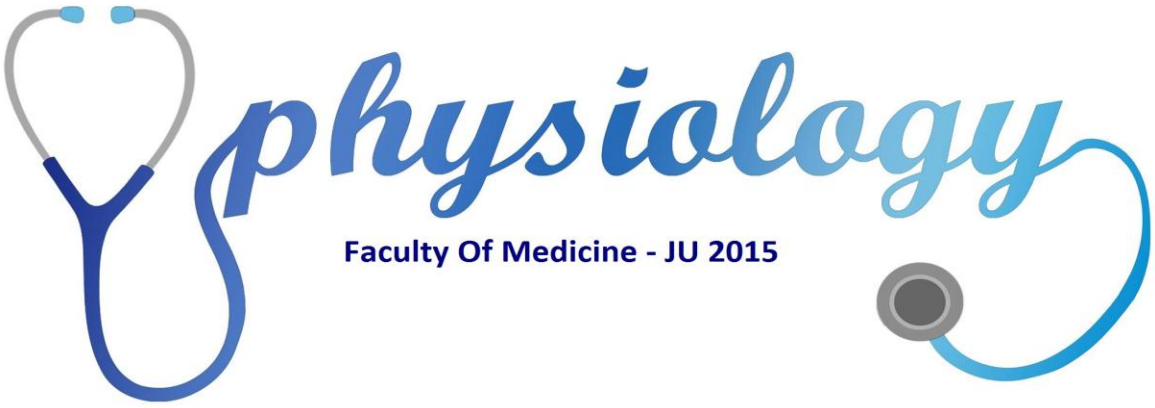

Lecture 16

Done by: Hanin Saleh

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Last time we discussed second messenger systems, such as cAMP and cGMP, and we talked about IP3 and DAG, so as we know those are also second messengers and are synthesized by an enzyme called **phospholipase C.**

Now phospholipase c is activated through a receptor system such as **G-protien coupled receptors,** or **Gq** (a specific isoform of G-protein coupled receptor). This **Receptor type protein kinase** can also activate phospholipase c.

Now we are going to talk about Gq, as we said it is a specific isoform of G-protein coupled receptor. Now this receptor produces DAG (di-acyl glycerol) as well as inisitol tri phosphate from **phosphatidylinisitol 4,5 bisphosphate**(It will slice into IP3 and DAG).

So Gq produces two molecules:

1- DAG which is attached to the inner layer of the plasma membrane and activates protein kinase C.

-protein kinase c is activated by DAG as well as calcium.

2- IP3 which is present in the cytosol and can go and activate calcium channels in the ER (as we know ER represents calcium storage)

-calcium level in the cytosol is very low so any sudden increase can lead to sudden changes of the cells activity.

NOTE: calcium level in the cytosol can either be increased by influx of calcium from outside of the cell or by efflux from the ER

So we call IP3 and DAG *second messengers* because they transduce the signal into either activation of protein kinase C in the case of DAG or increase in the intercellular calcium by IP3

-calcium can help DAG to produce protein kinase C

-calcium is a very important trigger for vesicle formation and exocytosis.

#This means that anything that requires secretion of vesicles for neurotransmitters or hormones it can use this signaling pathway we talked about in order to get calcium

Gq triggers PIP2>>PIP2 splits into DAG +IP3 >> IP3 releases calcium>>secretion of vesciles.

Calcium as a second messenger:

Remember>>a second messenger is any molecule that transfers a signal from the plasma membrane to the cytosol

Calcium binds to a certain calcium binding protein called **calmodulin**

When sudden increase of calcium in the cytosol happens calmodulin will be activated and now can bind to different types of proteins.

One of these proteins is called **calmodulin dependent kinase (ca-M-kinase),** once this kinase is activated, it autophosphorylates itself and becomes fully active and can activate or deactivate many other proteins.

Note: whenever you see the word *kinase* always does **phosphorylation**

-calmodulin can also bind to adenylate cyclase or phosphodiesterase to activate them, so calmodulins target isn't just ca-M-kinase. So calcium can be a second messenger to multiple kinase systems.

- adenylate cyclase can also be activated by ca-M-kinase

Calcium>>calmodulin>>kinase>>phosphorylation>>activation or deactivation of certain protein

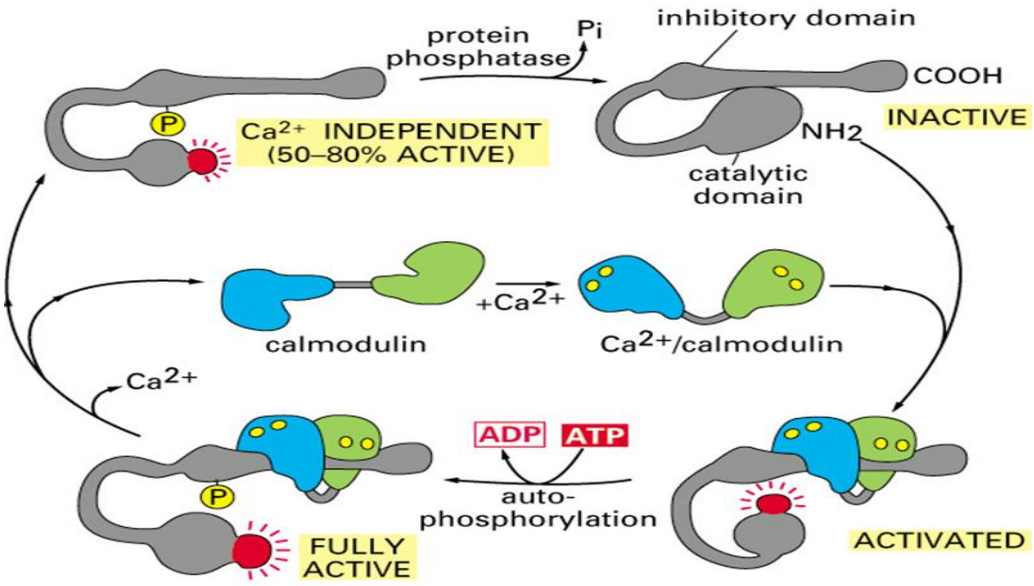

Figure 15–41. Molecular Biology of the Cell, 4th Edition.

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Epinephrine is a hormone that can utilize two systems of second messengers

Now we mentioned epinephrine when we talked about the ***beta adrenergic receptors*** as an example of G-protein coupled receptors >>when epinephrine binds to G-protein coupled receptor, it activates adenylate cyclase for production of cAMP.

The second receptor epinephrine can bind to is ***alpha adrenergic receptor***

-alpha adrenergic receptor is coupled to **Gq,** so that means epinephrine can increase the level of intracellular calcium, and Ca-calmodulin activation.

So epinephrine can change the intracellular activity depending on the receptor it is bound to.

- we can find high level of B-adrenergic receptors or Alpha or both depending on the type of cell,

PIP3 as a second messenger:

-also derived from the plasma membrane.

-PIP3 is basically PIP2 phosphorylated by a kinase called ***PI3 kinase*** and becomes a triphosphate.

-PIP3 is considered a second messenger in a signaling pathway important for survival of the cell (prevents cell death (apoptosis))

(This is all that you need to know about this second messenger you do not need to memorize the mechanism)

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-RAS and MAP kinase are important in cancer research

-JAK-STAT is also a pathway important in signaling (related with gene transcription)

-*This figure summarizes all the different types of second messenger pathways:

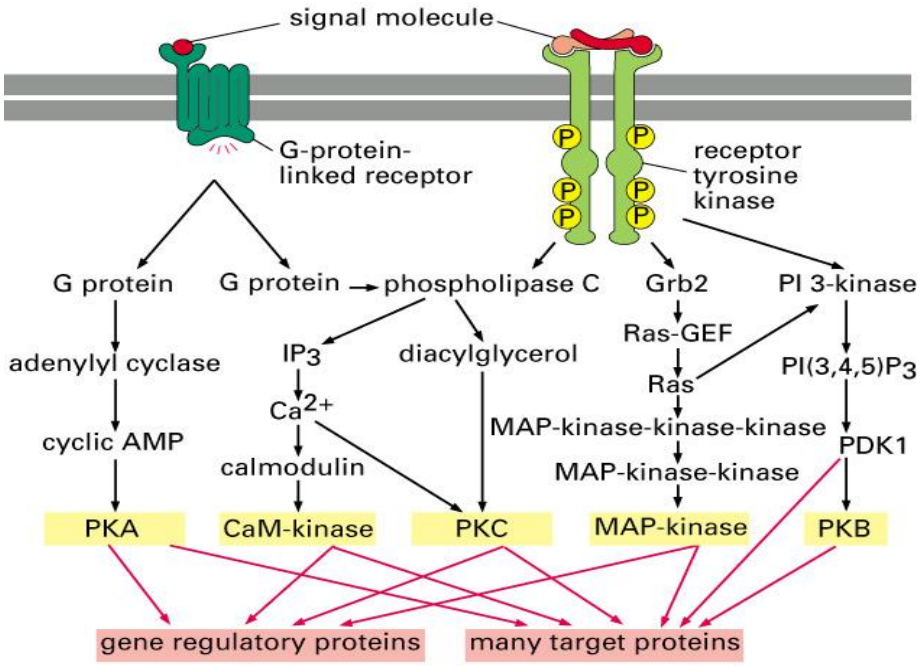

Figure 15–61. Molecular Biology of the Cell, 4th Edition.

-Neurotransmitters can either bind to ligand gated ion channels and then activate these channels in order to change the flow of ions or they can bind to a second type of channel that is linked to G-protein.

-so there are two types of post synaptic receptors

1-iono tropic (more details about it are found in pervious lectures)

2-metabotropic: linked to G-protein coupled receptor that is either linked to channel or a second messenger that can change the cell response or function

So neurotransmitters are not just for flow of ions, it can also change gene transcription, protein synthesis, cell activity..etc.

So any other changes neuro transmitters can make are by metabotropic receptors.

-Ionotropic receptors are very fast in responding (open fast and close fast)

-Metabotropic receptors are slow (it is coupled to G-protein and second messenger system so there are more steps in order to get response) and they are not always associated with a channel (could be linked to an enzyme or protein kinase) .

-many effects can occur with regard to metabotropic receptors.

-metabotropic effect lasts longer.

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So we covered everything we need to know about plasma membrane receptors, now we are going to talk about some hormones that don't necessarily requires channels to cross the plasma membrane (lipophilic) and bind to either cytosolic or nuclear receptors.

-these hormones are **steroids** and **thyroid** hormones as well as vitamin D.

-steroids such as estrogen, progesterone, cortisol.

-now these hormones in the blood plasma are bound to proteins to increase their half life and decrease their clearance

-When these hormones should cross the plasma membrane they need to dissociate from their bounding proteins.

1-steroids

-steroids can have their receptors either in the cytosol or nucleus

Now the receptors of the steroids have two binding sites, one for the steroid and the second for the DNA

-now both of these can cross the nuclear membrane and bind to a DNA binding site called ***hormone response element*** (each hormone has its own specific hormone response element which in eventually lead to functioning of this hormone)

-so there are DNA binding site and ligand binding site that are able to change the gene transcription

-receptors for steroids usually dimarise (become two identical receptors)to couple with the DNA or ligand response element

Remember:1- steroids can have cytosolic or nuclear receptors.

2-they have two binding sites

2-thyroids:

-thryroid binding to their receptors are present ***only*** in the nucleus

-thyroid is usually present as **T4** or **T3**

-the active form is **T3** (T4 must be converted into T3 in order to be active)

-T3 will bind to a receptor and this receptor dimerizes with another receptor which is not another thyroid hormone receptor instead it is a ***retinoic acid receptor (RXR)***

-retinoic acid is derived from **vitamin A (**it's important for thyroid action in the nucleus)

-9-cis-retinoic acid will bind to its receptor and then dimerizes then bind to the response element for thyroid.

-now gene transcription will occur and thryroid will form its function (will be translated).

-thyroid is important in CNS development and growth during infancy

-after puberty thyroid mainly affects metabolism.

-again thyroids functions depends on its response element.

Note: receptors must be dimerized in order to perform gene transcription.

Now we have an idea about the mechanism of lipophilic hormones.

-the equilibrium of free hormones and carrier bound ones is determined by the amount of release of hormones>>when a certain gland is stimulated>>release on one side leads to displacement from the reservoir of bound hormone >> increasing the amount of free hormones >>and they become available to enter the cell and bind to their receptors.

Factors that determine the cellular response of hormone: the amount of free hormones, the amount of hormone receptors, secretion of hormones, degradation of the hormone (metabolism).

Remember: lipophilic hormones are mainly present as ***bound*** in the plasma (blood plasma)

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

now what this figure shows is that:

The higher the protein binding percentage is>>the higher the plasma half life>>the lower the clearance.

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Hormone binding can be specific for certain proteins that are specific for certain hormones

Ex: thyroxin has a certain binding protein called thyroxin globulin.

-sometimes binding can be *non specific* (ex:albumin)

An example of signal transduction of hormone release:

- hypothalamus contains a releasing hormone called ***gonadotropin releasing hormone***

-this hormone binds to a G-protein coupled receptor present in the anterior pituitary gland>>G-protein contains Gq>>Gq binds to phospholipase C>>phospholipase C produces IP3>>IP3 releases calcium>>DAG stimulates PKC>>calcium will induce exocytocis of vesicles that contain certain hormones (ex:FSH and LH)

-PKC can function in protein synthesis .

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Third messenger

-sometimes used but not as important as second messenger

-Any signaling molecule going from outside to inside of nucleus or inside to outside is called third messenger.

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The sheet is now over I apologize for any mistakes

*special thanks to Abdullah Suliman and Omar Mahafza for the help .