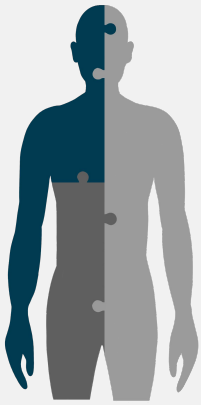


Revised & Approved



Introduction to Endocrine physiology

Objectives:

- ❖ **Hormones**
 - Definition
 - Chemical structure
 - Paracrine and autocrine
 - ❖ **Secretion/Transport and clearance of hormones**
 - ❖ **Mechanism of action of hormones**
 - Hormone receptors, down-regulation and up-regulation
 - Intracellular signaling
 - Second messenger mechanism (cAMP, IP₃)
-

Color index:

- ❖ **Important.**
- ❖ **Girls slide only.**
- ❖ **Boys slide only.**
- ❖ **Dr's note.**
- ❖ **Extra information.**

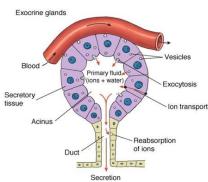


Editing File

Glands

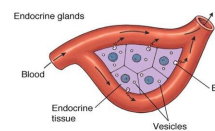
Exocrine gland⁽¹⁾

- ❖ Ducts
- ❖ Secretes enzymes
- ❖ Lumen and surfaces



Endocrine gland⁽²⁾

- ❖ No ducts
- ❖ Secretes Chemical Messengers
- ❖ Blood stream



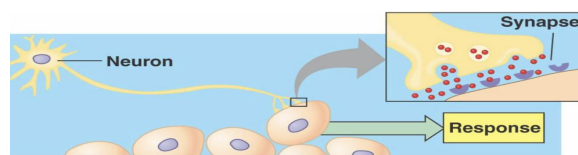
Chemical messengers

The activities of cells, tissues and organs are coordinated by chemical messengers:

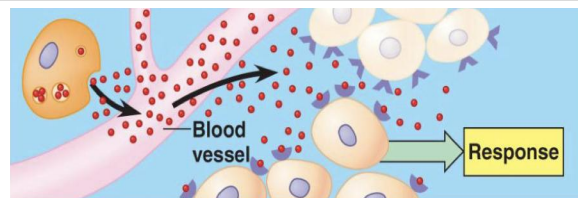
لازم نعرف لكل واحد:
 - جاي من وين ؟
 - فين released ؟
 - يشتغل على ايه ؟

Chemical messengers

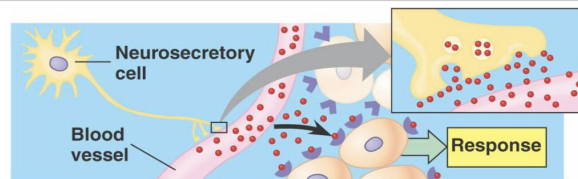
Neurotransmitters are released by axon terminals of neurons into the synaptic junctions and act locally to control nerve cell functions.*



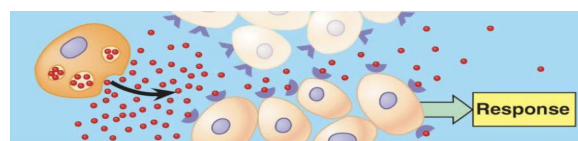
Endocrine hormones⁽³⁾ are released by glands or specialized cells into the circulating blood and influence the function of target cells at another location in the body.*



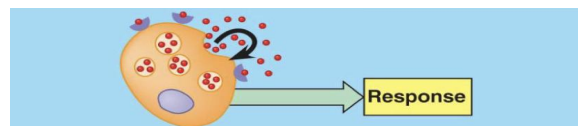
Neuroendocrine hormones⁽⁴⁾ are secreted by neurons into the circulating blood and influence the function of target cells at another location in the body.*



Paracrines⁽⁵⁾ are secreted by cells into the extracellular fluid and affect neighbouring target cells of a different type.
 - locally acting chemicals that affect cells other than those that secrete them.*



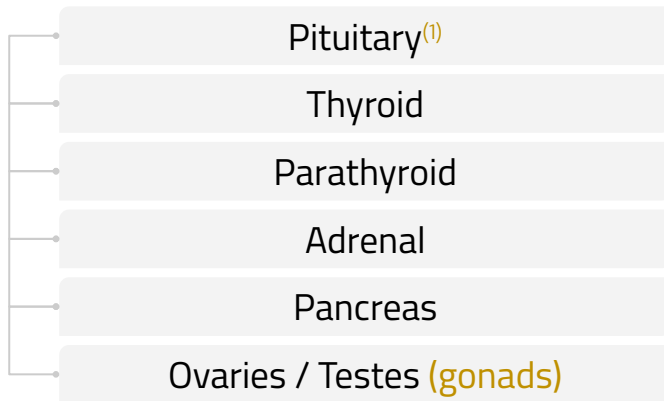
Autocrines are secreted by cells into the extracellular fluid and affect the function of the same cells that produced them.
 - Chemicals that exert their effects on the same cells that secrete them.*



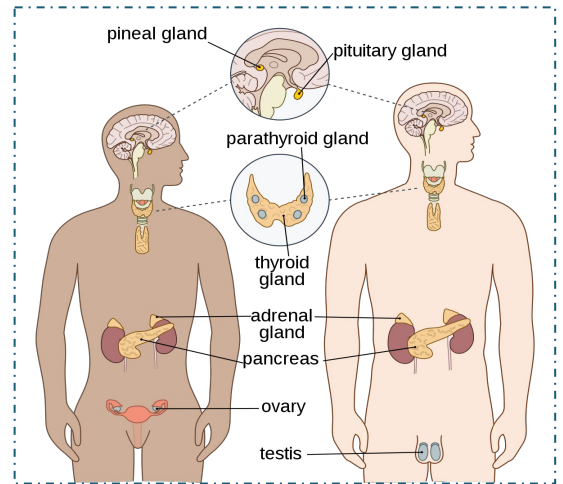
Cytokines are peptides secreted by cells into the extracellular fluid and can function as autocrines, paracrines, or endocrine hormones.
 Examples of cytokines include the interleukins, lymphokines and adipokines.*

- 1) E.x. Salivary gland, sweat gland and pancreas (which has both endocrine part and exocrine part).
- 2) Specialized cells surrounded by circulation secrete hormones directly into circulation.
- 3) Example: Hormone released from Anterior pituitary and travel through blood to ovary or testes
- 4) Neuro: from nerve cell. Endocrine: released in the circulating blood.
- 5) Hormone from Hypothalamus will affect the anterior pituitary

Endocrine glands



Placenta has endocrine function That secrete hormones.



What is hormone?

- Hormone is a chemical substance released by group of cells to control the function of other type of cells*
- Chemical substance secreted in a small amount from endocrine gland directly to the bloodstream in response to stimulus to cause physiological responses at the target tissues.*

Types of Hormones*

Affect many different types of cells (eg. GH (growth hormone) and Thyroxin).

Affect only specific target cells (eg. ACTH and estrogen).

The multiple hormone systems play a key role in regulating almost all body functions: so, it's very difficult to treat (اللعب بالهرمون زي اللعب بالنار)

Metabolism

Growth and development

Water and electrolyte balance

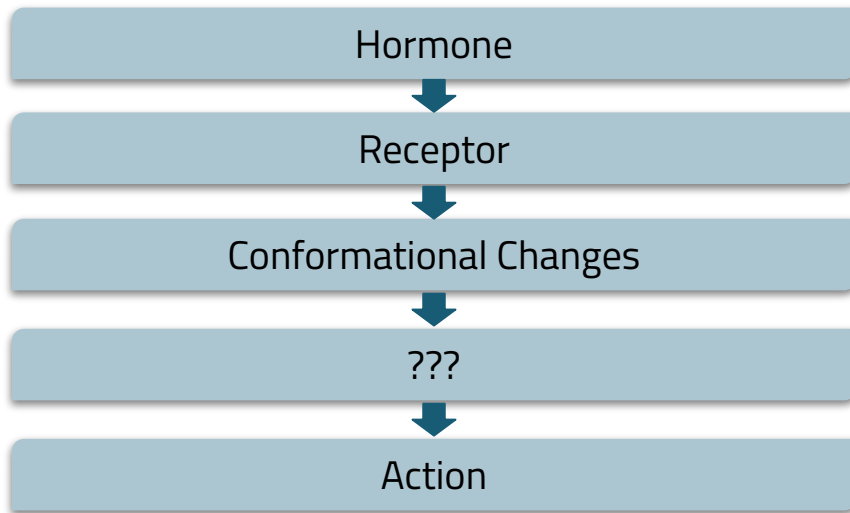
Reproduction

Behavior

1) Why is it considered the maestro? It Release hormones that affect the function of most of the other glands

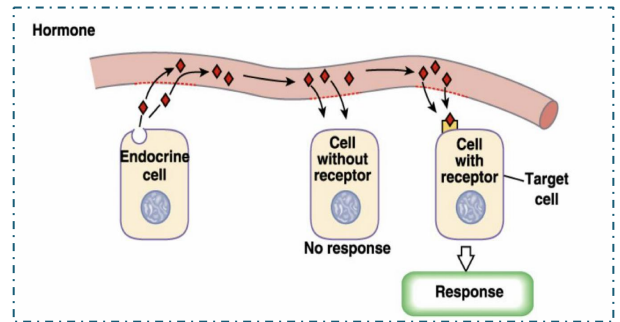
Target Tissue*

Mechanism of action:



What are target cells? *

Target cells refer to cells that contain specific receptors (binding sites) for a particular hormone.



Chemical Structure and Synthesis of Hormones

The text on the right was only found in females slides

Chemical Classification of Hormones	
<p>Proteins and/or polypeptides: <small>Depend on the number of amino acids</small></p>	<p>stored in vesicles until needed</p> <ul style="list-style-type: none"> • anterior and posterior pituitary gland • pancreas (insulin and glucagon) • parathyroid gland (parathyroid hormone)
<p>Steroid hormone: <small>Synthesis from smooth endoplasmic reticulum</small></p>	<p>diffuse across the cell membrane</p> <ul style="list-style-type: none"> • adrenal cortex (cortisol and aldosterone) • ovaries (estrogen and progesterone) • testes (testosterone)
<p>Amine hormone</p>	<ul style="list-style-type: none"> • thyroid hormones. • adrenal medulla (epinephrine and norepinephrine)/ <small>adrenaline and noradrenaline.</small>

- Unlike the enzymes only proteins.

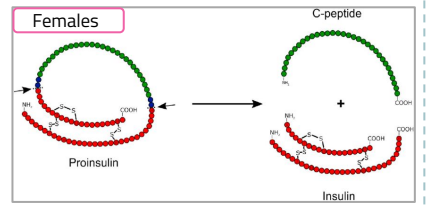


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1 Peptide (Protein) Hormones:

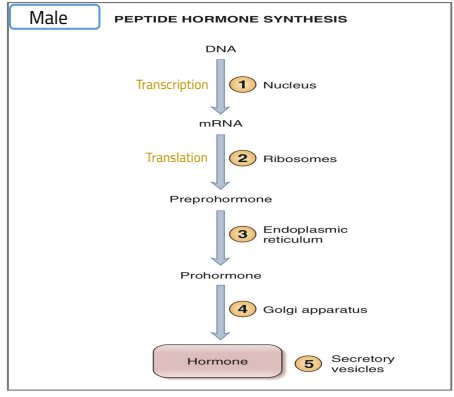
- ❖ Synthesized as preprohormone post-translational modification to prohormone then hormone.
- ❖ Example of protein hormone: **Insulin**.

لمعرفة مستوى الأنسولين C protein ممكن نقيس



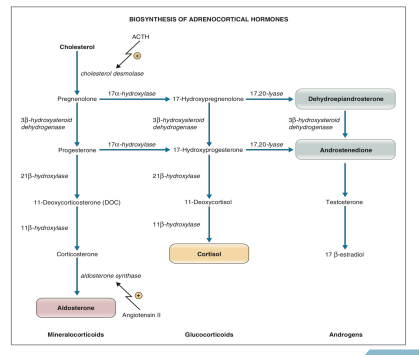
LINDA and doctor :

- 1- In the **nucleus**, the gene for the hormone is **transcribed** into an **mRNA**.
- 2- The mRNA is transferred to the cytoplasm and **translated** on the **ribosomes** to the first protein product, a **preprohormone**.
- 3- The signal peptide is removed in the **endoplasmic reticulum**, converting the preprohormone to a **prohormone**.
- 4- The **prohormone** is transferred to the **Golgi apparatus**, where it is **packaged in secretory vesicles**. In the secretory vesicles, proteolytic enzymes cleave peptide sequences from the prohormone to produce the final **hormone**.
- 5- The **final hormone** is stored in **secretory vesicles** until the endocrine cell is stimulated.



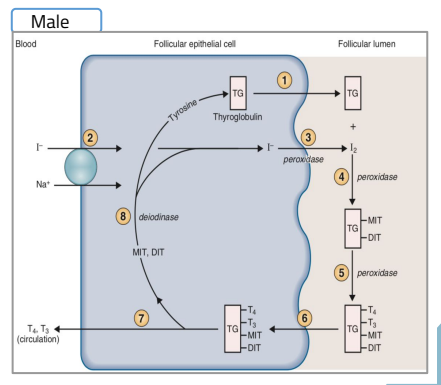
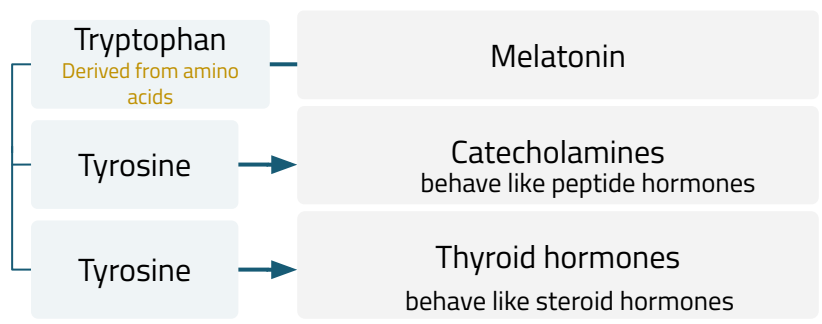
2 Steroid Hormones:

- ❖ Secreted by gonads, adrenals, placenta.
- ❖ Derived from cholesterol (**building blocks**) (lipophilic)
 - Cross membranes (no storage), **unlike the peptide hormones which storage in vesicles**.
- ❖ On-demand synthesis (SER)
- ❖ Usually bound to **Carrier** proteins in the circulation.



3 Amine Hormones:

- ❖ Derived from tyrosine or tryptophan.
- ❖ 3 groups:

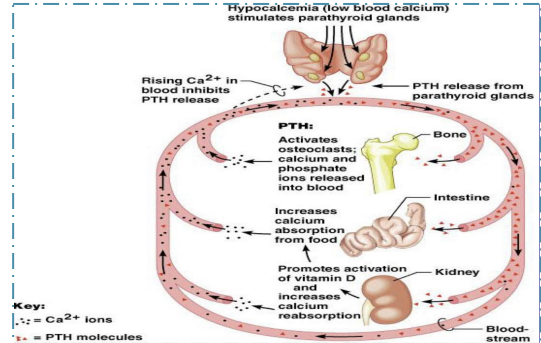
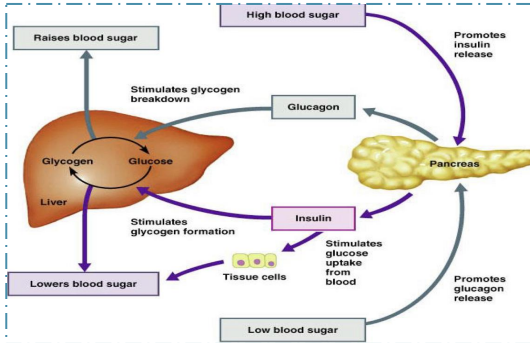


Classification of Stimuli*

1-Humoral Stimuli

Secretion of hormones in direct response to changing in blood levels of ions and nutrients

Examples:



- A) High blood sugar → Increase insulin secretion
- B) Low blood sugar → Glucagon is released → Glucose levels return back to normal

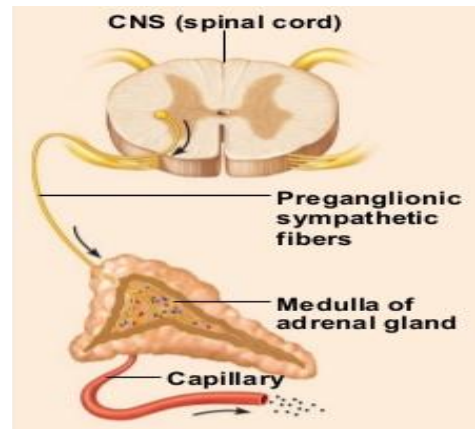
- A) Hypocalcemia → Increase in Parathyroid hormone release
- B) Increase in Ca^{++} levels → Calcitonin secretion from Thyroid gland)

2- Neural Stimuli

- ❖ Nerve fibers stimulate hormone release
- ❖ Example: fight or flight

Picture:

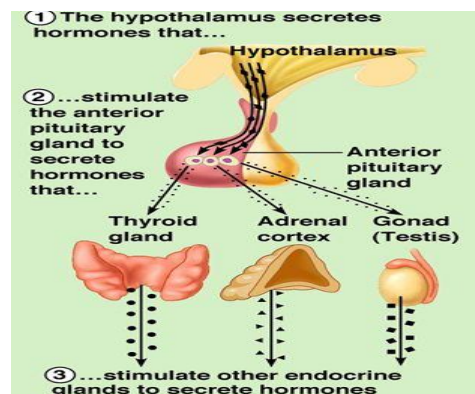
- A. Preganglionic sympathetic fibers stimulate the adrenal **Medulla**
- B. Secretion of catecholamines (Epinephrine and norepinephrine)



3. Hormonal Stimuli

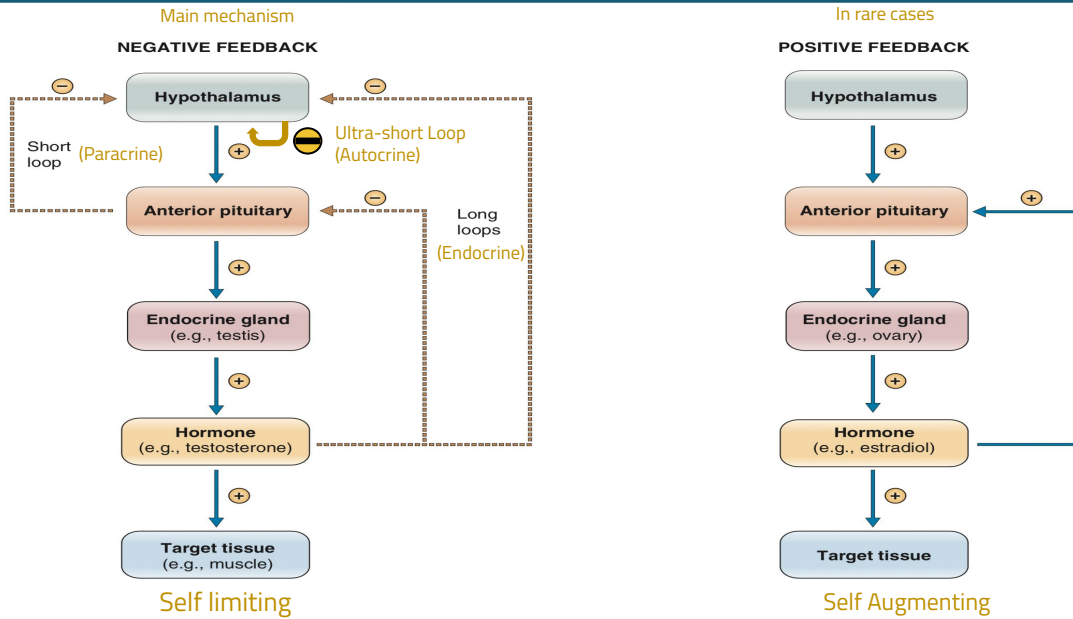
- ❖ Release of hormones in response to hormones produced by other endocrine gland.
- ❖ (Secretion of one hormone, will lead to the secretion of another hormone)

- Pituitary gland controls most of the secretion of other glands = المدير الكبير
 - pituitary > activates thyroid, adrenal cortex and gonads.



Regulation of Hormone Secretion*

1- Feedback mechanism Main mechanism



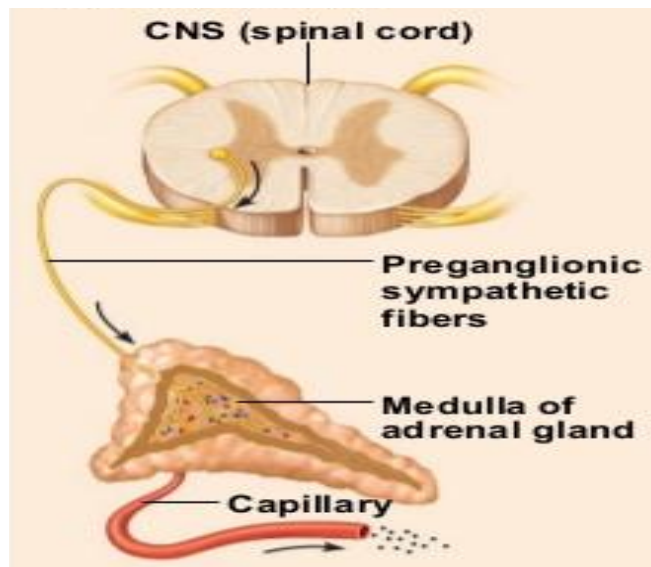
-Ve feedback is divided into:

- 1- Ultra short loop, which uses Autocrine signaling.
- 2- Short loop, which uses Paracrine signaling.
- 3- Long loop, which uses Hormonal signaling.

Example of +ve feedback:

During pregnancy Oxytocin is needed in higher levels as it increases uterus contraction and milk ejection

2- Neural mechanism



Controlled by catecholamines

Transport of hormones*

1. Water soluble hormones:

- ❖ Hydrophilic (peptides & catecholamines) dissolved in Plasma.

2. Fat soluble hormones:

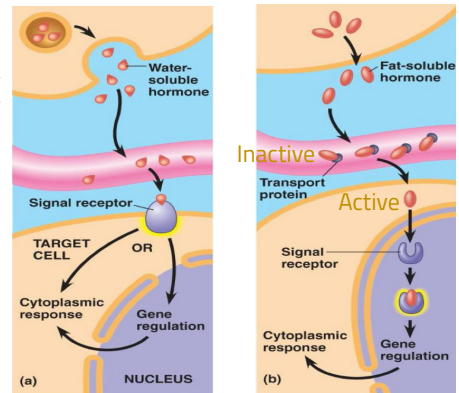
- ❖ Hydrophobic steroids and thyroid hormones transported bound to plasma proteins (90%) **inactive and only 10% is active.**
- ❖ Binding to proteins helps to:
 - Provide reservoirs.
 - Slow hormones clearance.

لأن ما عندي تخزين داخل الخلايا، فلازم نحافظ على الهرمونات عن طريق plasma protein .
تحميه من ال excretion and clearance

The differences between water-soluble & fat-soluble hormones*

- ❖ The active hormone will enter the cell and pass the cell membrane because it is fat soluble hormone, also will enter the cytoplasm and reach the nucleus (where it will affect the gene transcription).

الهرمون ما دخل الخلية إنما :
Hormone receptor complex
واللي بدوره يعمل التغيرات ويسوي ال response



Receptors*

Receptors:

- Hormonal receptors are large proteins.
- 2000-100,000 receptors/cell.
- Receptors are highly specific for a single hormone.

Receptor's location:

- On the surface of cell membrane (proteins, peptides and catecholamines).
- In the cell cytoplasm (Steroids).
- In the cell nucleus (thyroid hormones).

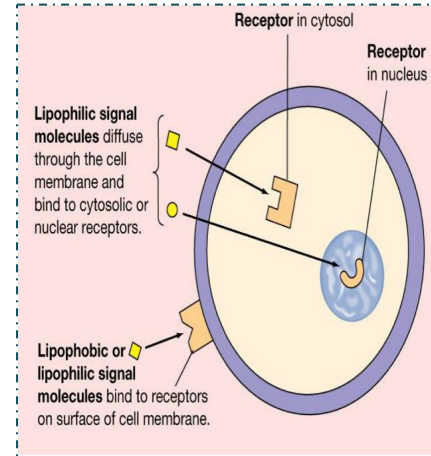
Receptor locations*

Cytosolic or Nuclear

- Lipophilic ligand enters cell
- Often activates gene
- Slower response

Cell membrane⁽¹⁾

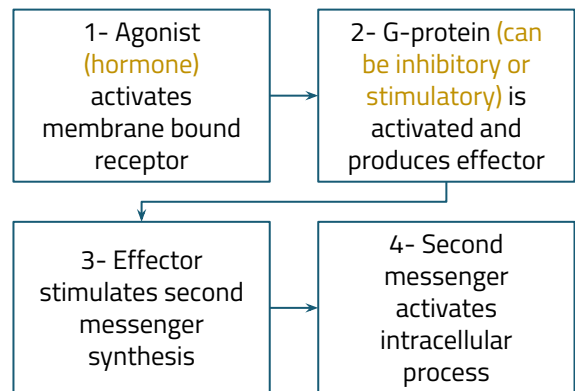
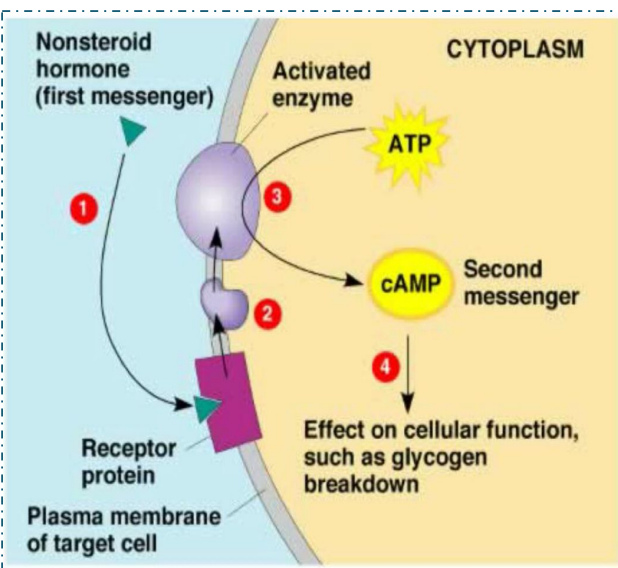
- Lipophobic ligand can't enter cell
- Outer surface receptor
- Fast response



Mechanism of action of hormones*

- 1 Hormone-receptor interaction (1st messenger)
- 2 Enzyme activation.
- 3 Release of the second messenger.
- 4 Effects on cellular function.

Mechanism of action of (Peptides and protein hormone)*⁽²⁾⁺⁽³⁾



Depending on the coupling of the hormone receptor to an **inhibitory** or a **stimulatory** G protein, it can either increase or decrease the concentration of cAMP & phosphorylation of key proteins inside the cell.

- 1) It has 3 mechanisms: 1. Adenyl cyclase mechanism (cAMP) 2. Phospholipase C 3. Tyrosine Kinase. (will be explained next slide)
- 2) The hormone will not enter the cell, will bind to receptors on the cell membrane.
- 3) Protein and peptide hormones need a second messenger because they can't enter the cell. So, the effects are done by the second messenger.

Second messengers

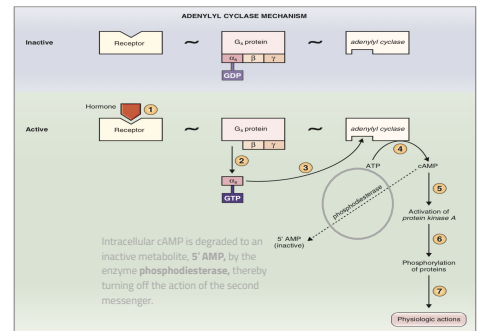
2nd Messenger Systems of Peptide and Protein Hormones:

1 Adenylate Cyclase-cAMP

LINDA: Hormone binds to its **receptor** in the cell membrane, producing a conformational change in the α s subunit (Step 1), which produces two changes: GDP is released from the α s subunit and is replaced by GTP, and the α s subunit detaches from the Gs protein (Step 2).

The **α s-GTP complex** migrates within the cell membrane and binds to and activates adenyl cyclase (Step 3). Activated **adenyl cyclase** catalyzes the conversion of ATP to cAMP, which serves as the second messenger (Step 4)

cAMP, via a series of steps involving activation of **protein kinase A**, phosphorylates intracellular proteins (Steps 5 and 6). These phosphorylated proteins then execute the final physiologic actions (Step 7).

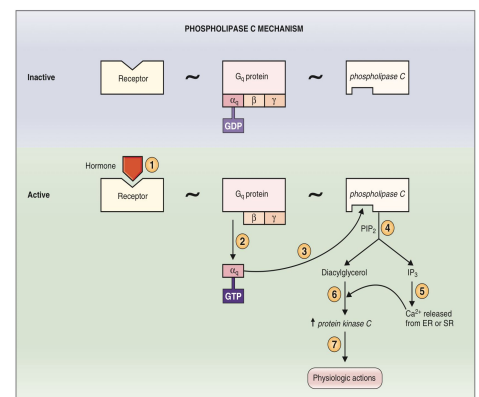


2 Phospholipase C-IP₃

LINDA: Hormone binds to its receptor in the cell membrane, producing a conformational change in the α s subunit (Step 1). GDP is released from the α s subunit, is replaced by GTP, and the α s subunit detaches from the G α protein (Step 2).

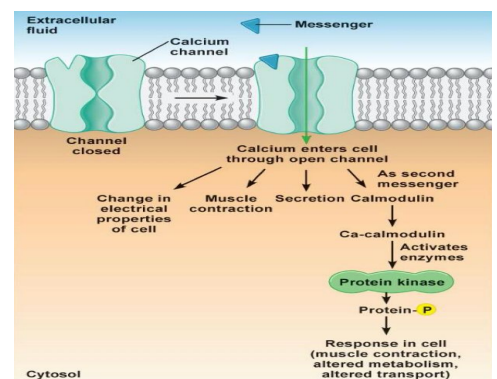
The **α s-GTP complex** migrates within the cell membrane and binds to and activates phospholipase C (Step 3). Activated **phospholipase C** catalyzes the liberation of diacylglycerol and IP₃ from phosphatidylinositol 4,5-diphosphate (PIP₂), a membrane phospholipid (Step 4). The IP₃ generated causes the release of Ca₂₊ from intracellular stores in the endoplasmic or sarcoplasmic reticulum, resulting in an increase in intracellular Ca₂₊ concentration (Step 5).

Together, Ca₂₊ and diacylglycerol activate **protein kinase C** (Step 6), which phosphorylates proteins and produces the final physiologic actions (Step 7).

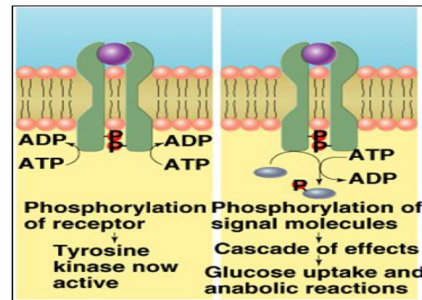
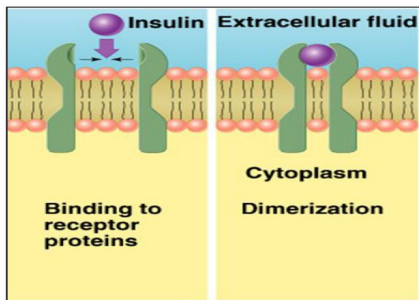


3 Calcium-Calmodulin complex*

1. Receptor operated by a ligand (hormone). The binding will cause a conformational change that will allow the Ca to enter the cell.
2. Once Ca level inside the cell rises, Ca will bind to calmodulin and form calcium-calmodulin complex (secondary messenger).
3. Ca-calmodulin complex will activate protein kinase by phosphorylation. Activated protein kinase will phosphorylate Protein-P and then will cause several cellular changes. #Med437

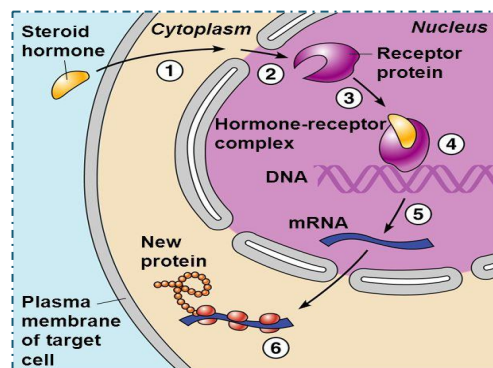
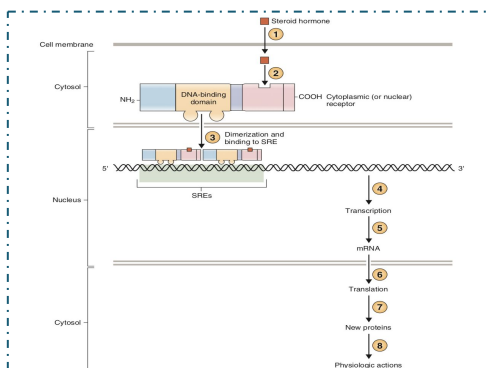


- ❖ Is used by insulin & many growth factors to cause cellular effects.
- ❖ Surface receptor is tyrosine kinase:
 - Consists of 2 units that form active dimer when insulin binds.
- ❖ Activated tyrosine kinase phosphorylates signalling molecules.
- ❖ Induction of hormone/growth factor effects.
- ❖ The receptor consists of an extracellular domain that acts as a binding site for the hormone, and a catalytic (enzymatic) domain in the cytoplasm. Upon hormone binding, a conformational change activates the cytoplasmic domain. #Med438



Mechanism of action of steroid hormones

- 1 The steroid diffuses through the plasma membrane and Binds an intracellular receptor.
- 2 The receptor-hormone complex enters the nucleus.
- 3 The receptor-hormone complex binds a hormone response element (a specific DNA sequence).
- 4 Binding initiates transcription of the gene to mRNA.
- 5 The mRNA direct protein synthesis.



Regulation Of Hormonal Receptors

❖ Receptors does not remain constant*:

- Inactivated or destroyed
- Reactivated or manufactured

❖ Factors in regulation of receptors*:

- Dose-response relationship. As we increase the dose the response increases.
- Sensitivity. The concentration which provides 50% of the maximum response (High sensitivity only needs a small concentration and vice versa.)
- Numbers. The higher the number of receptors the stronger the response.
- Affinity. قابلية الارتباط

Upregulation

- ❖ E.g: in case of Hypothyroidism
- ❖ Increase synthesis.*
- ❖ Decrease degradation.*
- ❖ Activation.*
- ❖ prolactin.*
- ❖ The hormone induces greater than normal formation of a receptor or intracellular signaling proteins.*
- ❖ Direct proportional.

Downregulation

- ❖ E.g: in case of Hyperthyroidism
- ❖ Decrease synthesis.*
- ❖ Increase degradation.*
- ❖ Inactivation.*
- ❖ T3.*
- ❖ Increase hormone concentration leads to decrease in the number of active receptors.*
- ❖ Most peptide hormones have pulsatile secretion⁽¹⁾ which prevent down regulation.*
- ❖ Inversely proportional.

- ❖ GH level is pulsatile, which means: As the hormone increase, the receptors will decrease. So, to maintain the number of receptors, we have to decrease the secretion of hormone> which leads to increase the receptors.

.ويكون أكثر خلال: During exercise and midnight

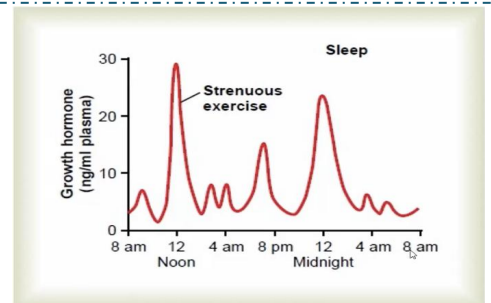


Figure 75-6

Typical variations in growth hormone secretion throughout the day, demonstrating the especially powerful effect of strenuous exercise and also the high rate of growth hormone secretion that occurs during the first few hours of deep sleep.

1) Which means it's not secreted in a constant manner, so that the receptor doesn't get bored and down regulate, however there's an exception, T3 & T4 are secreted in a linear manner, because they play a role in the body temperature, which has to be constant

Interaction of hormone at target cells

- ❖ Multiple hormones can affect a single target simultaneously*
- ❖ Three types of hormone interactions:

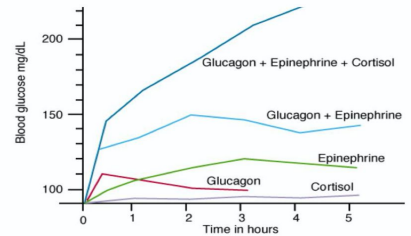
1

Synergism:

- ❖ **Combined action of hormones is more than just additive. Both hormones are acting**

- ❖ **Example:**

- Blood glucose levels & synergistic effects of glucagon, cortisol and epinephrine.



مثلاً نفترض أن فيه 3 هرمونات كل واحد ال action حقه = 5
يصير مجموعهم / ال combined action لهم = 15
لكن نجي نلاقي أن الثلاثة لما يشتغلوا يوصلوا ال 18-19.
لتسهيل الفهم: يد الله مع الجماعة، لأنهم اشتغلوا مع بعض ربنا ساعدهم زيادة
كمان.

The common example
Glucagon + epinephrine + cortisol: increase blood
glucose level > hyperglycemia.
When we combined them their effect increase
more than just additive.

2

Permissiveness:

الهرمون
المضحي

- ❖ **One hormone allows another hormone to have its full effect** (especially during growth). **Only one hormone is acting here**

- ❖ **Example:**

- ❖ Thyroid hormone have permissive effect on growth hormone action.
(thyroid give the GH the full action)
- ❖ Deficiency of thyroid hormone in infants leads to dwarfism.
- ❖ Presence of one hormone will potentiate the effect of another hormone, so as an example: If we say that 50ml of GH will give you 80% action. Then 50ml of GH mixed with thyroid hormone will give you 100% action.

3

Antagonism:

الهرمون
المعارض

- ❖ **Antagonistic hormones have opposing physiological actions.**

- Hormone B diminishes the effect of hormone A.

- ❖ **Example:**

- Glucagon antagonizes the action of insulin.

Glucagon: try to increase glucose level.
insulin: try to decrease glucose level.
So, they antagonize action of each
other.

Clearance of hormones

❖ Two factors control the concentration of a hormone in the blood:

- The rate of its **secretion/release**
- The rate of **Inactivation and removal from the body (metabolic clearance)**

سرعة تكوين الهرمون وسرعة التخلص من الهرمون هو الذي يحدد مستوى الهرمون.

❖ Hormones are cleared by:

- Metabolic destruction by tissues.*
- Binding with tissues.*
- Degrading enzymes*
- Excretion by the liver into bile (**Liver enzyme system**).
- Excretion by the kidney into urine.

❖ Clearance of protein bound hormones is slower than clearance of peptide hormones.

لأنني ما اقدر أخزنه بالأنسجة، نخزنه storage in plasma.

Schedules from Males slides



At the end of th block it will be easy for you as a revision

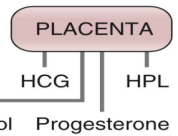
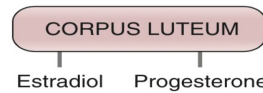
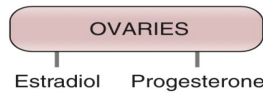
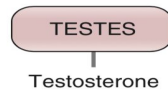
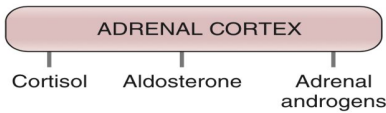
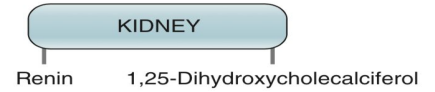
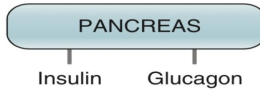
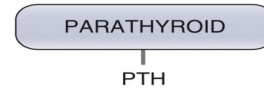
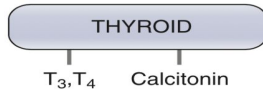
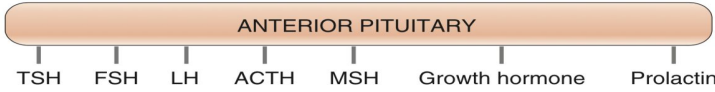
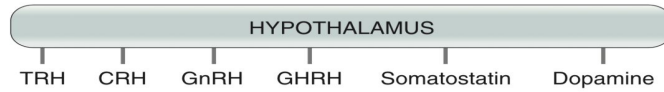


Table 9-1 Commonly Used Abbreviations in Endocrine Physiology

Abbreviation	Hormone	Abbreviation	Hormone
ACTH	Adrenocorticotrop hormone	LH	Luteinizing hormone
ADH	Antidiuretic hormone	MIT	Monoiodotyrosine
CRH	Corticotropin-releasing hormone	MSH	Melanocyte-stimulating hormone
DHEA	Dehydroepiandrosterone	PIF	Prolactin-inhibiting factor (dopamine)
DIT	Diiodotyrosine	POMC	Pro-opiomelanocortin
DOC	11-Deoxycorticosterone	PTH	Parathyroid hormone
FSH	Follicle-stimulating hormone	PTU	Propylthiouracil
GHRH	Growth hormone-releasing hormone	SRIF	Somatotropin release-inhibiting factor
GnRH	Gonadotropin-releasing hormone	T ₃	Triiodothyronine
HCG	Human chorionic gonadotropin	T ₄	Thyroxine
HGH	Human growth hormone	TBG	Thyroxine-binding globulin
HPL	Human placental lactogen	TRH	Thyrotropin-releasing hormone
IGF	Insulin-like growth factor	TSH	Thyroid-stimulating hormone

Table 9-3 Mechanisms of Hormone Action

Adenylyl Cyclase Mechanism (cAMP)	Phospholipase C Mechanism (IP ₃ /Ca ²⁺)	Steroid Hormone Mechanism	Tyrosine Kinase Mechanism	Guanylate Cyclase Mechanism (cGMP)
ACTH	GnRH	Glucocorticoids	Insulin	Atrial natriuretic peptide (ANP)
LH	TRH	Estrogen	IGF-1	Nitric oxide (NO)
FSH	GHRH	Progesterone	Growth hormone	
TSH	Angiotensin II	Testosterone	Prolactin	
ADH (V ₂ receptor)	ADH (V ₁ receptor)	Aldosterone		
HCG	Oxytocin	1,25-Dihydroxycholecalciferol		
MSH	α ₁ Receptors	Thyroid hormones		
CRH				
Calcitonin				
PTH				
Glucagon				
β ₁ and β ₂ receptors				

MCQ & SAQ:

Q1: Which of the following behave like steroid hormones?

- A. Epinephrine
- B. Thyroid hormones
- C. Parathyroid hormones
- D. Insulin

Q3: Which of the following is derived from Tryptophan?

- A. Thyroxine
- B. Epinephrine
- C. Melatonin
- D. Triiodothyronine

Q5: Which of the following cause upregulation of hormones receptors

- A.prolactin
- B.decrease synthesis
- C.T3
- D.increase degradation

Q2: Which of the following is secreted into the ECF and can function as autocrine, paracrine, or endocrine hormones?

- A.Neurotransmitters
- B. Neuroendocrine hormone
- C. Paracrines
- D. Cytokines

Q4: Which of the following is not a second messenger

- A.Tyrosine kinase system
- B. Phospholipase C-IP3
- C.Calcium-calmodulin complex
- D.Adenosine tri-phosphate

Q6: Dwarfism due to thyroid hormone deficiency is an example of

- A. Synergism
- B. Permissiveness
- C. Antagonism
- D. Negative feedback

6: B
5: A
4: D
3: C
2: D
1: B
key:
answer

1- List the body functions that are regulated by hormones?

2- Which type of hormone is synthesized as a Preprohormone?

3-List the ways hormones are cleared by?

4- List 4 Downregulators of hormonal receptors

A1: Metabolism, water and electrolyte balance, reproduction, behavior and growth & development

A2: Peptide hormone

A3: Page 15

A4: Decrease synthesis.Increase degradation,Inactivation,T3.

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