SIGNALING

- Different steps in signaling pathways
- The second messenger systems
- Function of signaling pathways for
  - Signal transmission
  - Amplification
- The role signaling pathways in regulation and integration of metabolism

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

By receptors

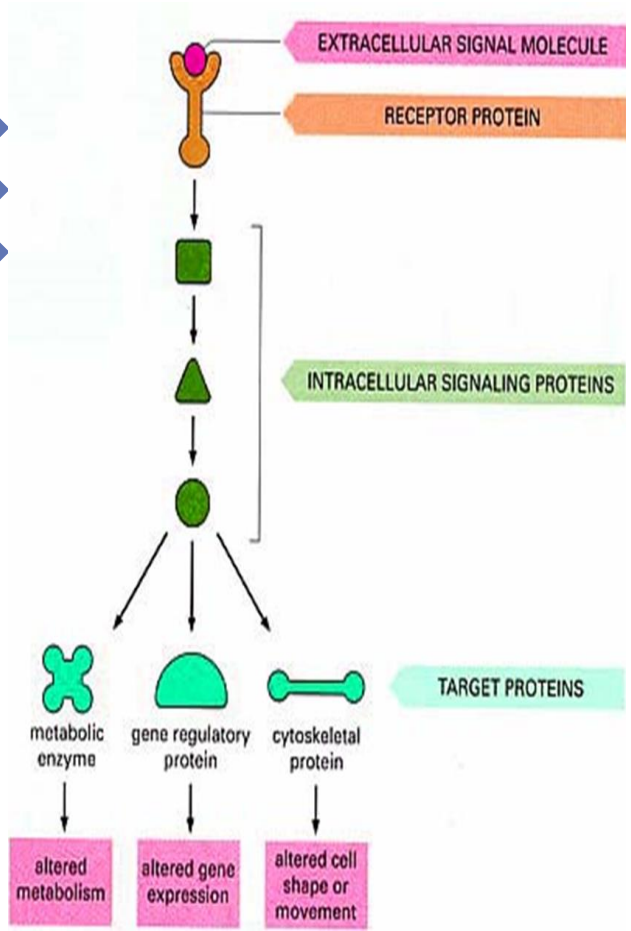
transduction

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

Effect

Modification of cell metabolism and function or the response of the cell

Signaling cascade



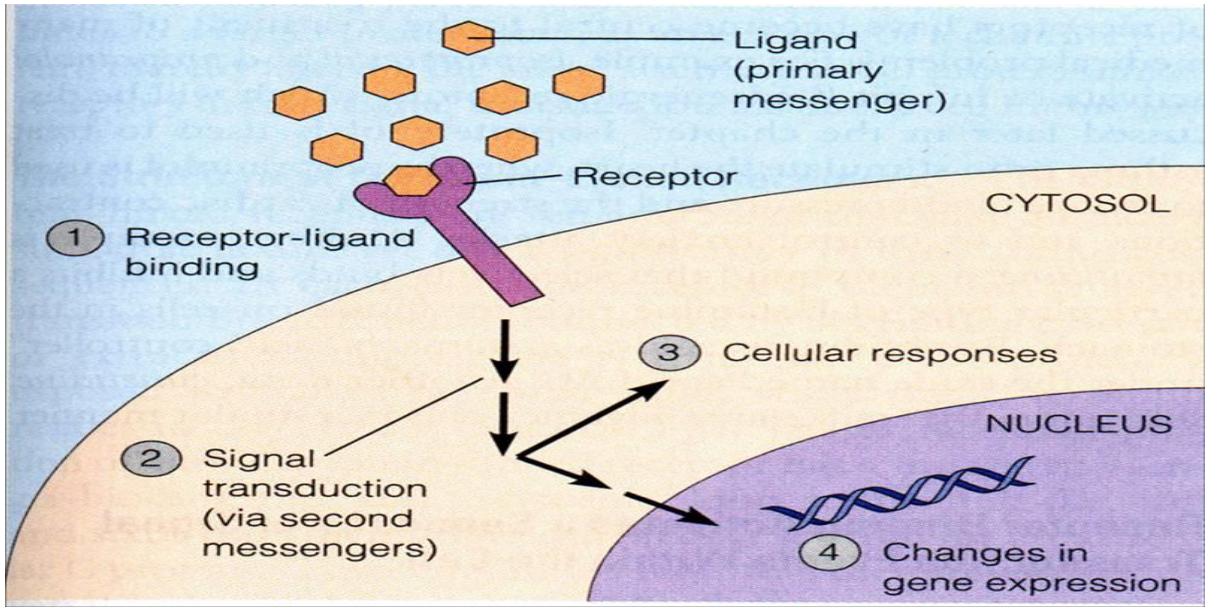
Recognition

1-Performed by receptors

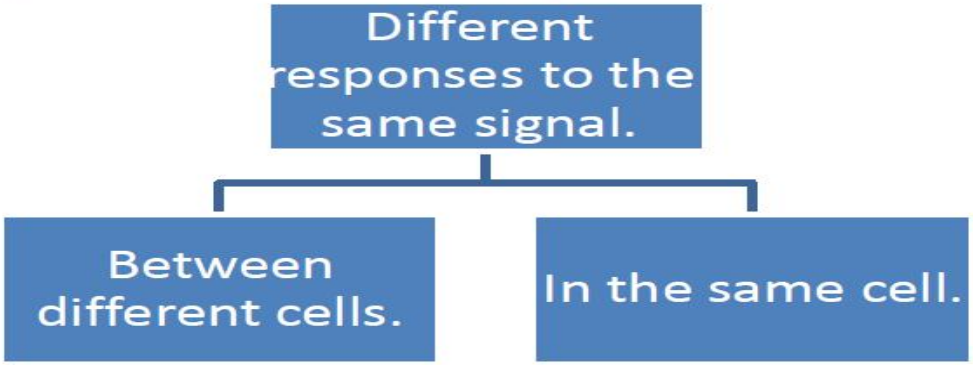
2-Ligand will produce response only in cells that have receptors for this particular ligand

3-Each cell has a specific set of receptors

General signaling pathway



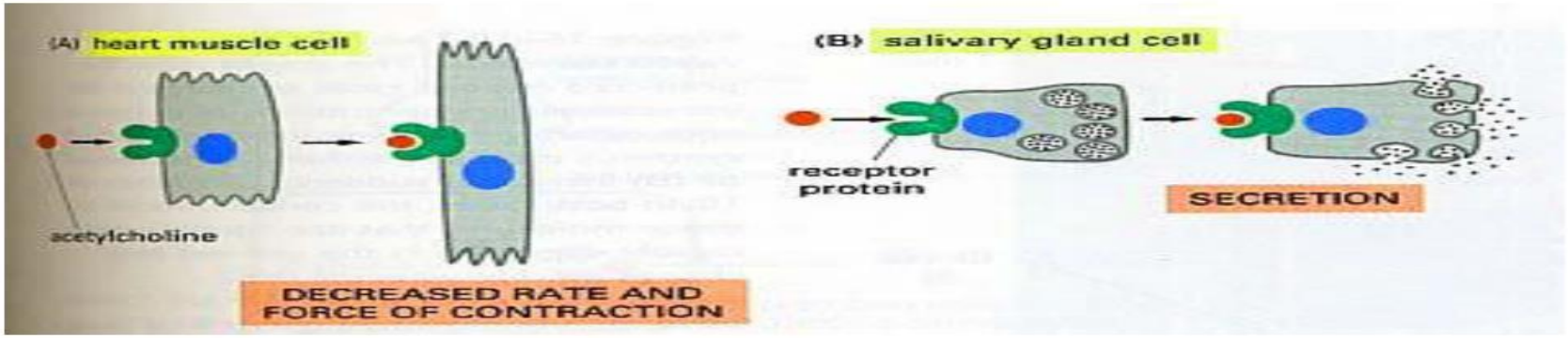
Different Responses to the Same Signaling Molecule



a) Between different cells

Concept: when I give cells the same signaling molecule, I can get different responses from different cells.

Examples of signaling molecules: Hormones (Testosterone, Insulin, etc.) or neurotransmitters such as adrenaline or Acetylcholine.



We can see from this picture that when Acetylcholine (Ach) came to the heart muscle cell, it **decreases** the rate and force of contraction. On the other hand, when the same signal (Ach) goes to salivary glands, it **increases** the secretion.

b) Different responses in one cell.

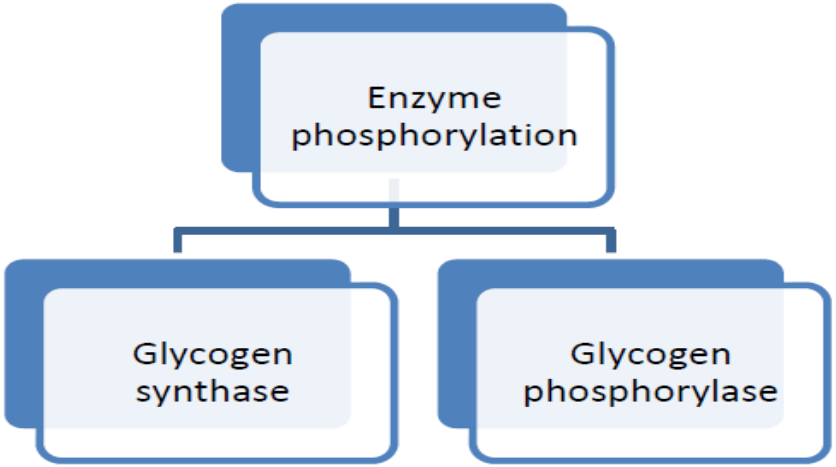
This happens when there are different **pathways** in one cell.

We will put an example to explain this process which happens in our bodies every day inside the liver cells (hepatoctes):

When you are feeling hungry, you blood glucose levels are usually low. This condition is named hypoglycemia (remember hypo means low). After that, a famous hormone called glucagon will be released. This hormone basically releases the stored glycogen from the liver to the blood (opposite to insulin).

What happens after that?

Glucagon has receptors in the hepatocytes. After that, Cyclic AMP (cAMP) is produced. cAMP leads to **enzyme phosphorylation**. We will talk about this process in detail after a while.



a) What happens when glycogen synthase is phosphorylated?

Glycogenesis is inhibited. **Glycogenesis** is the process of glycogen synthesis, it is how glucose is stored.

هذا الكلام منطقي, لأنه عندما تكون جوعان, من الغباء أن يقوم جسمك بتخزين الجلوكوز, ولذلك الكبد يقوم بالعكس بتثبيط هذه العملية.

b) What happens when glycogen phosphorylase is phosphorylated?

Glycogen phosphorylase stimulates **glycogenolysis**; which is the process of breaking down glycogen to glucose.

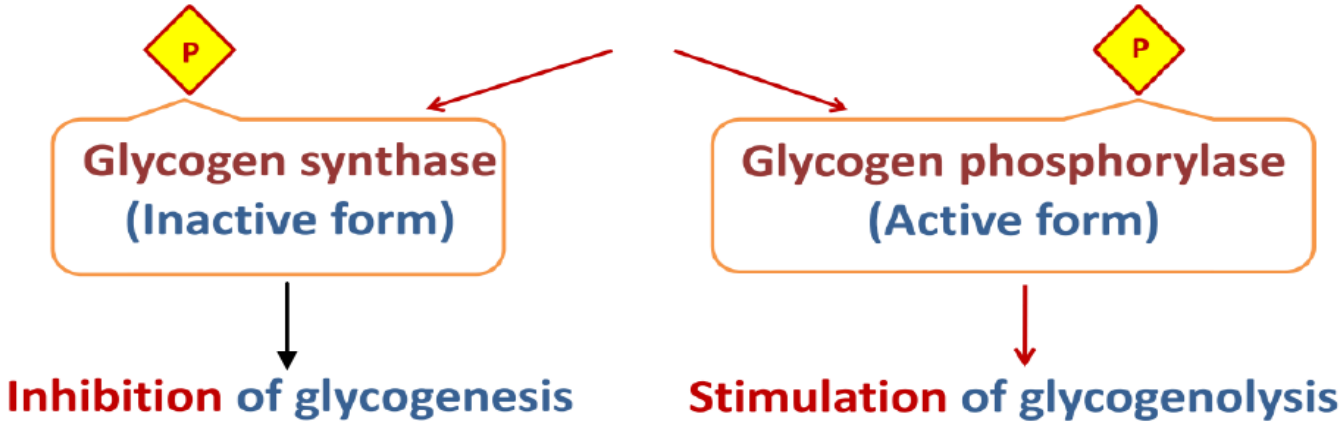
هذا الكلام منطقي لأنك جوعان فالكبد يقوم بتكسير الجلايكوجين إلى جلوكوز في محاولة ضبط مستوى السكر في الدم.

Remember: these two processes happen in the liver at the same time under the effect of the same molecule which is glucagon.

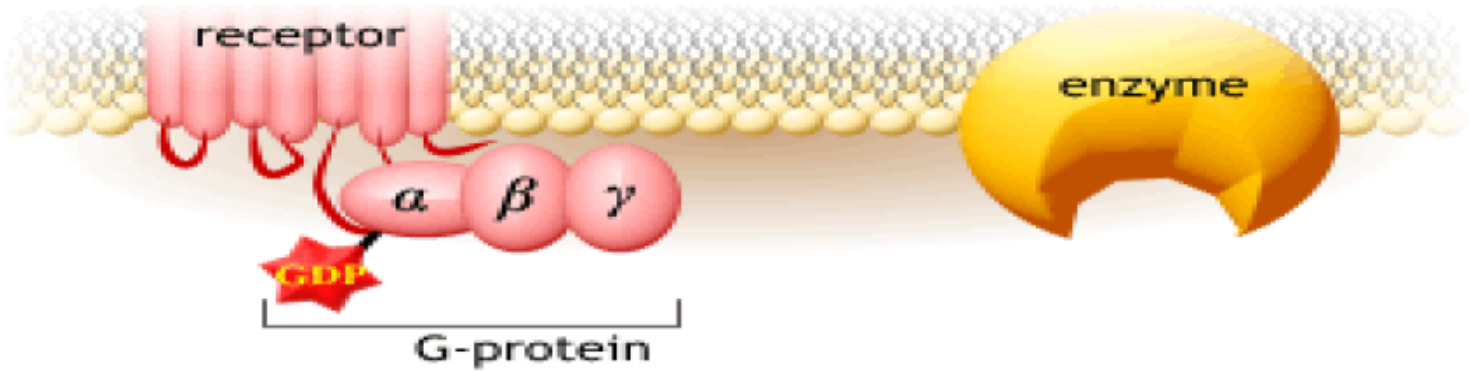
This is the slide the doctor used (I hope it makes sense now)

Different Responses to the Same Signaling Molecule
(B) One Cell but, Different Pathways

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



GTP- Dependent Regulatory Protein (G-Protein)



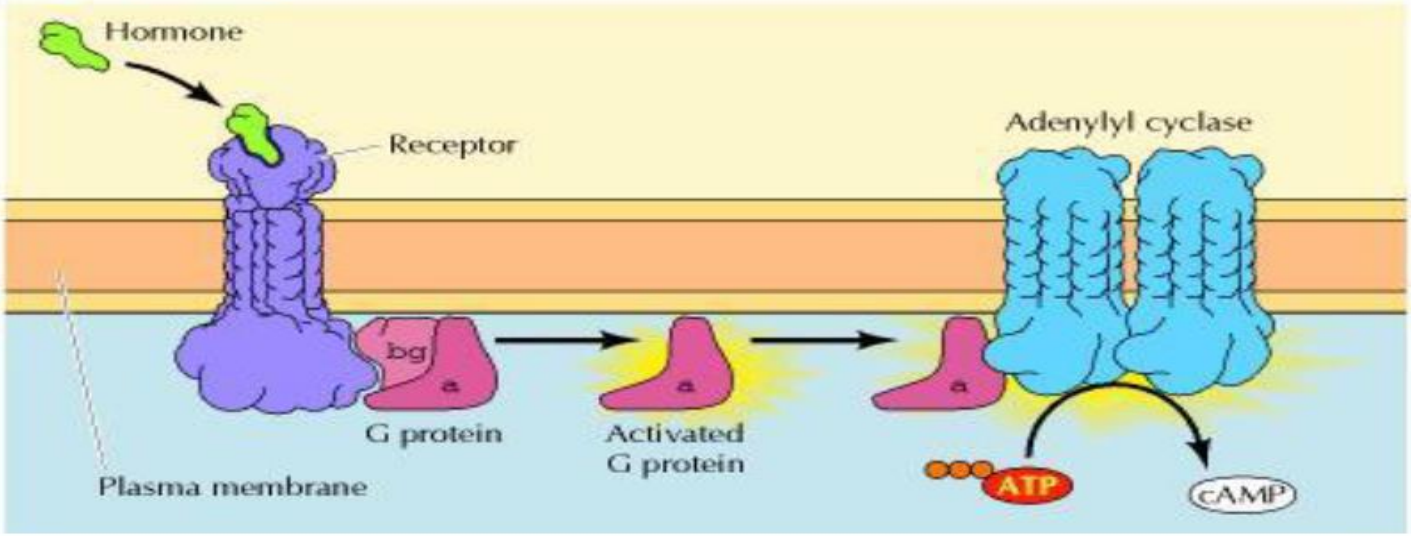
As you can see, the G protein has 3 subunits, that is why is is called **trimeric** protein. In addition, it is bound to the cell membrane.

When the G protein is bind to GDP, in is **inactive**, but when it is bound to GTP is becomes **active**.

As you can see, the alpha subunit is the one that has the GDP group.

يقول المثل الفلوس تغير النفوس. هذا ينطبق على الألفا سبيونيت. بالوضع الطبيعي زي هو موضح بالصورة, يكون الألفا سب يونيت معاها GDP وبالتي هي فقيرة فتحرص على أصدقائها البيتا والجاما سب يونيتس. ولكن عندما تصبح غنية وترتبط بالGTP, فتسحب على أصدقائها وتذهب بحثا عن الفلة (كما سيوضح لاحقا). لذا أخي/ أختي الطالبة, لا تحسب أنه طبائع الموليكيولز الصغيرة مختلف عن طبائع الكثير من البشر: والصديق وقت الضيق.

Adenylyl cyclase



We are coming to the whole process but for now just look at the adenylyl cyclase.

It is a membrane bound enzyme that converts **ATP** to **cAMP**. (we will discuss what cyclic AMP does later.)

Signaling pathways for regulation of metabolism

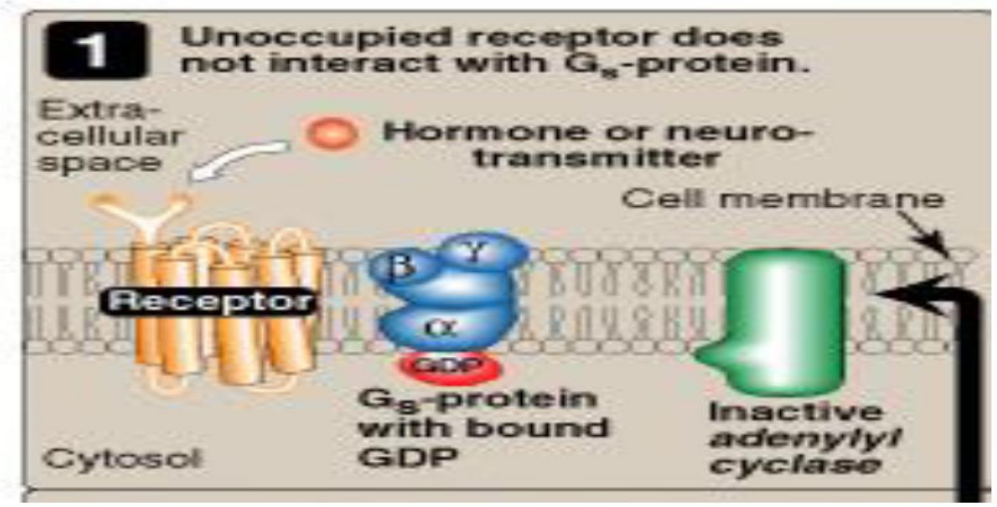
There are two important second messenger systems, Adenylyl cyclase system and phaosphatidylinositol system.

أخي الطالب/ أختي الطالبة, هذا الكلام كله موجود باختصار في لكتشر المحاضرة ولكننا نرى أنه من الأسهل والأجمل والأمتع أن تكتمل الصورة بإضافة بعضا من المعلومات والشرح. فمن حق طالب العلم أن يأخذ المعلومة بشكل واضح, أماطالب الإختبار فنسأل الله له الهداية.

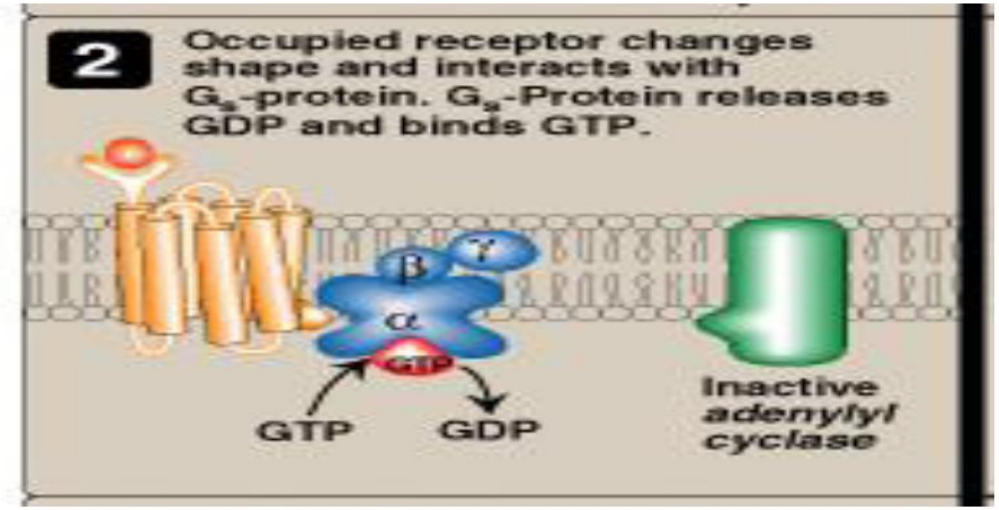
Adenylyl cyclase system:

Usually, the receptor has no signal, therefore there is no action in the cell.

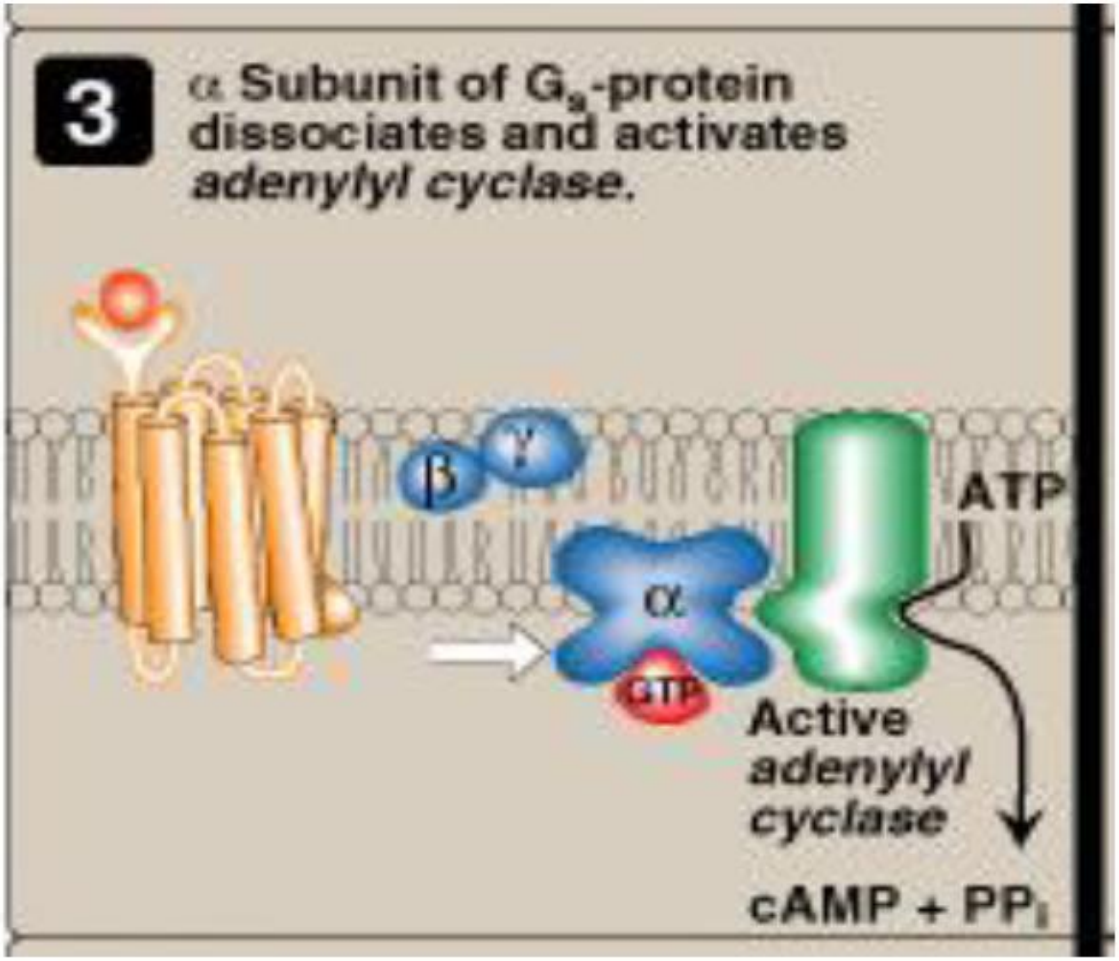
Once the receptor is activated by a signal (hormone or whatever) it is activated.



What happens when it is activated?

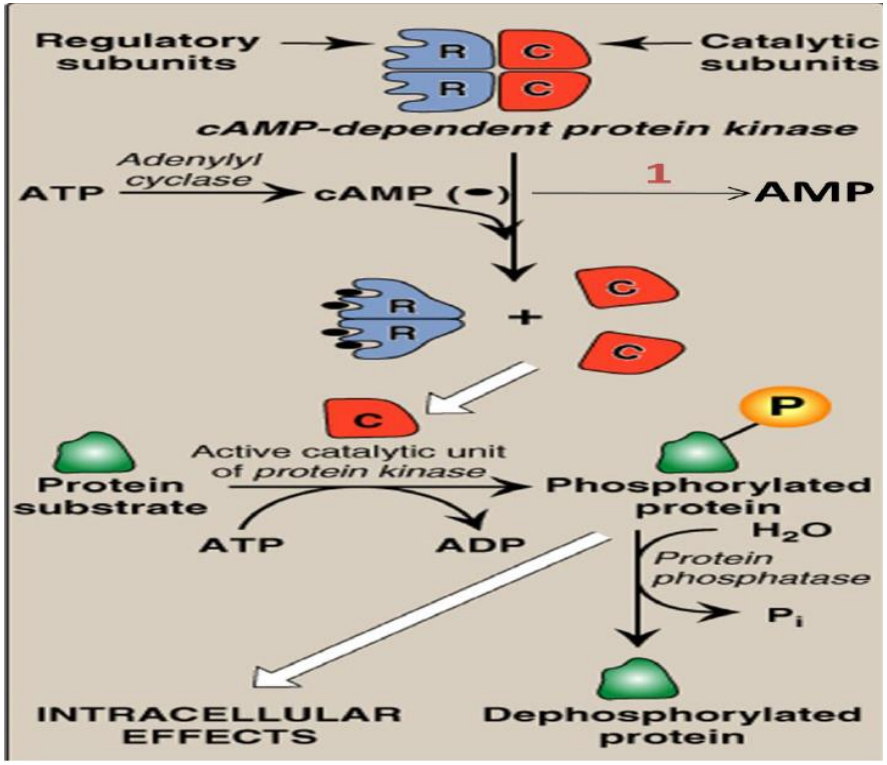


The G protein throws away the GDP & becomes RICH! (with GTP) & activated.



As you can see here, when the alpha subunit became rich it left its old friends, and goes to the adenylyl cyclaseيقولون الأدينيلايل سايكليز راعي فله و ألفا يدور على الفلة عقب ما زادت قروشه

Adenelyl cyclase will then convert ATP to cAMP. This cyclic AMP is said to be a **secondary messenger**; because it goes and creates other changes in the cell.



Look at the photo while you are reading.

cAMP will activate the **cAMP dependent protein kinase**.This dependent protein kinas (DPK) will phosphorylate many enzymes and is responsible for all the changes in the cell.

هذا البروتين دبندنت كاينيز هو اللي بيسوي كل الفرق أو بيسوي الهدف المرجو من الإشارة. مثلا, تذكرون مثال الكبد والجلوكاجون اللي تكلمنا عنه قبل شوي؟ هو اللي بيسوي فوفوريلايشون لهذيك المركبات اللي بتحفز الخلية تصرف جلوكوز وتمنعها من تخزينه.

ولأن ال cAMP هو اللي حفز البروتين كاينيز على فعل هذا الشيء سموه secondary receptor.

How is the signal stopped?

Keep looking at the picture as you read.

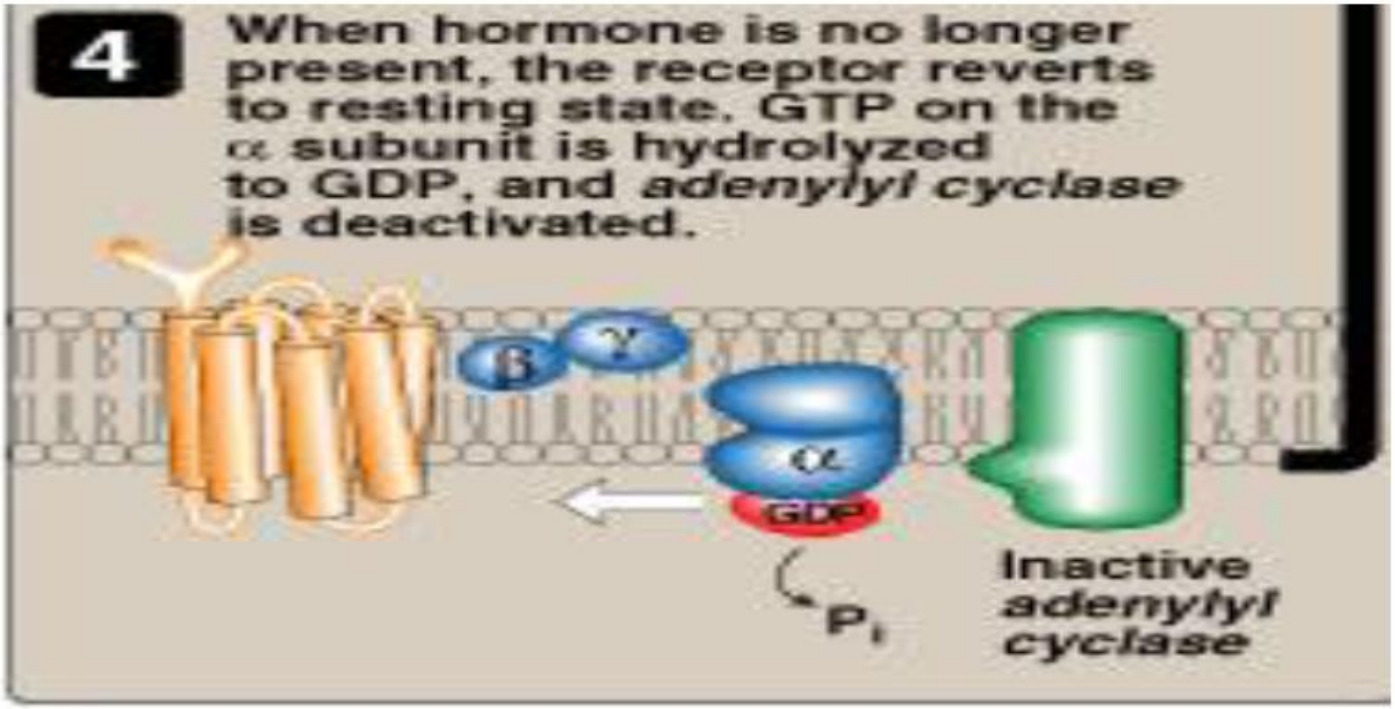
1)Look at **protein phosphatase** (bottom right of the picture). What it does is that it removes the phosphate from the activated protein, making it inactive. So protein phosphatase removes the phosphate and stops the signal.

You see the number 1 on the upper right corner of the picture? This is **Phosphodiesterase**. (we couldn't put it there because there is no space). What it does is that it transforms the cAMP to ATP. By doing this, cAMP isn't there to activate the cAMP dependent protein kinase. And the signal will be stopped.

So, phosphodiesterase lowers cAMP and, as a result, inactivates the cAMP dependent protein kinase.

بإختصار: نستطيع أن نوقف الإشارة أو المحفز بطريقتين. إما من الآخر نجي ونشيل الفوسفات باستخدام ال protein phosphatase. أو من الأول نشيل ال cAMPو نمنعه يسوي إشارة من الأساس.

2)And of course, when the signal (hormone) is no longer there, the GTP will go away from the alpha unit of the G protein. This will make it poor again, and it will go back to its friends in the resting mode.

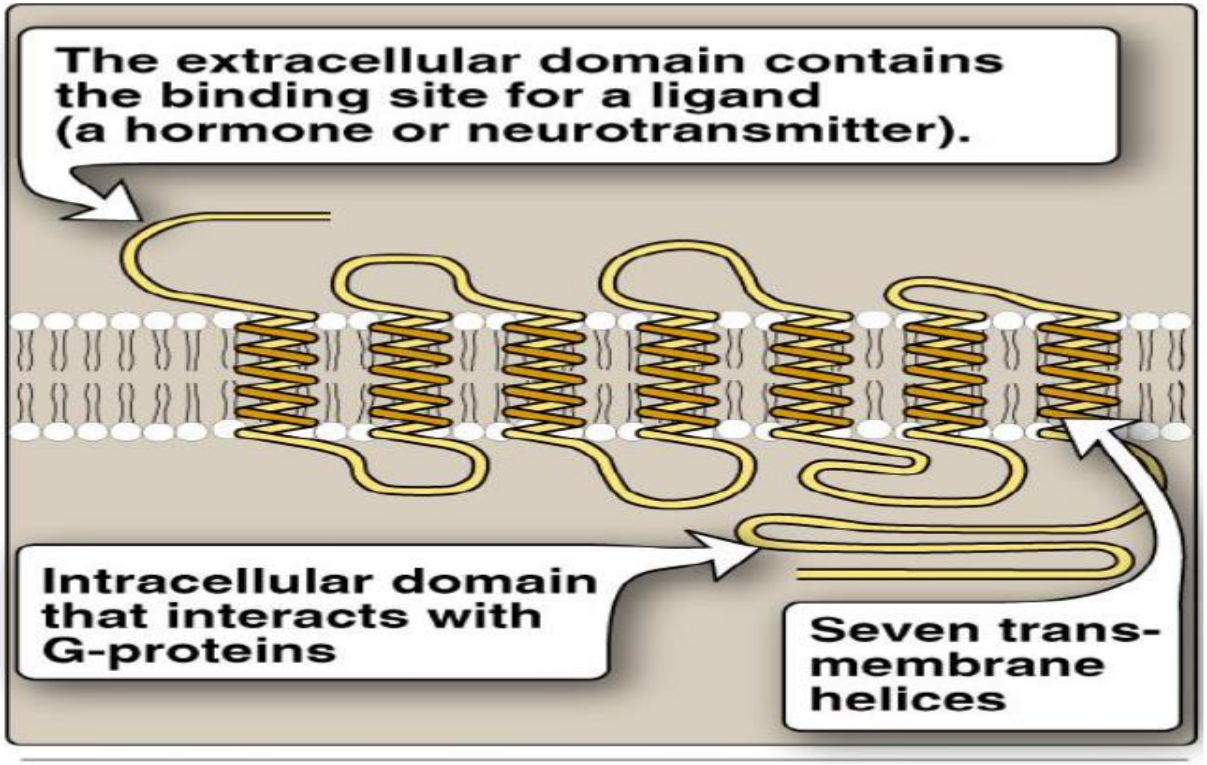


وهنا يتجلى لك أخي وأختي القارئة عظمة التسامح وأهميته. حيث أن البيتا والجاما سامحوا صديقهم القديم ألفا, بعد ما هجرهم, واحتضنوه. فلولا وجود التسامح لبقي الألفا يحفز الخلية ويودينا في داهية! فتذكروا جمال التسامح وخذوا البيتا والقاما سب يونيتس كقدوة حسنة لكم.

G protein coupled membrane receptor

Now that we learned about the G protein and anylyl cyclase, along with the cAMP and what happens after it activates protein kinase, it is the time to as the following question:

What is this receptor that has the G protein?

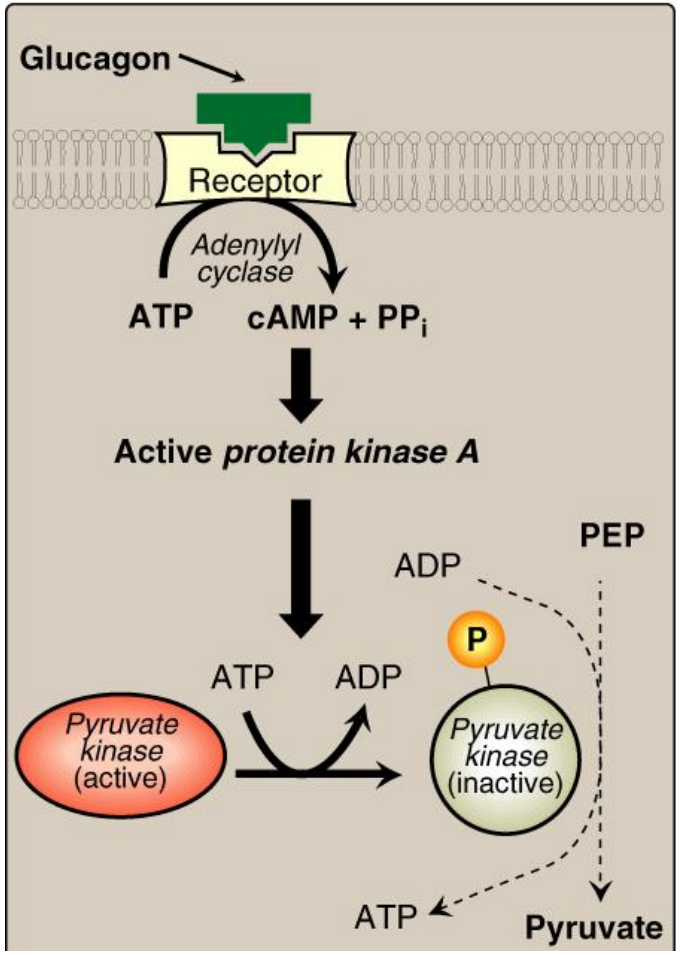


Please look at the picture

This is called a **seven pass receptor** because it crosses the cell membrane seven times.

It has an **outer domain** that receives the signal, and an **intracellular domain** that holds the 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.

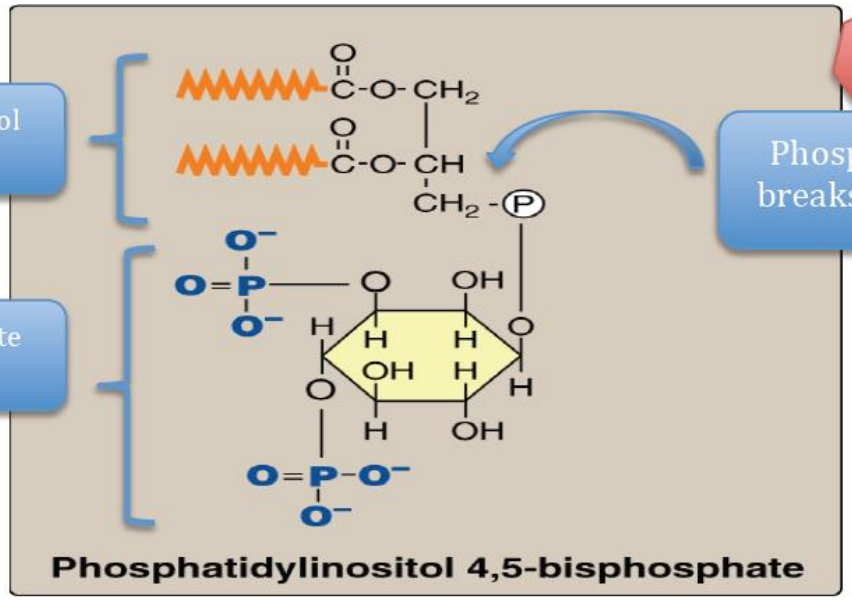
Calcium/Phosphatidylinositol System:

2

After it broke down the two compound are called

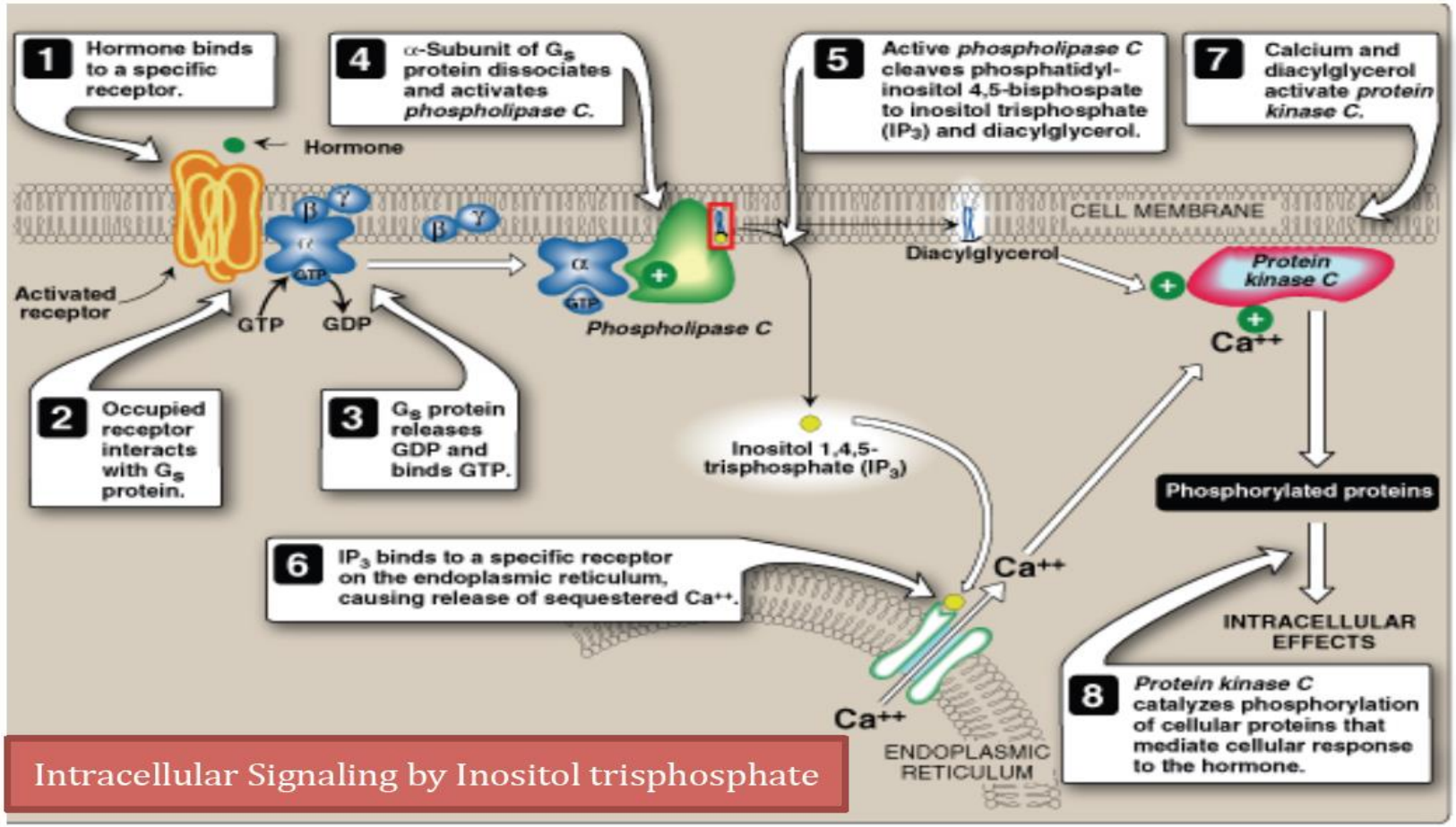
Diacylglycerol (DAG)

Inositol Trisphosphate (IP3)



1

Phospholipase C breaks this bound



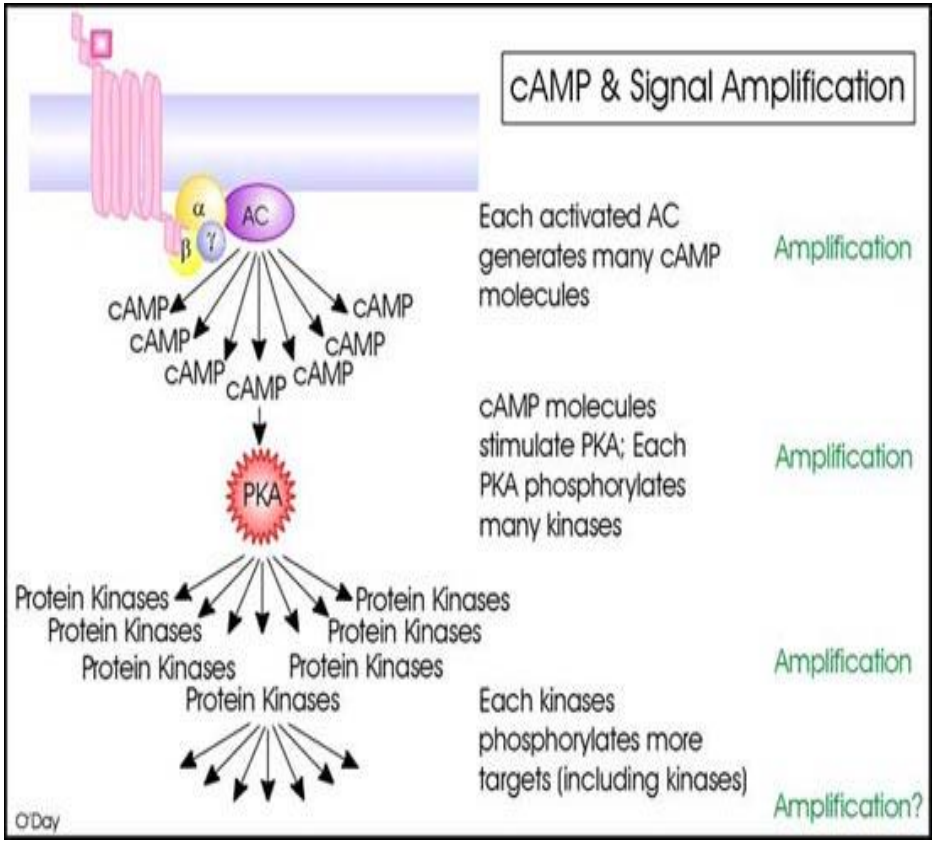
Intracellular Signaling by Inositol trisphosphate

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.



Take home message

Cell signaling allows

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

BIOCHEMISTRY TEAM:

QUIZ:
https://www.examtime.com/en/p/1566616

VIDEOS:
How Hormones Use G-protein Signaling Pathways:
http://www.youtube.com/watch?v=wC2_7Ror3qY
PIP2 secondary message system:
http://www.youtube.com/watch?v=FvPKbogo2pk

- محمد الخراز
- محمد الدماس
- أنس الزهراني
- اسامة عبدالقادر
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- لمى القحطاني
- نجود الرشيد
- حنان محمد
- رنا البراك
- فتون المطيري
- ارياف السلمة
- شيخة الدوسري
- نهى القويز
- مشاعل امين
- جمانة فطاني
- رنا الجنيدل
- لينة الجرف
- سارة المبرك
- أميرة بن زعير
- نوف العريني