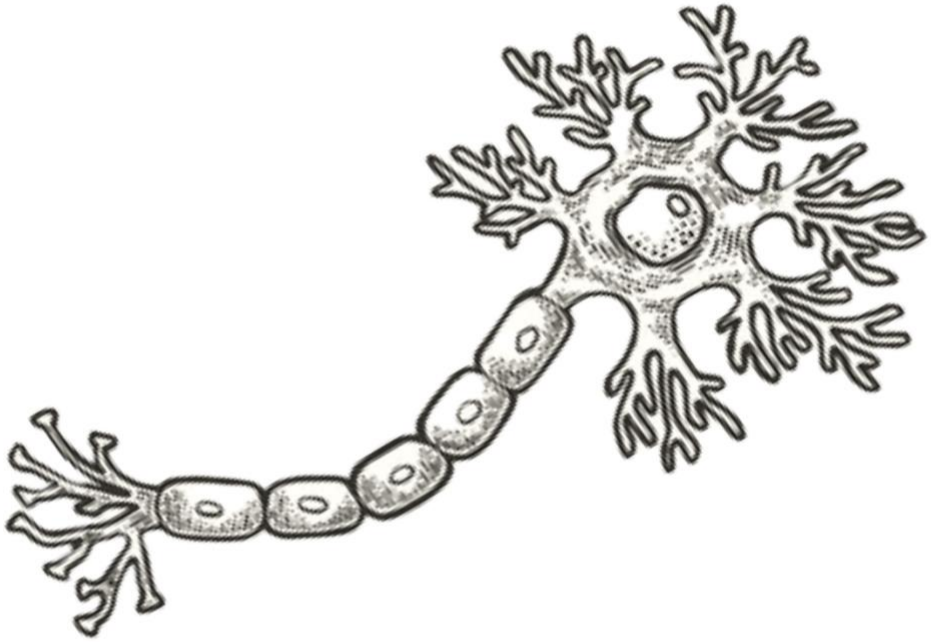
PHYSIOLOGY

SHEET NO.

20

والأخير



WRITTEN BY: Dental Student

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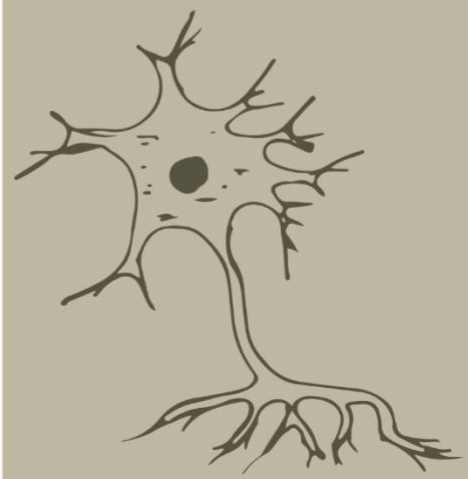
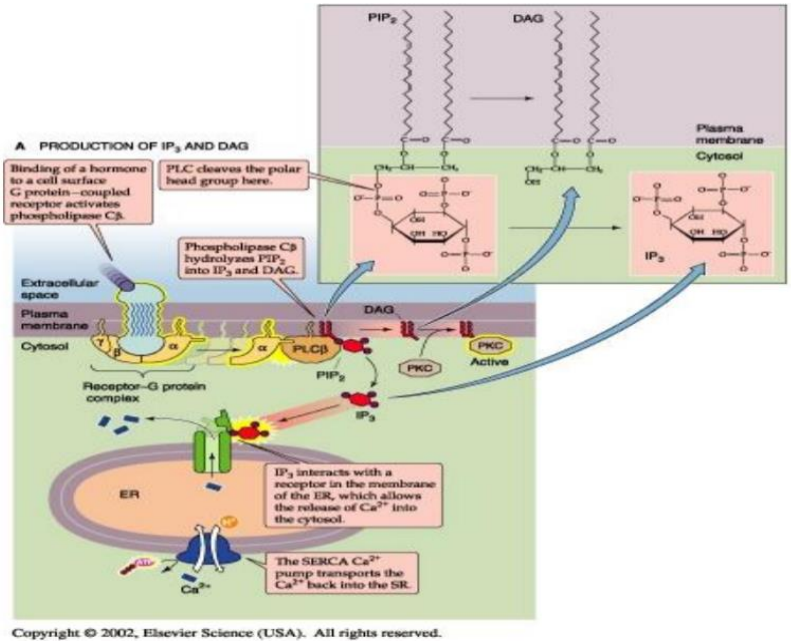


Signal Transduction

Second messengers: Phospholipase-C- Ca^{+2}



ملاحظة(للعناية بنفسيتكم): الشيت مش طويل بس فيه قصص غبية للمساعدة على الحفظ. بالتوفيق

As we can see in the picture above that (G Protein coupled receptor-q) can activate phospholipase Cβ from phospholipids (الموجودة بالغشاء أساسا) which will produce

1- **(DAG)** Diacylglycerol that remains anchored in plasma membrane.
2- IP3 or inositol-triphosphate that released in the cytosol, and it can bind to a receptor for IP3 that is considered as a (gate for Ca^{+2})and open this channel and releasing Ca^{+2} from ER. As a result, the ratio of Ca^{+2} will be higher at the cytosol. This Ca^{+2} increase influences the cell and serves as second messenger.

IP3 with Ca^{+2} with DAG will activate PKC (protein kinase C). Activated PKC will activate and make phosphorylation for other proteins and change its' functions.

And as we said before that Ca^{+2} concentration in the cell has been higher, and it will not stay high for ever, so we have a pump called (**SERCA Ca^{+2} pump)** in the SER will use ATP to pump the Ca^{+2} to the ER and save its natural concentration in the cytosol. NOTE: the natural concentration for Ca^{+2} in the cytosol is within (10^{-7} M).

SERCA:

مبين ليه سموها هيك، أول 3 احرف من مكانها، واخر حرفين شو بتنقل

قصة غبية للمساعدة على الحفظ:

هسا ال (Gp coupled receptor-q) الموجود بالغشاء بروح بفعّل جاره بالغشاء الي اسمه(PLCβ) الي بروح بنشّط شغلتين اللي همه ال DAG اللي بضل ملزّق بال plasma memb وال IP3 اللي بيسرح وبيمرح بالسايتوسول .المهم وهو بسرح وبمرح بروح على channel موجودة على ال ER وبيرتبط فيها وبخليها تشتغل وتطلّع الكالسيوم اللي عندها وبتصير عمالة أطفال وبتشتغل هاي الكالسيوم شغل ال second massenger.
بس هل بعد ما عمل هيك يقعد ويركز؟ لأ طبعا . بروح بسحب حاله وبؤمر الكالسيوم مع ال DAG اللي حكينا عنه قبل انهم بيروحوا بيتحركشوا بال PKC فبيعصّب ال PKR وبصير يمشي بالخلية وبفشّ خلقه بالبروتينات والبروتين اللي ما بعجبه شغلة بغير وظيفته. طبعا ال SER قاعده وبتتفرج كيف انه ولادها الكالسيوم صار تركيزهم بالخلية عالي وما بصير يضل هيك الموضوع للأبد –هو لعب ولاد ضغار كاين!- فالمهم ما بعجبها الوضع وبتطلع بتلم ولادها وبتنادي عليهم وبتضّخهم بمضخة اسمها SERCA لجوّا البيت اللي هو ال ER– طبعا زي ما لاحظتوا جدا الاسم مبتكر ☺ حيث انه اول 3 احرف اسم المكان ، واخر حرفين اسم ولادها اللي بتنقلهم.

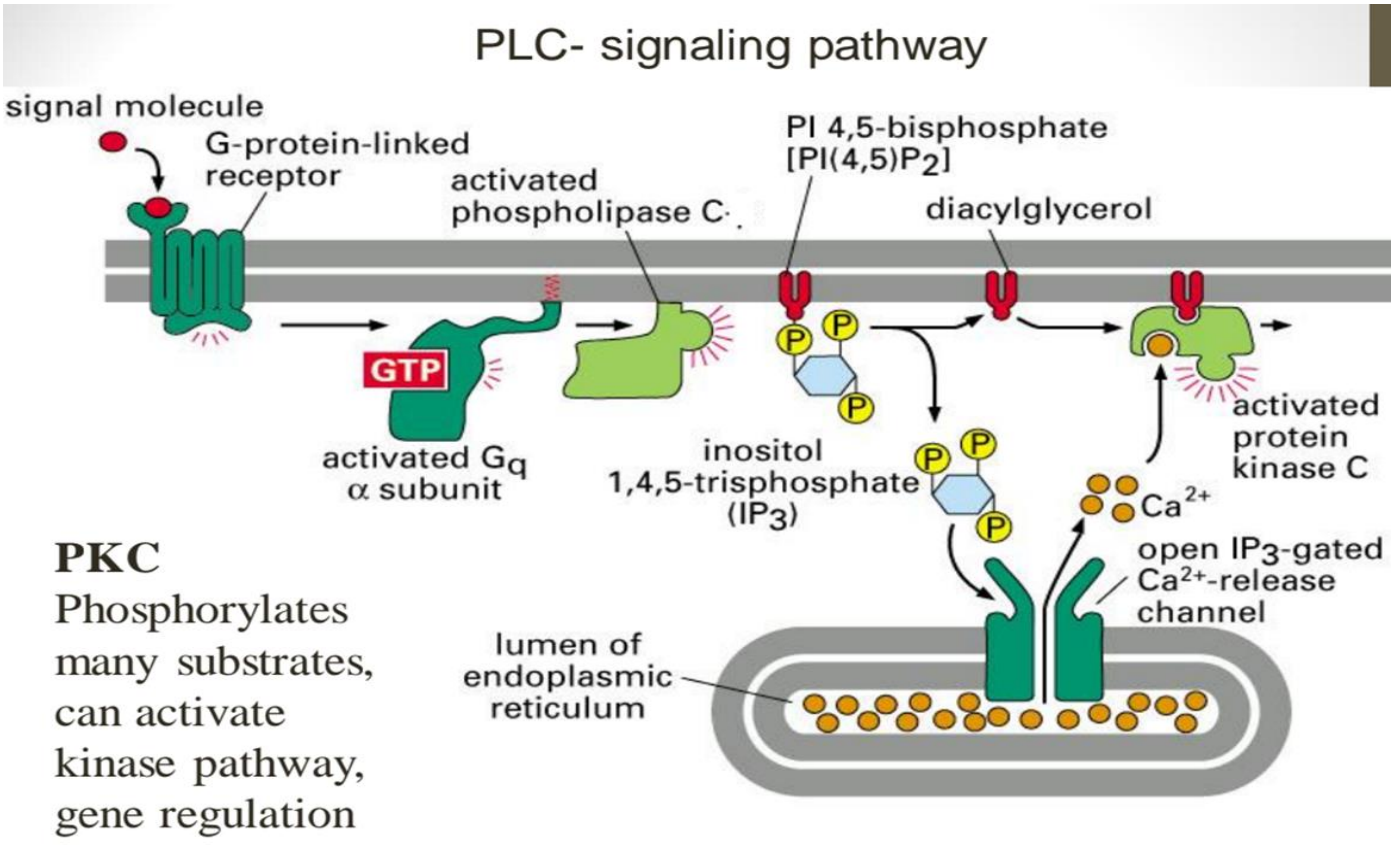
وسلامتكم يلا نكمل بالشيت.

We should know that DAG and IP3 may be:

1- Activated by G protein coupled receptor-Q.
2- Or produced by enzyme linked receptors like phospholipase Cγ which can be activated by enzyme linked receptors.

Phospholipase Cγ is activated by enzyme linked receptors, but β is activated by GP coupled-q receptors.

فهدول الاثنين (β,γ)ممكن ينتج عنهم ال(Ca^{+2} ,DAG,IP3) و بنسميهم سوا (شلّة ال second messenger)



Ca^{+2} is also considered as a 2nd messenger.

Because when the intracellular concentration gets higher will make changes in the cell and transient signaling like: it can bind to PKC with inositol triphosphate activating PKC , also it can bind to specific protein called calmodulin.

When Ca^{+2} binds to calmodulin, the shape of calmodulin will change, as a result it will be able to bind enzymes and activate them. These activated enzymes will be able to phosphorylate other enzymes.

Also, the enzymes that have been activated by the calmodulin are (target types for this process):

1- **Ca^{+2}-Calmodulin dependent kinases (CaM-kinases):** Special enzymes that activated only by calmodulin-Ca^{+2}.
2- **Or other enzymes** like adenylyl cyclase, and phosphodiesterase, causing change in conformation and activation of these proteins.

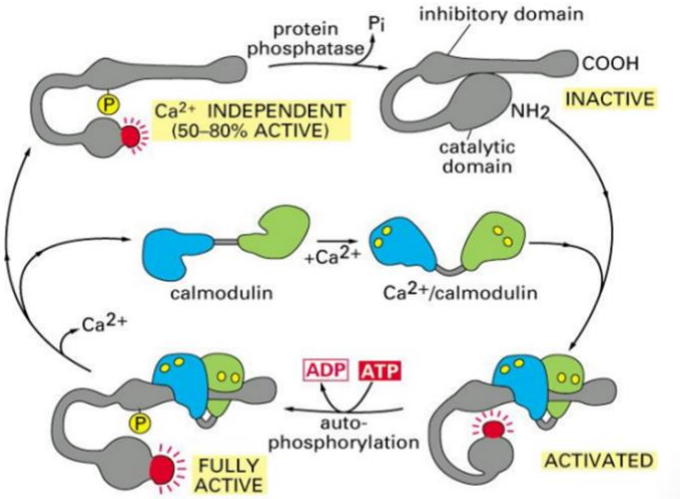


Figure 15–41. Molecular Biology of the Cell, 4th Edition.

At the red picture below, **we can see how the same ligand** (**as example: hormone epinephrine**) **can bind to more than one receptor and can make more than one 2nd messenger**.

The doctor comment on this picture is:

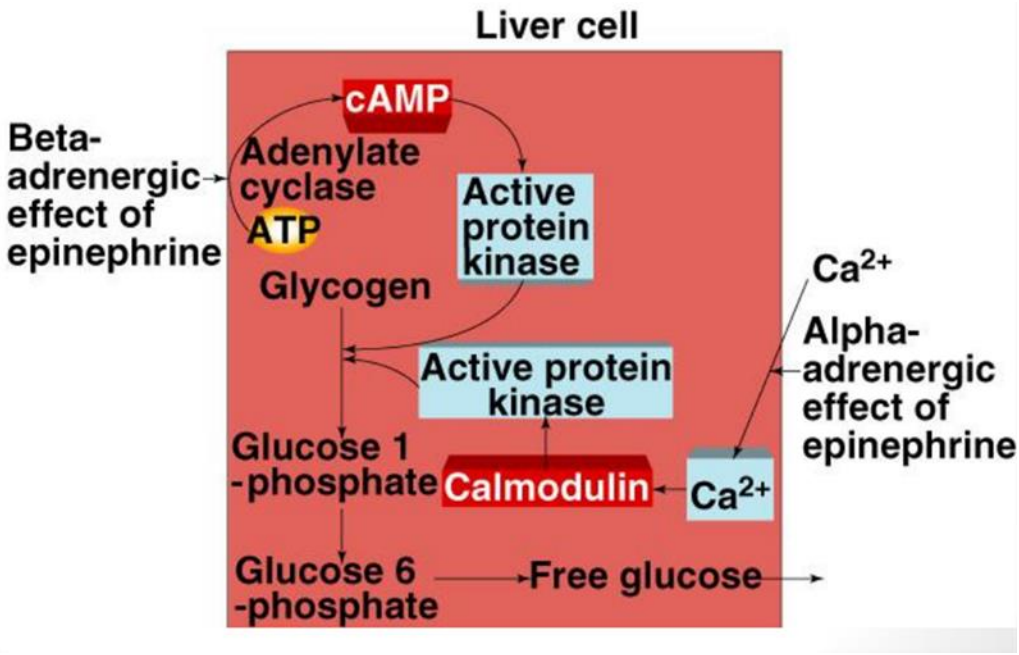
This is the liver cell or hepatocyte. So, the liver cell in the fight or flight condition, the epinephrine will bind to (β or α) adrenergic receptor.

(β) will release cAMP → then active protein kinase.

(α) will release Ca^{+2} →then calmodulin → active protein kinase.

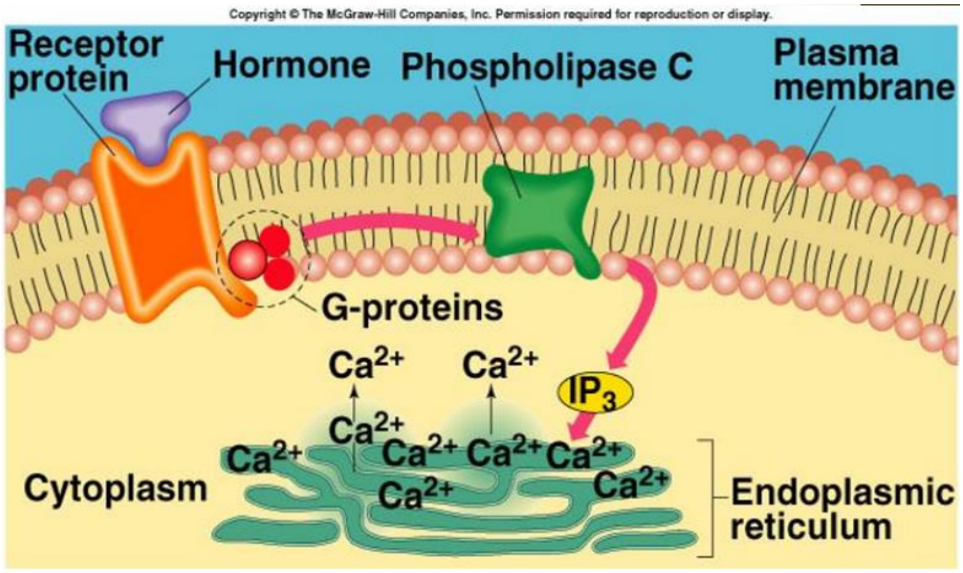
Then the active protein kinases from either will involve in breakdown of Glycogen to **Glucose** which is important for the body to make the response of (fight or flight).

2 second messengers here were the cause of the 2 types of signal receptors that have been activated by epinephrine **in the same cell.**



<u>I'll put now another picture from the slides that talking about (Ca^{+2}- calmodulin) then I'll put the description from slides below it.</u>

<u>هانت يا جماعة هاانت ☺</u>



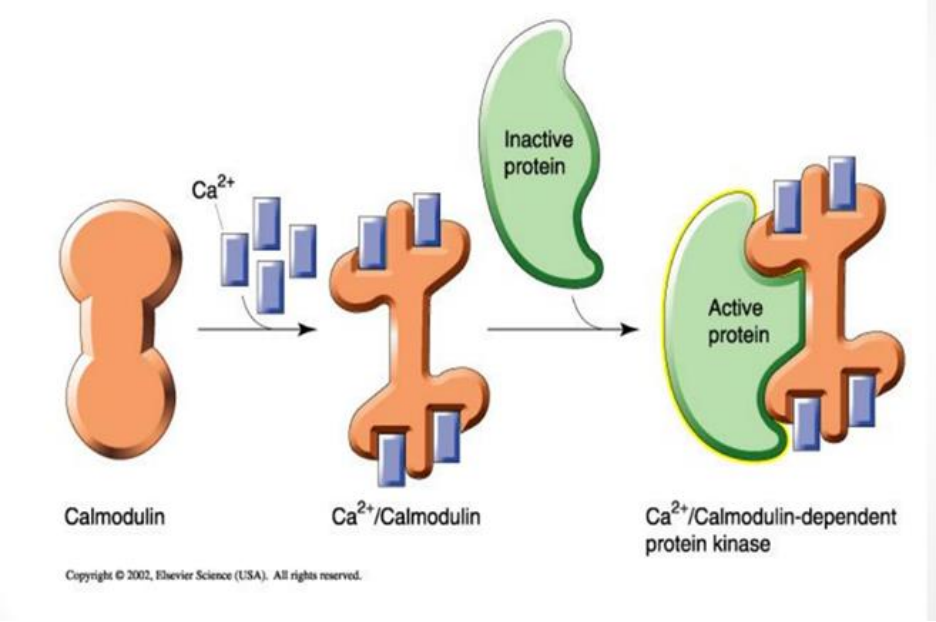
طبعا الخرابيط اللي فوق إذا بدي أساعدك بحفظها فممكن نحاول نربطها انه لما سمع الكبد انه في عملية كرّ وفرّ fight or flight التخم وحس إنه الموضوع ضروري بسرعة يصير

فشغّل أكثر من نوع 2nd messengerواكثر من نوع مستقبل (نوعين همه)عشان يقدر يلحق يعطي الجسم سكر الجلوكوز يا سكر انت يا حلاوة

- Ca^{+2} diffuses into the cytoplasm.
- Ca^{+2} binds to calmodulin.
- Calmodulin activates specific protein kinases enzymes.
- Alters the metabolism of the cell producing the hormone's effects.

حاليًا انظر عزيزي المتابع للأخ Calmodulin كيف بغيّر شكله عشان يقدر يترتبط بالانزيمات لبعدين ويغيّر شكلها وال activity من inactive إلى active عن طريق

Conformational or structural changes



Guanylate cyclase (GC) receptor

-Membrane receptor – ANP (we talked about it in previous lectures in enzymes linked receptors).

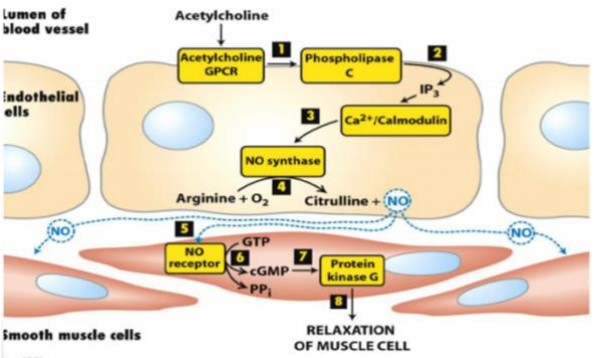
-Soluble receptor – NO, CO → NO: nitric oxide gas

It's hormone, vasodilator, anti-platelet factor and **very important signaling molecule in the body.**

NO Signaling

NO Signaling is in the blood vessels.

Blood vessel (except capillaries) wall consists of 2 layers: endothelial cell layer and smooth muscle cell layer. So, the signaling happen in two layers as:



1- In the endothelial layer: acetylcholine binds to a receptors called **epithelial acetylcholine receptors (αo< GP coupled to q)** → so it activate the phospholipase Cβ → which release Ca^{+2} → then Ca^{+2} will bind to calmodulin → the active Ca^{+2} / calmodulin activate an enzyme called **(NO synthase)** which produce **nitric oxide (NO)** from amino acid called **Arginine** in this equation:

Arginine + O_2 → **Citrulline** + **NO** (gas)

This NO gas will exit the endothelial cells and enter the smooth muscle cells (because its gas and freely enter) to complete signaling.

2- In smooth muscle cells: when the NO enters < it has a receptor which located in the cytosol called **NO receptor** that is guanylyl cyclase, too. So, this receptor will transform **GTP** to **cGMP** + PPi, then the cGMP will bind to a specific kinase called **PKG** → and this kinase will make phosphorylation for proteins that will cause relaxation of the smooth muscle (vasodilation/relaxation for the smooth muscle call). → the thing will increase the blood flow on the tissues.

PIP3 (phosphatidyl inositol triphosphate): another second messenger.

PIP3 is also produced from PIP2, which is in the plasma membrane, which is phosphorylated by kinase called **PI3 kinase**. PI3 kinase will add phosphate on PIP2 to transform it to PIP3 in the membrane.

PIP3 involved in preventing apoptosis (apoptosis inhibition signaling)

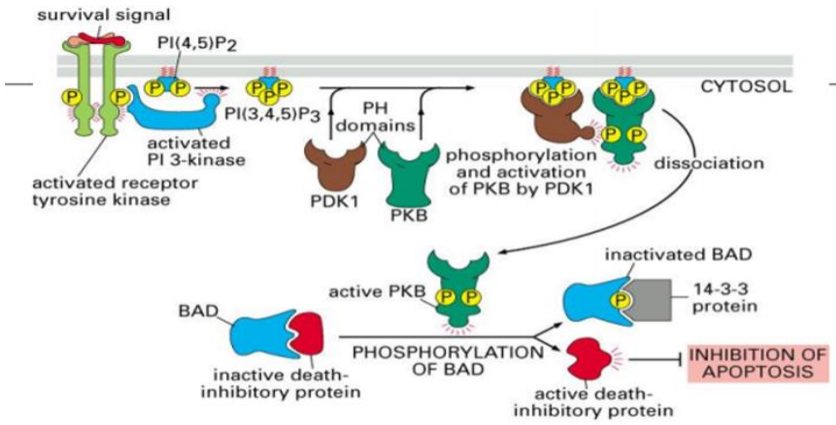


Figure 15–60. Molecular Biology of the Cell, 4th Edition.

Akt signaling functions in the apoptosis but we don't have to know any details we are required to know that the one above is PIP3 which is classified as a 2nd messenger produced by PI3 kinase from the PIP2 then it functions in apoptosis inhibition signaling

Signaling cascades

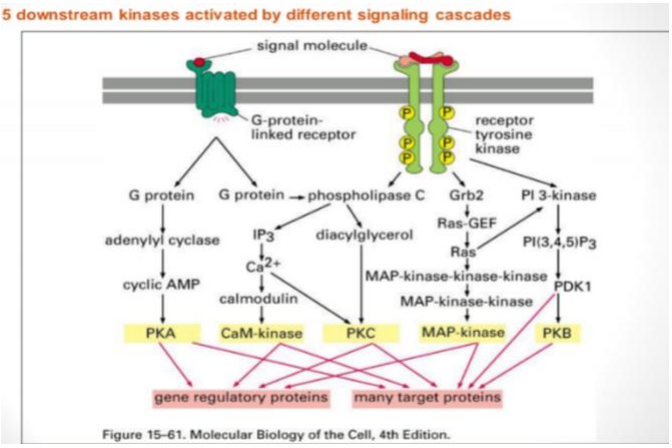
In signaling, we have divergences and convergences, sometimes different receptors activated at the same time, or some enzyme that is activated by certain receptor may also be activated by another receptor, or different signaling pathways may be activated by different enzymes.

Signaling pathways are complex and not working in one direction.

Every signaling will make activation of certain enzymes that will change:

1- Gene expression
2- activity of the enzyme
3- phosphorylation of enzyme

هاي الصورة بس هيك يعني عشان تعرف انه معقد وهي مش للحفظ

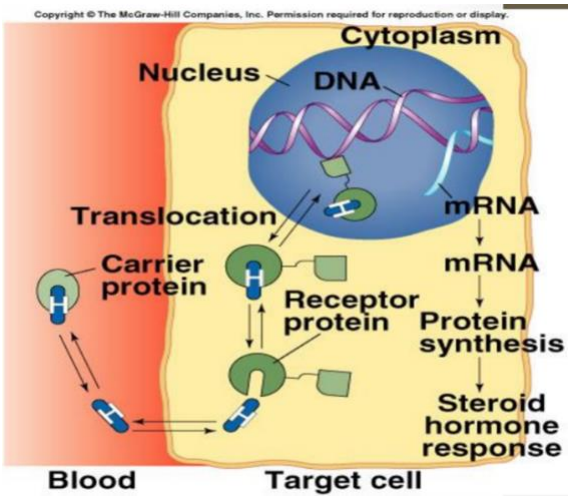


Hormones that bind to nuclear receptor portions

Hormones that can entering the cell (lipophilic hormones):

1-steroids 2- T_3, T_4 (thyroids hormones)

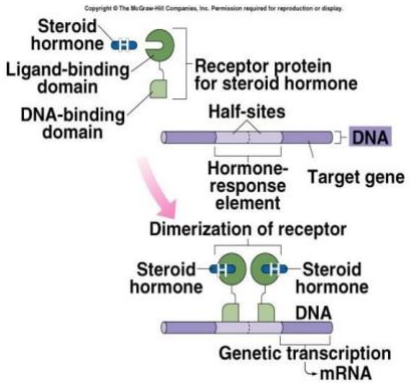
Those hormones in blood → they are attached o plasma carrier proteins because they are not soluble in water (plasma), so they need a carrier. Surely, they are released when they reach the target cell.



When they enter freely, they bind to cytosolic receptor in its binding site→ then become activated → translocation to the nucleus → in the nucleus bind to a DNA binding site because that the receptor has DNA binding site and hormone or ligand binding site → the change in exertion start.

The general mechanism of steroid hormone action

Steroids have a receptor in the cytoplasm and nucleus.



1- In cytoplasm: the steroid hormone will bind with the receptor → translocation to the nucleus.
2- In the nucleus it will bind to a DNA response element that specific to this hormone example:(testosterone will bond to testosterone response element) and so on.

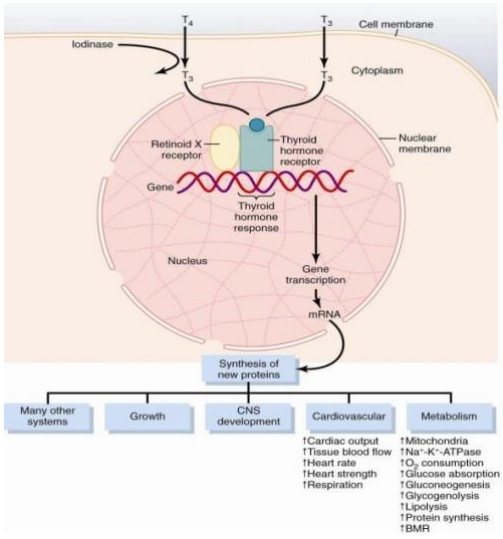
And the receptor will not go alone. Dimerization occurs between the same type of receptor what we call it (homodimers) and they will bind together with 2 halves of the response element.

They bind as homodimers with response elements on the DNA. After this, the gene expression starts. Start with initiation of transcription, and producing proteins that are important for this hormone function. We called it homodimer because it is from the same type, same receptor, same hormone.

Thyroid signaling

In our blood we have T3 and T4 (T4 is the majority).

The receptors are for T3 not for T4, so we need to convert T4 in the plasma membrane to T3. Then the T3 binds with its receptor, The dimerization happens with receptor from another type, this receptor is called RXR receptor (for 9-cis-retinoc acid) / a derived molecule from vitamin A. They dimerize with each other and bind with the two halves of respond element and start to make gene expression. And then the thyroid hormone genes transcription is done.



We can call the dimers here heterodimers because they are not of the same type.

Steroid or thyroid hormones or both if they bind to intracellular receptors, they make gene expression and affect the transcription and translation. The thing that leads to produce proteins, enzymes, receptors, cytoskeleton and change the function of the cell.

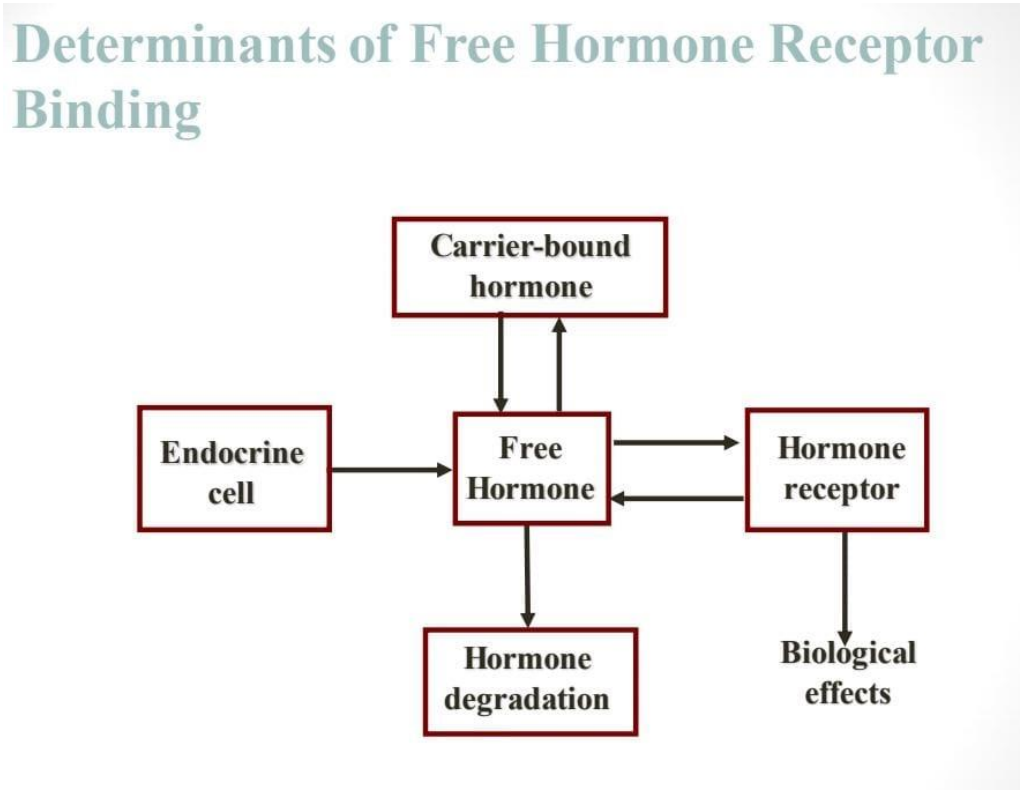
Actions of the Thyroid Hormones have wide and various effects by changing the gene expression. Some of these effects are:

Increase the metabolism of the body and the activity of the cardiovascular function. It has a role in the development and growth of the central nervous system CNS especially in the infancy (babies before they come to this amazing world!)-I wish I were in my mum uterus right now. At least, I will not study and have exams \:

***NOTE:**Thyroid hormones are very important for the development of their CNS for them and for growth.

Now let's talk about

Factors That Affect the free hormone level



A free hormone is the hormone that is not bonded with anything and just waiting to enter the target cell.

1- Endocrine cell release -> the rate of secretion by it will affect the construction of the free hormone.
2- Carrier bound to hormone-> are they available or not.

Remember: Lipophilic that have Carriers

الفكرة هون انه اذا مرتبط بال carrierما رح يكون free hormone

فكل ما زدنا تركيز الهرمون اكثر كلمت صار ازاحة للهرمونات من ال carriersعشان تصير هي freeيعني "تحرر" لذلك بنحكي انه ال free hormone levelمعتمد على انه كم هو مرتبط بالبروتين وكم هو free هاد ال carrier

3- Metabolism of hormone علاقة عكسية

كلما زاد ال metabolism or clearanceللهرمون بقل ال free level

لانه اذا كان مرتبط ببروتين رح تقل ال clearance تبعته لإنه بصير حجمه أكبر وبحميه من انه يروح للكلية وانه يطلع برا الجسم لانه زي ما بنعرف الكلية فيها ثقوب يا عزيزي فالبروتين ما رح يمر منه ،بينما لما يكون اشي lipid solubleومش مرتبط ببروتين (اوبروتين صغير أو peptide)رح يمر في هاي الثقوب ويضل داعس يا معلم ويضل رايح. الاشي اللي بأثر على ال clearanceوما رح يطول حضرته بالجسم .

والشق الثاني من النقطة انه حسب وجود ال metabolic enzymesاللي رح تعمل الي تكسير للهرمون الاشي اللي بأثر على ال levelوعلى العمر تبعه بالجسم (يعني كم رح يضل obind)

وبالأخير ال free hormoneهو اللي رح يرتبط بال receptorسواء كان جوا الخلية او على الغشاء وبعدها بتحدث ال biological efference

والنقاط اللي فوق بتأثر على نسبة ال free hormone وبالتالي بتأثر على ال response

In this table

Correlation of Plasma Half-Life & Metabolic Clearance of Hormones with Degree of Protein Binding

Hormone	Protein binding (%)	Plasma half-life	Metabolic clearance (ml/minute)
Thyroid			
Thyroxine	99.97	6 days	0.7
Triiodothyronine	99.7	1 day	18
Steroids			
Cortisol	94	100 min	140
Testosterone	89	85 min	860
Aldosterone	15	25 min	1100
Proteins			
Thyrotropin	little	50 min	50
Insulin	little	8 min	800
Antidiuretic hormone	little	8 min	600

عليك عزيزي/تي الدكتور/ة انه ما تحفظ الأرقام, لكن لازم تعرف مين الارتباط تبعهم عالي ومين قليل وتعرف تقارن بينهم مين الارتباط تبعه اعلى من الثاني وهكذا وتحفظ الأمثلة (ربك بعين ☺)

This table talks about the relationship between binding of the hormone to proteins in blood/plasma and the half-life.

Let's talk about it:

The thyroids (T3,T4) bind a lot (look at the percentage), as a result they have a high half-life (in days).

But if we look at the proteins

اه هون في ملاحظة غبية انه يعني جماعة البروتين مش رح يكونوا مرتبطين ببروتين لانهم اصلا بروتين ! :)

وطبعا كالعادة سهل انه يصير الهم clearance لما يصير filtration in the kidney

لانهم not protected لذلك اذا تطلعنا على ال half life تبعتهم بنلاقيها قليلة (دقائق)

Like the (Thyrotropin, insulin, Antidiuretic hormone -ADH-) which have a very very little binding or not having binding at all (Free).

بالمختصر عندك علاقة طردية بين ال binding وال half-life

وال Clearance بكون عكسي مع ال half-life and binding

If we compare Cortisol with Testosterone or Aldosterone, you will find out that cortisol and Testosterone have a longer half time because they are bonded more than aldosterone.

Another table here.

الدكتورة هون حكت انه الجدول مو مطلوب بس قرات النوع الثاني و اختصاراته فكونوا على علم فيه اضمن الكم

1-Specific transport proteins: بروتينات منقرفة بس بترتبط بهرمونات معينة

2-Nonspecific transport proteins: بنت عالم وناس وبترتبط بأي هرمون

Like albumin that bind with any steroid hormone for example

Circulating Transport Proteins

Transport Protein	Principle Hormone Transported
Specific	
Corticosteroid binding globulin (CBG, transcortin)	Cortisol, aldosterone
Thyroxine binding globulin (TBG)	Thyroxine, triiodothyronine
Sex hormone-binding globulin (SHBG)	Testosterone, estrogen
Nonspecific	
Albumin	Most steroids, thyroxine, triiodothyronine
Transthyretin (prealbumin)	Thyroxine, some steroids

The last thing in this course

We know now that the hormone is released, it's bind to receptor, then it induces signaling pathways, and do functions and activities.

So…. What releases that hormone? Or What is the mechanism that facilitate or mediate the release of hormones?

It's **Another signaling.** As usual it's another gland that releases a hormone that stimulates the release of the other hormone.

As example: the **Hypothalamus** will release hormones called **releasing hormones, (**which considered as the link between the nervous and Endocrine systems). And when the (releasing hormone) is released, it goes to work on the gland that it supposed to release the hormone that we need and do a signaling for it.

By:

Ex: Hypothalamus released the GnRH (Gonadotropin releasing hormone) in the blood circulation (by the capillaries) and it arrived the **anterior pituitary / factor system of the anterior loop of the pituitary.** Here it will bind with a receptor in the anterior pituitary gland/glandular cells.

This receptor is G protein coupled receptor-q that will do release for (DAG, IP3 and Ca^{+2}) الشلة اللي حكينا عنها في أول هالمحاضرة

Ca^{+2} binds to that vesicles that contain (FSH or LH) hormones and Ca^{+2} will release those hormones from the anterior pituitary by exocytosis.

Now **FSH and LH** when they go to the target cell (testes or ovary as an example) they will bind to their receptors their like: G protein coupled receptors and they will increase cAMP in follicular cells or whatever in the target.

بالمختصر كان عندي هرمون او factorمعين ادى لل

stimulation for secreting cell or for the gland to do the release

كل هرمون اله قصة بس احنا هاد المثال المطلوب منا فقط الله يعطينا ألف ألف ألف عافية

The end of this sheet #20, subject and the **Semester**

أي حد وصل لهون أنا بحب اقلك إنه انت انسان رائع ومكافح

الفصل هاد ما كان سهل بس هينا بحمد ربنا وكرمه قدرنا نخلصه

وكلجنة شيتات بنعتذر عن أي غلط وسامحونا اذا قصرنا بيوم من الأيام، حاولنا نعمل كل اللي قدرنا عليه فان احسننا فمن الله وان أسأنا فمن نفسنا والشيطان

اذكروا أي شخص ساهم بنجاح الشيتات بدعوة، الله يوفقكم جميعا

♡فالكم العلامات العالية يا تيجان ♡