Endocrine system

1

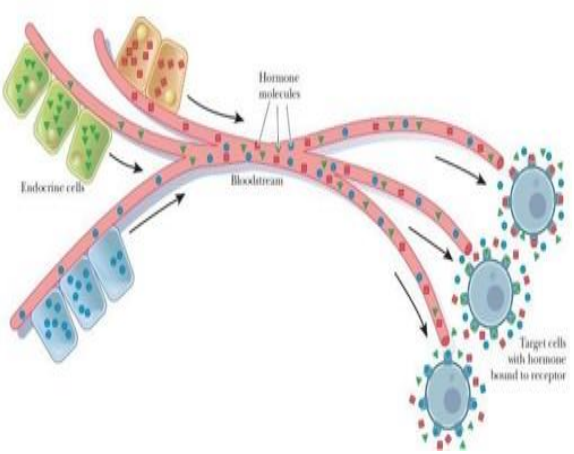
Biochemistry

Writer: Alaa Bany Amer

Corrector: Rahaf Turab

Doctor: Nafez Abu-Tarboush

Hormones: The Remote Controllers.



❖ **What are hormones?**

Hormones are **organic** substances (proteins, lipids, steroids and catecholamines) released to blood in **small amounts** with specific source and target. Also, they perform their function by binding to certain receptors in or on cells.

Note: It is very important to know that hormones are secreted in very **small quantities**. If there are two substances whose concentration is high in the blood, you must exclude **hormones and enzymes.**

❖ **Functions:**

-They help maintain homeostasis.

-Mediate responses to external stimuli.

-Play roles in growth and development.

Very helpful video for overview:

https://youtu.be/9sF_h-bAnIE

❖ **What is the way hormones are released?**

The effect of hormones is very large although they are secreted in very small quantities, so the best way to prevent the over stimulation of receptors is to be released in a **pulsatile manner**.

Recall that the signal that results from the binding of the hormone to its receptor is **amplified. Thus, a greater response occurs despite the lack of its concentration.

❖ **Classes:**

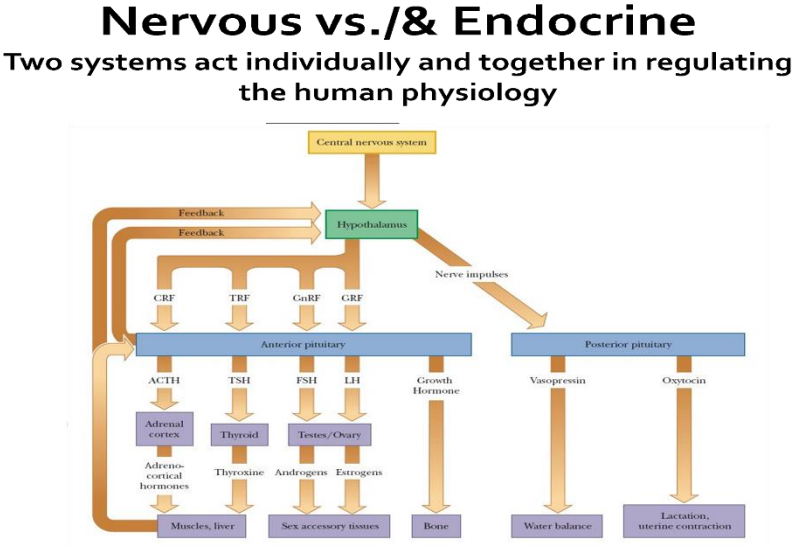
Previously it was thought that hormones are released from a **ductless source** to **blood stream** to act **distally** (away from the source), then it was found that there are molecules (hormones) which are released from a **ductless source** affecting **nearby tissues** without reaching blood stream, according to that, hormones are classified into:

- Endocrine hormones: explained above^
- Paracrine hormones: released without reaching blood stream and effect **different type of cells.**

- Autocrine hormone: released without reaching blood stream and effect **same type of cells.**

Nervous vs./ endocrine

- metabolism is mainly controlled by **central nervous system** and **endocrine system** and, so both integrating their actions to regulate and control metabolic activities in human body and maintain homeostasis.
- Both endocrine system and CNS are regulated and controlled in the same manner by **+/- feedback.**



The target cell concept

- Understanding the endocrine system from a physiological, pathological and anatomical point of view may be somewhat easy, but understanding it from a biochemical point of view may be difficult and complex, but why is understanding it biochemically difficult?
  - You can imagine that there are about **200 types of differentiated cells** in the human body that make up more than **75 trillion cells**, and this huge number of cells is controlled by **less than 50 known hormones** only! And what makes things more and more difficult is that:
    - One hormone can bind to several cell types.
    - One cell type might be affected with several hormones.
    - One hormone can have several effects in different types of cells.

  - What explains this complexity is the differences between cells in protein expression induced from this hormone.
    e.g: hormone binds its receptor-which is the same in all cells- induces the same signal transductions in all cells but the effect is different in each cell type according to the **protein expression** occur in that cell.
    *Each different tissue contains different protein expression.

To bring the concept closer: All cells contain the same DNA content, but what makes them different? The protein expression varies according to the function of each cell.

Here I will present the students' answers and the doctor's interpretation of what is incorrect about the hormone's ability to cause different effects in different cells despite the presence of a small number of hormones compared to the number of cells:

Student 1: one hormone can bind to different receptors causing different effects.

Doctor's answer: biochemically that's not true, because hormones have a fixed structure→They bind to the same receptor every time.

An example of this is insulin. It binds to the same receptor-tyrosine kinase receptor-, yet different effects occur in each organ-liver, muscles and adipose tissue-.

Student 2: the different effect is induced by different signal transductions.

Doctor's answer: logically the transduction mechanisms are same in same receptors (what binds to the receptor intracellularly is same).

Student 3: hormones might have different binding sites.

Doctor's answer: assuming different binding sites → different receptors and that's not true. An example: thyrotropin releasing hormone -that is secreted from hypothalamus to anterior pituitary gland- consists of only 3 amino acid فشو بده يلحق ليلحقif it has different binding sites.

❖ Several factors determine the response of target cell to a hormone:

Factors affect the concentrations of the hormone at the target cell:
the rate of synthesis and secretion of the hormone.
The proximity of the target cell to the hormone source (dilution). Distance will affect the dilution (further = more dilution).
The Kd of the hormone-receptor complex. Recall that hormone binds to its own receptor due the presence of affinity, and the only parameter that expresses affinity is Kd. Thus, when Kd is low means low concentration, and strong binding → high affinity and vice versa. (Kd= concentration)

The rate of conversion of inactive form to the fully active form
The rate of clearance from the plasma. Hormones are designed to be degraded and cleared after a certain limit and in different rates→ effecting the concentration of those hormones at the site of action→different efficacy.
Displaceable binding between hormone and receptor. Not covalent binding: *Competition between hormones. * To release the hormones to bind again. *to prevent the consistent stimulation of target cells.

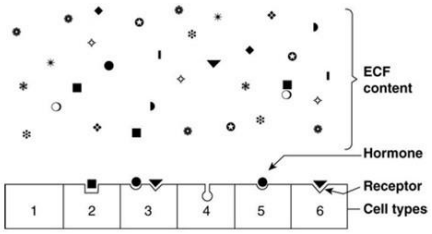
❖ Several factors determine the response of target cell to a hormone:

Factors effecting the target cell response:
the number, relative activity, and stage of occupancy of receptors.
The metabolism(activation/inactivation) of the hormone in target cell.
The presence of factors within target cell necessary for the response.
Up-or-down-regulation of the receptors upon interaction with ligand. ****post-receptor desensitization of the cell.**

Receptors Discriminate Precisely

❖ Major challenge:

- Atto- to nano-molarrange (10–15 to 10–9 mol/L) vs. Structurally similar molecules (sterols, amino acids, peptides, and proteins): micro- to milli-molar (10–6 to 10–3 mol/L) range.



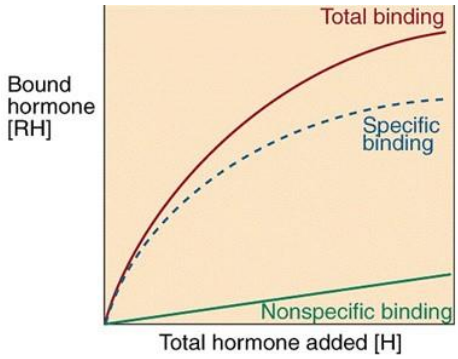
**The nature of hormones is organic and it is known that the differences between the structures of organic compounds are few , meaning that they are very similar, in addition to the fact that these compounds are present in very large quantities, which poses a great challenge to hormones that are secreted to blood in small quantities in a pulsatile manner

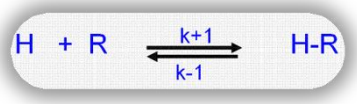
crossing large distances to reach their target without being diluted + binding to their receptors and causing effect !!!! . طب شو الحل بهيك حالة ؟

- Solution: is to increase the affinity between the receptor and hormone- low kd- و هاد بخلي الريسبتور يلقط الهرمون تلقيط

Accordingly, Hormone-receptor interaction

- Should be specific: **displaceable** by agonist or antagonist.
- Should be **saturable**.
- Should occur within the concentration range provided.



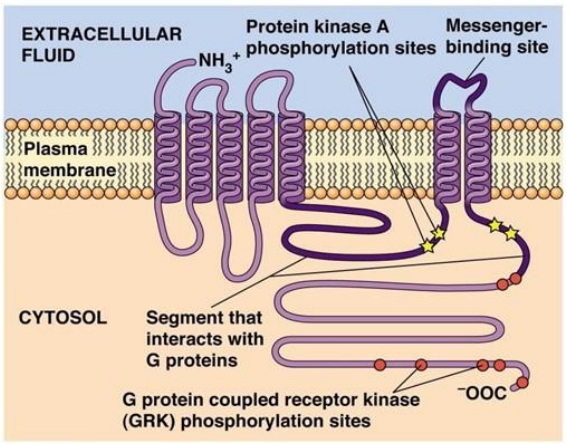


- Should occur within the concentration range provided.
- Dissociation constant $K_{d.}$
- K_d = {[H]X [R]} / [H-R].
- **20 X dissociation constant** is enough to saturate the receptor.
- **K_d** values for many hormones range from 10^{-9} to 10^{-11} M.

Receptor domain

- Receptors are always **proteins**→ to resemble their functions through **confirmational changes** (receptors are proteins that change their confirmation as a result of binding).
- Receptors of hormones are classified according to the location of the receptor into **surface receptors** and **intracellular receptors** and -each type has at least 2 domains-:
  1) Recognition domain. 2) Coupling or signal transduction domain.

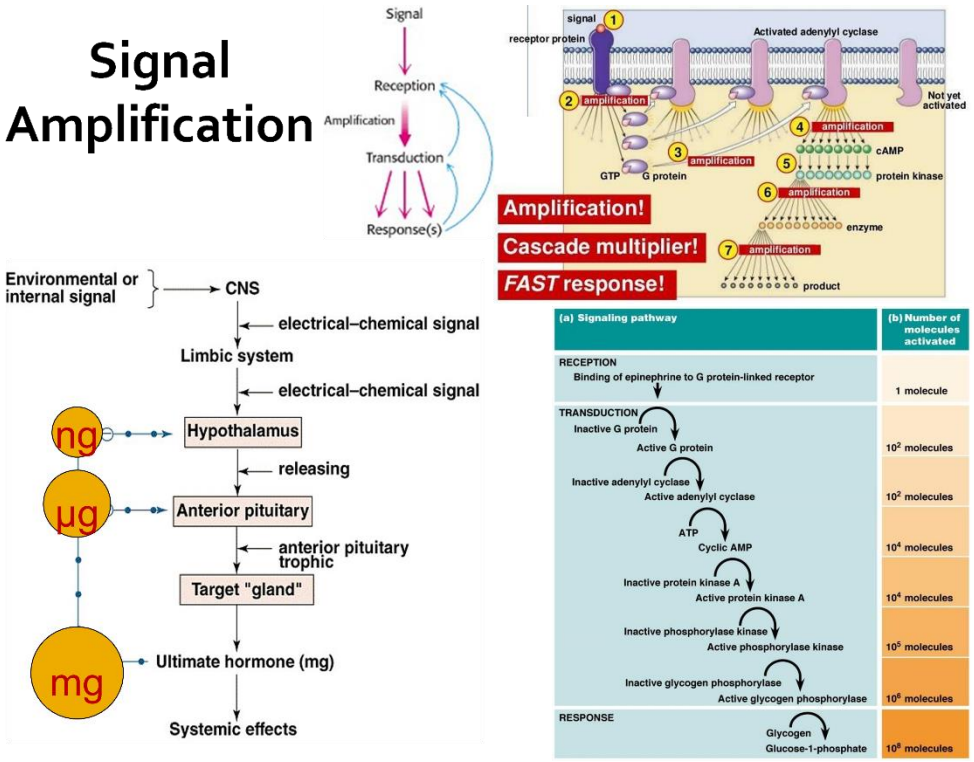
  Recall: domain is a part of the protein that if it is cleaved it will behave in the same manner.



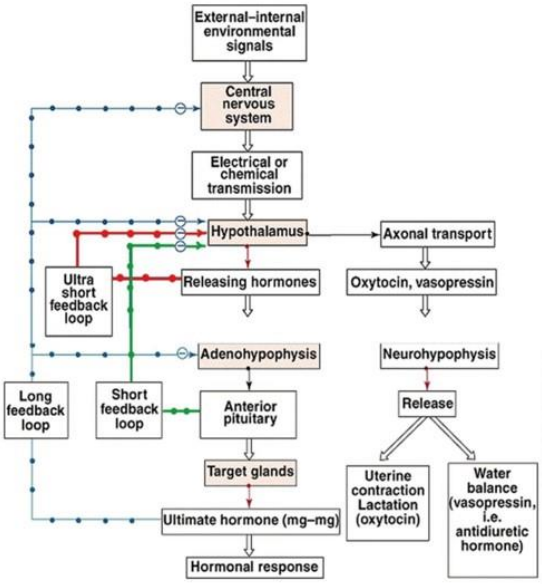
- Receptor–effector coupling provides the first step in amplification.

	Surface receptors	Intracellular receptor
domains	**Recognition domain or hormone binding domain (outside the cell).**	**Recognition domain or hormone binding domain.**
	Coupling or signal transduction domain (inside the cell). Part of the receptor that transmit the signal inside the cell.	**DNA binding domain**. The destination of intracellular receptors is mainly DNA, so these receptors bind to DNA on HRE (hormone response element) to initiate protein expression process. eg: co-regulator proteins binding site, cellular trafficking proteins binding site.
How the coupling occurs?	**Changing the activity of an enzyme**	**Direct.**
Examples (hormones)	**Polypeptide & catecholamines.**	**steroids, retinoids, and thyroid hormones.**

Amplification

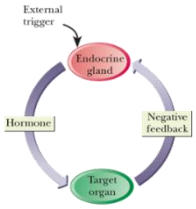


How the release is controlled?



❖ **feedback inhibition:** controlling the release of hormones over the body in a very tight manner and at more than one level so when the levels of the hormones increase → feedback inhibition→ either on cells that release the hormones or on another cell that contributed to the secretion of a hormone, stimulating other cells to secrete that hormone whose levels have risen.through:

- **Ultra-short loop.**
- **Short loop.**
- **Long loop.**

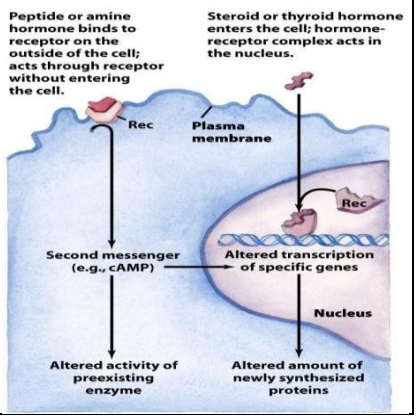


Classification of hormones/chemical structures

Can be classified according to **solubility** (water-soluble/lipid-soluble); **location of receptors** (intracellular receptors/ surface receptors); **nature of the signal used to mediate hormonal action**; or according to **chemical composition**:

- Polypeptides: Pituitary hormones; Hypothalamic releasing hormones; Insulin, Growth factor.
- Amino acid derivatives: Adrenalin, Thyroid hormones.
- Steroids.

Classification of hormones/MOA

<table>
<tr><th></th><th colspan="4">Hormones that bind to cell surface receptors</th><th colspan="3">Hormones that bind to intracellular receptors</th></tr>
<tr><td rowspan="2">classification</td><td colspan="4">According to second messenger:</td><td colspan="3">-</td></tr>
<tr><td>cAMP:
β adrenergic factor, glucagon, ACTH</td><td>cGMP:
atrial natriuretic factor, Nitric oxide</td><td>Calcium or phosphatidyl inositol:
oxytocin, TRH</td><td>Kinase or phosphatase cascade:
insulin, GH</td><td>Calcitriol, retinoic acid</td><td>Steroids</td><td>Thyroid</td></tr>
<tr><td>Notes:</td><td colspan="4">Another challenge faces hormone: 30 hormones mediate their effect through cAMP.
Solution: **cAMP→ PKA → phosphorylation. While Ca++ mediate their effect through PKC.
** different timing, environment and conditions →different concentrations → different strength of binding → different confirmational changes → different amount of cAMP to be produced → different effect.</td><td colspan="3">*Transport proteins.
* Long Half- life (hrs-days).
 
</td></tr>
</table>

General features of hormone classes

	Group I	Group II
Types	Steroids, iodothyronines, calcitriol, retinoids	Polypeptides, proteins, glycoproteins, catecholamines
Action	Slow	Fast Second messenger
Solubility	Lipophilic	Hydrophilic
Transport proteins	Yes	No
Plasma $t_{1/2}$	Long (hrs - days)	Short (minutes)
Receptor	Intracellular	Plasma membrane
Mediator	Receptor-hormone complex	cAMP, cGMP, Ca^{2+}, kinase cascades, metabolites of phosphoinositols

Things that bind to the DNA causing protein expression will act slowly, so the half lives of the hormones will be longer.