Introduction to metabolism + signaling

Lecture 9+10

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What is a pathway?

- A multi-step sequence of chemical reactions. The product of first reaction becomes a substrate for second reaction.
- Different pathways can intersect, forming an integrated and purposeful network of chemical reactions "The Metabolic Map"
- Pathways that regenerate a component are called cycles.

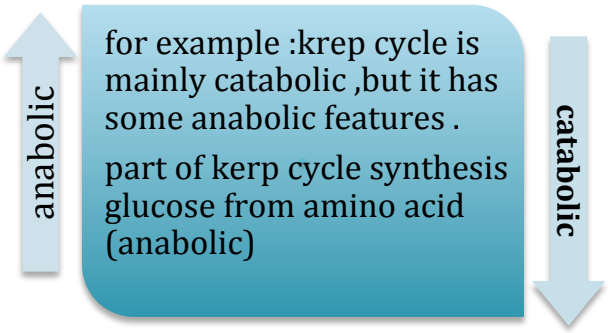
Metabolism: All the chemical reactions taking place inside a cell. It consists of Anabolic (energy consuming) and catabolic (energy producing).

Comparison of Catabolic and anabolic pathways:

Anabolic	Catabolic
Simple to complex	Complex to simple
Endergonic (use ATP)	Exerognic (produce ATP)
Reductions	Oxidation
Require NADPH	Requires NAD+
Divergent process	Convergent process

Amphibolic pathways

Amphi:dual
Amphibolic means : dual pathway

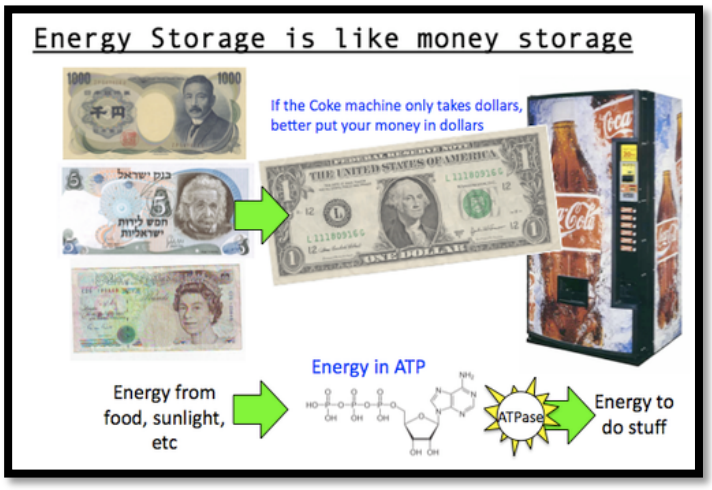


Energy currency: ATP

The Free energy liberated (gained) in Hydrolysis of ATP (Adenosine Triphosphate) is used to reaction that used energy.

$$ATP + H2O \rightarrow ADP + Pi$$

ATP is oxidized (loss Electron) and turns to ADP.
This ATP-ADP cycle is the fundamental mode of energy exchange in biological systems



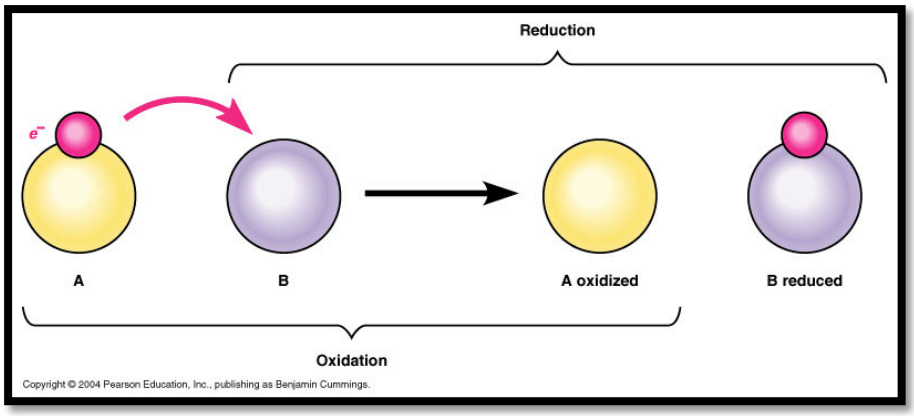
Oxidation-Reduction in Metabolism:

Reduction

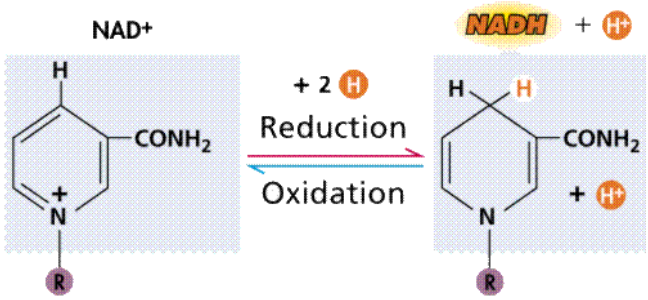
- Gain of hydrogen
- Gain of elctron
- Loss of Oxygen

Oxidation

- Loss of hydrogen
- Loss of electron
- Gain of Oxygen



NAD+ and NADH:



Regulation of metabolism:

Regulation will be discussed with more details in next lectures.

1. Intracellular signals (inside the cell):
   - Substrate availability:
   - Product inhibition
   - Allosteric activators
2. Intercellular communications (Between the cells):
   Chemical signaling (hormones):

By Second messenger: after the substrate binding to the receptor. The receptor forms a signal inside the cell to the target e.g. to ribosomes. Some examples for second messengers:

Cyclic AMP, cyclic GMP
Ca/phosphatidylinositol

Metabolic fuel

carbohydrates & lipids mainly used for energy production.
proteins are little extent comered to carbohydrates and lipids

EXAMPLE OF METABOLIC FUEL : glucose , faty acid and amino acid.

clucose is the major metabolic feule of most tissue

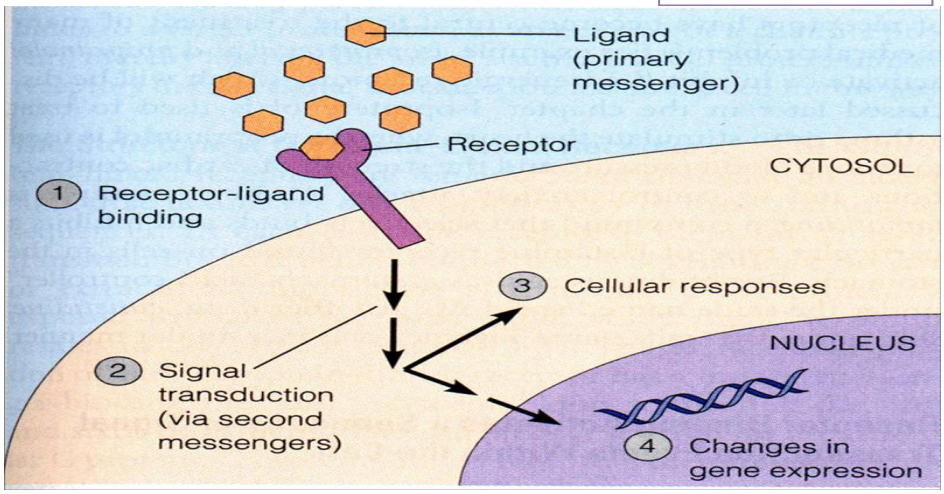
No cell lives in isolation

You should know that cells

- Communicate with each other
- Send and receive information (signal)
- Signal is relayed within cell to produce response.

Signaling Process:

Recognition of signal	Transduction	Effect
By Receptor.	Transofer external signal into intracellular message with amplication and formation of second messenger.	Modification or response of cell.



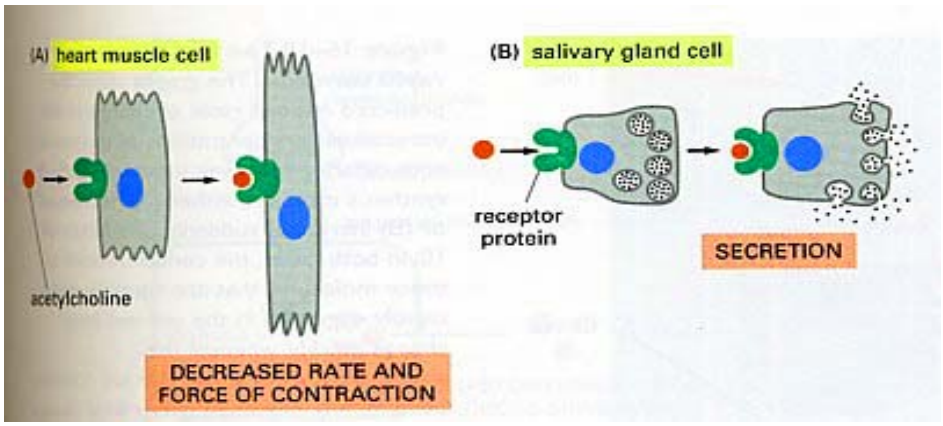
Recognition: (by receptors)

Ligand will produce response only in cells that have receptors for this particular ligand. And each cell has specific receptors.

Transduction:

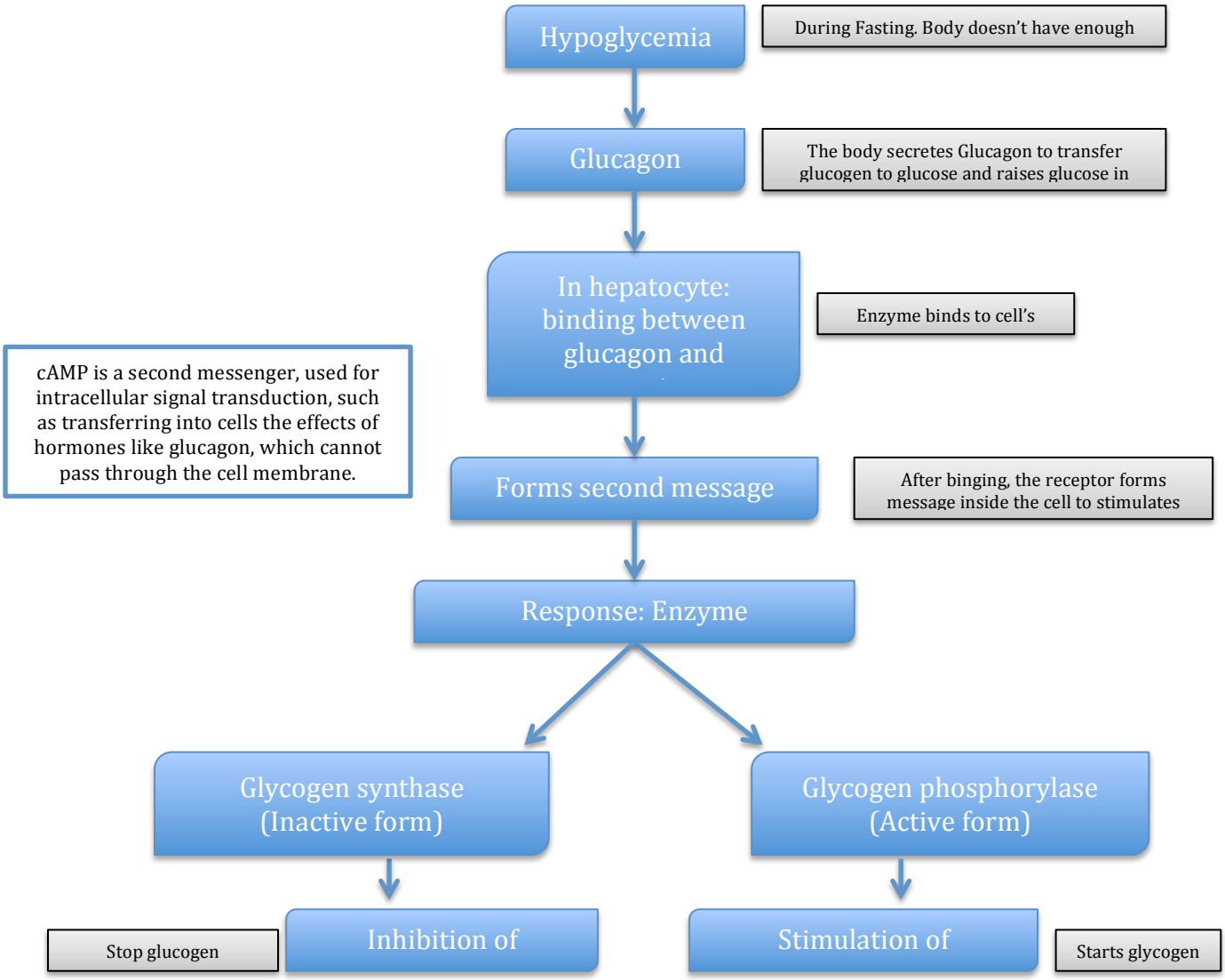
Different response to the same signaling molecule:

I. Different cells:



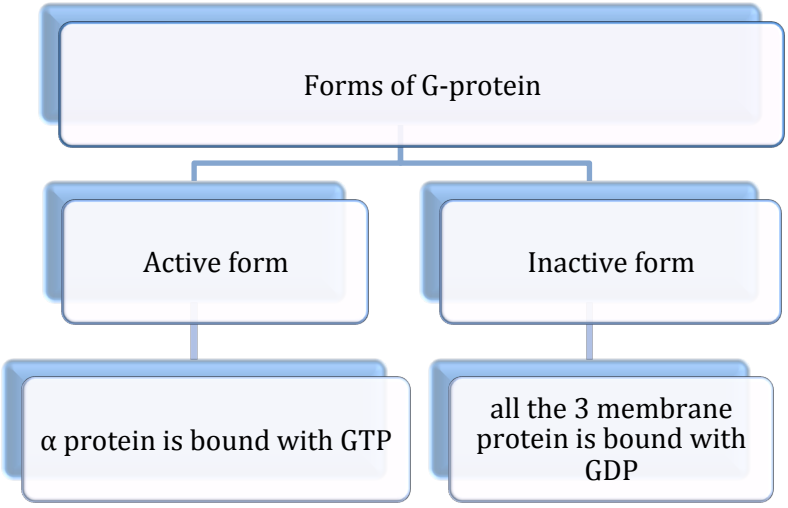
Acetylcholine affects two different cells: Heart muscle cell and salivary gland cell.

II. One cell but different pathways:

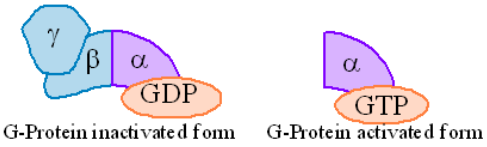


GTP-dependent regulatory proteins (G-proteins):

G-protein is Trimeric (3 polypeptide) membrane proteins (αβγ). It can be either G-stimulatory (Gs) or G-inhibitory (Gi). And it binds to either GTP or GDP.

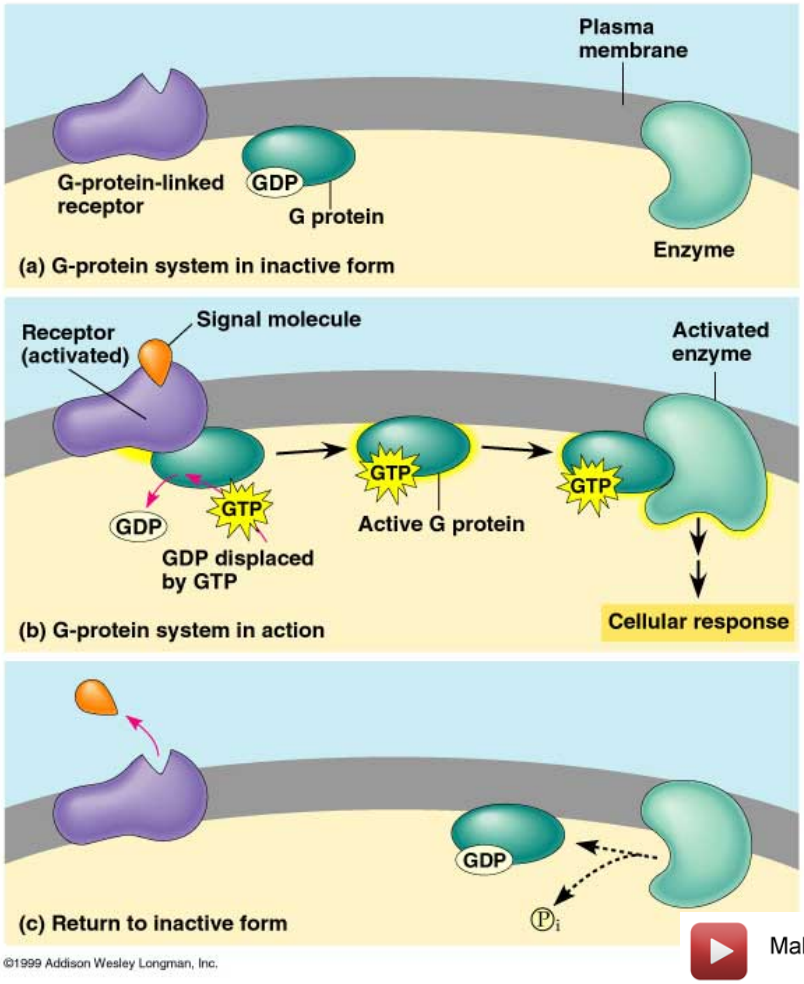


NOTE: we call it G-proteins because it has the ability to bind to GDP or GTP



G-Protein inactivated form G-Protein activated form

The α-subunit has intrinsic GTPase activity, resulting in hydrolysis of GTP into GDP and inactivation of G-proteins.(since when we do something it has to comeback to the normal state or position α-subunit has intrinsic GTPase which is responsible for converting GTP to GDP during binding of all subunits α to βγ)



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Second messeger systems:

1. Adenylyl cyclase system.
2. Calcium/phosphatidylinostol system.

Adenylyl cyclase system

What is it?

Membrane-bound enzyme

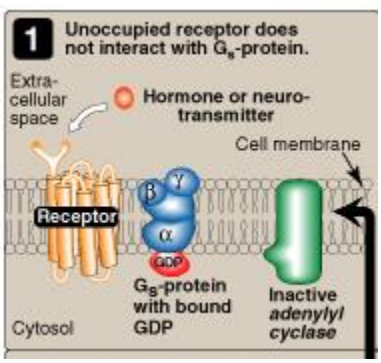
Converts ATP to cAMP

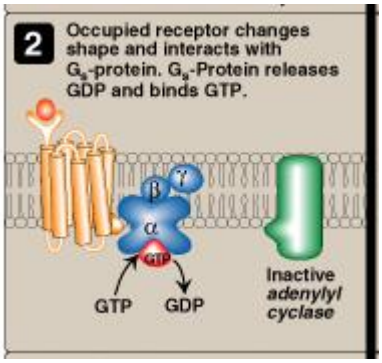
Signal: Hormones of neurotransmitters. (e.g. Glucagon and epinephrine) or toxin (e.g. cholera and pertussis toxins)

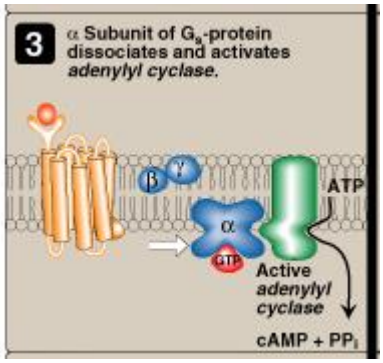
Receptor: G-protein

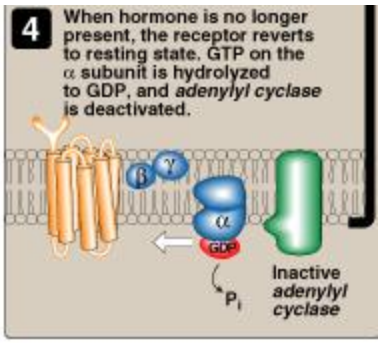
Respnse: Activation or inhibition of protein kinase A (it is called Kinase A because it is dependent on cyclic ADP).

Kinase: enzyme can add phosphate to other protein





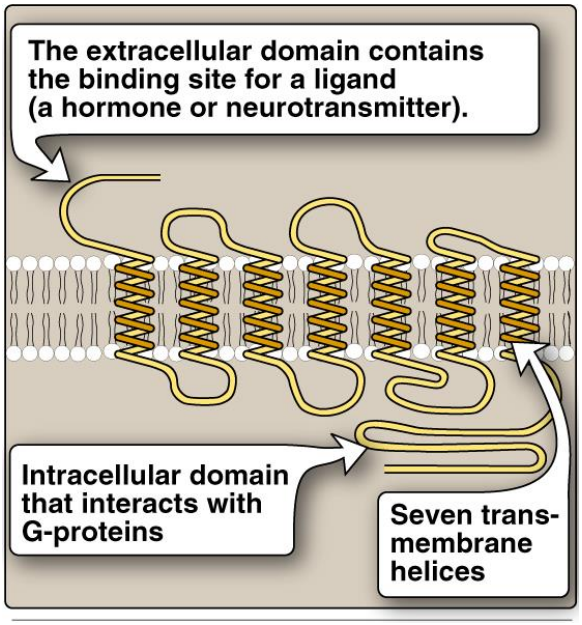




Termination: the aim is to transfer the protein to protein without phosphate again. It has three stages:
Termination A: 'Phosphodiesterase' enzyme breaks a phosphodiester bond of cAMP (secondary messenger) and transfers it to AMP(which is an inactive form). Phosphodiesterase will decrease the amount of cAMP which causes inactivation of protein kinase.
Termination B: When ligand (hormone) is no longer present, the receptor reverts to its resting state. GTP on the α subunit is hydrolyzed (by intrinsic GTPase activity)to GDP, and cAMP is deactivated.

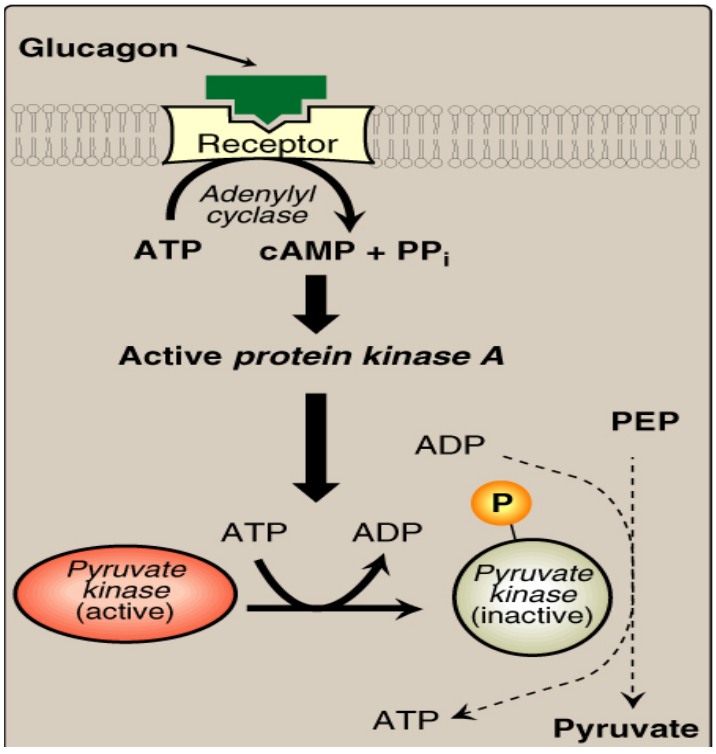
Termination C: hormone or neurotransmitter is removed things get back to rest state.

G-protein coupled membrane preceptor.



The picture illustrates the structure of G-protein.

Pyruvate Kinase Regulation: Covalent Modification



Glucagon binds to receptor in order to increase the number of glucose in the blood stream. Pyruvate is compound from glucose. When the Pyruvate is active, it will decrease the number of glucose (Burning it down). BUT here the enzyme is Glucagon (it wants to increase the rate of the glucose). Glucagon will prevent burning of Pyruvate. So, Glucagon dephosphates Pyruvate and shuts it down.

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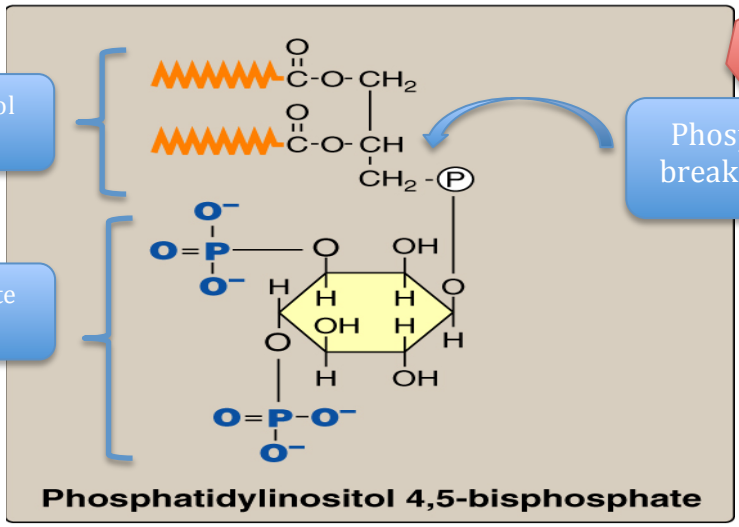
Calcium/Phosphatidylinositol System:

2

After it broke down the two compound are called

Diacylglycerol (DAG)

Inositol Trisphosphate (IP3)



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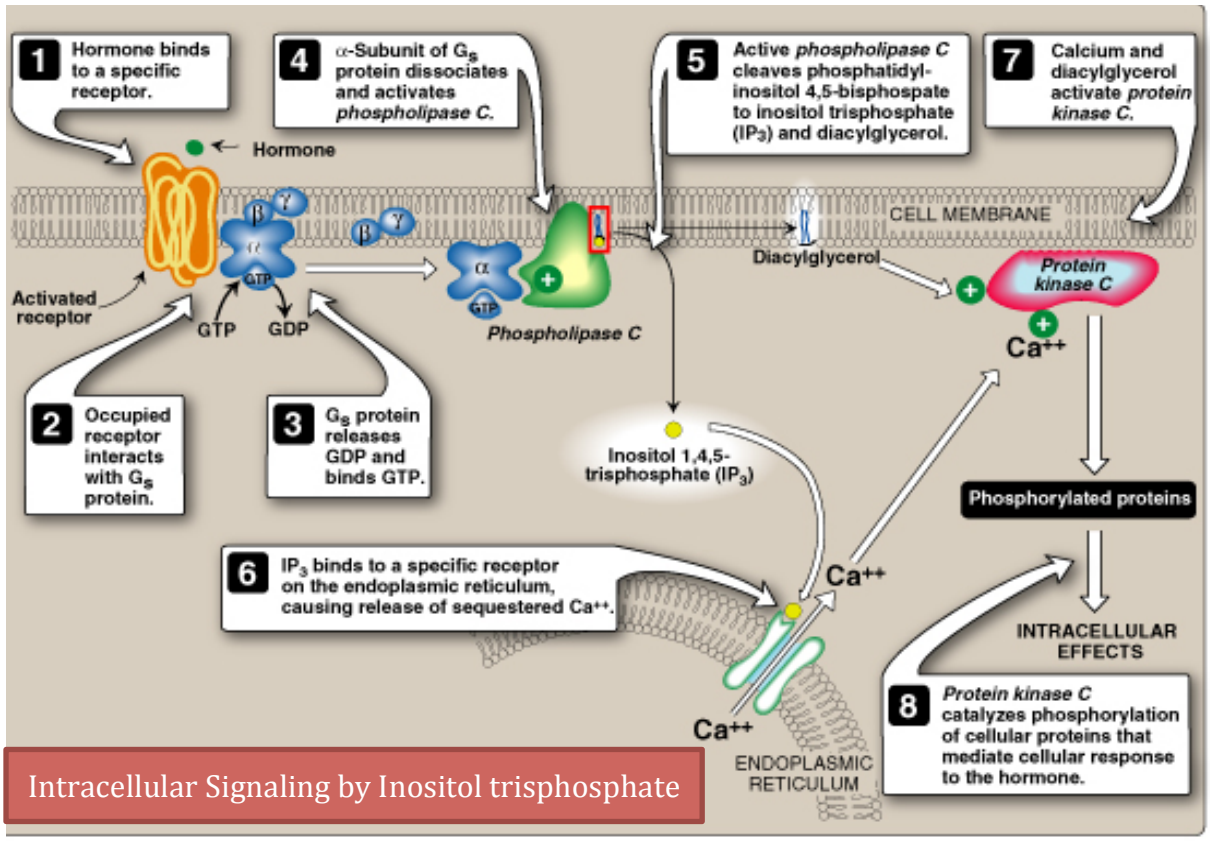
Phospholipase C breaks this bound



Intracellular Signaling by Inositol trisphosphate

Example for this pathway is Antidiuretic hormone (ADH) or Acetylcholine

Name of hormone	Glucagon / epinephrine	Antidiuretic hormone or acetylcholine
Enzyme	Adenylyl cyclase	Phospholipase C
Substrate	ATP	phosphatidylinositol 4 5-bisphosphate
Second messenger	cAMB	diacylglycerol

Signal Amplification: One hormone will stimulate a lot of second messages.

* and if the series is long. There are a lot multilevel inhibition (in pharmacology the drug can inhabit any step of this long series of steps.