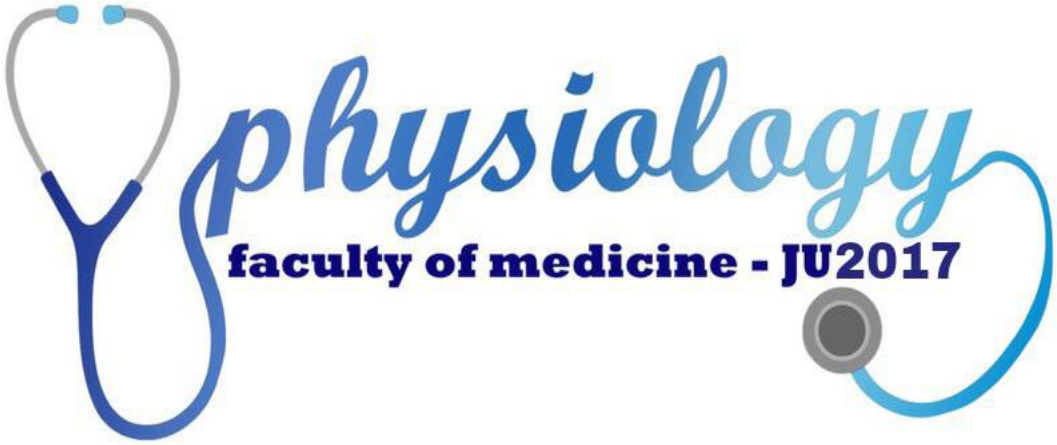

◉Sheet ○Slides

Number

23

Done by:

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Revision of previous lectures

G-proteins coupled receptors mechanism:

- When a hormone binds to G-protein coupled receptor, GTP replaces GDP which will activate the alpha subunit. The alpha subunit dissociates and activates the effector enzyme adenylate cyclase.
- Activation of adenylate cyclase converts ATP into cAMP, then the cAMP will bind to the regulatory subunit which will activate catalytic subunit causing it to phosphorylate enzymes or channels proteins. The catalytic subunit may enter the nucleus where it activates "cAMP response element binding protein".
- Once this protein is activated, it goes to the and binds to a specific site in the DNA in order to start gene transcription process to form new proteins.
  Note: phosphorylation of proteins or enzymes is relatively faster than the process of forming new proteins. However, ionotropic receptors mechanism is the fastest.

phosphorylation doesn't always mean activation of protein, it may also cause inactivation of the protein. In both cases the result is a change in the behavior (biological effect).

how the signal is turned off?

- By phosphorylation of specific phosphodiesterase "cAMP dependent phosphodiesterase" which converts cAMP to 5'-AMP.

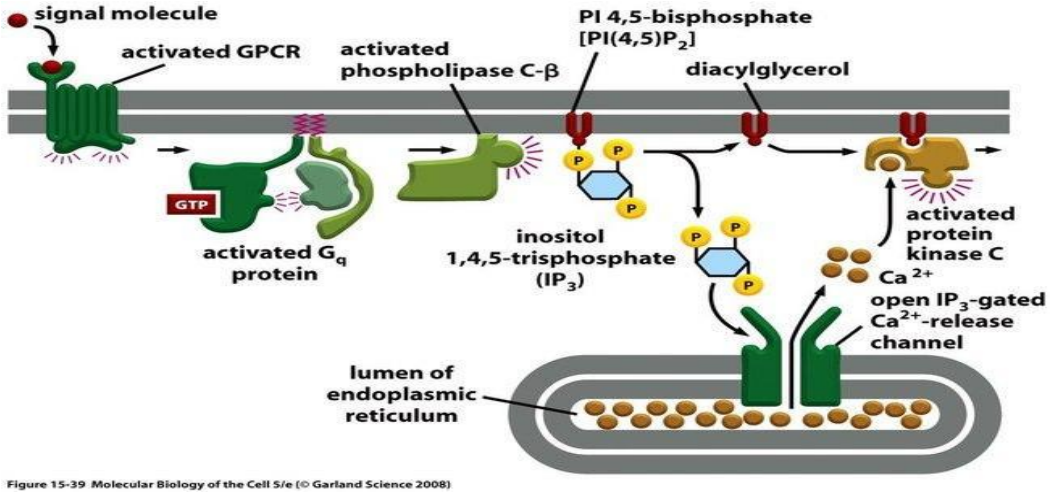
signal amplification:

- Whatever the 2nd messenger is, its function is amplification of the signal; only one ligand (e.g. epinephrine) but the end result is millions of phosphorylated proteins leading to cellular response

phospholipase c activation:

- epinephrine binds to alpha adrenergic receptors → G-proteins → phospholipase C → Phospholipase C removes the middle carbon "C" leaving the 2 fatty acid derivatives "DAG" and producing IP3. DAG doesn't split from the membrane and IP3 goes down to ER and causes release of Ca.
- DAG and Ca will activate protein kinase C which will cause proteins phosphorylation

- Once it binds to the process is activated
  The three types of protein kinases don't phosphorylate the same proteins or amino acids which means they have different actions. However, the end result is always a change in the behavior.



11:00

- After releasing Ca++ into the cytoplasm, it binds to calmodulin.
  Calmodulin activates specific protein kinase enzymes.
  That alters the metabolism of the cell, producing the hormone's effects.

☆ Each Calmodulin can bind 4 Ca++ ions, and it's almost found in every cell

☆ Protein Kinases differ from cell to another, if the cell contains protein kinase B, calmodulin activates it and so on.

<u>NT-Receptor Binding</u>

1. Transmitter is synthesized and stored
2. Action Potential reaches the terminals of presynaptic membrane.
3. Depolarization: open voltage-gated Ca2+ channels.
4. Ca2+ enter cell and causes vesicles to fuse with presynaptic membrane.
5. NT is released (exocytosis).
6. NT binds to postsynaptic receptors, causes Opening or closing of postsynaptic channels
7. IPSP or EPSP occurs to change excitability of the cell.
8. Retrieval of vesicles from plasma membrane (endocytosis).
9. Inactivation of the NT: it can be recycled in presynaptic terminal or can be broken down by enzymes within the cell.

Receptors of NT

- Large, dynamic proteins that exist along and within the cell membrane.
- Dynamic: they can increase in number and avidity for their neurotransmitter according to circumstances.
- Classified into two types:

1- **Ionotropic receptors:** NT binding results in direct opening of specific ion channels, so changing the permeability.
   - ***a.*** It is coupled with ion channels, so It works very fast; has important role in fast neurotransmission.
   - ***b.*** Each is made of several subunits 4 or 5 (together form the complete receptor).
   - ***c.*** The center of the receptor is a channel or pore to allow flow of ions.
   - ***d.*** Not coupled with second messenger.
   - ***e.*** At rest: receptor channels are closed
   - ***f.*** When the ligand binds: channel immediately opens
   - ***g.*** When the ligand leaves binding site: channel quickly closes.

2- **Metabotropic receptors:** binding of NT initiates a sequence of internal molecular events which in turn open specific ion channels.
   - ***a.*** It is coupled with G-protein and works more slowly than ionotropic receptors.
   - ***b.*** It works by activating other proteins called G proteins.
   - ***c.*** Each is made of one subunit of several transmembrane regions.
   - ***d.*** When the ligand binds to the receptor, it activates G-protein.
   - ***e.*** When G-protein is activated, Alpha subunit of the G-protein dissociates and it can :
   - Stimulate or inhibits the opening of ion channels in the cell membrane.
   - Stimulate or inhibit certain effector enzyme, which acts as second messenger and activates protein kinase.

Characteristics	Ionotropic receptors	Metabotropic receptors
Structure	4 or 5 subunits that assemble in the cell membrane	1 subunit
Mechanism of action	Contain an intrinsic ion channel that opens in response to neuro-transmitter or drug binding	Activate G proteins in response to neurotrans-mitter or drug binding
Coupled to second messengers?	No	Yes
Speed of action	Fast	Slower

Note: Most effector enzymes controlled by G-proteins are involved in synthesis of second messengers. [First messenger=ligand Second messenger=effector enzyme]

Other Metabotropic Receptors

1. They do not possess a channel or pore and work more slowly than ionotropic receptors

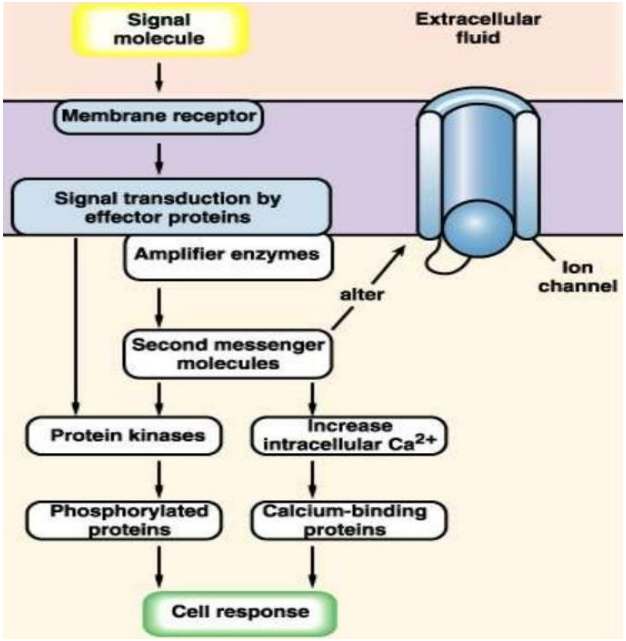
2. Though it takes longer for postsynaptic cell to respond, response is somewhat longer-lasting.

3. They Comprise a single protein subunit, winding back-and-forth through cell membrane seven times (transmembrane domains).

Second messengers

1) Activate Protein Kinases
2) Protein kinase is hepta-subunit protein, there is many types of protein kinase.
3) Protein Kinases work by:

✓ Affecting: NT production, no. synapses formed, sensitivity of receptors, or expression of genes (long term effects).
✓ Amplification -interconnections.
✓ Phosphorylation of proteins or enzymes.



Remember that:

- Upregulation: increasing the number of receptors in the membrane.
- Downregulation: decreasing the number of receptors in the membrane.
- Ligand is the signal molecule.
- Agonist: it binds to the same receptor of the ligand and causes the same respond from the cell like the ligand "hormone or NT".
- Antagonist: it binds to the same receptor but doesn't cause the effect of the ligand. It blocks the receptor.

The General Mechanism of Water-Soluble Hormones

The hormone circulates in a free form in the blood 》》 it binds to its receptors which are located in the membrane of the target cells 》》 activates G-protein 》》 Alpha subunit activates adenylate cyclase 》》 the activated adenylate cyclase converts ATP to cAMP 》》 cAMP activates protein kinase 》》 causes phosphorylation of proteins 》》 phosphorylated proteins cause reactions 》》 produce physiological responses 》》 phosphodiesterase inactivates cAMP.

22:00

Lipid Soluble Hormones:

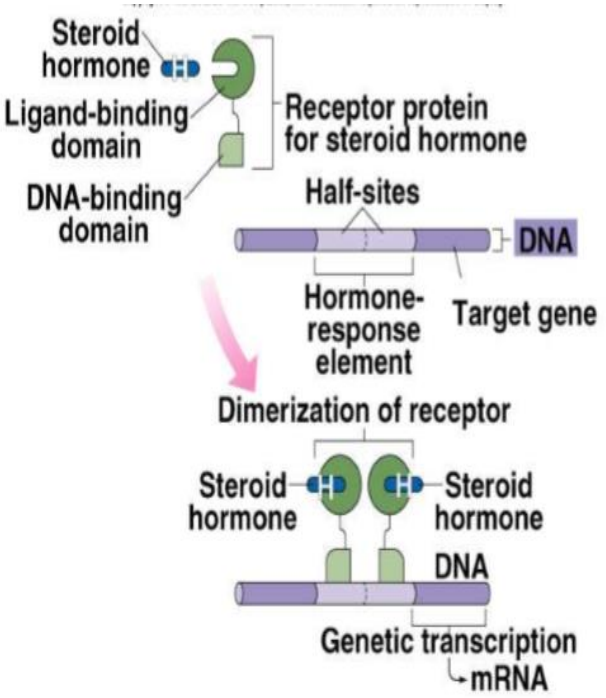
-They need a transport protein (Also called plasma carrier proteins) to transport them through the blood capillaries throughout the body, these proteins could be specific or non-specific.

-Once the hormone gets to the target cell they disassociate form the carrier and diffuse into the target cell (They are lipid soluble, so they don't need receptors on the cell membrane to enter the cell).

-Once they are in the cytoplasm, they bind to their receptors in the nucleus (Called the nuclear hormone receptor, They can also bind to receptors on the cytoplasm then enter the DNA) , which are dedicated for gene transcription, the mRNA is then translated in the cytoplasm by ribosomes to produce proteins that alter the cell's activity.

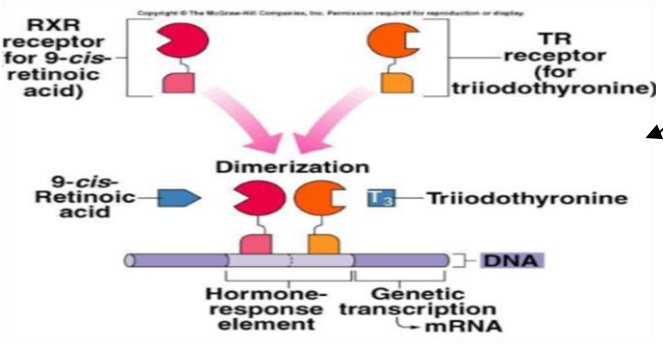
-The Nuclear hormone receptor has two binding sites (Two domains), one that binds to the receptor, and one that binds to the DNA, once the receptor is activated by its Hormone, it binds to the DNA on a region called the Hormone responsive element (HRE), which activates gene transcription. The HRE is always located adjacent to the gene that will be transcribed.

-Usually The Genetic transcription starts after the Dimerization of the hormone receptor



Dimerization is the process of 2 receptor units coming together at the half sites (the HRE is split into half sites, see picture to the left).

-Dimerization does not necessarily require two identical receptors, two different receptors for different hormones may dimerize to perform the same function.



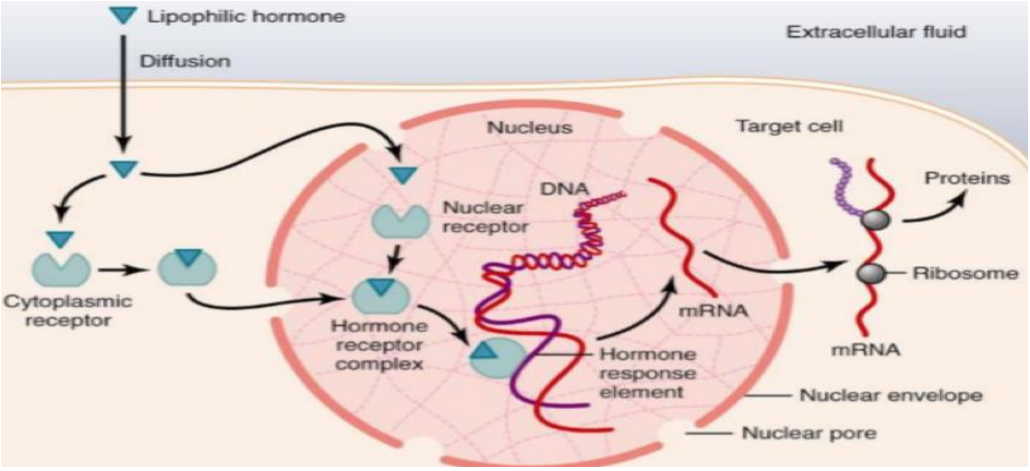
For Example:

1. **Aldosterone** is a hormone that causes increase in sodium reabsorption, it does that by forming more sodium channels that work on sodium reabsorption.

Note: The protein formed could be any protein that function in the cell, it does not have to be a channel protein, and every hormone produces a certain protein that preforms a certain function.

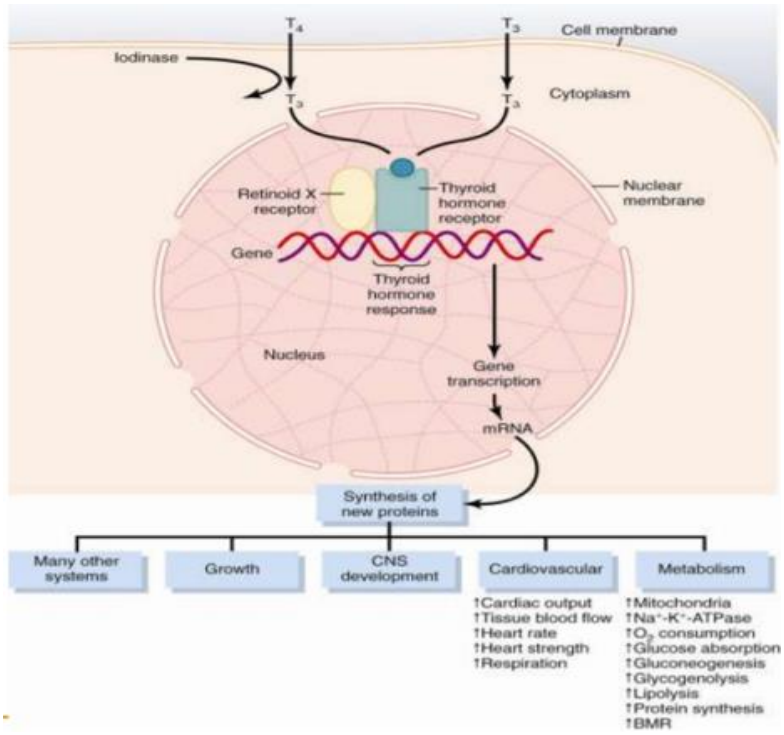
2. **Thyroid Hormone:** T3 and T4 are liposoluble tyrosine-based hormones (amines) that are primarily responsible for regulation of metabolism. T4 is transported from the blood into the cytoplasm and is converted to T3 by enzyme deiodinase which binds to its ligand binding domain in the nucleus, the other half of Dimerization is not a T3 receptor, it is actually a Vitamin A derivative (called "9-cis-retinoic acid" which binds to the RXR receptor), once both of these receptor's DNA-Binding domain binds to the half site, transcription of genes is Stimulated and new proteins are produced.

33:00



T_3/T_4 and the Central nervous system

- The newly formed proteins might be growth proteins which are important for the CNS development in the first 2 years after birth
- T_3 and T_4 are essential for the development of the central nervous system and the cerebral cortex *(which is responsible for voluntary movements and motor control)* in the first 2 years of age after birth



Congenital hypothyroidism

Before birth, the fetus takes T3 and T4 through the placenta because they are lipid soluble.

hypothyroidism is a condition of thyroid hormones (T3 and T4) deficiency present at birth. It prevents full development of CNS. Babies born with congenital hypothyroidism must be treated, If untreated for several months after birth, severe congenital hypothyroidism can lead to **growth failure** (the person is short) and **permanent intellectual disability/mental retardation**.

That's why newborn screening is done, babies at the age of 1 week are exhibited to T_4 blood test, if there is a deficiency in T_4, they are given a daily dose of thyroid hormone throughout their lives.

- In general, hormone deficiency cases are easy to treat, the patient has to be given the hormone as a drug and they will be healthy and normal.
- T3 and T4 are important for CNS development which is completed after 1.5 years (approximately). At this age if the CNS is fully develped, babies obtain the ability to walk, speak, and voluntarily urinate.

40:00

Hyperthyroidism

T3 and T4 increase basal metabolic rate, this means that more ATP is requires. 75% of ATP is released as heat, so a person who has hyperthyroidism will feel hot even if it's cold. A person with hypothyroidism can't tolerate cold weather.

Free and bound hormones

The relation between them is reversible; as one increases the other decreases.

42:00