forming the second messenger (e.g.cAMP).



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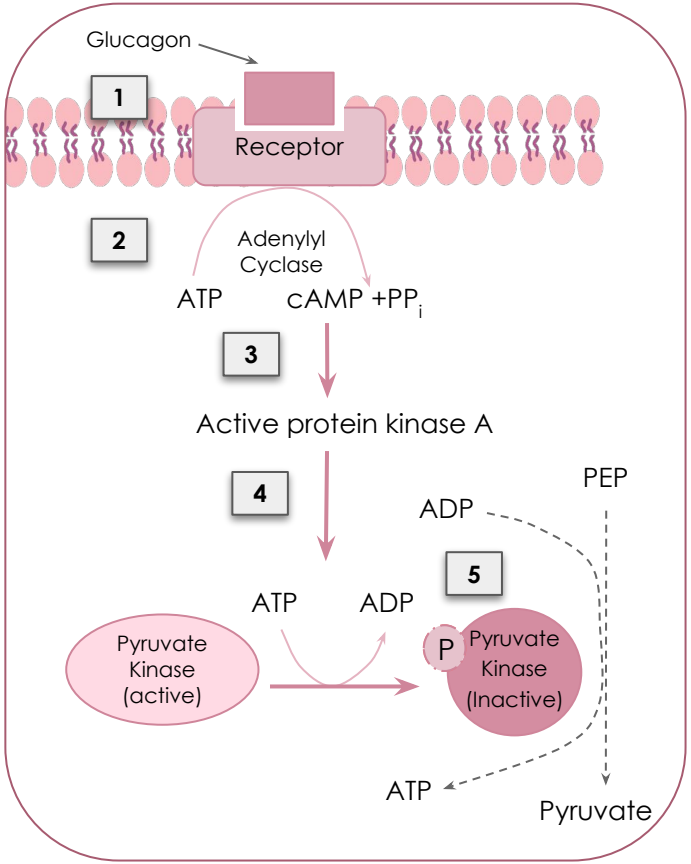
1. Adenylyl cyclase system (AC), Contd...

Pyruvate Kinase Regulation: Covalent Modification

- Glucagon hormone can go to other normal cells to tell them that they should reduce the amount of glucose they use, Why? cuz they normally use glucose for cellular respiration to produce energy so glucagon inhibits glucose degradation there " cuz we need glucose to rise blood glucose levels not for using them to produce energy"
- **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.

- We are talking about the last step in Glycolysis.

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.
5. After that it becomes Inactive, So the Glycolysis is stopped



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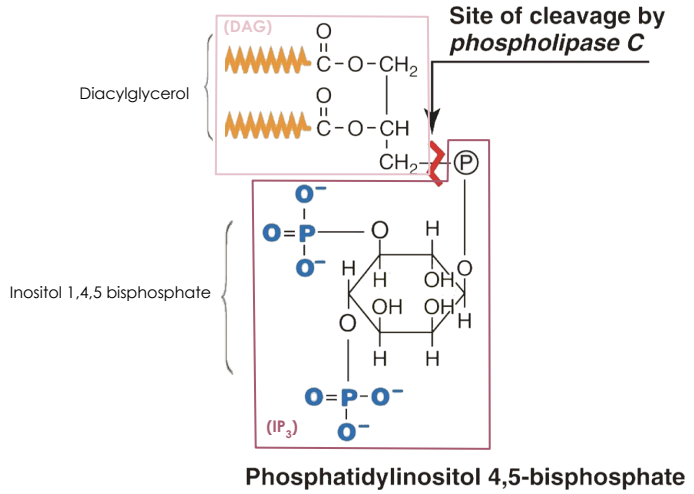
Signaling Pathways for Regulation of Metabolism

Two important second messenger systems"

2. Calcium/phosphatidylinositol system (PLC)

2. Calcium/phosphatidylinositol system (PLC)

- This is a minor phospholipid (Phosphatidylinositol 4,5-bisphosphate),and is a component of the cell membrane.
- After the breakage of the bond by **Phospholipase C**, inositol 4,5- bisphosphate takes the phosphate group (PO_4) with red arrow becoming Inositol 1,4,5 triphosphate



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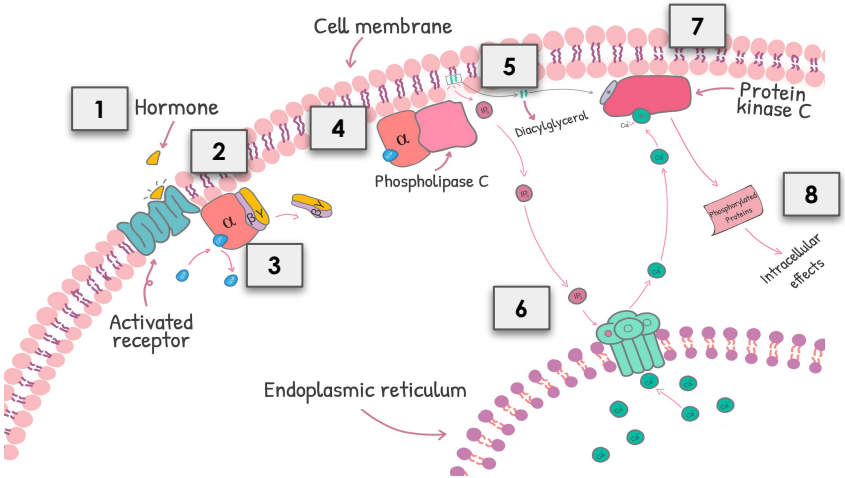
2. Calcium/phosphatidylinositol system (PLC), Contd...

Intracellular Signaling by Inositol trisphosphate

A helpful video

1. A specific Ligand "first messenger" (hormone or neurotransmitter), binds to G-protein coupled receptors.
2. Receptor interacts with G_q protein.
3. G_q protein stimulates its release of GDP and replaces it with GTP, therefore activating it.
4. a-subunit disassociate from G-protein, binds to **Phospholipase C** activating it in the process.
5. Phospholipase C breaks **phosphatidylinositol 4,5-bisphosphate** into Inositol trisphosphate (**IP_3**) + diacylglycerol (DAG) .
6. **IP_3** "second messenger" binds to Endoplasmic Reticulum (ER), a major store of Calcium ions, causing the release of Calcium ions.
7. Protein Kinase C responds to second messengers, in this case they're Calcium from ER and signals from DAG.
8. Protein Kinase C phosphorylates proteins in response to the signals from DAG and **IP_3** that cause intracellular effect and response to the hormone.

(remember that kinase proteins function in phosphorylating proteins).



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

★ extra explanation
Thank to #Med436

The system	Adenylyl cyclase	Calcium/Phosphatidylinositol
Enzyme	Adenylyl cyclase	Phospholipase C
Secondary messenger	cAMP	Diacylglycerol (DAG) & Inositol 1,4,5 triphosphate (IP_3)
Protein	Protein kinase A (A stands for cAMP)	Protein kinase C (C stand for Ca^{++})
Signal	- Hormones or neurotransmitters (e.g. Glucagon and Epinephrine) - Toxins (e.g. cholera and pertussis toxins)	Acetylcholine (Ach) and Antidiuretic Hormone (ADH)

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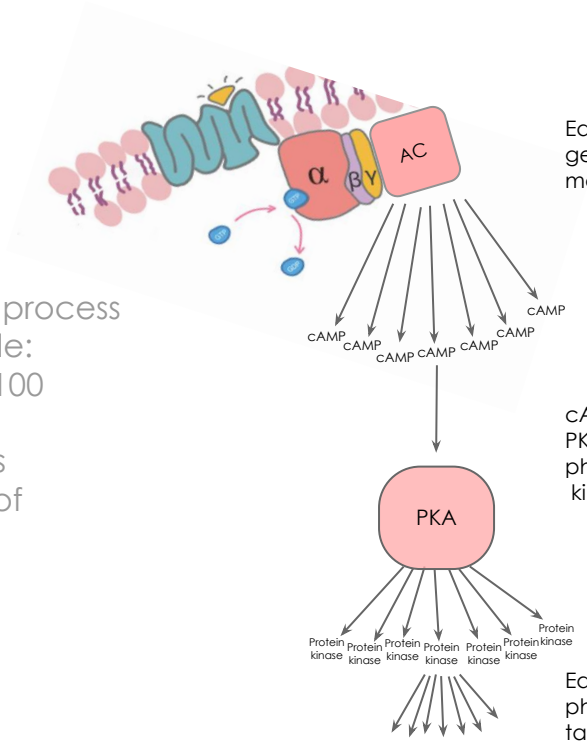
Signal Amplification

- 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



Take home messages

Cell signaling allows :

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

Quiz

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
Q5 : G protein are:			
A) Tetrameric	B) Trimeric	C) Dimeric	D) None

SAQs :

Q1: What's the main function of Adenylyl cyclase?

★ **MCQs Answer key:**

1) A 2) B 3) D 4) C 5) B 6) D

★ **SAQs Answer key:**

1) Converts ATP into cAMP

Girls team:

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Shaden Alobaid
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Sadem Alhazmi
Somow Abdulrahman
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Abdulaziz alrabiah
Saud alrasheed
Abdullah almazro
Hamad almousa
Ahmad alkhayat

"One small positive thought can change your whole day ."

☆Special thanks to **Maram Aldeej** for her amazing drawings

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