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MED437
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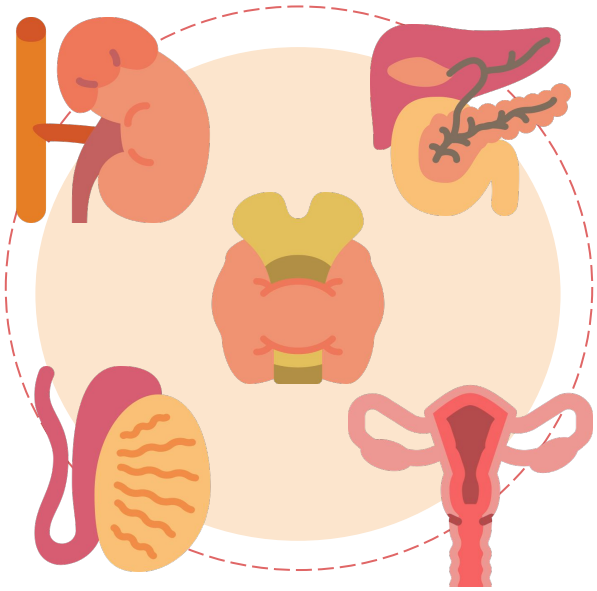

Introduction to The Endocrine Physiology

Objectives:

- Endocrine vs exocrine gland
- Chemical messengers Hormone
  - Definition
  - Chemical structure
  - Paracrine, autocrine, endocrine, neuroendocrine
  - Transport and clearance
- Mechanism of action
  - Receptors, down-regulation and up-regulation
  - Intracellular signaling
  - Second messenger (cAMP, IP3)

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Colour index:
- Important
- Numbers
- Extra

وَأَن لَّيْسَ لِلْإِنسَانِ إِلَّا مَا سَعَىٰ

Types of Glands

Exocrine Gland

- Ducts
- Lumen and surfaces

Endocrine Gland

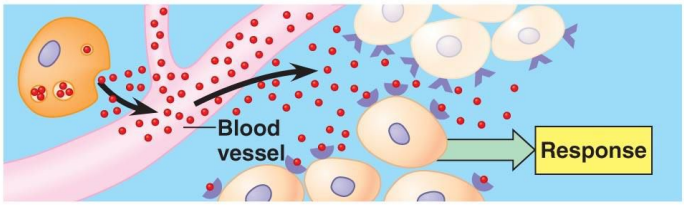
- Chemical messengers
- Blood stream

Chemical Messengers:

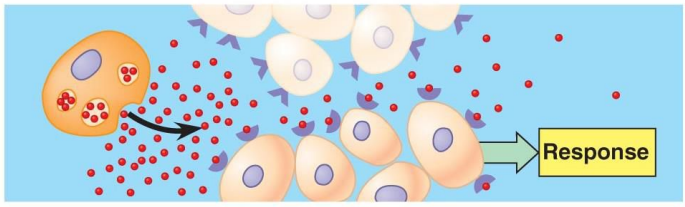
The activities of cells, tissues and organs are coordinated by chemical messengers:

- Neurotransmitters
- Endocrine hormones
- Neuroendocrine hormones
- Paracrines
- Autocrines
- Cytokines

Types of Signaling:

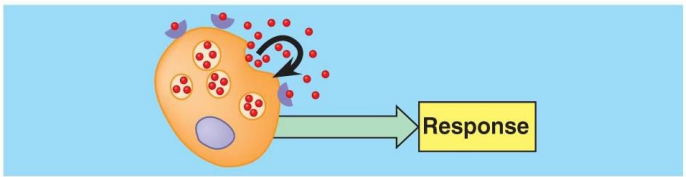


(a) Endocrine signaling



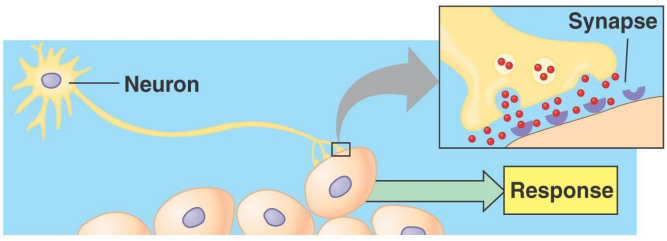
(b) Paracrine signaling

Locally acting chemicals that affect cells other than those that secrete them. Without reaching systemic circulation

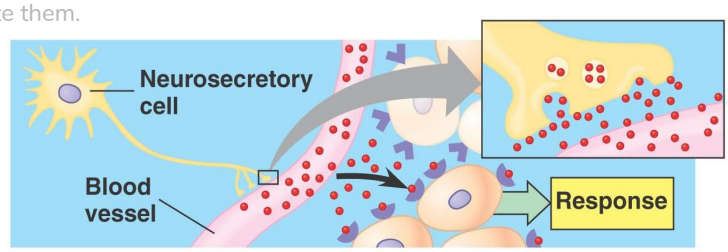


(c) Autocrine signaling

Chemicals that exert their effects on the same cells that secrete them.



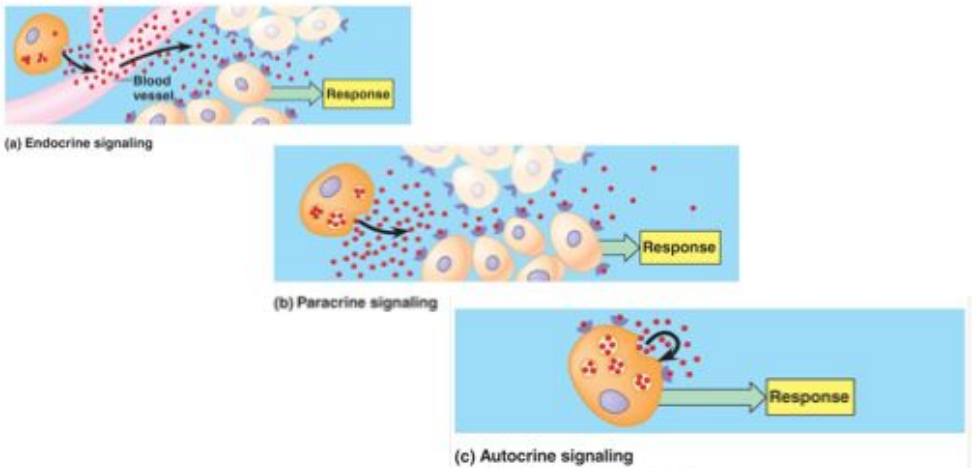
(d) Synaptic signaling



(e) Neuroendocrine signaling

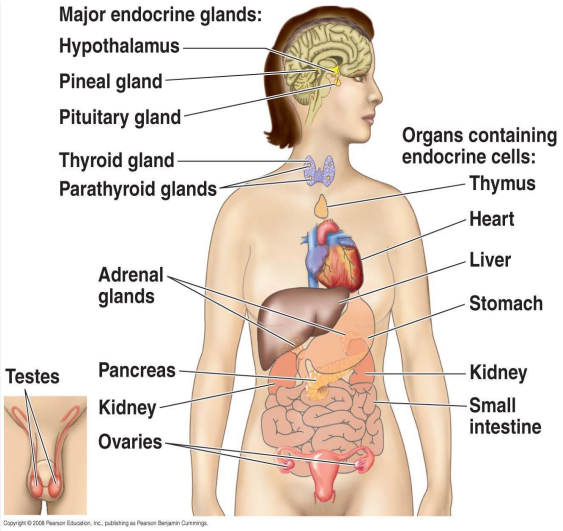
Cytokines:

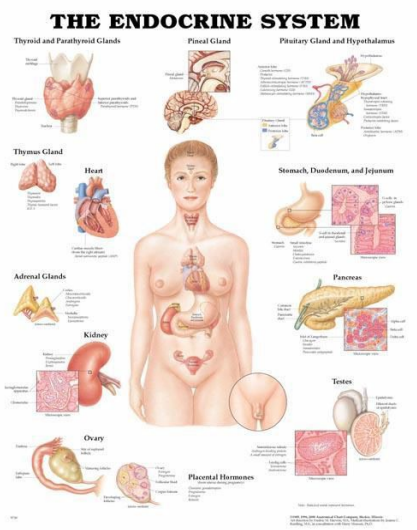
- Peptides **(interleukins**, **lymphokines**, **adipokines)**.
- Secreted by cells into extracellular fluid.
- Can function as: **Endocrine signaling**, **Paracrine signaling** and **Autocrine signaling.**



Endocrine Glands

- Pituitary
- Thyroid
- Parathyroid
- Adrenal
- Pancreas
- Ovaries
- Testes





The multiple hormone systems play a key role in regulating almost all body functions:

- Metabolism
- Growth and development
- Water and electrolyte balance
- Reproduction
- Behavior

Hormones

Definition :

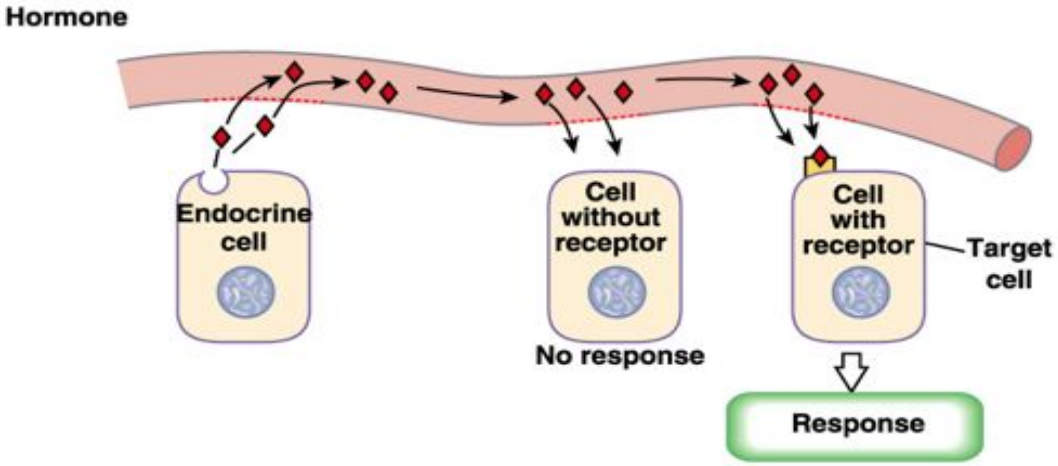
Hormone is a chemical substance released by group of cells to control the function of other type of cells.

Types of hormones:

- Affect many <u>different</u> types of cells (eg. GH and Thyroxin)
- Affect only <u>specific</u> target cells (eg. ACTH and estrogen)

What are target cells?

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



Chemical structure of hormones ,**Three general classes of hormones:**

1. **Proteins** and polypeptides (anterior and posterior **p**ituitary, **p**ancreas and **p**arathyroid hormones) stored in vesicles until needed.

   "Produced from different types of amino acids". PPP

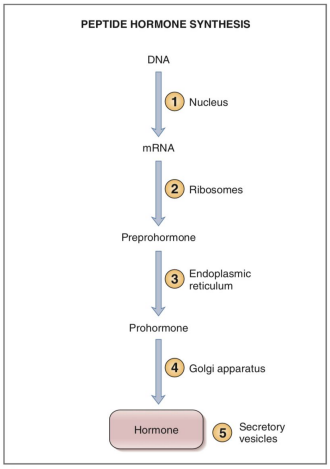
   Pituitary, Pancreas, Parathyroid

2. **Steroids** (adrenal cortex, ovarian and testicular hormones) diffuse across the cell membrane. Also the placenta, all are cholesterol derivatives.

3. **Derivatives of amino acid tyrosine** (thyroid hormones and catecholamines) and dopamine.

1- Peptide (Protein) Hormones:

- Synthesized as **preprohormone** → post-translational modification to **prohormone** → then **hormone** .



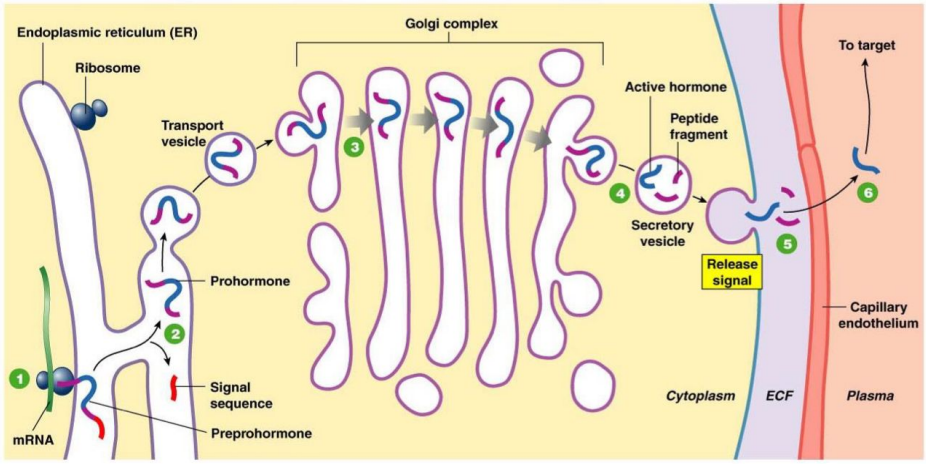
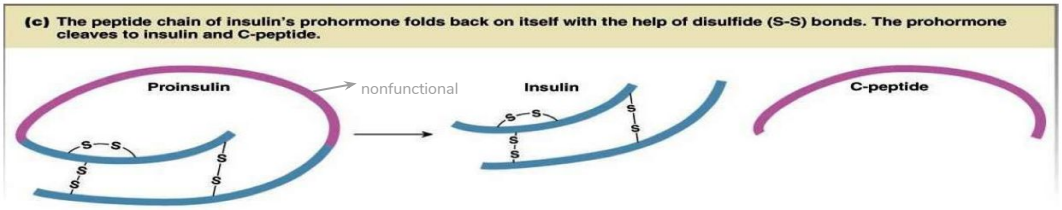


Fig. 9.2 Steps involved in the synthesis of peptide hormones. See the text for an explanation of the circled numbers. *DNA*, Deoxyribonucleic acid; *mRNA*, messenger ribonucleic acid.

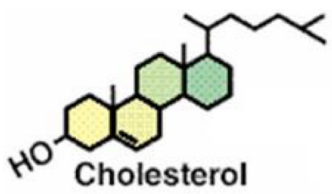
Example of protein hormone: Insulin.



The prohormone is made of insulin and C-peptide to make it active we have to cleave the c-protein chain. we can use the c-protein chain to detect the amount of insulin being released in the body

2- Steroid Hormones:

- Secreted by gonads, adrenals, placenta
- Derived from cholesterol (lipophilic)
  - Cross membranes (no storage)
- On-demand synthesis (SER) synthesized when needed
- Usually Bound to Carrier proteins



3- Amine Hormones:

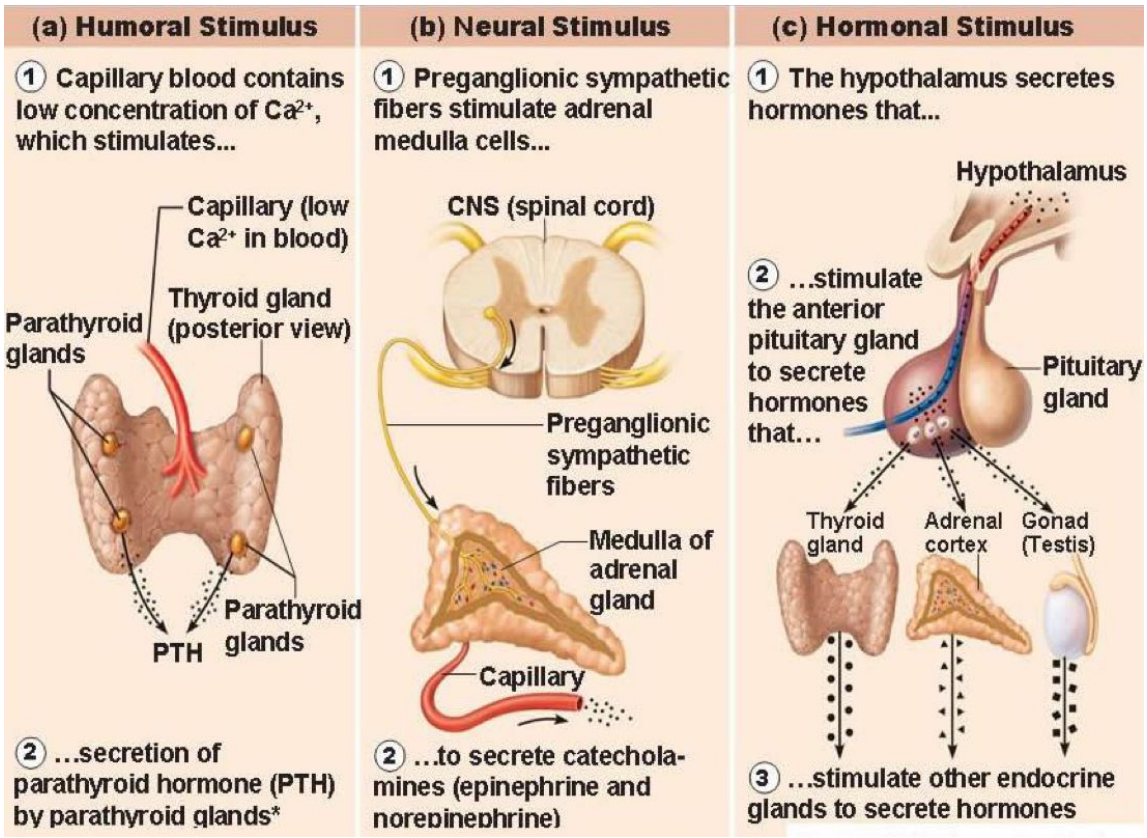
- **Derived from tyrosine or tryptophan** One type of amino acid (tyrosine).
- **3 groups:**

1. **Tryptophan → Melatonin**
2. **Tyrosine → Catecholamines**
   - behave like peptide hormones
3. **Tyrosine → Thyroid hormones**
   - behave like steroid hormones

Types of stimuli

Humoral Stimuli	Neural Stimuli	Hormonal Stimuli
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.

For better understand:



Transport of hormones: Within the blood

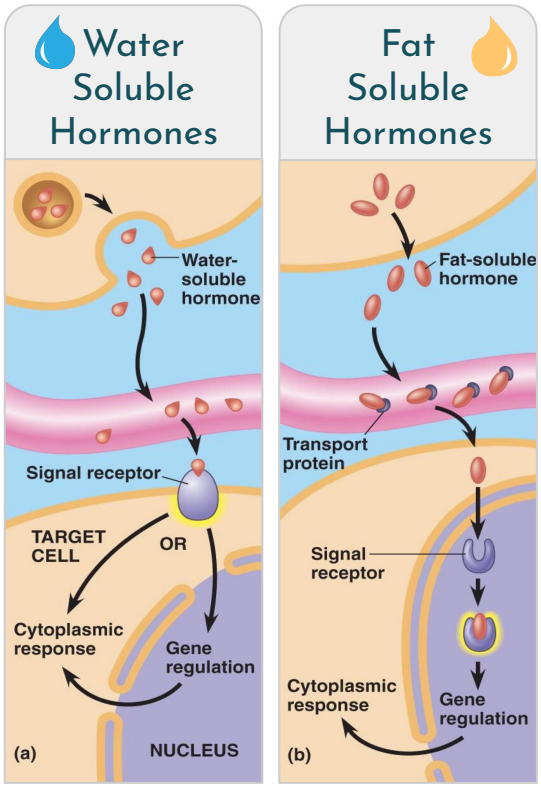
- **Water soluble hormones**- hydrophilic (peptides & catecholamines) dissolved in plasma.
- **Fat soluble hormones** – hydrophobic Steroids and thyroid hormones transported bound to plasma proteins (90%),

Fat soluble hormones binding to proteins helps to:

1. Provide reservoirs
2. Slow hormones clearance

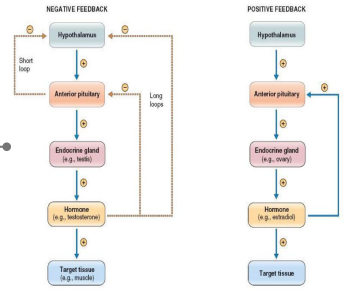
Differences between Water & fat soluble hormones:

Water soluble	Fat soluble
Stored within vesicles	No storage
Transport freely in the blood	Binds to plasma protein
Need to receptors on the cell membrane to get in	Diffuse through the cell membrane
Produce the action once gets inside the target cell	Have receptors inside the target cell to produce its action

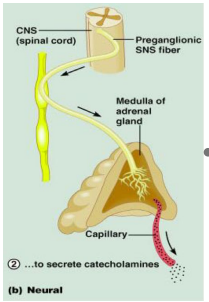


Regulation of hormone secretion

Feedback mechanism



Neural mechanism



Hormones & Receptors:

Receptors:

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

Receptor's Locations:

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

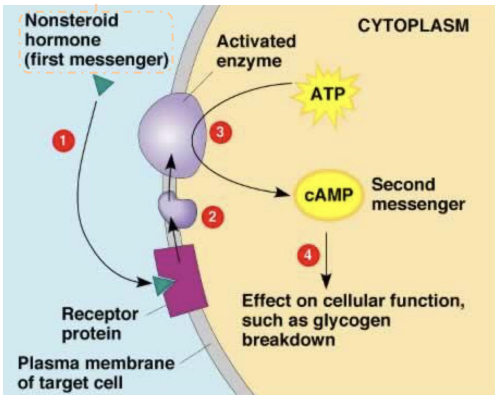
1. Lipophobic hormones (proteins) will bind with a receptor on cell membrane.
   - Faster and through 2nd messenger.
2. Lipophilic hormones (steroid and amine) will bind to a receptor either on cytoplasm or nucleus.
   - Slower and through transcription and translation.

Mechanism of action of hormones:

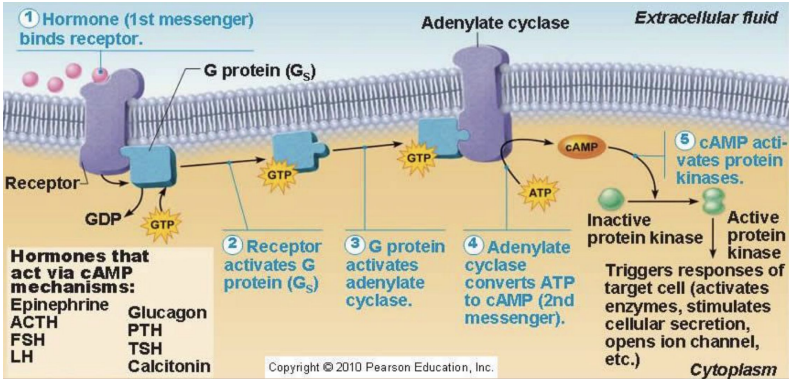
(peptides and protein hormones)

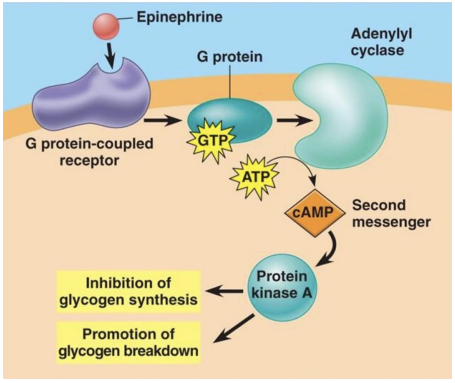
Action gets magnified with each step

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



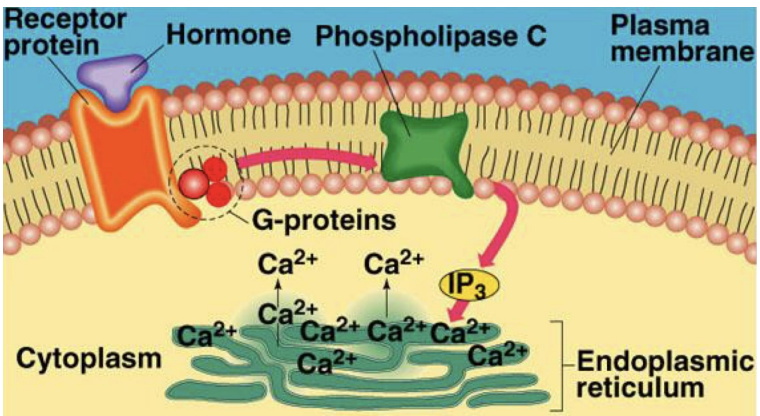
Second messenger (Adynylate cyclase-cAMP):





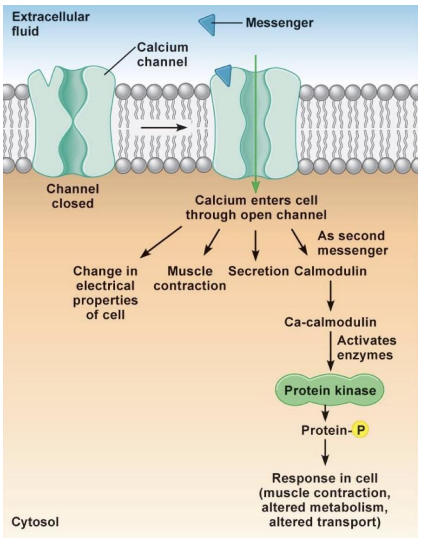
1. Hormone binds with the receptor on cell membrane
2. The receptor is bound to G-protein which is bound to GDP after the hormone is connected with the receptor the G-protein will get activated by acquiring GTP and releasing GDP (enzyme activation)
3. The changes to G-protein will make it move across the cell membrane to the adenyl cyclase receptor that will convert ATP to cAMP (release of secondary messenger)
4. cAMP will then activate protein kinase which will cause the effect on cellular functions

Second messenger (Phospholipase C-IP3):



1. Hormone binds with receptor that is connected to inactivated g-protein (bound to GDP).
2. The binding will activate the G-protein which will move across the membrane to activate the phospholipase C (enzyme activation), then cleaves the inositol phospholipid into two parts IP_3 and DAG.
3. The IP_3 (secondary messenger) will go to the endoplasmic reticulum and stimulate the release Ca, the increase of Ca will cause the effect on cellular functions.

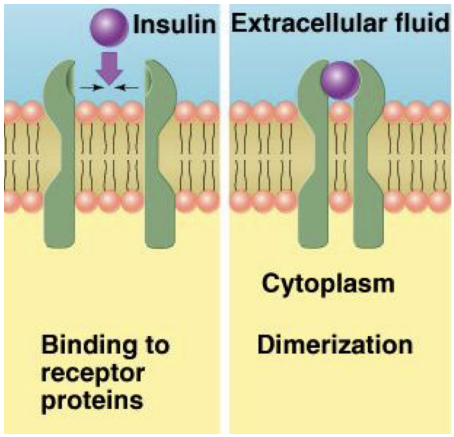
Second messenger (calcium-calmodulin complex):

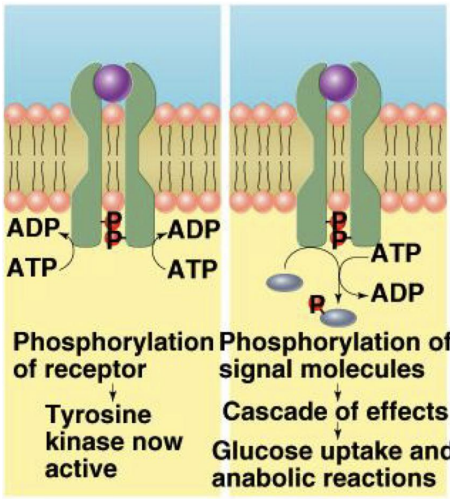


1. Receptor operated by a ligand (hormone). The binding will cause a conformational change that will allow the Ca to enter the cell.
2. Once Ca level inside the cell rises, Ca will bind to calmodulin and form calcium-calmodulin complex (secondary messenger).
3. Ca-calmodulin complex will activate protein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

Second messenger (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 signaling molecules.
- Induction of hormone/growth factor effects.





Tyrosine kinase receptor has two domains, when insulin binds to the receptor the domains will come together (dimerization). Activation will cause phosphorylation of the receptor by ATP, and the receptor will phosphorylate other signaling molecule that will produce the action of insulin which is opening some channels that brings glucose inside the cell.

All the previous four were on the surface of the cell membrane, the next one is in the plasma.

Mechanism of action (steroid hormones)

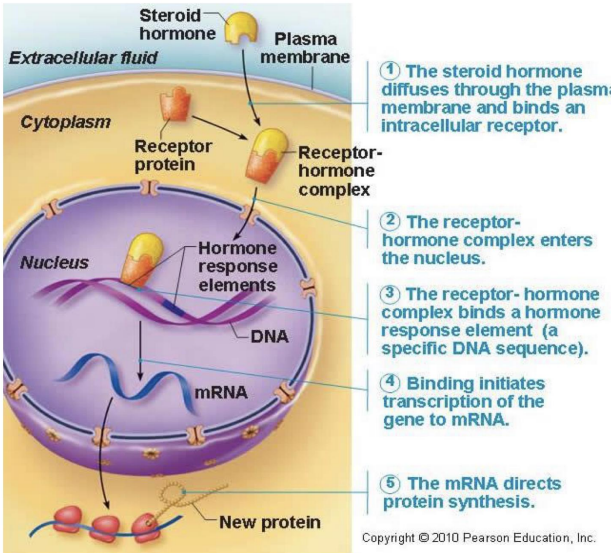


TABLE 9.3 Mechanisms of Hormone Action

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				

cAMP, Cyclic adenosine monophosphate; *cGMP,* cyclic guanosine monophosphate; *IP_3,* inositol 1,4,5-triphosphate.

Regulation of hormonal receptors

- **Receptors does not remain constant**
  - Inactivated or destroyed
  - Reactivated or manufactured
- **Downregulation**
  - Increase hormone concentration leads to decrease in the number of active receptors.
  - Most peptide hormones have pulsatile secretion which prevents downregulation.
  - Decrease synthesis, increase degradation, e.g. T_3
- **Upregulation**
  - The hormone induces greater than normal formation of a receptor or intracellular signaling proteins
  - Increase synthesis, decrease degradation, e.g. PRL

For example; at the end of pregnancy oxytocin receptors and the proteins inside the cells will increase.

- **Dose-response relationship**
- **Sensitivity**
- **Number**
- **Affinity**

First mechanism is the feedback mechanism, if it is not resolved, the body will proceed to regulation of receptors (down or up)

Clearance of hormones

- **Two factors control the concentration of a hormone in the blood:**
  - The rate of its secretion
  - The rate of its removal (metabolic clearance)

- **Hormones are cleared by:**
  - Metabolic destruction by tissues
  - Binding with tissues
  - Excretion by the liver into bile
  - Excretion by the kidney into urine

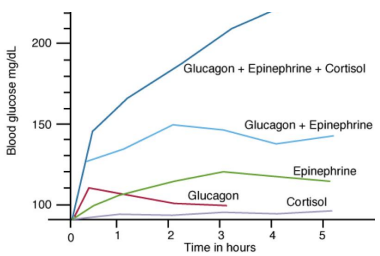
  Hormones clearance will be affected by liver diseases like a male with liver cirrhosis will develop gynecomastia.

- **Clearance of protein bound hormones is slower than clearance of peptide hormones.** Peptide hormones takes seconds, while Steroids may take days.

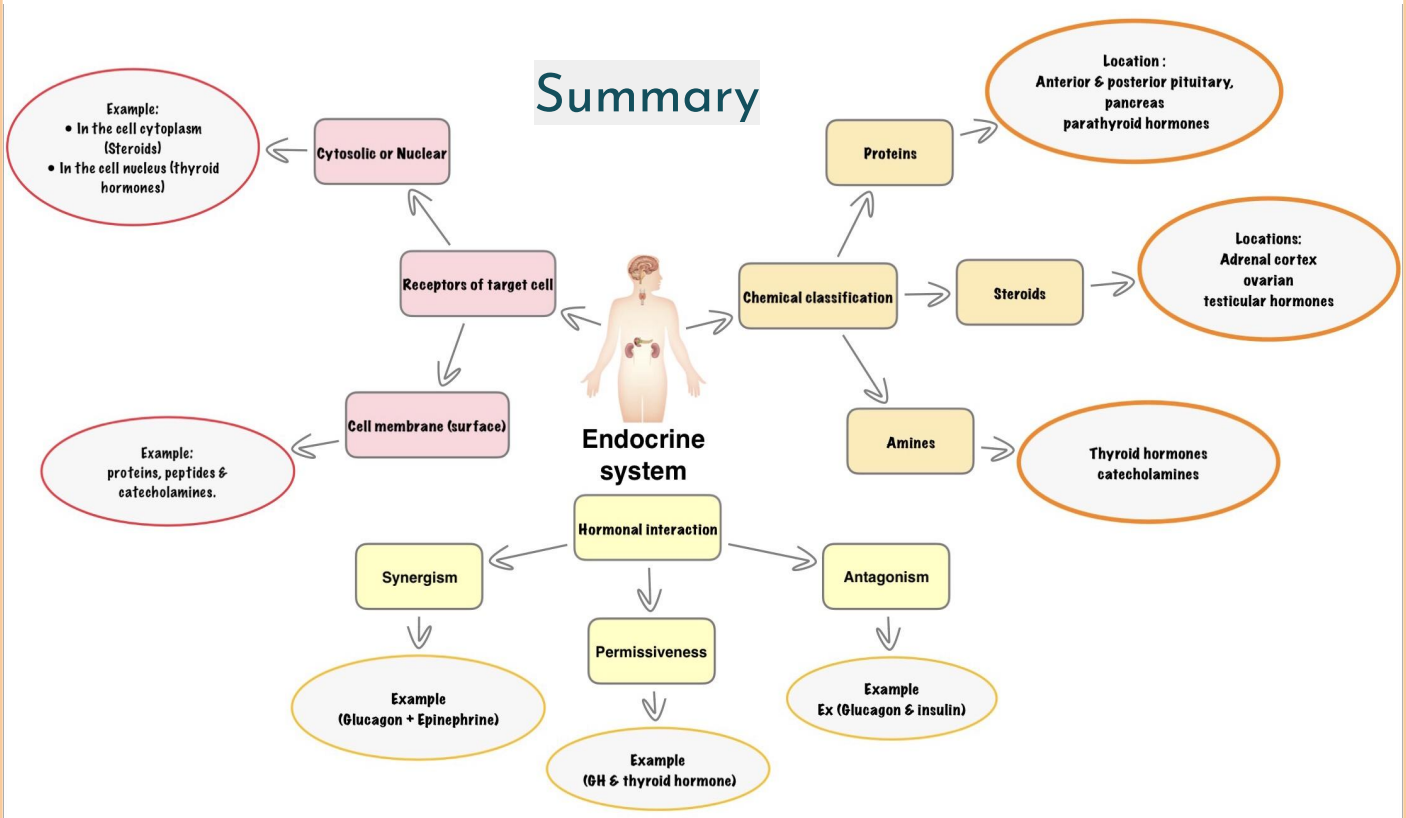
Hormone interactions

- **Multiple hormones can affect a single target simultaneously.**

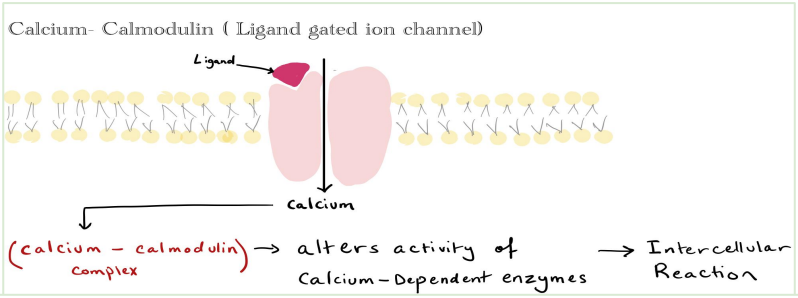
Three types of hormone interactions:

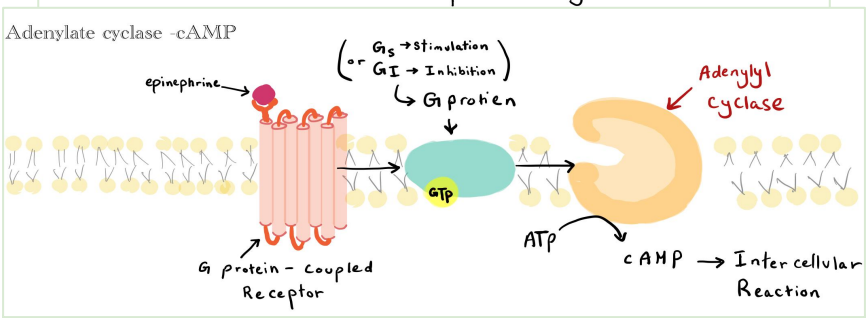
	Synergism	Permissiveness	Antagonism
Definition	**Combined action of hormones** is more than just additive!	**One hormone allows another hormone to have its full effect,** especially during growth	**Antagonistic hormones have opposing** physiological actions (Hormone B diminishes the effect of hormone A)
Examples	Blood glucose levels & synergistic effects of glucagon, cortisol and epinephrine.	Thyroid hormone have permissive effect on growth hormone action. Deficiency of thyroid hormone in infants leads to dwarfism.	Glucagon antagonizes the action of insulin
Notes	Effect of combined hormones is greater than effect of individual hormones. 	Presence of a hormone will potentiate effect of another hormone. Is not necessary that hormones have a similar effect. زي واحد يتمرن لحاله يواجه صعوبة في رفع الأثقال ولكن اذا جاء واحد يشجعه بتسهل عليه عملية رفع الاثقال.	Calcitonin antagonizes the action of parathyroid.

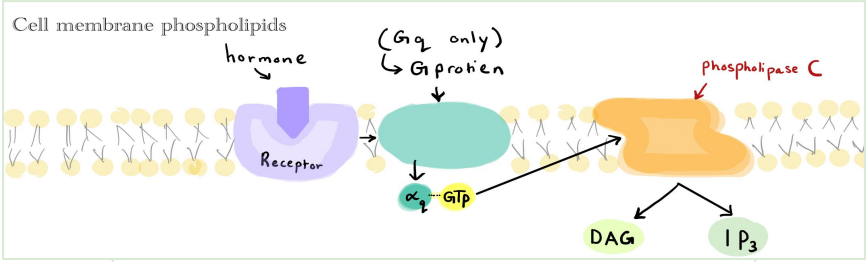
Summary

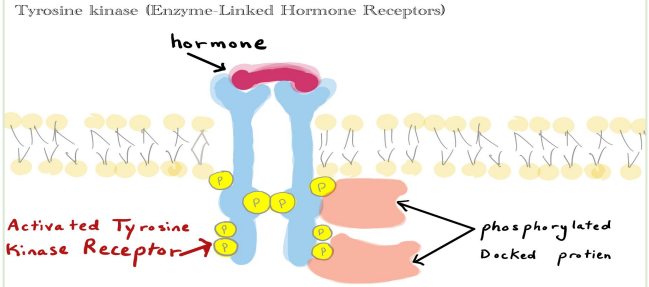


Mechanism of action of peptides & protein hormones- Red is the secondary messengers

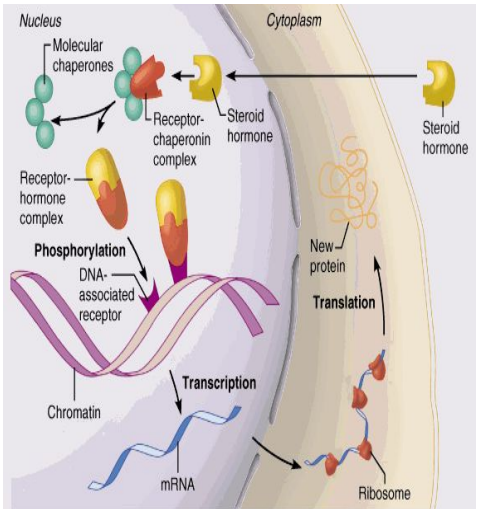








Mechanism of action of steroid & thyroid hormones



MCQs

Q1: Which one is considered a 2nd messenger :

A) Phospholipase C
B) G protein
C) cAMP
D) Adenylate Cyclase

Q2: Calcitonin and Parathyroid hormone have what type of interaction?

A) Antagonism
B) Synergism
C) Permissiveness
D) None of the above

Q3: Which hormone has its receptor in the cytoplasm?

A) Cortisol
B) Insulin
C) Growth hormone
D) Oxytocin

Q4: Melatonin is: :

A) Derived from Tyrosine and behaves like peptide hormones
B) Derived from Tyrosine and behaves like steroid hormones
C) Derived from Tryptophan
D) A steroid hormone

Q5: Ductless glands that produce hormones released directly into the blood are:

A) Paracrine glands
B) Endocrine glands
C) Autocrine glands
D) Exocrine glands

Q6: Which of the following statements about peptide or protein hormones is usually true ?

A) They have longer half-lives than steroid hormone
B) The have receptor on the cell membrane
C) The have a slower onset of action than both steroid and thyroid hormones
D) The are not stored in endocrine-producing glands

SAQ: what is the interactions of hormones at the target tissue ?

1- permissiveness
2- synergism
3-antagonism

Answers
Q1: C
Q2: A
Q3: A
Q4: C
Q5: B
Q6: B