By the name of Allah

Receptors function and signal transduction (Hormones and receptors Types)

We were talking about receptors of the neurotransmitters; we have 2 types of receptors:

1- Ionotropic receptors (ligand-gated channels); the receptor itself is an ion channel (When the hormone binds to the receptor it changes the permeability of the ion channel). The ion is the center of the receptor.

2- Metabotropic receptor (G protein-coupled receptors); bounding of a neurotransmitter to the receptor activates "G protein "and the alpha subunit disassociates and targets an ion channel nearby. (It changes the permeability of the ion channel).

** Ionotropic receptors are very fast and work faster than metabotropic receptors.

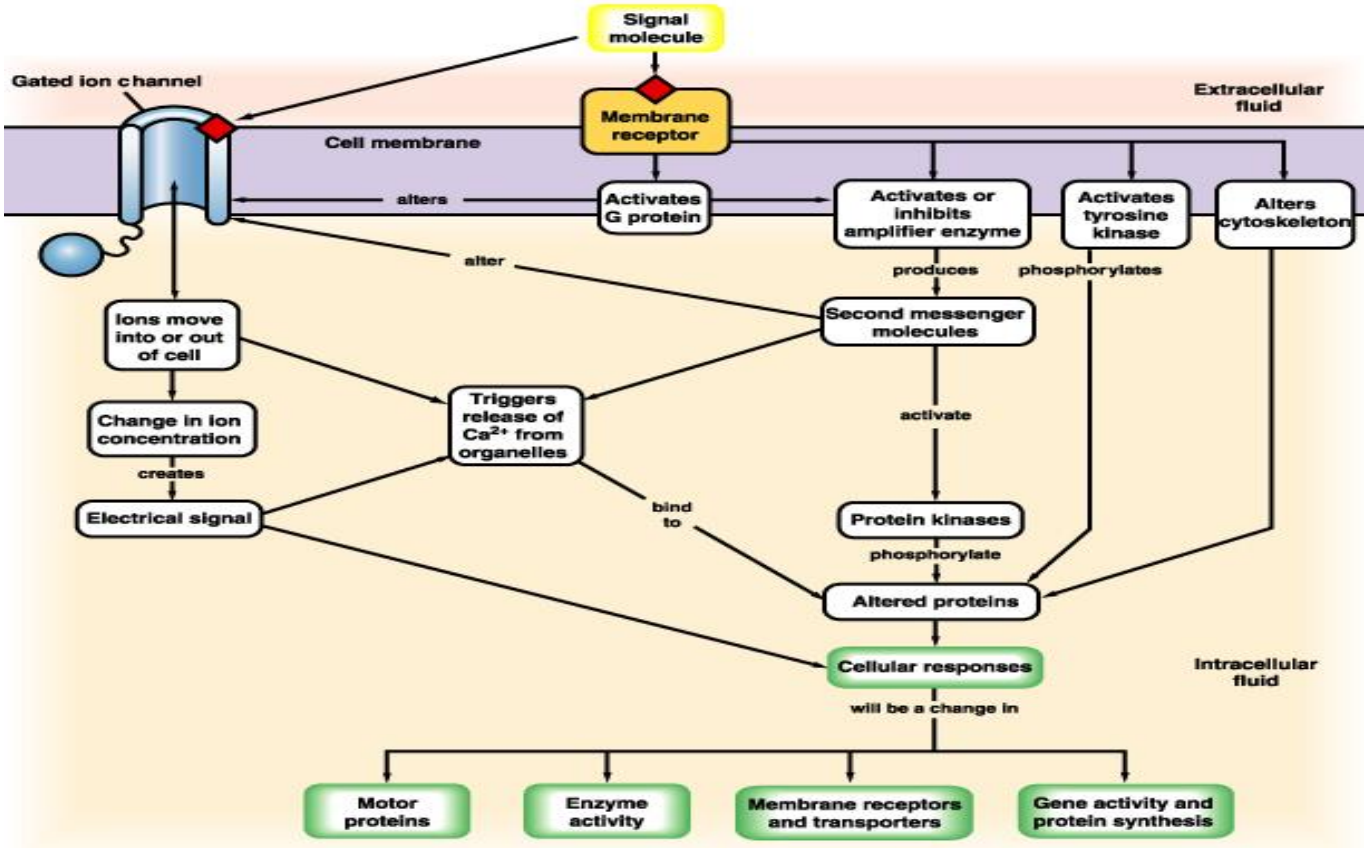
** An advantage for metabotropic receptors is that they last longer.

Sometimes metabotropic receptors work by second messenger mechanism ; bounding of a neurotransmitter activates the G protein , then the alpha subunit of the G protein activates an effector enzyme (Amplifier) (eg. Adenylate or Guanylate cyclase) adenylate cyclase converts ATP →cAMP (cAMP is the second messenger) , then cAMP can either work on a channel or activate protein kinases , protein kinases act on its substrate. So they have much longer effect than Ionotropic receptors.

- Second messenger might perform directly on the ion channel or phosphorylates protein kinases(indirectly).

** Another second messenger is IP3(activation of phospholipase C by α subunit causes degradation of phospholipids and leads to diacylglycerol and IP_3) which goes to the ER and causes an increase in the intracellular Ca++ by releasing it and Ca^{+2}

binds to calcium binding protein (calmodulin) and activates specific protein enzymes.



On this figure: Ca^{+2} could be released from electrical signals; that is the ion channels in the cell when opened or closed change the membrane electrical potential and this affects the voltage gated Ca^{+2} channels so this increases the Ca^{+2} in the cytoplasm indirectly (by electrical potential). In the end they work on protein kinases and cause cell response.

Each receptor has a primary ligand which binds to it to cause an effect, but receptors can have Agonists and Antagonists.

*Agonist: may be with higher or lower affinity than the ligand but has the same or increased effect of the primary ligand.

*Antagonist: blocks the receptor → will not have an effect.

*That means when we say: this is epinephrine agonist → it has the same effect of epinephrine, and if we say: this is epinephrine antagonist → it blocks the action of epinephrine.

***NOTE:**

When we say it is sympathomimetic drug, it mimics the effects of transmitter substances of the sympathetic nervous system (agonists) And the same goes with parasympathetic nervous system, **Parasympathomimetic drugs.**

PLC-Signaling pathway:

Signal molecule →activates G protein → activated alpha subunit (GTP) → activates phospholipase C →which break down phospholipids into : 1-Diacylglycerol

2-IP3(1,4,5-triphosphate) : which causes Ca++ release from the endoplasmic reticulum.

Together Diacylglycerol and Ca++ activate protein kinase C → which phosphorylate proteins.

- It is not necessary that the same proteins are phosphorylated by the same kinases. Proteins are formed from different types of amino acids and each amino acid can be phosphorylated by a different kinase, for example protein kinase A phosphorylates threonin and protein kinase B phosphorylates lysine... whatever so the kinases have different sites of phosphorylation → different sites means different actions. To sum up phosphorylation means to add phosphate to amino acid or proteins enzyme despite which type. And this activates kinase pathway, gene regulation.

**It is not necessary that the cell contains all types of protein kinases, some cells have one, two... or maybe all .

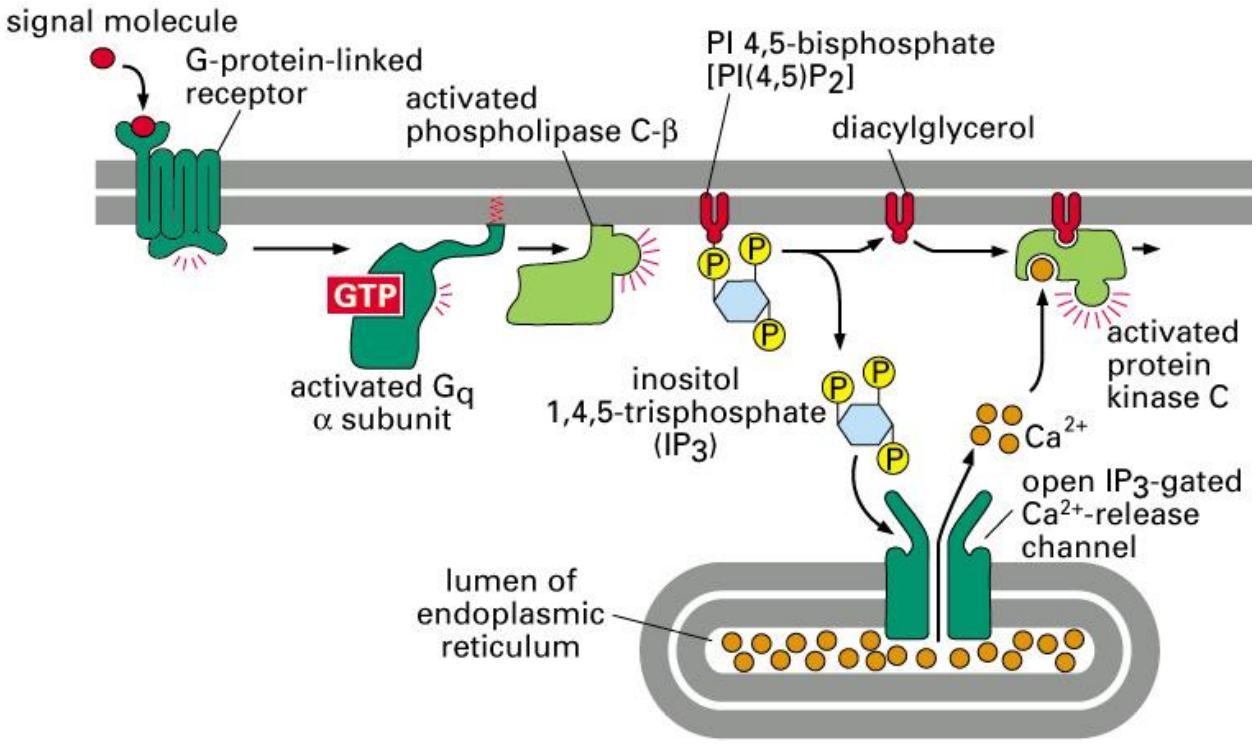


Figure 15–36. Molecular Biology of the Cell, 4th Edition.

Receptors Superfamilies: (Summary):

1-Ionotropic receptors: ligand gated channels.

2- Metabotropic receptors: G protein coupled receptors.

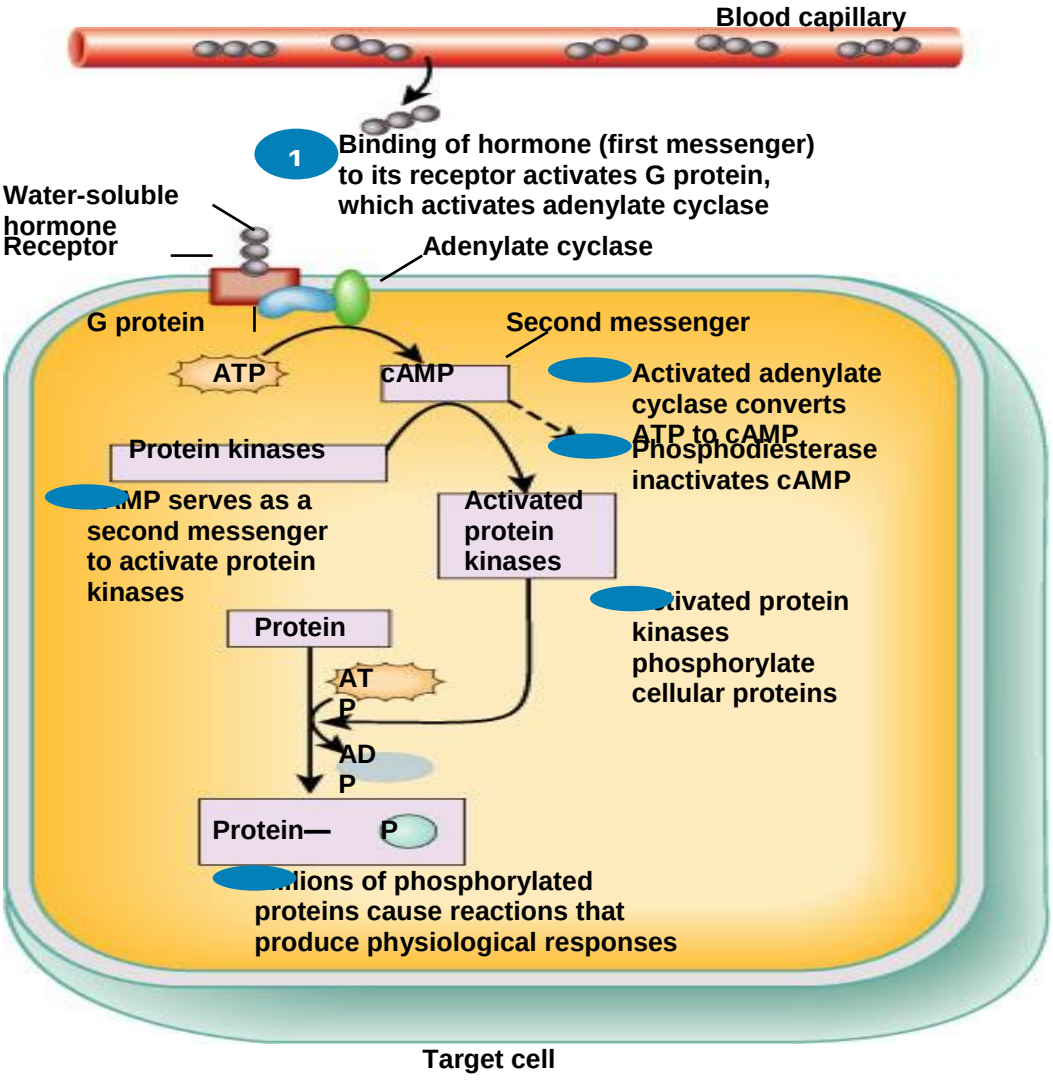
3-Tyrosine kinase.(we mentioned protein kinase A,B and C but we also have other special kinases like Tyrosine kinase, JAK kinase, lysine kinase). Kinase → Phosphorylation.

Ionotropic vs. Metabotropic ;)

	Speed	Lasts	Mechanism	# of subunits	2nd messen.
Ionotropic	Faster	Shorter	Direct activation(change the channel permeability)	4-5 subunits assemble the channel in the membrane	Not coupled
Metabotropic	Slower	Longer	G protein activation	1 subunit	Coupled

Water soluble hormones (e.g. epinephrine and norepinephrine) summary:

- The receptors are found on the cell membrane.
- And the response is amplified; we started with one hormone and we ended up with millions of phosphorylated proteins.→ this is called amplification process.
- We stop the reaction by activation of phosphodiesterase that inactivates cAMP by converting it to AMP. We also have phosphodiesterase for cGMP.



Some hormones work by 2 mechanisms on the same cell because it has 2 types of receptors; epinephrine has alpha and beta receptors, if it binds to its alpha receptors it will increase Ca++ influx , meanwhile if it binds to its beta receptors it will increase cAMP by activating G protein, and then cAMP will activate protein kinases. It has multiple actions.

Lipid soluble hormones (e.g. Lipophilic steroid and thyroid hormones):

- They are unable to dissolve in water so they need a water soluble transporter to move in blood , after they reach their target cells they detach and diffuse in the cell to bound to their receptor. It is found in the cytoplasm or the nucleus and eventually they are translocated to the nucleus after binding even if the receptor was in the cytoplasm.

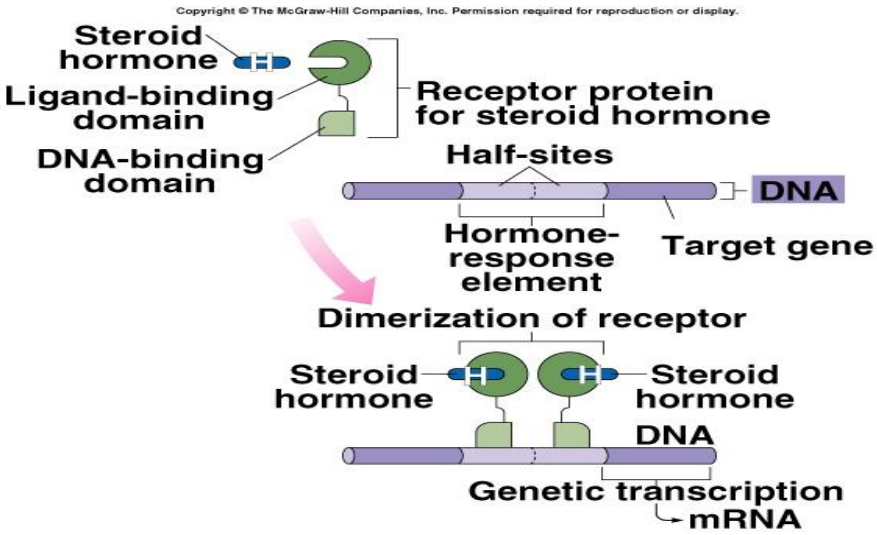
1-Steroid hormones action:

(Each nuclear hormone receptor has 2 regions-binding sites):

- A ligand (hormone)-binding domain.
- DNA-binding domain.

An activated receptor-hormone complex is formed (by binding of the hormone to the receptor), 2 complexes dimmerize then bind to a specific place on the DNA that is called hormone responsive element HRE (has 2 sites because the dimmer needs 2 sites) to cause a gene transcription of the nearby DNA part to form a protein . Each hormone has a specific gene→ specific action.

*The new protein synthesized could be a channel, receptor, enzyme, hormone and a transporter.



2-Thyroid hormones action:

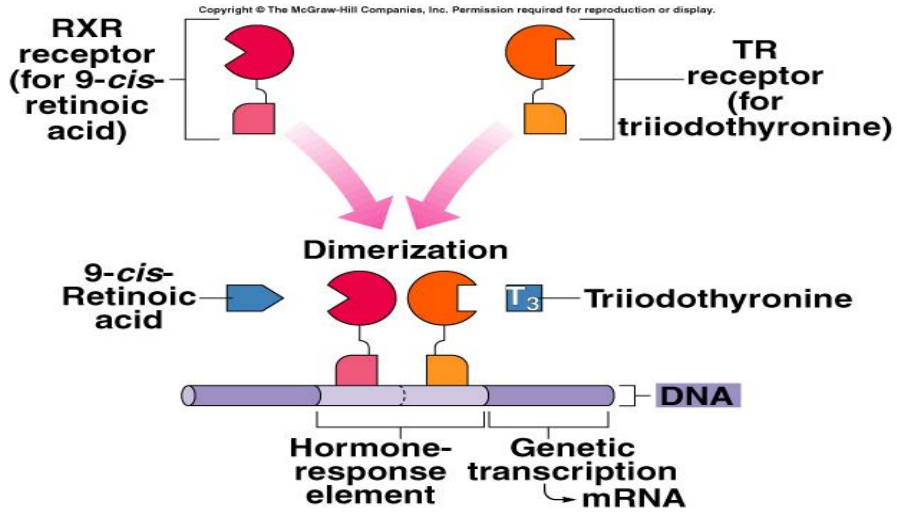
They also need carriers through blood.

**Remember: As T4 enters the cell it is converted into T3 because it is more active.

The thyroid hormone receptor is in the nucleus and has 2 binding sites one for T3 and one for binding with the DNA.

The dimerization (these receptors always work as dimers) happens with one receptor-hormone complex containing T3 receptor and the other half site is for vitamin A derivative (9- cis-retinoic acid receptor).

After binding the dimmer with the HRE of the DNA , gene transcription happens to form a protein that affects growth, CNS development, metabolism, cardiovascular and many other systems...



For example if the formed protein is a β receptor when added to the heart cells we will have more sympathetic innervation.

T3 and T4 are very important in development of the CNS (central nervous system) for 2 years after birth, so after birth the doctors should check the levels of these hormones (before birth it is not important to check the level because the embryo takes the hormones from the mother), if there is deficiency in these hormones this person will suffer from congenital HYPOTHYRODISM (shortness and mental retarded) if not treated.

*Treatment: by giving him T4 hormone for the rest of his life and the CNS will develop normally and maintain normal growth → one (100mlg) tablet of T4 once a day and this will save him. Each packet contains 100 tablets for 3 months.

**Endocrine cells secretes free hormones , if there is excess free hormones they will they will form carrier – bound hormone (hormones bounded to the carrier proteins in the blood) , if there is more bound hormones they will go to free hormones (balance).

Half life & Metabolic clearance:

Bound hormones have different half lives.

** Plasma Half life: is the time required for the hormone to reach its half concentration.

** **Metabolic clearance:** is the amount of hormone consumed (ml/minute)

The more the half life the less the metabolic clearance will be .

Hormone / comparison	Half life	Metabolic clearance
Thyroxin (T4)	6 Days	0.7 ml/minute
Aldosterone	25 minutes	1100 ml/minute
Cortisol	100 min	140ml/minute

As we mentioned before carrier proteins are water soluble proteins, they might be specific or nonspecific.

Only the lipid soluble proteins are bound proteins.

	Transport protein	Hormone transported
Specific	*Corticosteroid binding globulin (CBG, transcortin)	Cortisol, Aldosterone
	*Thyroxin binding globulin (TBG)	Thyroxin, triiodothyronine
	*Sex hormone-binding globulin (SHBG)	Testosterone, estrogen
Nonspecific	Albumin	Most steroids, thyroxin, triiodothyronin
	Transthyretin (prealbumin)	Thyroxin, some steroid hormones

Feedback mechanism:

*Negative feedback: 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.

*Positive feedback: the endocrine cell secretes 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 increase→ response increase.

ختامها مسك

Good luck everyone ;)