

Receptors and hormones :

activity of hormones depends on the receptor , so hormones affect specific target tissue because of the presence of specific receptor .

Receptor are protein whether they are intracellular or membranous .

they're dynamic (not static) with constantly synthesized and broken down .

Upgration (up-regulation) is the increase in the number of receptors and thus the circuit will be more sensitive .

Downgration (down-regulation) is the decrease in the number of receptors where the cell becomes desensitized or less active .

The number and sensitivity of hormone receptors are regulated by :-

The effects of hormone depends on : the hormone concentration and the number of receptors , both are directly proportional .

Also when it's saturated , that is when all receptors are fully occupied so no more hormones will affect .

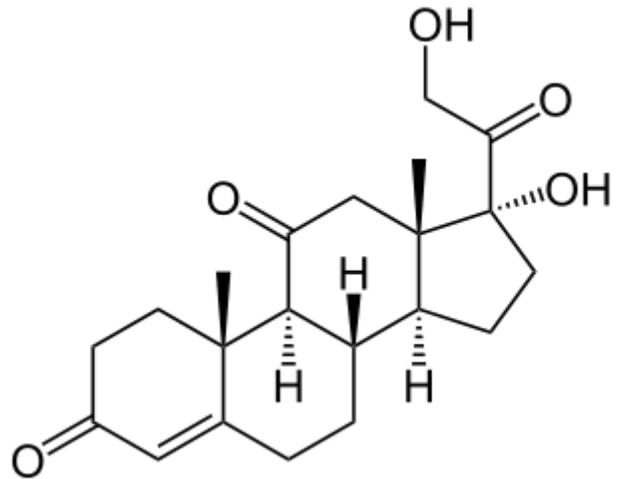
- 1) upgration increase in the number of receptors on the target cell in response to a particular hormone especially if the circuit is dormant (not active) after a while the number of receptors will be increased so any small amount of the hormone will be highly affective and the response will be more than usual .
- 2) downgration especially for water soluble hormones (polypeptide hormone) for sometimes there would be a high availability of water soluble hormones , the number of receptors will be decreased by internalizing the receptors (exposing them to the intracellular compartment rather than exposing them to the extracellular compartment) so they are not exposed to the hormone therefore there would be no further response , e.g. insulin in adipose tissue .

How is hormone secreted :-

Hormones are not secreted continuously, they are rather secreted in a pulsatile form (like pulses at a time there is a secretion after a while this secretion is stopped then another secretion then it's stopped and so on).

The advantage of this pulsatile form that it decreases the downgration process .

e.g. Cortisone is secreted in higher amount in the morning compared to the afternoon and its importance comes because it makes the person alert , awake and pleased (that's why 8 am lecture is important :P).



Hormones and their half life :-

Half life of hormones : is the time required for the hormone to decrease its concentration to half the original value e.g. half life of thyroxin is about 7 days so you don't need to give the hormone thyroxin to the patient three time per day so it's satisfactory to give him one dose every week . One the other hand the half life of insulin is between 10 to 20 minutes so insulin shall be given to the patient more frequent.

Drug	Anti-inflammatory strength*	Dose equivalent (mg)	Relative sodium retention**	Plasmatic half-life (minutes)	Biologic half-life (hours)
Hydrocortisone	1	20	1	90	8 - 12
Cortisone	0.8	25	0.8	30	8 - 12
Prednisone	4	5	0.2	60	12 - 36
Prednisolone	5	4	0	180	12 - 36
Methylprednisolone	5	4	0	180	12 - 36
Triamcinolone	5	4	0	300	12 - 36
Betamethasone	25	0.5	0	100 - 300	24 - 72
Dexamethasone	25	0.75	0	100 - 300	24 - 72

Figure 2. Glucocorticoid equivalence for systemic administration.

* Glucocorticoid effect

** Mineralocorticoid effect

Adapted from reference 3.

The difference between physiological and pharmacological concentration :-

Physiological range of hormone is the normal concentration of hormone that is produced inside our body, so the effect of hormone is perfect if the hormone is present in the physiological range.

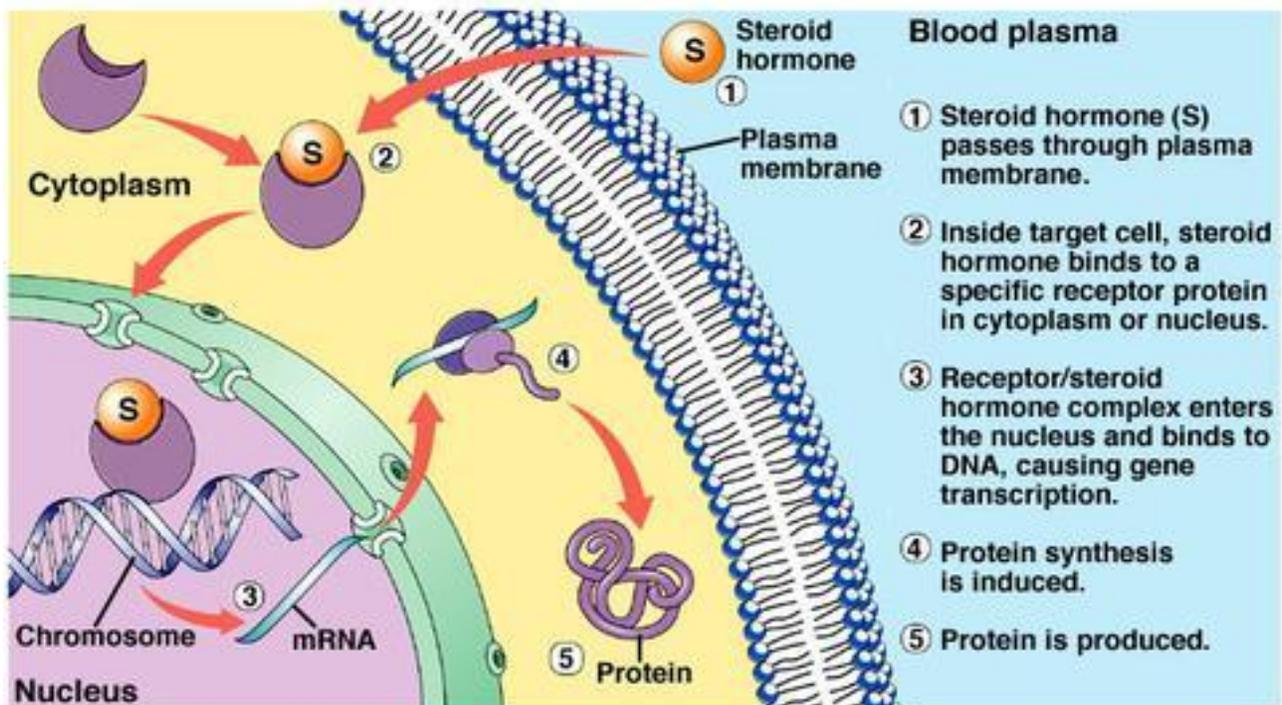
Pharmacological concentration is the concentration of hormone in drugs, and the concentration is different from the physiological because it is used for treatment.

The different mechanisms of binding between water soluble and lipid soluble hormones :-

- 1) Water soluble hormones (peptide hormones) have receptors that are membranous e.g. insulin, also called lipophobic. These hormones usually act through second messenger.
- 2) Lipid soluble hormones e.g. steroid, thyroxin, they pass through the membrane so their receptors might be found in the cytosol or nucleus. If they are cytosolic receptors they will bind to it and then translocate to the nucleus thus their effect is over the DNA (gene transcription and translation), also called lipophilic.

so in the end they have to enter the nucleus.

Steroid Hormone Action



Some mechanisms

Synthesized hormones or drugs acts similarly upon the receptors of the normal hormone .

- 1) Antagonists (the blockers) opposite action , by binding to the same hormone receptor (as it has the same structure) they will block the action of the hormone because the normal hormone can't bind any longer to its receptors .
- 2) Agonist same action of the hormone .

Affinity of the receptors to the hormone is the tendency of hormone to bind to the receptor , therefore high affinity requires only small amount of the hormone to have its effect and low affinity need a very high concentration to have the same effect .

Intercellular signaling after hormone receptor activation :-

Ligand molecule (hormone) transduce signal where the binding initiates a certain mechanism inside the cell

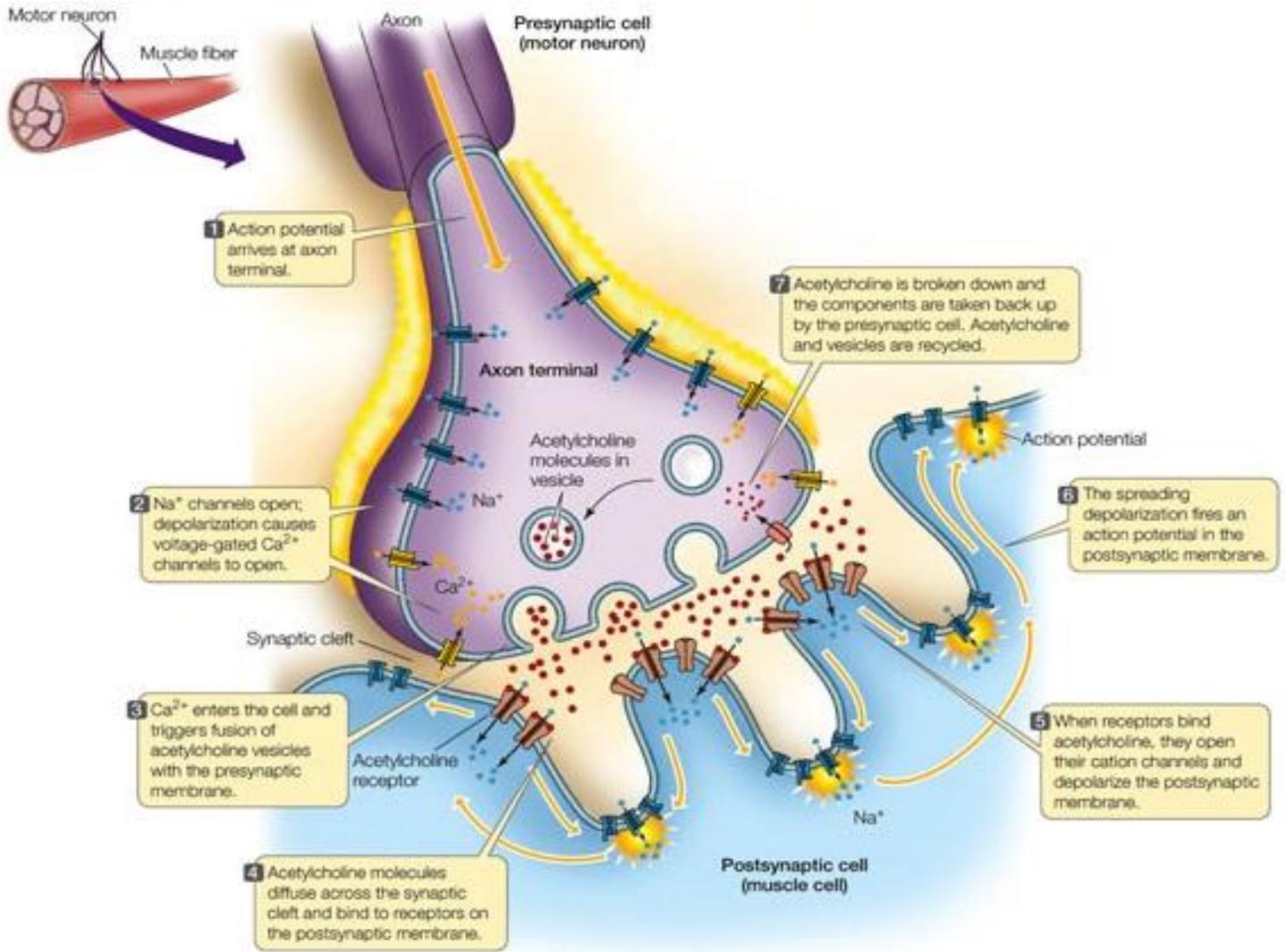
1) Activation of channels :-

When a ligand binds to its receptor this activates G protein , the activation of G protein will induce activation on specific channel such as Na channels , for example :

Acetylcholine when it binds on its receptors on the membrane it changes the permeability of ionic channel (could be cationic or anionic) which will open cationic channel usually Na this will cause depolarization as the membrane potential becomes less negative .

ACh also acts upon synapse , as the neurotransmitter vesicles reaches the presynaptic knob , calcium channel will open (voltage gated) and calcium will move into the knob by simple diffusion down its concentration gradient this will stimulate the fusion of vesicles to the membrane of the knob which results in the releasing of the neurotransmitters , these will bind to Na channels on the postsynaptic membrane which will open them .

note : Acetylcholine (ACh)
channels are pentameric and open
due to rotation



2) Second messenger

The main function is amplification (so one hormone will produce a couple of second messengers and every second messenger might function on about 10 proteins)

G protein , present on the membrane which consist of three subunits (intracellular) alpha , beta and gamma , seven helices and extracellular binding site . They're bound to GDP in the "off" state but when GTP binds to the G protein it will be switched on and the alpha subunit will be released , this alpha subunit has function in the cell .

G proteins belong to the larger group of enzymes called GTPases (which hydrolyze GTP) . The alpha subunit might cause the opening of ionic channels.

alpha subunit can go to the DNA to affect transcription and translation so it change the protein formation

c-AMP as a second messenger

The alpha subunit could activate a membranous enzyme e.g. adenylyl cyclase which changes ATP to c-AMP or guanylyl cyclase which changes GTP to c-GMP

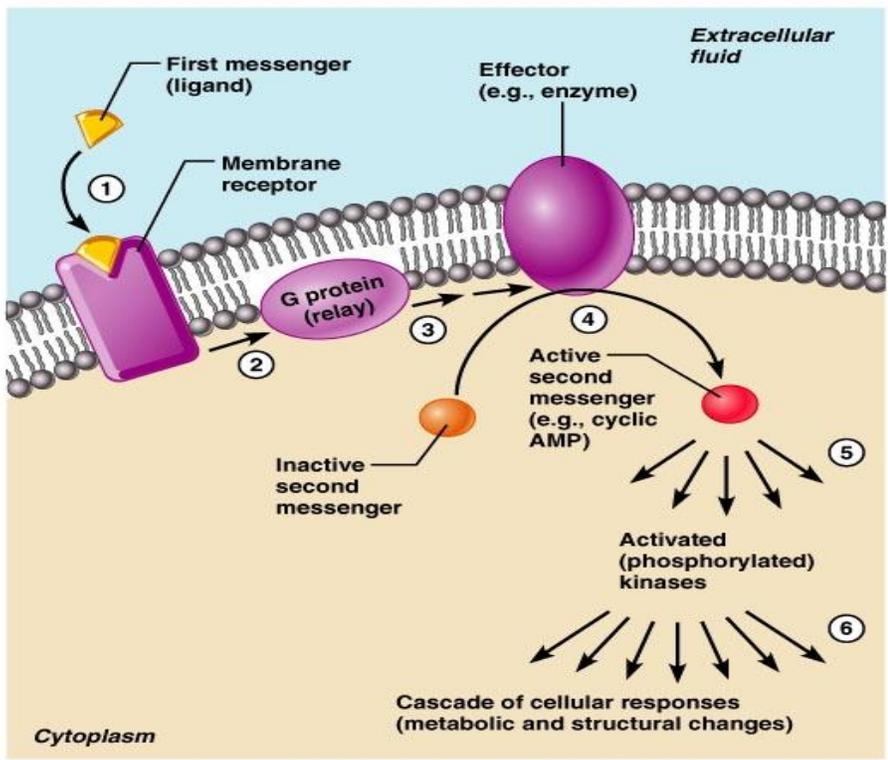
c-AMP will activate a c-AMP dependant protein kinase (protein kinase A) which will phosphorylate a protein which cause a change in activity inside the cell

Ca as a second messenger

In this pathway phospholipase C is activated . This enzyme breaks down PIP₂ into DAG and IP₃ . IP₃ induces the release of Ca from ER into cytosol where it binds to and activates a protein called calmodulin . The activation of calmodulin triggers Ca dependant cellular response by altering activity of other functional proteins inside target cell .

Handout 1 has explained cellular events after binding of ligand to its receptor

Though no one can go back and make a brand new start, anyone can start from now and make a brand new ending.



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