Faculty of Medicine 2012

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Date : March - 19th - 2013

lecture no. : 6

PHYSIOLOGY

Sheet

Medical Committee
The University of Jordan

Price :

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Hormones That Bind to Nuclear Receptor Proteins

Hormones bind to their receptors .Whether the receptor is found in the nucleus or the cytoplasm, at the end they are translocated to the nucleus because they have to bind to specific sites on the DNA that's called hormone response element (HRE)

Binding to this hormone response element causes protein formation through transcription and translation of the DNA

So here when they bind to the DNA, transcription occurs, and the resulted messenger RNA is translated, forming a new protein.

The resulted proteins might be receptors,enzymes, transporters, channels … etc., it depends on the action of the hormone

The lipophilic steroids (lipid soluble) pass through the membrane by diffusion after they dissociate from their carrier in the plasma, after that if their receptors are found in the cytoplasm, the receptor with the hormone will be translocated to the nucleus and in the nucleus they bind to specific sites (HRE)

REMEMBER:In the DNA, parts are called introns and other parts are called exons .The exons are the parts of the DNA that are transcribed.

The receptors for lipophilic hormones are known as nuclear hormone receptors, so once they are translocated to the nucleus it activates transcription through forming mRNA leading to protein synthesis and steroid response

Steroid responses are located in the cytoplasm, functions within the cell, and activates genetic gene transcription - mRNA formation.

Each nuclear hormone receptor has two regions:

A ligand hormone binding domain→binds the receptor

A DNA binding domain→binds to the DNA (to specific areas (HRE))

So in the DNA binding domain , receptors are activated by dimerization , they comes at the dimer through binding with specific region on the DNA called HRE , located adjacent to the gene that will be transcribed (on the introns).

The cytoplasmic receptor binds to steroids, then it is translocated to the nucleus, the DNA binding domain binds to HRE that has two sides , one side for this receptor and the other side for another receptor.
So here the hormone response element on this half and the other half is the intron. ??!
After forming the dimers , transcription occurs forming mRNA.
So dimerization is the process of two receptor units coming together at 2 half sites stimulating transcription of particular genes
The dimers can be homogenous (the same) or heterogeneous (different)like thyroxin.
The receptors for thyroxin differ from each other , the receptors for T4 (prehormone) is converted to T3 because T3 is more active than T4
So T4 passes to the cytoplasm , and is then converted to T3 , T3 binds to a ligand binding domain . The other part of the receptor is the RXR (retinoic x receptor) which is a derivative of vitamin A
Again it's not necessary that the dimers are homogenous, they could be heterogeneous
These two receptors (RXR & TR thyroxin receptor) bind to the same HRE , and dimerize , They do not stimulate the gene transcription unless they dimerize, so dimerization is essential

T_3 binds to ligand-binding domain. Other half-site is for vitamin A derivative.

DNA-binding domain can then bind to the half-site of the HRE.

Two partners can bind to the DNA to activate HRE Stimulating transcription of genes.

The proteins that are formed by the T3/T4 are receptors , they can be beta receptors.

If it forms beta receptors , then the T3/T4 are considered to be activating the sympathetic , if we increase the sympathetic receptors the activity increases .

This is why a person with high amounts of T3/T4 , has a very fast heart rate , because T3/T4 causes an increase in the formation of beta receptors , which stimulates the sympathetic , and then the sympathetic causes the increase in the heart rate .

Also , T3/T4 hormone stimulate the formation of NA/K pump leading to an increase in the consumption of ATP and the metabolism (catabolism of glucose , formation of metabolism enzymes , and so on)

(75% of the ATP that is consumed is produced as heat, this is why a person who has a high concentration of thyroxin has an intolerance to heat .

So since thyroid and steroids are lipid soluble they pass the membrane by diffusion and bind to their receptors , if their receptors are in the cytoplasm or in the nucleus , at the end they are translocated to the nucleus , the hormone receptor then binds to the HRE , after that dimerization occurs , they have to form 2 , then they cause transcription of the genes .

Action of the thyroid hormones
Thyroid hormone cause the formation of new proteins which can be involved in :
1. many other systems
2. Growth (which is why the thyroxin Is also known as the growth hormone like hormone , newborns with congenital hypothyroid (they do not have thyroxin) become dwarfs , also those with hypopituirism (do not have pituitary growth hormones) are going to be dwarfs , the difference between the two cases is that thyroxin is essential for CNS , not like growth hormone which is not essential for CNS especially after delivery , before that the baby will take it from his/her mother and this causes mental retardation)

3. CNS development
4. Cardiovascular (increase in cardiac output , tissue blood flow , heart rate , heart strength and increase in respiration), all this is due to the formation of beta receptors.
5. Metabolism (increase the mitochondria metabolism , which is the cytochrome system ,increase in $Na^{+}K^{+}$ ATPase , O_2 consumption , glucose absorption , gluconeogenesis , glycogenolysis , lipolysis , protein synthesis and increase in BMR)

All of these effects are due to the activation of enzymes and formation of proteins.

Note : T4 is converted to T3 before binding to the receptor , however the receptor can still bind to T4 but the affinity of the receptor to T3 is higher that its affinity to T4.
The lipophilic hormone effects are slower than hydrophilic hormone because it acts on gene transcription , which is a slow process.

What determines the amount of free hormones

First of all , free hormones are secreted from the endocrine cells as free hormones, especially those that are lipid soluble proteins , then they are carried through the plasma as carrier bound hormones, after that they will be freed from their carriers and uptaken by cells through hormone receptors. Hormone receptors either free the hormones again or put them to work causing biological effects (if there is too much effect the receptors free the hormones (negative feedback)). Also free hormones are degraded after a while .
So this is what determines the hormone concentration : the action (biological effect) and the hormone degradation

Correlation of plasma half-life & metabolic clearance for hormones with a degree of protein binding

We have talked before about the half – life for some hormones
The half life can range between minutes to days ,
The shorter the half life is the higher the metabolic clearance will be
The thyroid hormones (thyroxine&Triiodothyronine) are bound to proteins because they are lipid soluble - about 99% of them are bound to proteins -.
The thyroxine has a half-life of 6 or 7 days while the half-life of Triiodothyronine is 1 day , which is why the metabolic clearance for Triiodothyronine is higher than that of Thyroxine.

The half life for steroids is a little shorter than than of throidhormones , which is why the metabolic clearance for them is higher than that of thyroid hormones.

As for insulin the half life is 8 minutes , (we have said before that it ranges between 5 and 20 minutes depending on the type of insulin we have) , and a metabolic clearance of 800
Antidiuretic hormone has a half life of 8 minutes , and a metabolic clearance of 600
thyrotropin (TRH) has a half life of 50 minutes and metabolic clearance of 50

This is important to know when we study the hormones because it tells us how frequent can we give the hormones to a patient , for example we can't give a patient thyroxin hormone three time a day because it has a low metabolic clearance and a long half life

The protein binding percentage affects the half life , proteins like Antidiuretic hormone, insulin &thyrotropin)are water soluble and they do not need carriers which is why the protein binding percentage is low , however lipid soluble hormones are bound to transporters through the plasma and these transporters are proteins , so the protein binding percentage is high.

Transport proteins
The transporters can be specific or nonspecific
Of The nonspecific transporters for the lipid soluble hormones is the albumin.
The albumin is a nonspecific transporter for too many lipid soluble hormones , it might even carry some inorganic ions like the calcium.
Prealbumin transporter is also nonspecific

Specific transporters
For the thyroxine there is a thyroxine binding globulin
For steroids there is a steroid binding globulin
For corticosteroids there is a corticosteroid binding globulin
For sex hormones there is a sex hormone binding globulin

The most important transporters are the specific transporter , however if for some reason the specific transporters are congenitally not formed , then the

nonspecific will cover some of the burden the specific transporters should have carried and the person will not suffer a deficiency of the hormone.

Steroid & Thyroid Hormones – Receptors

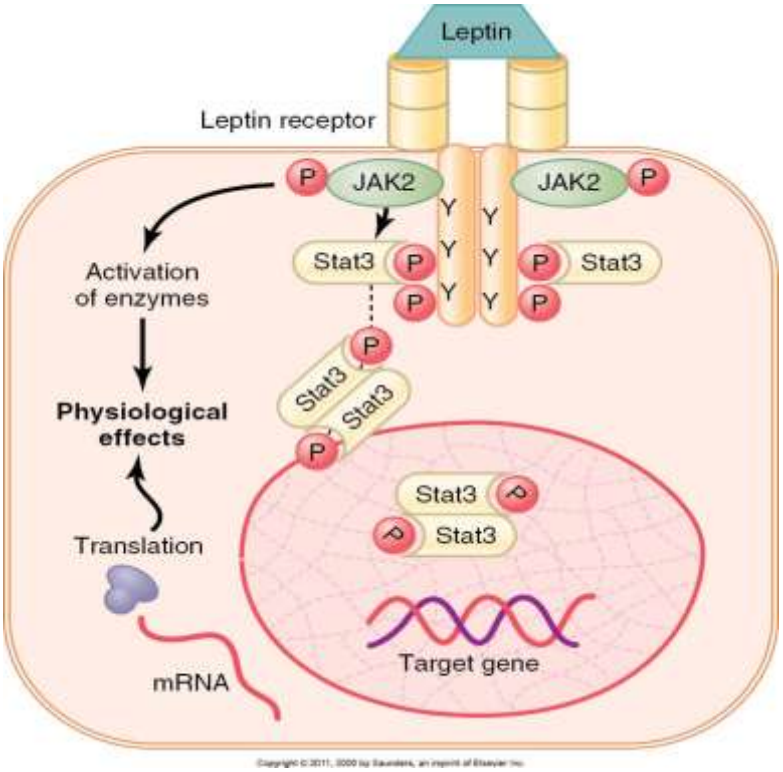
Sometimes the receptors are very complex

For example , even though glucocorticoid ,vitamin D, mineralocorticoid, estrogen and progesterone are all steroids , each has a specific receptors.

Thyroid hormones also have different specific receptors

* All of the kinases we have mentioned before like cAMP are nonspecific kinases

Other than the general differences between hormones like water and lipid soluble , there are certain specific diffrences between hormones.

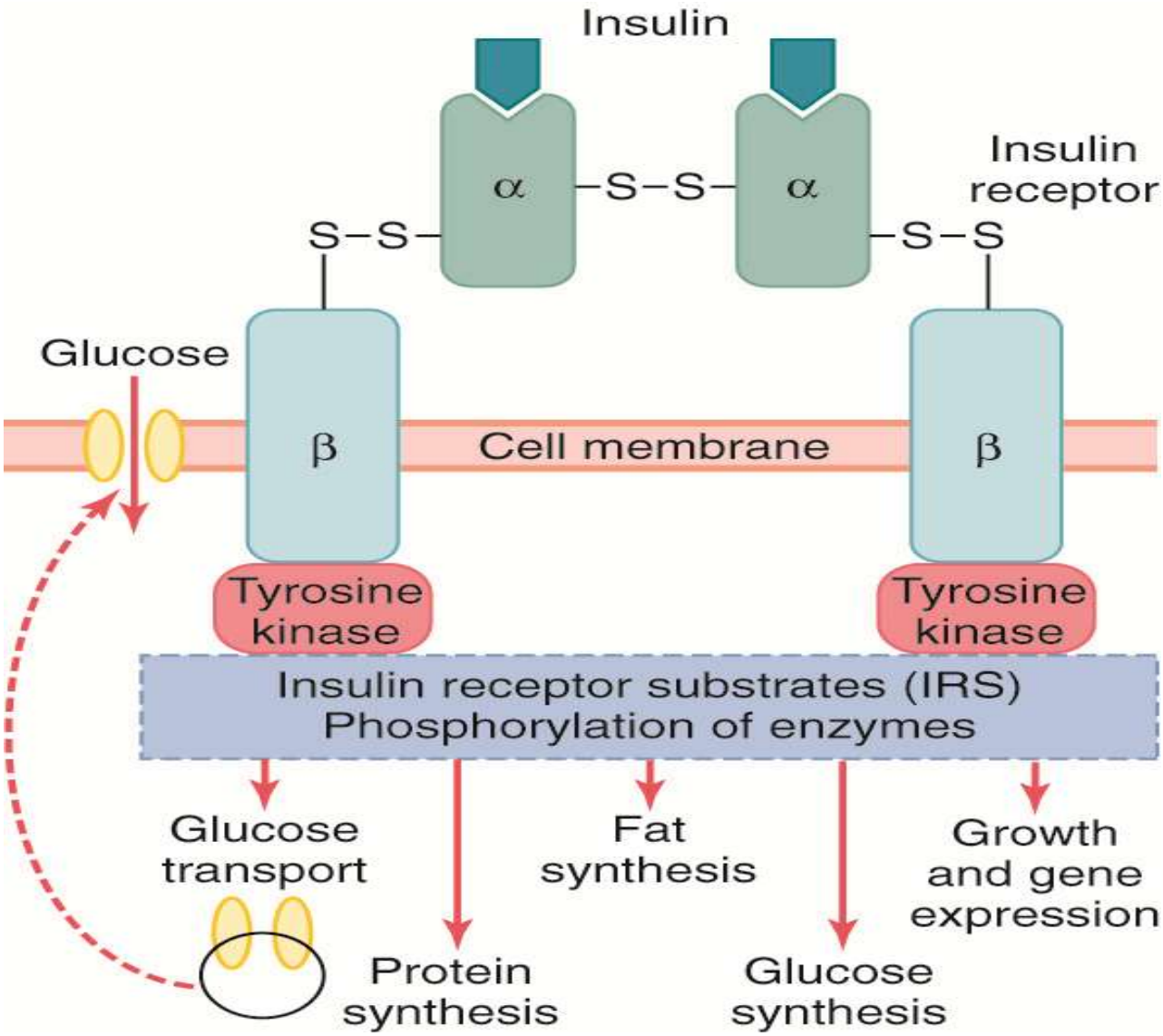


For example the leptin hormone which is incriminated for weight gain and is water soluble has a receptor on the cell, and when leptin passes through the receptor , the receptor itself is a kinase , and when the leptin binds to the receptor , the kinase is phosphorylated and activated. This receptor is called JAK , Janus kinase or Just Another Kinase. So leptin will bind to a receptor and tansit In diemericreceptor , it activates a kinase (JAK). So the receptor here is auto phosphorylated (bcause it is a kinase itself) , after that it goes and phosphorylates a substrate called Signal Transducer and Activator of Transcription (STAT) which then goes and activated gene transcription.

Sometimes however the JAK itself changes the phosphorylation of certain enzymes and then it activates the enzyme through gene transcription or gene translation.
So, leptin binds to its receptor (which is composed of two subunits),
The receptor is composed of two subunits, the intracellular part of the receptor is a kinase itself, it's phosphorylated after binding of the hormone to the receptor, when this kinase is a receptor it phosphorylates intracellular substrates. These intracellular substrates are called STAT. This STAT goes to the nucleus and causes gene transcription and formation of new proteins.
JAK activates certain enzymes and goes the other way around.

There are other kinases than JAK like tyrosine kinase or .
The intracellular part of receptor itself is a tyrosine kinase , which means that it is a kinase that phosphorylates tyrosine.
The tyrosinkinase can also be tyrosine phosphatase, this kind of receptor is for insulin , so here when the hormone binds to the receptor , this activates auto phosphorylation of tyrosine kinase , which activates intracellular signaling.
This is especially important for insulin

Again : Insulin receptor is a tyrosine kinase , it consists of 2 subunits that dimerise when bound to insulin which auto phosphorylates tyrosine kinase intracellulary , causing an increase in the activity of the kinase, activating signal molecules which Stimulate glycogen, fat and protein synthesis and insertion of GLUT-4 carrier proteins (glucose channels). All of this increases the uptake of glucose (which is the effect of insulin) , which causes a decrease in the glucose concentration in the plasma.



"Travelers, there is no path, paths are made by walking." Antonio Machado