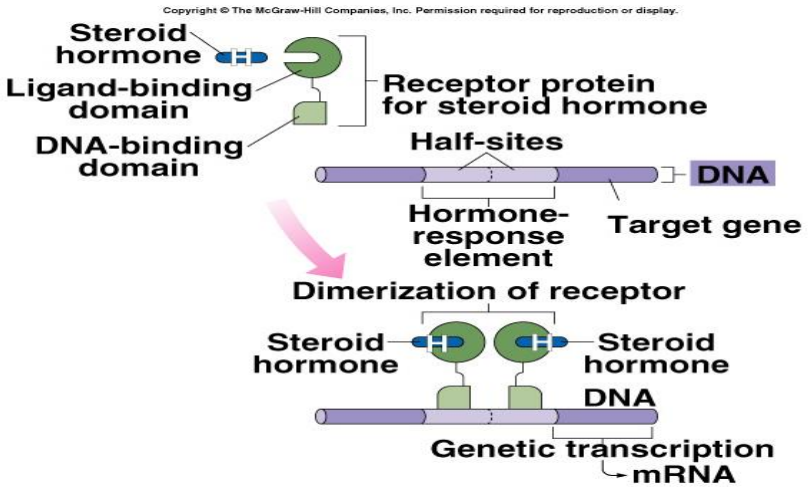
Receptors function and signal transduction

General types of hormone receptors :

Lipid soluble hormone receptors :

- **Steroids receptors** (lipid soluble hormone receptors) :
* They are intracellular receptors
* They have two binding sites:
  - one binding site for the hormone
  - The other binding site for the DNA.
* These hormone receptors have to dimerize before acting
* When they bind to the DNA site, they bind to a specific area called hormone response element "HRE" , that has a nearby area for gene transcription → the result is new protein formation → ((which is the cell response)).



** The hormones USUALLY travel in the plasma in the bound form (mo8eeden) because they are lipid soluble , but when they act on targets , they act as FREE >> means >> they are secreted in the free state , then they are circulated as carrier >> then they go to the intracellular receptors (boundary receptors) after unbound from their carrier >> They work as free here when they bound to their receptors

خطوة التحرر من الناقل العصبي

Done by Nour Al-Deen Abu Zant Corrected by Ala'a Shaban & Shatha Tailakh

The amount of free is a balance how much is secreted , how much is going to be degraded , how much is bound. If there is more free they go to the bound form, if there is a less free they dissociate from the bound to the free form

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Half life

- **Half Life** for these hormones is directly proportional to its percentage of bound (if the percentage of bound is less >> means their half life is shorter and vice versa.

** **Note** : we should remember this term
" Metabolic Clearance Rate " that means :
((how much is being cleared from this hormone)) or
The volume of biological fluid completely cleared of drug metabolites as measured in unit time .

- Case -1- if the bound hormone percentage is high >>> the half life is high and the metabolic clearance is low ..
Eg : Thyroid hormones .. very high percentage of bound >> they have long half life and the metabolic clearance is low.

- Case -2- : if the bound hormone percentage is low >> the half life is low and therefore the metabolic clearance is high .
eg : the steroids hormones have less percentage of bound >> they have less half life >> they have more metabolic clearance .

Eg : proteins are water soluble (they don't need to be bounded) they have very little percentage of bound >> low half life >> the metabolic clearance is very high such as : the insulin which has less bound and therefore its half life is less and (this is important) its metabolic clearance is high (therefore, insulin is given frequently to the patient.. that we give the diabetic patients 2-3 doses per day).

إنّ التحلّل السريع لهرمون الإنسولين يجعلنا نكرر عدد الجرعات اليومية لمريض السكري نظرا لسرعة تحلّله

The transporters of hormones are classified into :

1) Specific: Corticosteroid binding globulin (CBG, transcortin) - Thyroxin binding globulin (TBG) -Sex hormone-binding globulin

2) Non-specific: means that they can bind too many hormones not just one type of hormones, eg. Albumin - Transthyretin (prealbumin)

** These transporters are usually formed from the cells in the nearby from where the hormones are formed (for example: the sex hormones are formed in the sex glands, thyroid hormones are formed in the thyroid gland)

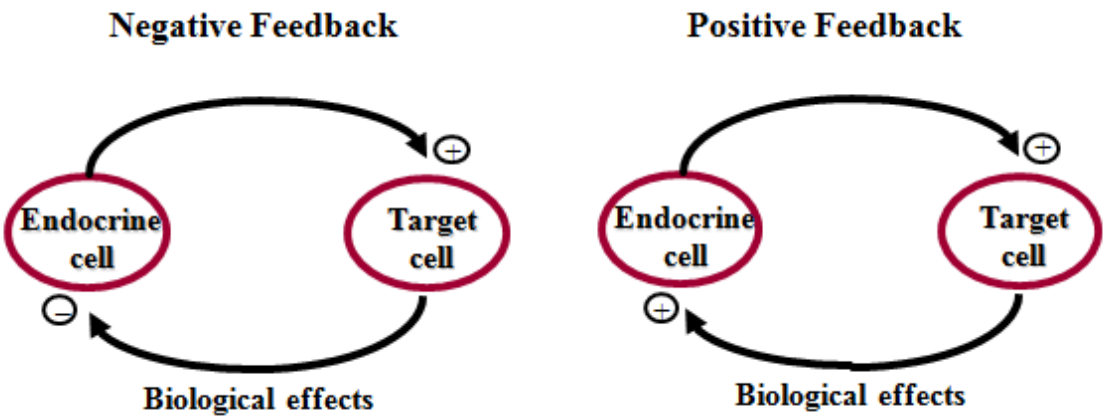
Feedback mechanisms

The Last paragraph in the last sheet was about the feedback mechanism :

1) The positive feedback : *the response is in the same direction of the stimulus* .
the endocrine cells secrete the hormone and the hormone has a positive action on the target cell and the target cell will make positive action on the endocrine cell.
*Stimulus increases→ response increases.

** Increase in the hormone → increase in the biological effect.
** This is abnormal, except for some cases which are considered normal.

2) The negative feedback : increase the secretion of the hormone → goes to the target cell → there is more biological effect → this effect suppress the endocrine gland secretion
increase in the secretion of hormone when endocrine cells secrete a hormone and the hormone increases the response, the increase in the response itself will cause suppression in the endocrine cell activity.
* Stimulus increase→ response decrease.
** this is normal.



This point was repeated ! I know ! But (here we should put in our mind this result from the last paragraph : the response in positive feedback is in the same direction of the stimulus) therefore , we talked that (the increasing of stimulus means the increasing of response)

Remember :

In the receptors of the lipid soluble hormones , we find 2 binding domains (sites) :

1) hormone binding site 2) DNA binding site

* We talked about general types of receptors (lipid soluble & water soluble)

Other kinds of receptors : Enzyme-linked receptors

The leptin hormone and its mechanism

Leptin is :
- a peptide hormone
- it is secreted from the lipid cells
- and it may be the reason for the obesity because it affects on the Appetite .

** How does this hormone works ?! (water soluble hormone)

since its water soluble (it's a peptide), it has receptors on the target cell's membrane when the leptin bind to its receptor (the receptor itself is an enzyme- linked receptor) >> it activates kinase activity in the receptor >> the kinase or janus kinase phosphorylates the substrate (signal transducer and activator of transcription "stat3") or sometimes this janus kinase or just another kinase activates enzymes >> then this "stat3" goes to the nucleus and activates transcription of certain genes (which means formation of proteins)

→ so either directly (through activation of enzymes) or indirectly (through formation of proteins)they have their physiological effect.

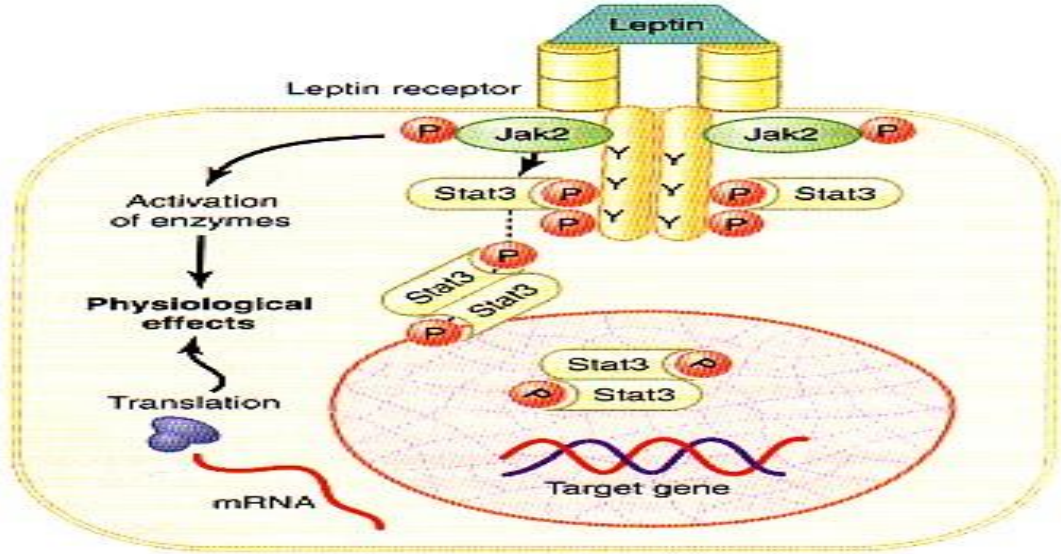
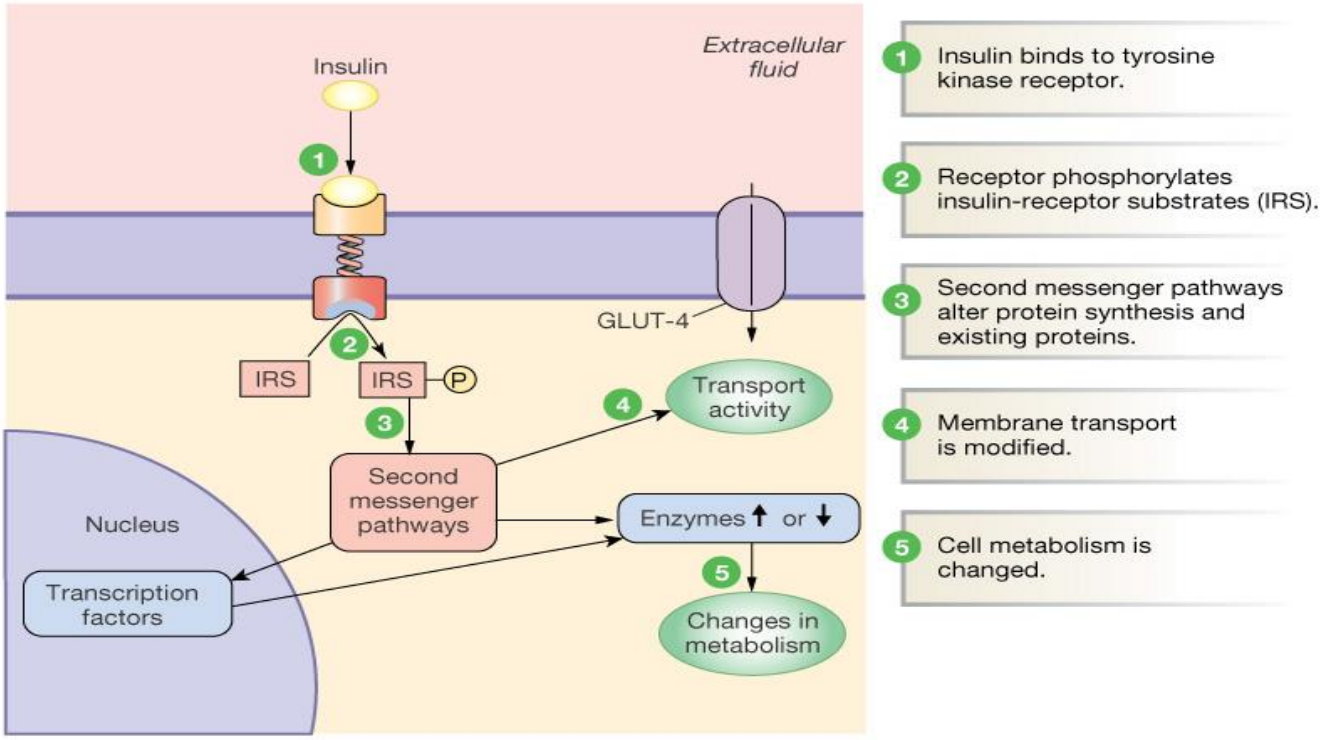


Figure 74–5

An enzyme-linked receptor—the leptin receptor. The receptor exists as a homodimer (two identical parts), and leptin binds to the extracellular part of the receptor, causing phosphorylation and activation of the intracellular associated janus kinase 2 (JAK2). This causes phosphorylation of signal transducer and activator of transcription (STAT) proteins, which then activates the transcription of target genes and the synthesis of proteins. JAK2 phosphorylation also activates several other enzyme systems that mediate some of the more rapid effects of leptin.

Tyrosine kinase: from its name it's phosphorylation of tyrosine

Tyrosine kinase is a receptor for certain hormones such as Insulin, it's found in the conformation of diamers, this receptor when the hormone (ex: Insulin) is bound to it, diamerizes and this autophosphorylates the receptor.



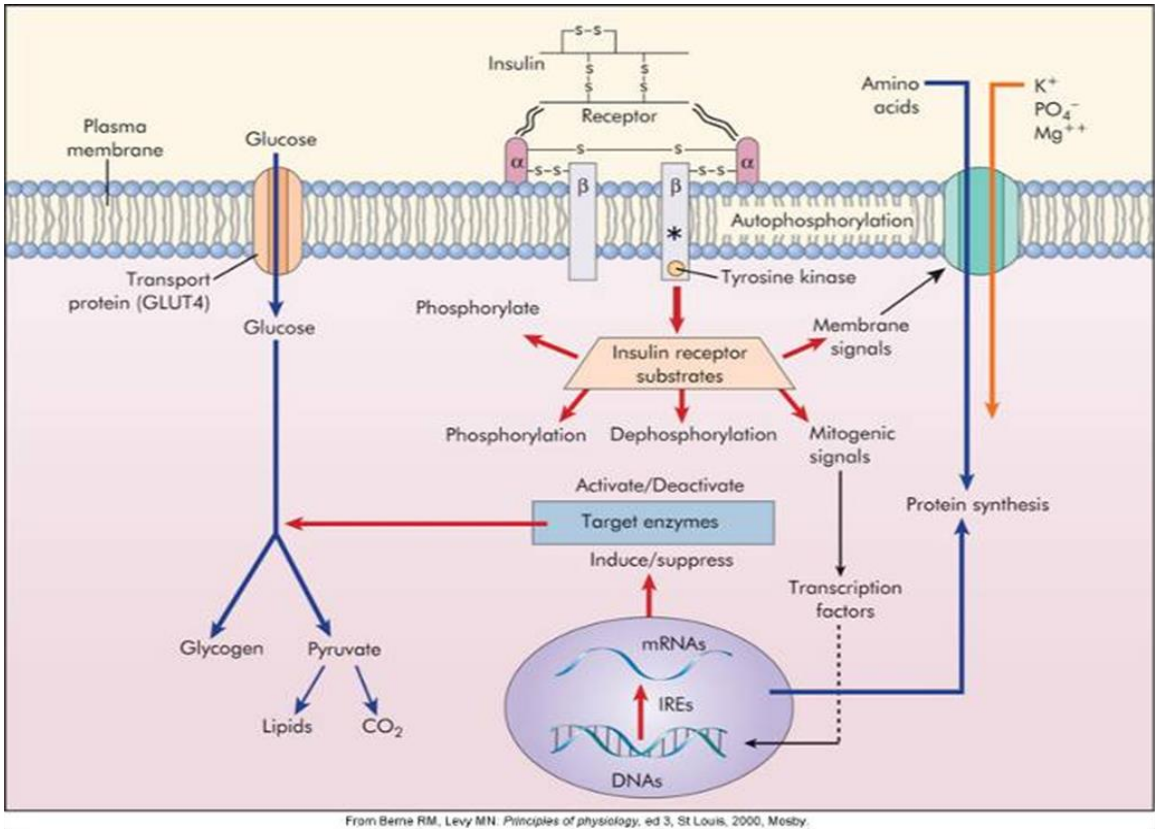
The receptor consists of two subunits (intracellular beta subunits – extracellular alpha subunits)

(((The binding of the hormone to the alpha subunits autophosphorlates the beta subunits >> the autophosphorlation of the beta subunits activates the kinase (the beta subunits act as the kinase itself) ..... these steps take place in this arrangement)))

Then the kinase phosphorylates the intracellular substrates this will affect on the biological state of the cell, these substrates might go to the nucleus and therefore activates the gene transcription .

The substrates will go to the gene transcription (this is the most important point according to what Doctor said) therefore , they induce changes in the cell activity by initiating the synthesis of proteins,

Insulin action:



From Berne RM, Levy MN. *Principles of physiology*, ed 3, St Louis, 2000, Mosby.

Insulin is very specific and it is water soluble, it binds to the alpha subunit causing it to diamerize, this will autophosphorylates the beta subunit of the receptor and we will have now active tyrosine, this will cause phosphorylation of insulin receptor substrate that might give synthesis of fat or glycogen synthesis or growth hormone and might go to the nucleus and lead to gene transcription for new protein synthesis and the protein that is synthesized might be a transporter (Glucose transporter) which goes to the plasma membrane and gets inserted there as channels in the plasma membrane.

Note : If we increase the transporters of hormones >>> the permeability of cell to glucose will increase and that is the action of Insulin. Because of that we give the diabetic patients insulin to decrease the glucose level in the blood by increasing the uptake of glucose by the cells (Glucose will enter the cells more)

عند دخول السكر إلى الدم – بوجود كميات الانسولين – تمتصه خلايا الدم الحمراء هذا السكر سريعا جدا وبالتالي تقلّ كميّته في البلازما

→ the amounts of glucose will enter inside the RBC throughout the presence of the insulin in the circulation .

Note: the insulin receptor substrate might go and open channels in the plasma membrane such as Potassium channels or aminoacids channels.

Medical application

when we give any person the insulin , we have to care about the concentration of the potassium in the blood (WHY ?!?) because the insulin will open the potassium channels and therefore it will go out according to the electrochemical gradient MEANS → the potassium concentration in the cells will decrease and that might lead to hypocalemia.

Note : we should know that the insulin increases the amount of amino acids by going to the nucleus and synthesizing proteins that make the aminoacid channels (therefore the insulin is described as growth hormone as you need aminoacids and mitogenic transciption).

الإنسولين هو يوصف بأنّه هرمون نمو لكن ليس هو هرمون النمو المعروف باسم ((somatropin or GH

You must know that Insuline doesn't work through second messenger (CAMP or CGMP) this is a special kind of receptors called enzyme-linked receptor such as tyrosine kinase, serine kinase and leucine kinase.

Like other examples of the protien hormones is TRH (Tripeptide hormone) it is the simplest peptide in our body, it works on the pituitary and activates the release of TSH which is a glycoprotein, as what we said the glycoprotein consisits of alpha and beta subunits, alpha is general (the same for all glycoproteins) Beta is specific, Beta subunit of TSH bound to its receptor activates G-Protein system tha affect a nearby enzyme called adenylcyclase it converts ATP to CAMP that activates protein kinase A and you can do the phosphorylation through this thyroid gland and the activation of the hormone formation and secretion.
Iodine which is found in the plasma, we have to uptake it by Iodine pump followed by Iodination.
* TSH activates all the processes needed to the formation of T3 and T4

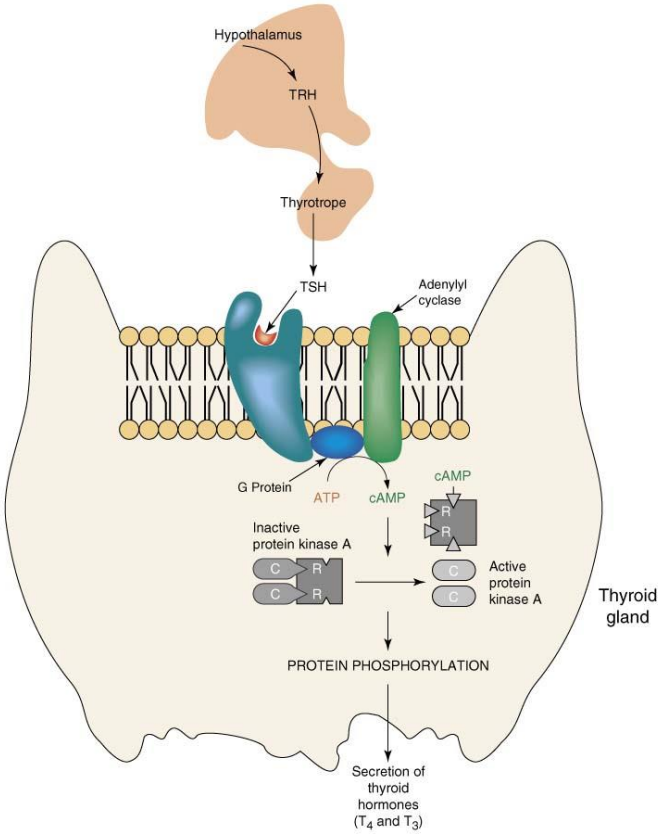


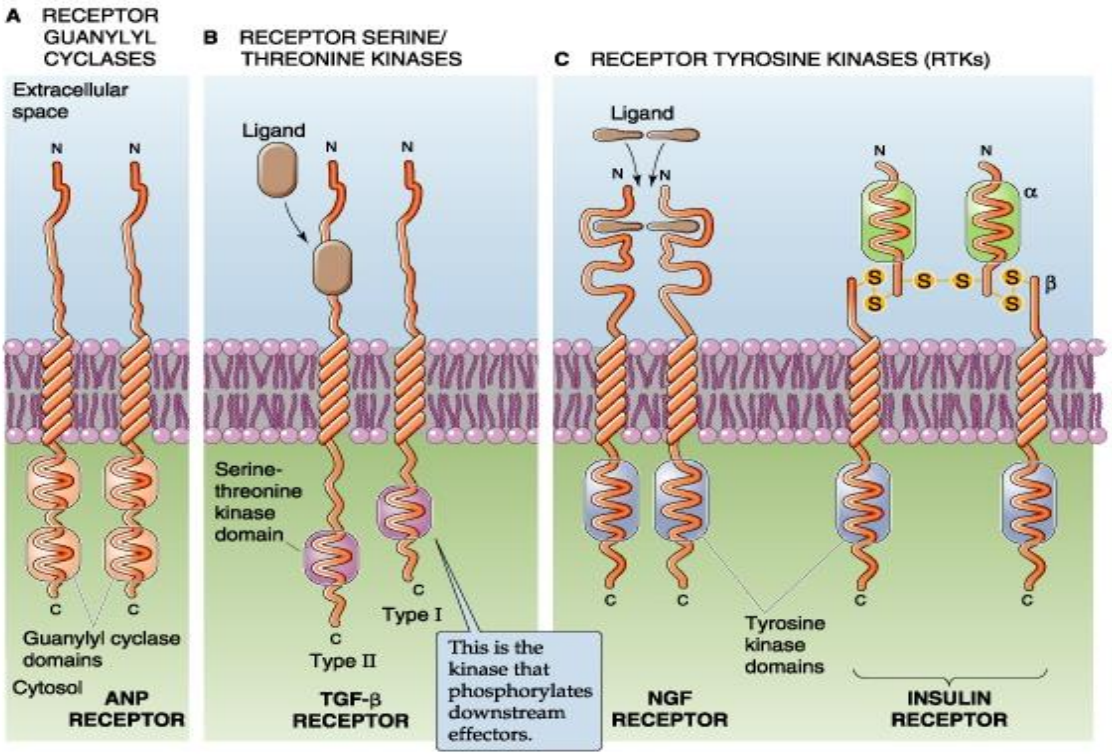
Figure 23.16. Effect of TSH on secretion of thyroid hormone.

Textbook of Biochemistry With Clinical Correlations, *Sixth Edition*, Edited by Thomas M. Devlin. Copyright © 2006 John Wiley & Sons, Inc.

Another enzyme is
LH:

It is a glycoprotein so it activates Alpha subunit which is common and Beta subunit which is specific activation of these subunits will activate G-Protein system, G-protein here is not coupled to CAMP, It is coupled to cyclic Phospholipase C which activates phospholipids that will convert the acid into diacylglycerol and IP3, IP3 goes to the endoplasmic to release Ca and then IP3 with Ca activate protein kinase C that will have an effect on the gland.

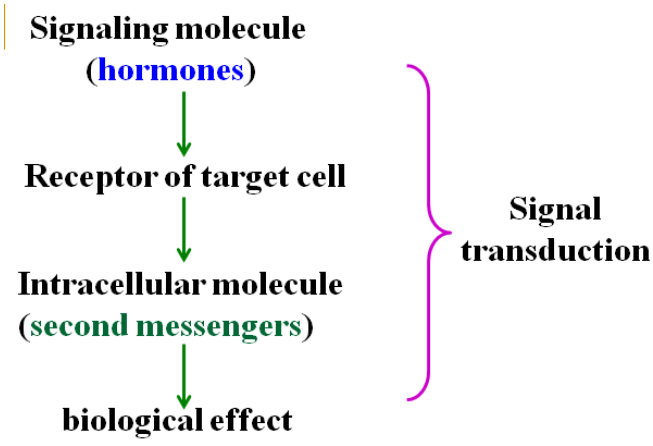
*Doctor comments on slide #36 at min #28



The signal transduction

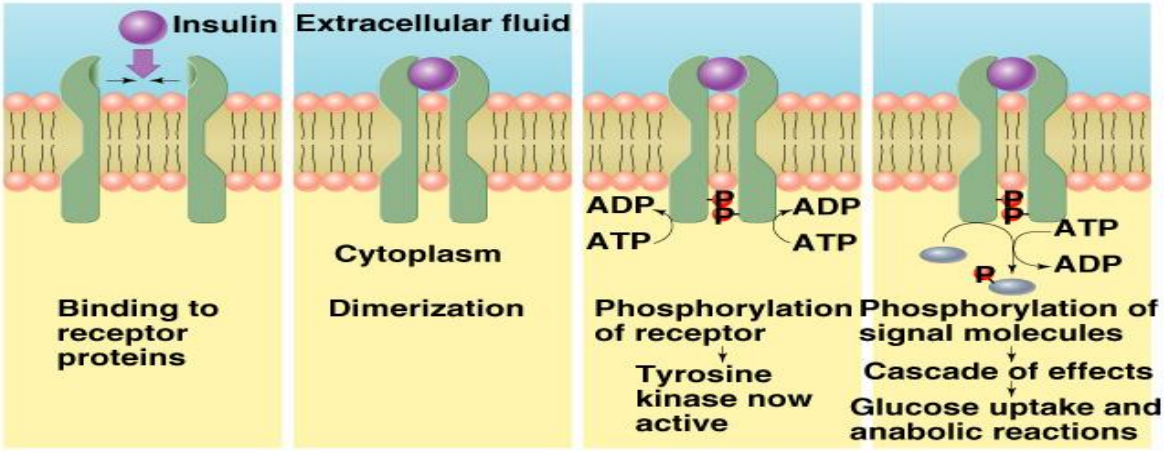
signaling hormone >>> receptor of target cell >>> intracellular molecule (2nd messengers)>>> biological effect

*Doctor comments on slide #37 at min #30



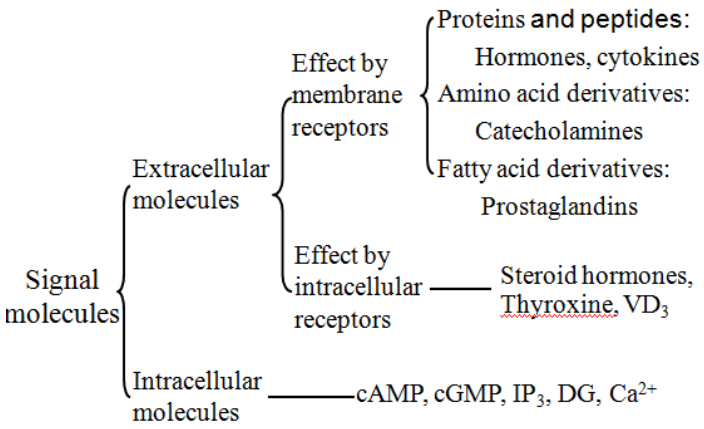
Review

insulin receptor consists of 2 units that diamerize when they bind with insulin (The insulin binds to ligand-binding site on the plasma membrane , activating enzymatic site in the cytoplasm → Autophosphorlation occurs , increasing tyrosine kinase activity → activates the signaling molecules (stimulate glycogen ,fat and protein synthesize , and stimulates insertion of GLUT-4 carrier proteins)



 # Third messengers are the molecules which transmit message from outside to inside of nucleous or from inside to outside of nucleous, also called DNA binding protein.

Doctor comments on slide #39 at min #31



Signal transduction (for reading)

occurs when an extracellular signaling molecule activates a specific receptor located on the cell surface or inside the cell

In turn this receptor triggers a biochemical chain of events inside the cell, creating a response . Depending on the cell the response alters the cell's metabolism, shape, gene expression, or ability to divide .

. The signal can be amplified at any step. Thus, one signaling molecule can cause many responses