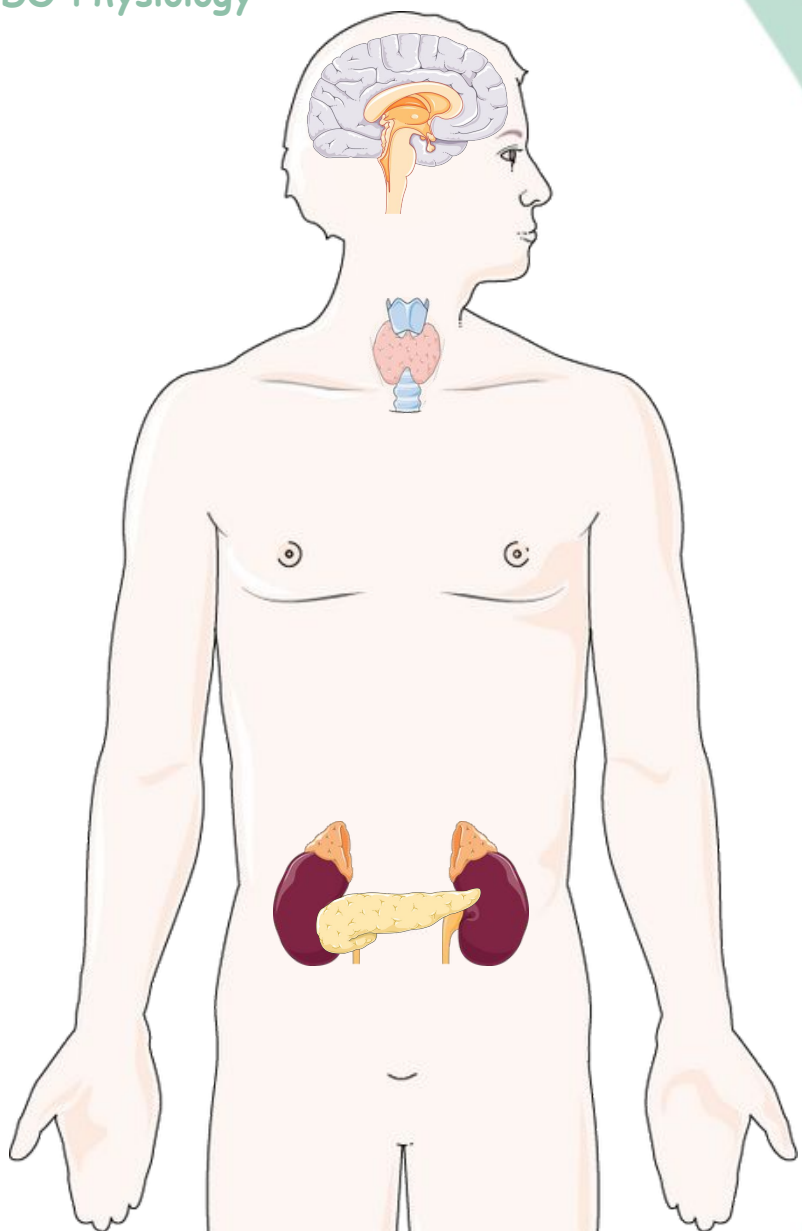
Introduction to Endocrine physiology

ENDO Physiology



Editing File

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- Main Text
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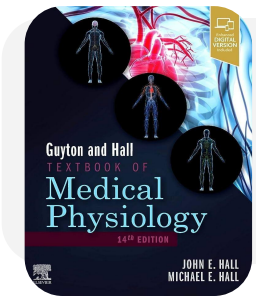
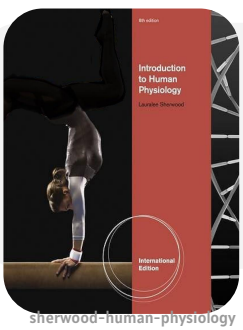
Objectives

- **Endocrine vs Exocrine gland**
- **Chemical messengers**
- **Hormones**
  - Definition
  - Chemical structure
  - Paracrine and autocrine, endocrine, neuroendocrine
- **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)

Resources

Only ENDO chapters included





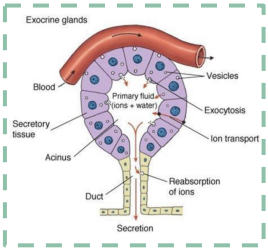
sherwood-human-physiology

This lecture was presented by:
Dr. Hana Alzamil - Prof. Abdulmajeed Aldrees

Osmosis: Anatomy & physiology of endocrine (14min)

What is the difference between Endocrine and Exocrine

Gland

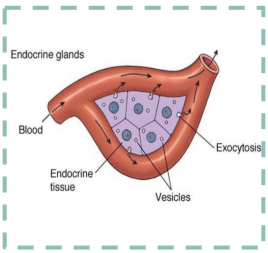


Exocrine gland (1)

- ❖ Ducts
- ❖ Secrets enzymes
- ❖ Lumen and surfaces

Endocrine gland (2)

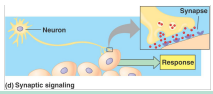
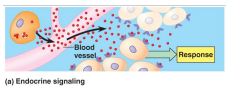
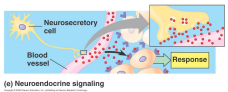
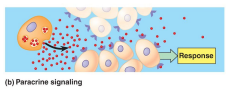
- ❖ No ducts
- ❖ Secrets Chemical Messengers
- ❖ Blood stream



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

Chemical messengers

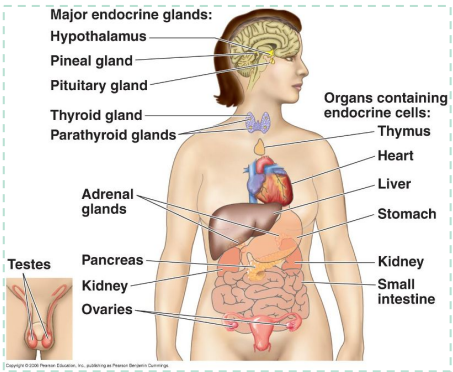
The activities of cells, tissues and organs are coordinated by chemical messengers:

Chemical messengers	Dif	Picture
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. .(thyroid test only order for TSH,T4,T3 but not for T12H because it's paracrine not shown in blood	
Autocrines	Are secreted by cells into the extracellular fluid and affect the function of the same cells that produced them. (Same cell mean hypothalamus cell) - 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:

- Pituitary (6)
- Thyroid
- Parathyroid
- Adrenal
- Pancreas
- Ovaries / Testes (gonads)



Placenta has endocrine function That secrete hormones.

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

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

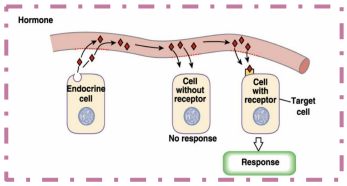
- Affect only specific target cells (eg. ACTH and estrogen).
- Affect many different types of cells (eg. GH (growth hormone) and Thyroxin).

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

What are target cells?

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



Target Tissue

Mechanism of action:

Hormone → Receptor → Conformational Changes → ??? → Action

More than one mechanism

Chemical Structure and Synthesis of Hormones

Female

Chemical Classification of Hormones

Proteins and/or polypeptides:
Depend on the number of amino acids

Stored in vesicles until needed
- Anterior and posterior pituitary gland
- Pancreas (insulin and glucagon)
- Parathyroid gland (parathyroid hormones)

Steroids:
Synthesis from smooth endoplasmic reticulum

Diffuse across the cell membrane
- Adrenal cortex (cortisol and aldosterone)
- Ovaries (estrogen and progesterone)
- Testes (testosterone)

Derivatives of Amino acid tyrosine
Amine hormone

- Thyroid hormones.
- Catecholamines e.g. adrenal medulla (epinephrine and norepinephrine)
  adrenaline and noradrenaline.

What's the difference between "Peptide", "Polypeptide", and "Protein hormones?
Peptides: fewer than 50 amino acids.
Polypeptides: 50 to 100 amino acids.
Protein hormones: composed of one or more polypeptide chains; so more than 100 aa.
You need to differentiate for next lectures to use the proper terminology for each hormone.

- Unlike the enzymes only proteins.

Female slides

Hormones

- Peptide (Protein) Hormones:
- Steroid Hormones:
- Amine Hormones:

1 Peptide (Protein) Hormones:

- Synthesize as the **preprohormone** post-translational modification to **prohormone** then **Hormone.**
- Example of protein Hormone: **insulin**

Is C protein active? Yes it is. What its benefit? To measure insulin in the blood.

- **LINDA :**

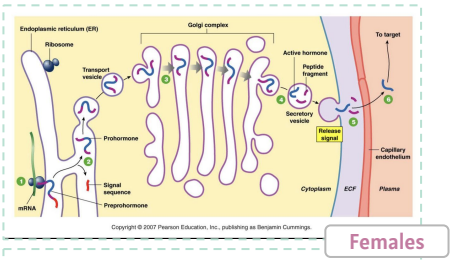
I- In the **nucleus**, the gene for the hormone is transcribed into an **mRNA.**

2- The mRNA is transferred to the cytoplasm and translated on the **ribosomes** to the first protein product, a **preprohormone.**

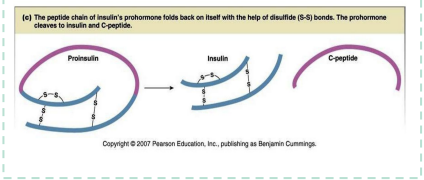
3- The signal peptide is removed in the **endoplasmic reticulum,** converting the preprohormone to a **prohormone.**

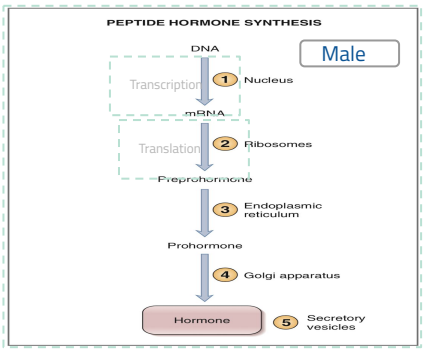
4- The prohormone is transferred to the **Golgi apparatus**, where it is packaged in secretory vesicles. In the secretory vesicles, proteolytic enzymes cleave peptide sequences from the prohormone to produce the final **hormone.**

5- The final hormone is stored in **secretory vesicles** until the endocrine cell is stimulated.



Females

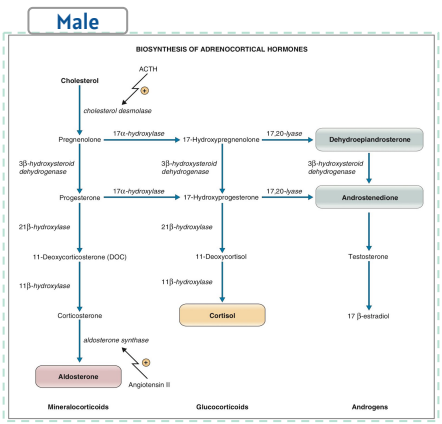




2 Steroid Hormones:

- Secreted by gonads, adrenals, placenta.
- Derived from cholesterol (building block) (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.

Male

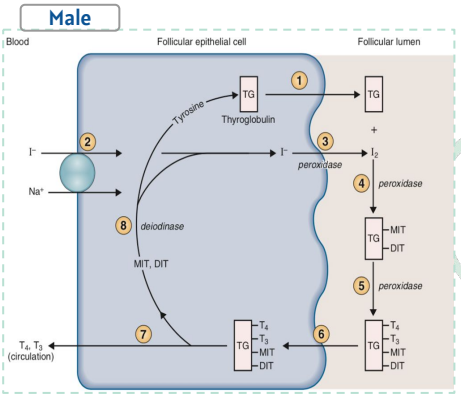


3 Amine Hormones:

- Derived from tyrosine or tryptophan?
- 3 group:

Tryptophan Derived from amino acids	**Melatonin**
Tyrosine	**Catecholamines** behave like peptide hormones
Tyrosine	**Thyroid hormones** behave like steroid hormones

Male



Male slides

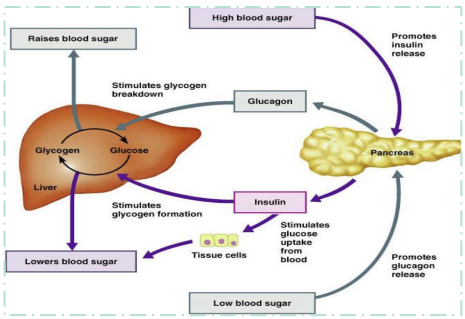
Classification of Stimuli

1-Humoral Stimuli	2- Neural Stimuli	3. Hormonal Stimuli most common
Secretion of hormones in direct response to changing in blood levels of ions and nutrients	Nerve fibers stimulate hormone release	Release of hormones in response to hormones produced by other endocrine gland.

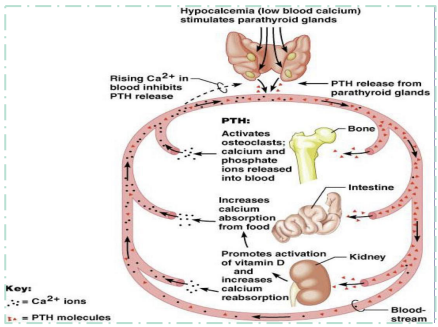
1- Humoral stimuli

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



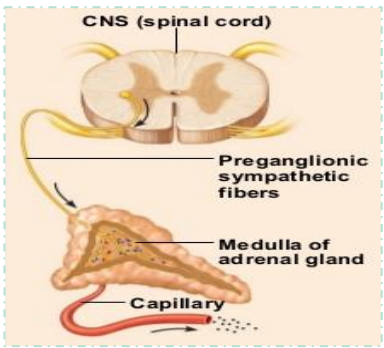
A) Hypocalcemia → Increase in Parathyroid hormone release
B) Increase in Ca++ levels → Calcitonin secretion from Thyroid gland)

2- Neural stimuli

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

Picture:

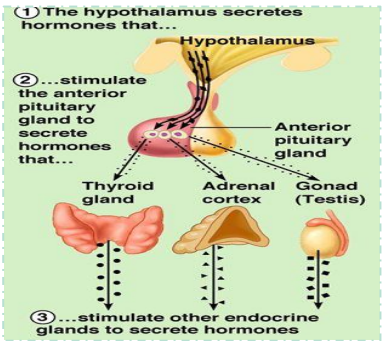
A. Preganglionic sympathetic fibers stimulate the adrenal **Medulla**
B. Secretion of catecholamines (Epinephrine and norepinephrine)
C. Response to stress:
Acute >Epinephrine and norepinephrine
Chronic > cortisol



3- Hormonal stimuli most common

- 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.



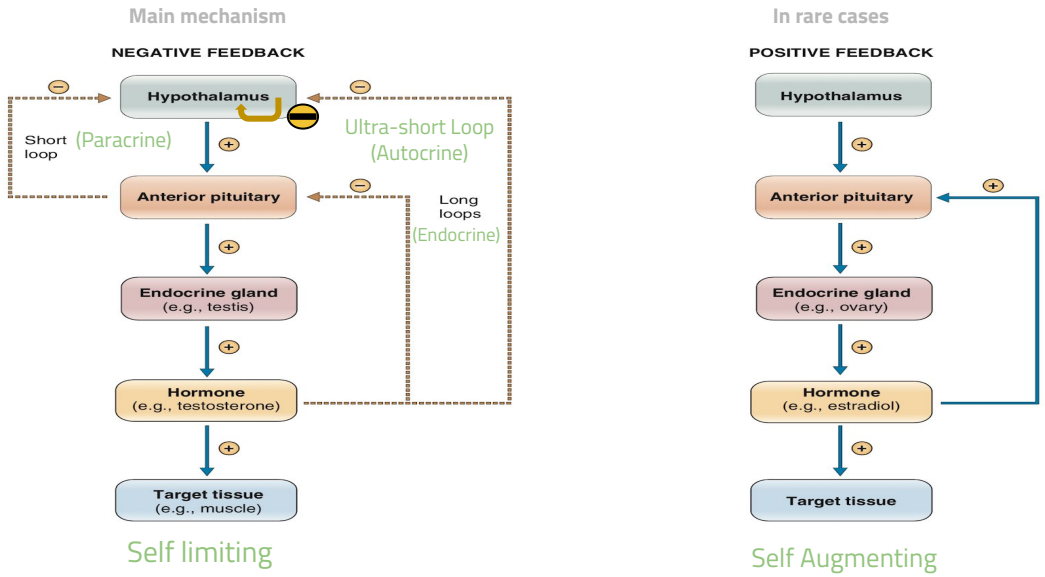
Male slides

Regulation of Hormone Secretion

- 1- Feedback mechanism
  - Negative feedback
  - Positive feedback
- 2- Neural mechanism

1- Feedback mechanism

Main mechanism



Self limiting

Self Augmenting

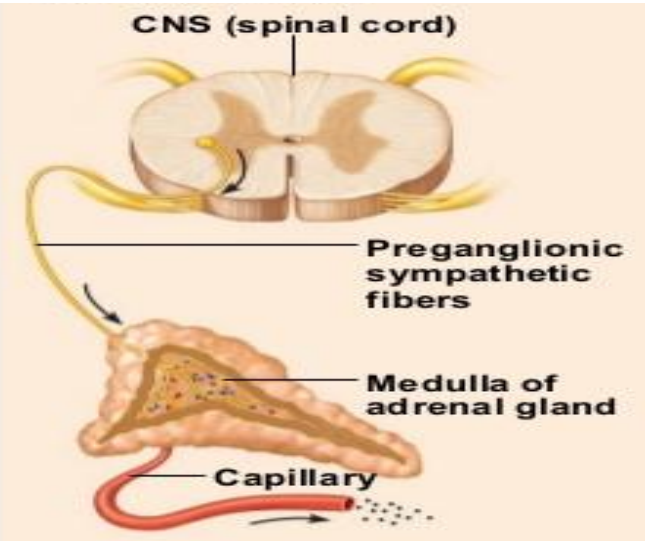
-Ve feedback is divided into:

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



Depends upon stress

Controlled by catecholamines

Transport of Hormones

Female slides

1- Water soluble Hormones:

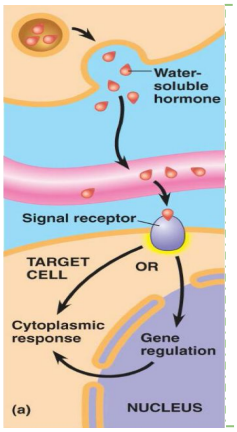
- Hydrophilic (peptides & catecholamines) dissolved in Plasma.

2- Fat soluble Hormones:

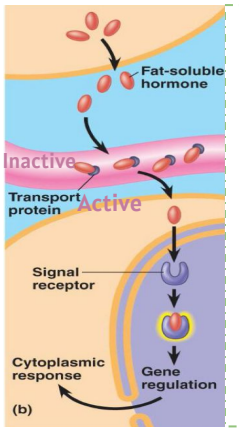
- Hydrophobic steroids and thyroid hormones transported bound to plasma proteins (90%) inactive and only 10% is active.
- Binding to proteins helps to:
  - Provide reservoirs.
  - Slow hormones clearance.

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



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



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).

Female slides

Receptors

Receptors :

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

Receptor's location:

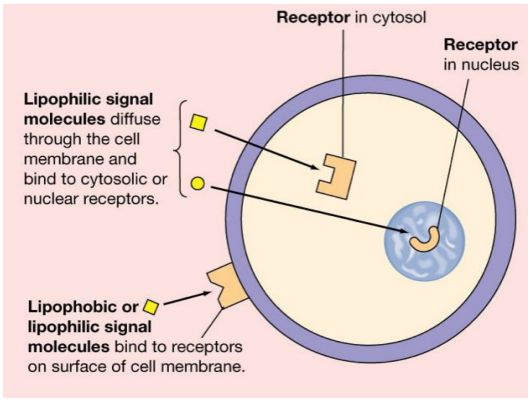
- On the surface of cell membrane (proteins, peptides and catecholamines).
- In the cell cytoplasm (Steroids).
- In the cell nucleus (thyroid hormones).

Receptor locations

Male slides

Cytosolic or Nuclear
- Lipophilic ligand enters cell
- Often activates gene
- Slower response

Cell membrane (I)
- Lipophobic ligand can't enter cell
- Outer surface receptor
- Fast response



Mechanism of action of hormones

Female slides

(at the level of cell membrane (water soluble))

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

Mechanism of action of (Peptides and protein hormones) (2)+(3)

Female slides

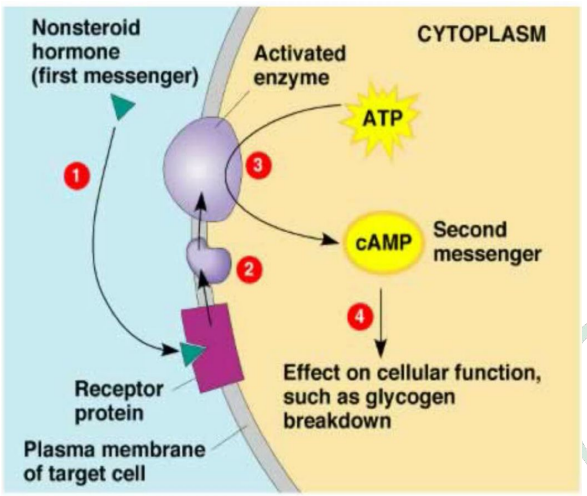
4- Second messenger activates intracellular process

3- Effector stimulates second messenger synthesis

2- G-protein (can be inhibitory or stimulatory) is activated and produces effector

I- Agonist (hormone) activates membrane bound receptor

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.

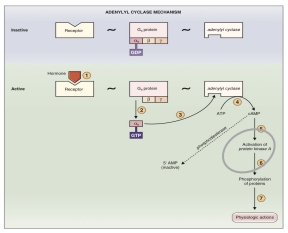


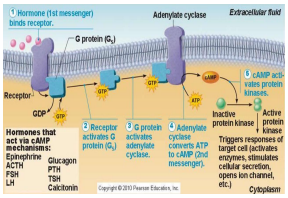
I) It has 3 mechanisms: I. Adenylyl cyclase mechanism (cAMP) 2.Phospholipase C 3. Tyrosine Kinase. (will be explained next slide)
2) The hormone will not enter the cell, will bind to receptors on the cell membrane.
3) Protein and peptide hormones need a second messenger because they can't enter the cell.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

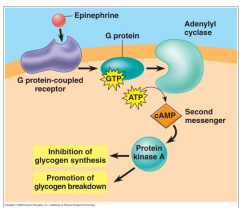
Second messengers

2nd Messenger Systems of Peptide and Protein Hormones:

Adenylate Cyclase-cAMP:





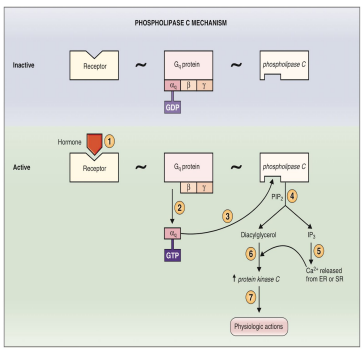


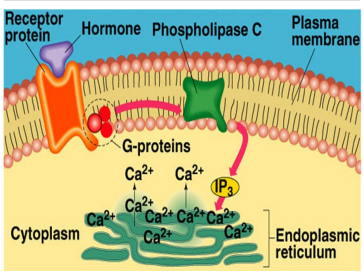
LINDA: Hormone binds to its **receptor** in the cell membrane, producing a conformational change in the αs subunit (Step I), which produces two changes: GDP is released from the αs subunit and is replaced by GTP, and the αs subunit detaches from the Gs protein (Step 2).

The **αs-GTP complex** migrates within the cell membrane and binds to and activates adenylyl cyclase (Step 3). Activated **adenylyl 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).

Phospholipase C-IP3:





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

The **αq-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).

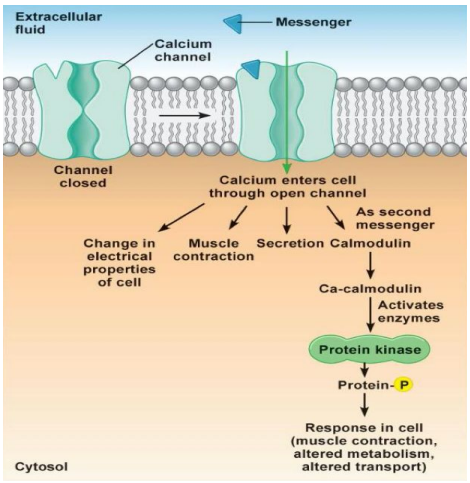
Together, Ca2+ and diacylglycerol activate **protein kinase C** (Step 6), which phosphorylates proteins and produces the final physiologic actions (Step 7)

Second messengers

2nd Messenger Systems of Peptide and Protein Hormones:

Calcium-Calmodulin complex:

Female slides

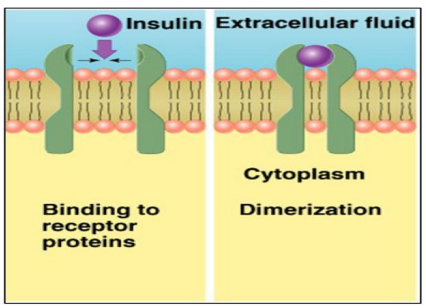


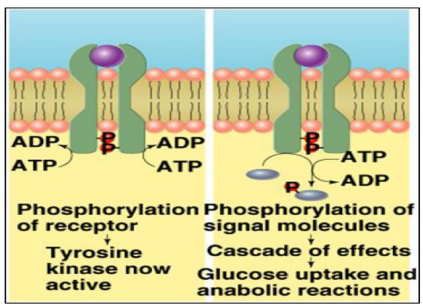
1. Receptor operated by a ligand (hormone). The binding will cause a conformational change that will allow the Ca to enter the cell.

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

Tyrosine kinase system:





❖ Is used by insulin & many growth factors to cause cellular effects.

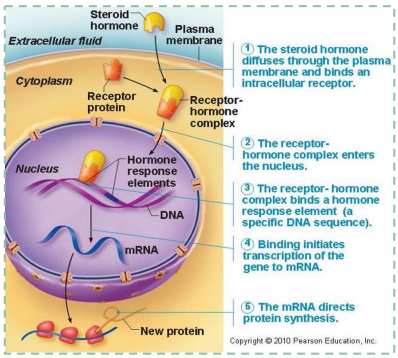
❖ Surface receptor is tyrosine kinase:
Consists of 2 units that form active dimer when insulin binds.

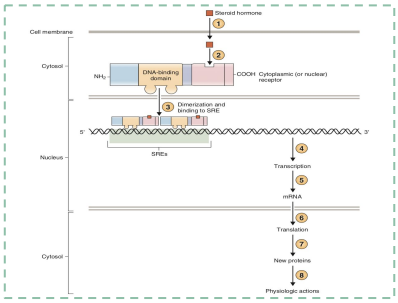
❖ Activated tyrosine kinase phosphorylates signalling molecules.
❖ Induction of hormone/growth factor effects.

❖ 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. #Med43

Mechanism of action of steroid hormones

1. The steroid hormone 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.





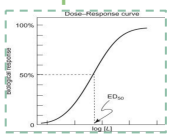
Regulation Of Hormonal Receptors

Receptors does not remain constant:

1. Inactivated or destroyed
2. Reactivated or manufactured

Factors in regulation of receptors:

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



Upregulation

- E.g: in case of Hypothyroidism
- Increase synthesis.
- Decrease degradation.
- Activation.
- Eg: prolactin.(2)
- 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.
- Eg: T3.
- Increase hormone concentration leads to decrease in the number of active receptors.
- Most peptide hormones have **pulsatile secretion**(1) which prevents down regulation.
- Inversely proportional.

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.
2) Prolactin will increase its receptors in the breast during lactation

- Example: 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: exercise and midnight

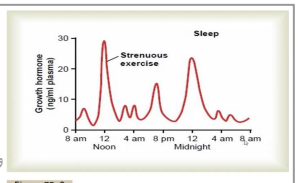


Figure 75–6

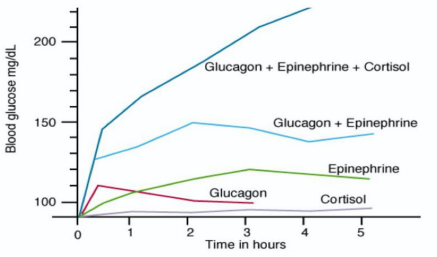
Typical variations in growth hormone secretion throughout the day, demonstrating the especially powerful effect of strenuous exercise and also the high rate of growth hormone secretion that occurs during the first few hours of deep sleep.

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.



مثلًا نفترض أن فيه ٣ هرمونات كل واحد ال action حقه = 5
يصير مجموعهم / الـ combined action لهم = 15
لكن نجي نلاقي أن الثلاثة لما يشتغلوا يوصلوا ل 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:

- 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:

1. The rate of its secretion/release

2. The rate of Inactivation and removal from the body (metabolic clearance)
سرعة تكوين الهرمون وسرعة التخلص من الهرمون هو اللي 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.
storage in plasma لأني ما اقدر أخزنه بالأنسجة، نخزنه

Schedules from Males slides

Male slides

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

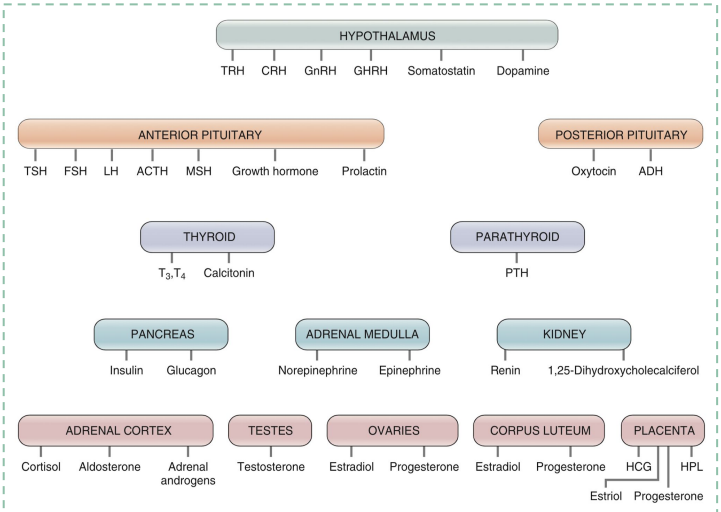


Table 9–1 Commonly Used Abbreviations in Endocrine Physiology

Abbreviation	Hormone	Abbreviation	Hormone
ACTH	Adrenocorticotropic 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				

MCQs:

Q1: Which one of the following is released by a neural stimulus?

- A.Epinephrine from adrenal medulla
- B.Thyroxine from thyroid gland
- C.ADH
- D.Parathyroid hormone from parathyroid gland

Q2: Where do hydrophilic hormones have their receptors?

- A.Cytoplasm
- B.Plasma membrane
- C.Nuclear
- D.Endoplasmic reticulum

Q3:What is the mechanism of regulation of the chemicals released by a cell to the ECF to act on the same cell?

- A. Paracrine
- B. Neuroendocrine
- C. Endocrine
- D. Autocrine

Q4:Which of the following is considered as release of hormones due to humoral stimulus?

- A.Parathyroid gland secreting parathyroid hormone
- B.Thyroid gland secreting thyroid hormone
- C.Adrenal gland secreting catecholamines
- D.None of them

Q5: Which of these is secreted into ECF and affect nearby cells?

- A.Paracrine
- B.Neuroendocrine
- C.Endocrine
- D.Autocrine

Q6:Hormones that have permissive effect?

- A.Cortisol and norepinephrine
- B.Thyroid and growth hormone
- C. Thyroid and ACTH
- D. Dopamine and growth hormone

Q7: Which of the following is false about cortisol?

- A. It's bound to plasma protein
- B. Injections lead to rise in arterial pressure
- C. Is inactivated in the liver and excreted in the bile
- D. Inhibit release of ACTH from the anterior pituitary gland

Q8:Which of the following hormones is synthesized by tyrosine amino acid?

- A. Epinephrine
- B. TSH
- C.ADH
- D.FSH

Q9: Which of the following behave like peptide hormones?

- A.Triiodothyronine
- B.Estrogen
- C.Testosterone
- D.Epinephrine

Answers: A/B/D/A/A/B/C/A/D

SAQ :

1. **List 3 types of stimulus & examples?**
2. List the body functions that are regulated by hormones?
3. Which type of hormone is synthesized as a Preprohormone?
4. List the ways hormones are cleared by?
5. List 4 Downregulators of hormonal receptors

A1: page 6
A2: Metabolism, water and electrolyte balance, reproduction, behavior and growth & development
A3: Peptide hormone
A4: Page 14
A5: Decrease synthesis.Increase degradation,Inactivation,T3.

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Almas Al Mutairi

Afnan Al Ahmari

Rawan Al Qahtani

Faisal Al Showier

Abdullah Al Assiri

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Zeyad Al Otaibi

Aban Basfar

Feras Mazen

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