# MEDICINE 438's

# ENDOCRINE PHYSIOLOGY

## LECTURE I: Introduction to the Endocrine Physiology

EDITING FILE

IMPORTANT | MALE SLIDES | EXTRA | FEMALE SLIDES | LECTURER'S NOTES

# 1 INTRODUCTION TO THE ENDOCRINE PHYSIOLOGY

Lecture One

## OBJECTIVES

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

## Introduction

**What are hormones?** Chemical substances secreted in a small amount from endocrine gland directly to the bloodstream in response to stimulus to cause physiological responses at the target tissues.

### Exocrine Glands

- Ducts
- Secrete enzymes
- Secretion into lumen of ducts and body surfaces (e.g. sweat glands)

### Endocrine Glands

- No ducts
- Secrete chemical messengers
- Secretion into bloodstream

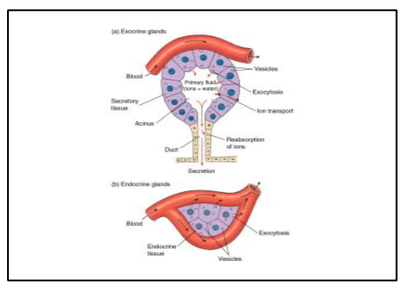



**Figure 1-1**

## Types of Hormones

**The activities of cells, tissues and organs are coordinated by chemical messengers, these can be classified in the following manner:**

1. **Neurotransmitters:** Chemical substance released from the axon of one neuron across a synaptic cleft to act on another cell.
2. **Endocrine Hormones:** Chemical substance released by mostly glands into the bloodstream.
3. **Autocrine Secretions:** Chemical substance secreted by a cell into the ECF to affect the function of the same cell that produced them.
4. **Paracrine Secretions:** Chemical substance secreted by a cell into the ECF to affect the function of adjacent cells other than those that produced them.. (e.g. histamine by ECL cells)
5. **Cytokines[1]:** Chemical substance released by cells into the ECF and can function as autocrines, endocrines and paracrines. Peptides (interleukins, lymphokines, adipokines)
6. **Neuroendocrine Hormones:** Chemical substance released by neuronal axons directly into the bloodstream.

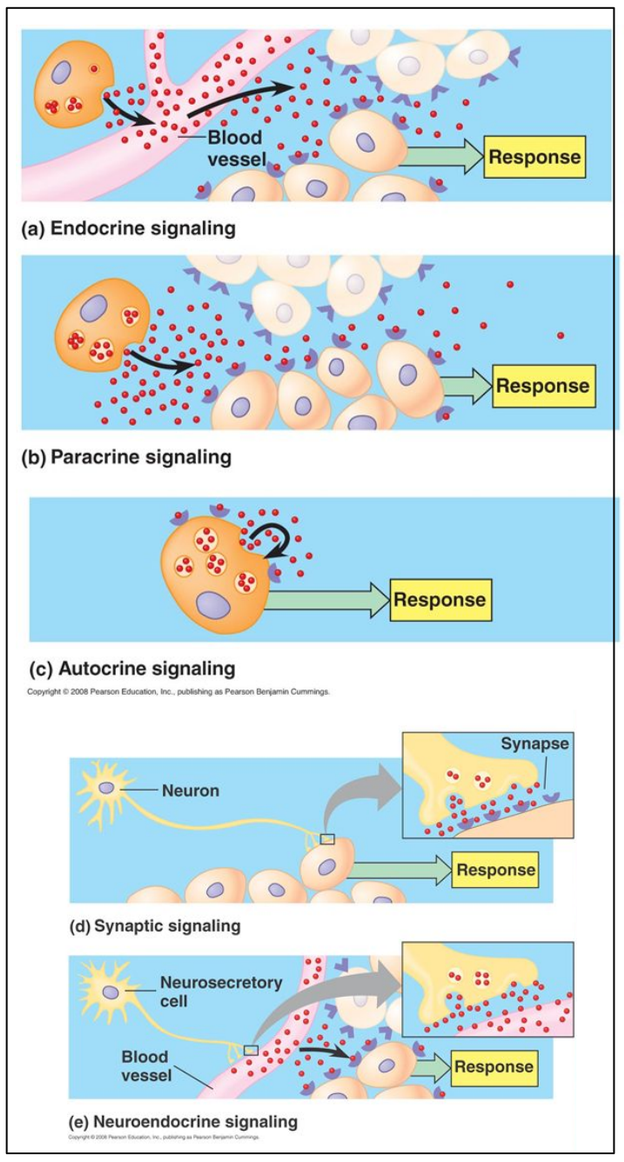



**Figure 1-2**

## According to Chemical Structure

| Peptides and Proteins | Steroid Hormones | Amines (hormones derived from the amino acids tryptophan and tyrosine) |
|---|---|---|
| Parathyroid, pancreatic and pituitary hormones. Stored inside vesicles until needed. | Adrenocortical hormones (adrenal cortex), ovaries, testes and placenta. Diffuse across cell membranes and are not stored inside vesicles. | Thyroid hormones (tyrosine-derived), catecholamines from adrenal medulla (tyrosine-derived), melatonin (tryptophan-derived). |

## According to Target Cells

1. Affect many different types of cells (eg. Growth hormone and thyroxin)
2. Affect only specific target cells (eg. ACTH[2] and estrogen)

## According to Stimuli

| Humoral: Secretion of hormones in direct response to changing in blood levels of ions and nutrients | Neural: Nerve fibers stimulate hormone release. | Hormonal: Release of hormones in response to hormones produced by other endocrine gland. |
|---|---|---|

## FOOTNOTES

1. The distinction between cytokines and hormones is that hormones tend to be released by glands and are present in higher concentrations. But no definite distinction exists.
2. Released by anterior pituitary to stimulate adrenal cortex. Specificity depends if the cells express receptors for that particular hormone.

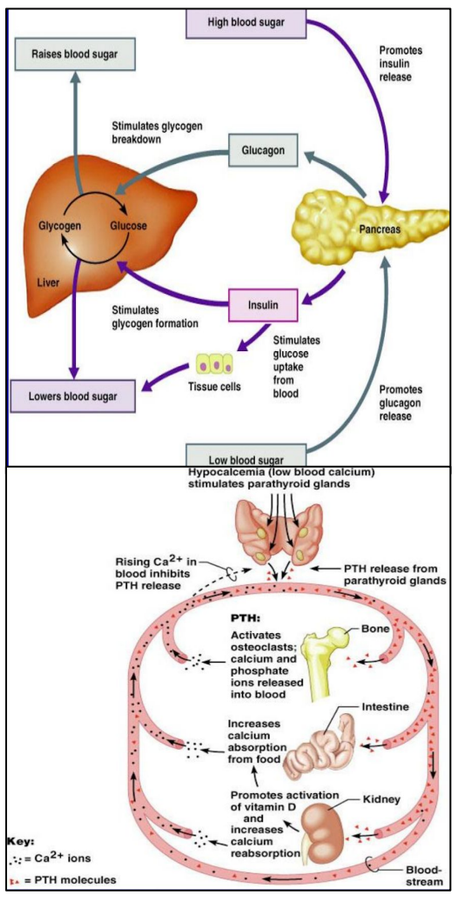



**Figure 1-3** Humoral stimuli for hormonal secretion. Will be explained later in-depth in upcoming lectures.

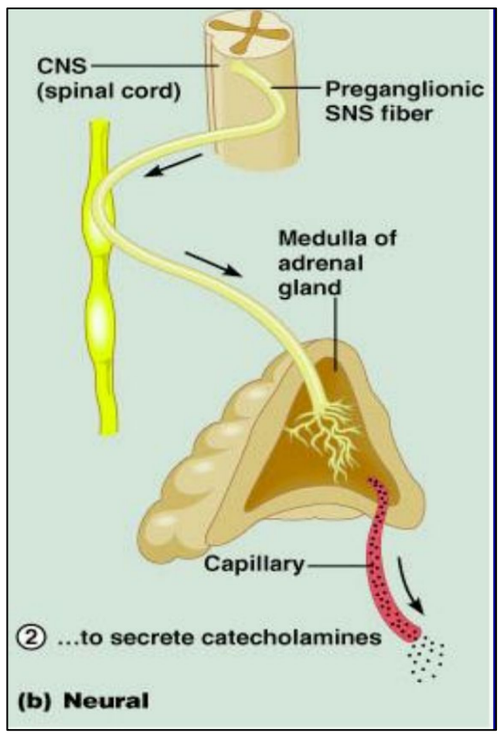



**Figure 1-4** Neural stimuli for hormonal secretion, the adrenal medulla medulla, unlike neurons, secrete four times as much epinephrine than norepinephrine.

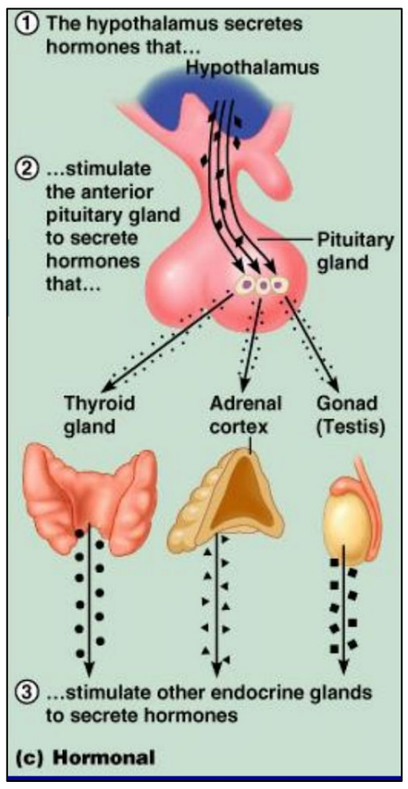



**Figure 1-5** Hormonal stimuli for hormonal secretion. Will be explained later in-depth in upcoming lectures.

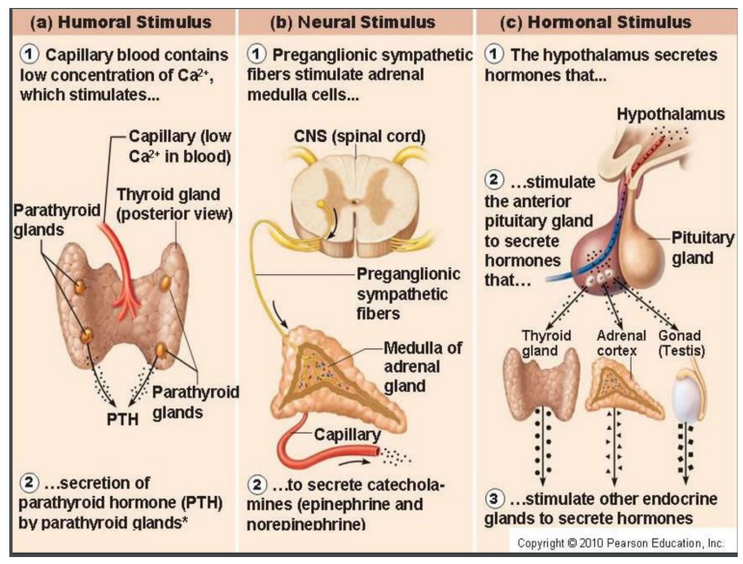



**Figure 1-6** Stimuli for hormonal secretion.

## Endocrine Glands and Key Roles of Hormones

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

1. Metabolism (thyroxine)
2. Growth and development (Growth hormone)
3. Water and electrolyte balance (ADH)
4. Reproduction (FSH, LH and sex hormones)
5. Behavior (Oxytocin, increases during hugging and orgasmic activities)

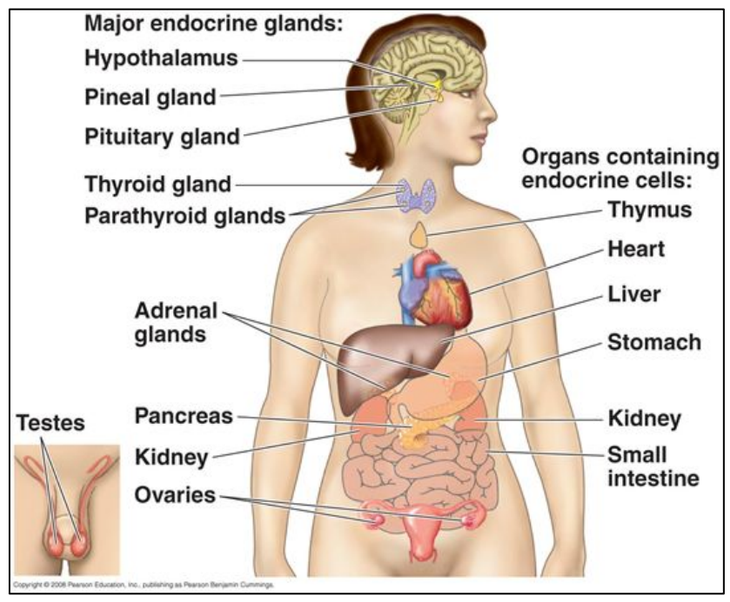



**Figure 1-7** Shows endocrine glands, the key endocrine glands are: (1) Pituitary, (2) pancreas, (3) testes, (4) ovaries, (5) adrenals, (6) thyroid, (7) parathyroid, (8) placenta.

## Receptor Types and How Hormones Exert Their Effects

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

**Receptors:** Hormonal receptors are large proteins.

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

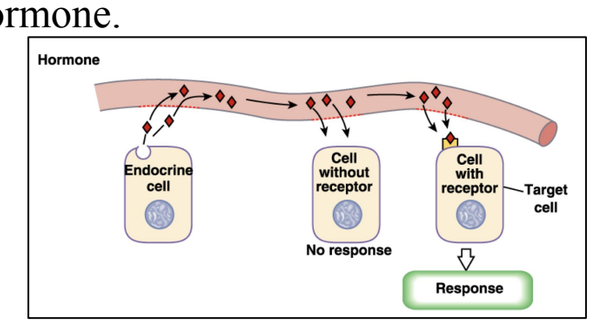



**Figure 1-8**

**Receptor Locations:**

1. **Cytosolic or Nuclear:** Lipophilic ligand enters cell, often activates gene, and slower response.

A. **Cytosolic:** Steroid hormones
B. **Nuclear:** Thyroid hormones

**2. On the Surface of Cell Membrane:** Lipophobic ligand can't enter cell, outer surface receptor and faster response.

- **Peptides, proteins and catecholamines**.

## Mechanism of Action

1. Hormone-receptor interaction (1st messenger)
2. Conformational changes

**From here most hormones cause:**

3. Enzyme activation
4. Release of the second messenger
5. All hormones: effects on cellular function

## Transport of Hormones

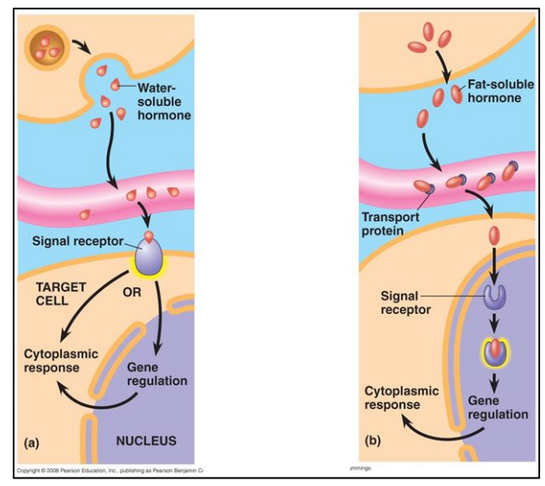



**Figure 1-9**

**Water soluble hormones: hydrophilic** (peptides & catecholamines) dissolved in plasma.
**Fat soluble hormones: hydrophobic** (steroids and thyroid hormones) transported bound to plasma proteins (90%),
binding to proteins helps to

- Provide reservoirs
- Slow hormones clearance

## Peptide and Protein Hormones

(Pituitary, pancreatic and parathyroid hormones)

### Synthesis

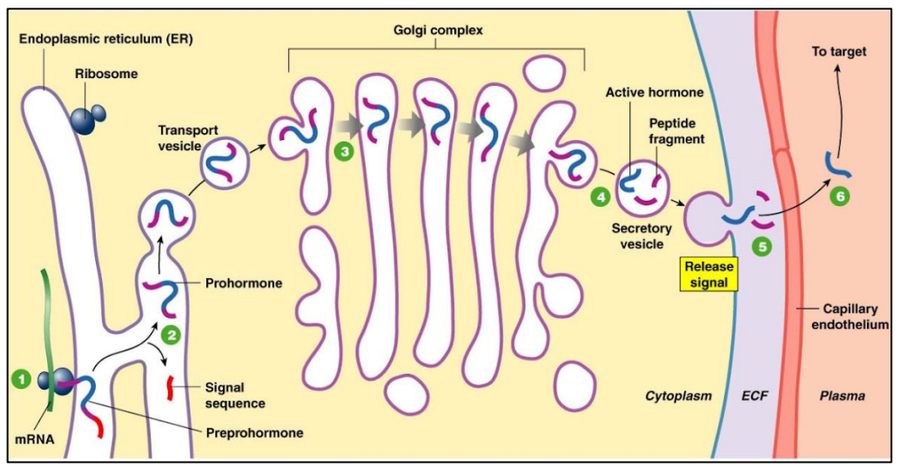



**Figure 1-10** Synthesized as preprohormone → post-translational modification to prohormone → then hormone.

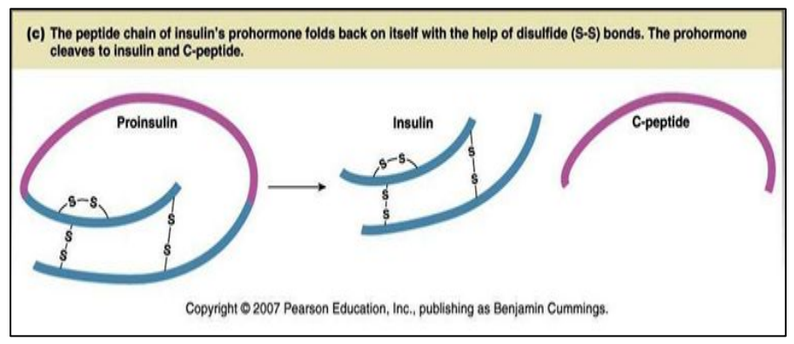



**Figure 1-11** Example of protein hormone, insulin.

In other words: The gene hormone is transcripted into mRNA → translated in the ribosomes into the hormone with an extra amino acid sequence that serves as a "docking peptide" → attach to ER, the hormone plus the docking peptide are called "preprohormones" → docking peptide is chopped off → preprohormone enters the ER as a prohormone (there are still some remaining amino acids that keeps the hormone inactive) → these extra amino acids are cleaved in golgi apparatus, and then the hormone along with the chopped off peptide are released into ECF.

### Mechanism of Action

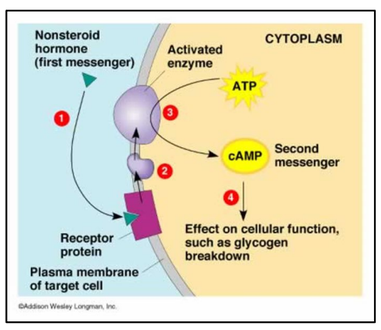
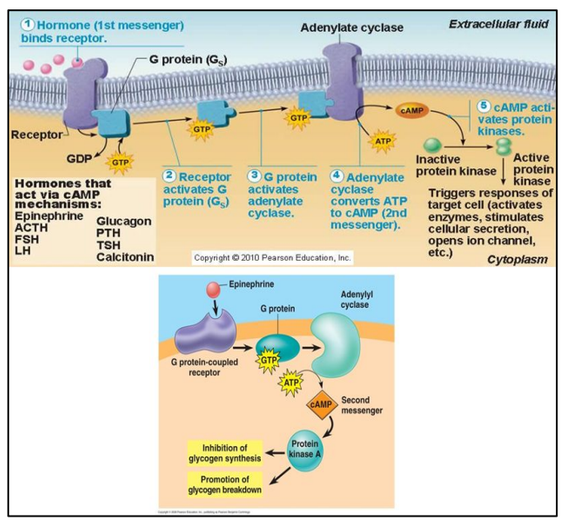
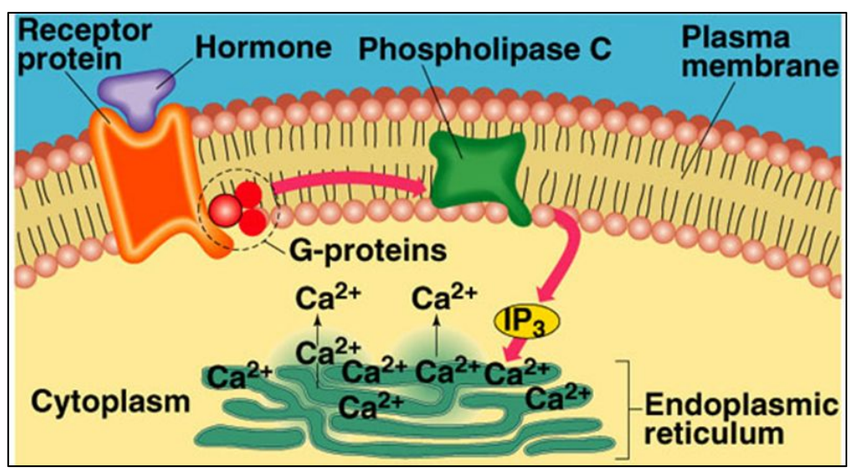



**Figure 1-12**
Peptide hormone exert their effect through 2nd messenger systems.

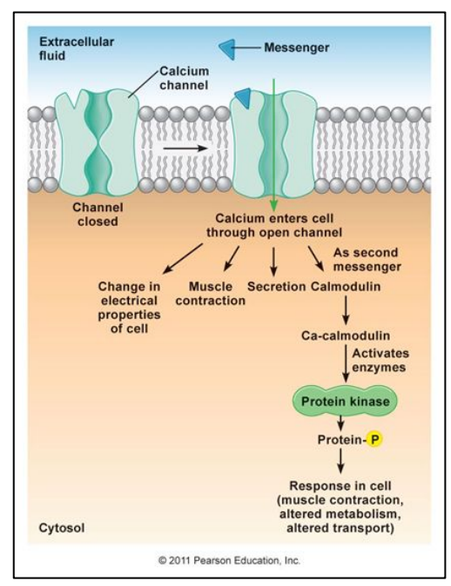
**Figure 1-13: 2nd Messenger Systems of Peptide and Protein Hormones: (a) Adenylate Cyclase-cAMP, (b) Phospholipase C-IP3/DAG (c) Calcium-calmodulin complex, (d) Tyrosine Kinase System**



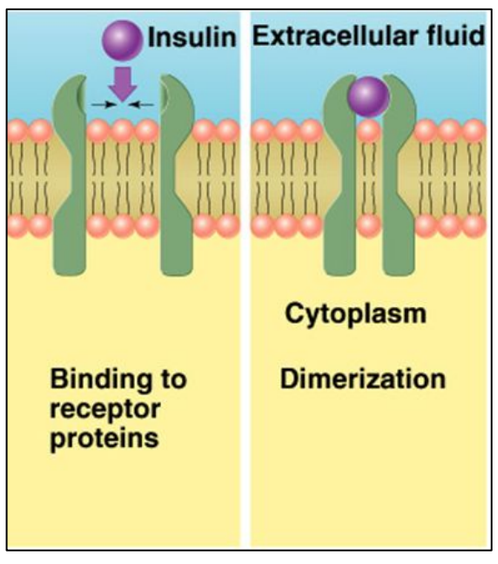

(a) **Adenylate Cyclase-cAMP**

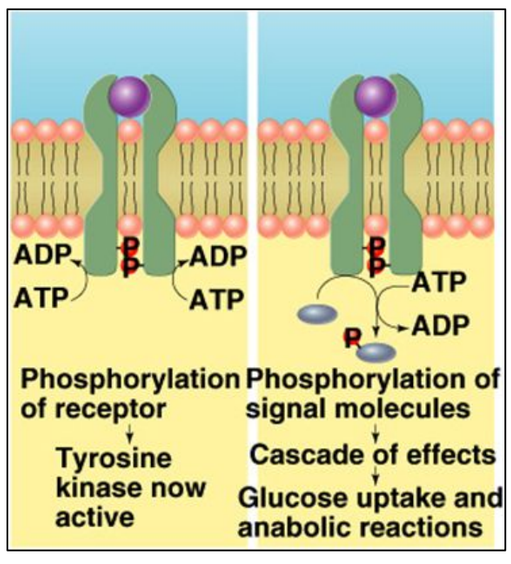



(b) **Phospholipase C-IP3/DAG:** Binding of hormone: Hormone binds → Alpha subunit of G-protein detaches → Activates PLC → Cleaves a phospholipid in cell membrane (PIP2) into DAG and IP3 → IP3 releases calcium from mitochondria and sER, DAG activates protein kinase C → Cell effects.




**(c) Calcium-calmodulin complex**




**(d) Tyrosine Kinase System:**

- Used by insulin & many growth factors to cause cellular effects.
- Surface receptor is tyrosine kinase: consists of two units that form active dimer when insulin binds.
- Activated tyrosine kinase phosphorylates signaling 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.

## Steroid Hormones
(Adrenal cortex, placenta, ovaries and testes)

**Synthesis**

- Derived from cholesterol (lipophilic)
- Cross membranes (no storage)
- On-demand synthesis (SER)
- Usually bound to carrier proteins

**Mechanism of Action**

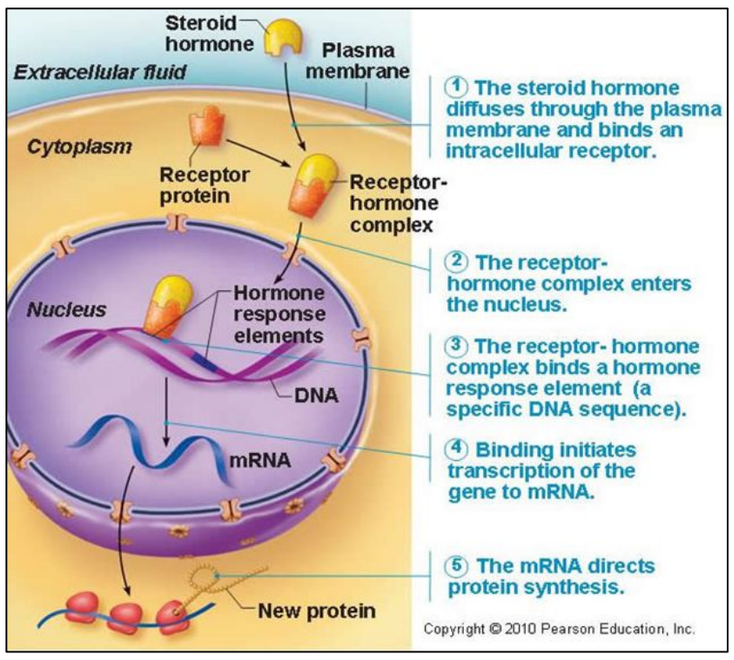



**Figure 1-14** Hormone response element, is a DNA segment on which the receptor-hormone complex will bind to adhere to the DNA. The complex acts as a transcription factor to initiate gene transcription, and therefore protein synthesis.

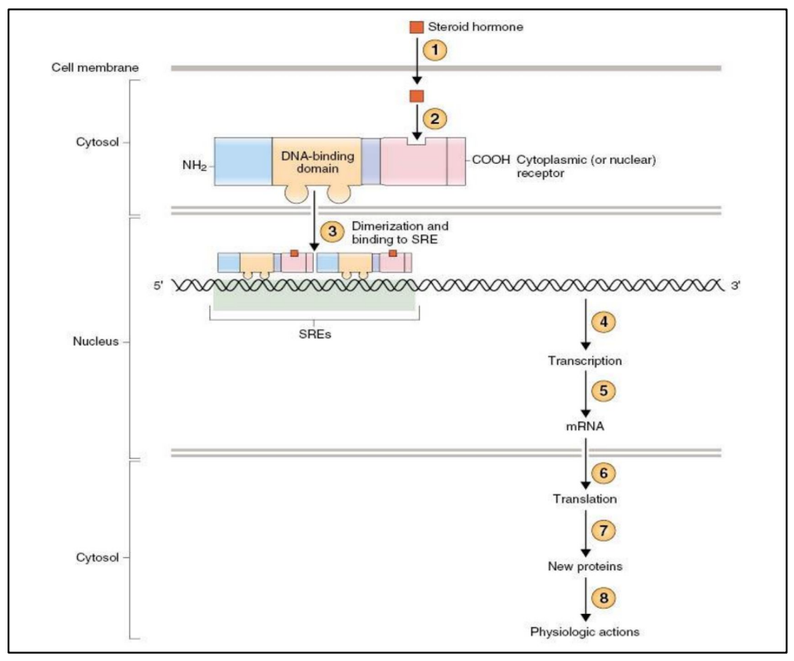



**Figure 1-15**

## Amine Hormones
(Tyrosine-derived: Thyroid hormones, catecholamines. Tryptophan-derived: melatonin)

**Synthesis**

**Tryptophan-derived:** Melatonin

**Tyrosine-derived:** Catecholamines

- Behave like peptide hormones[1]

**Tyrosine-derived:** Thyroid hormones

- Behave like steroid hormones[1]

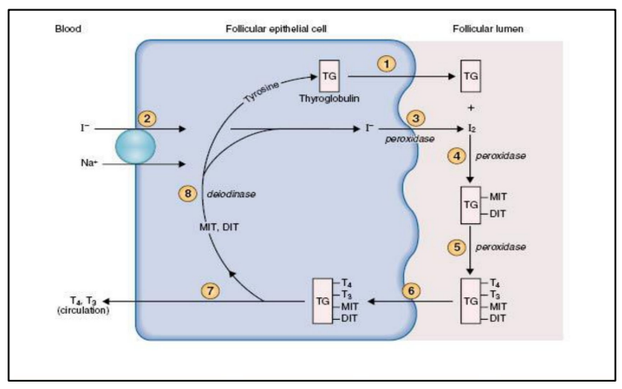



**Figure 1-16** Mainly for your knowledge only.

**Mechanism of Action**

**Catecholamines:** same as peptide hormones

**Thyroid hormones** act via nuclear receptors.

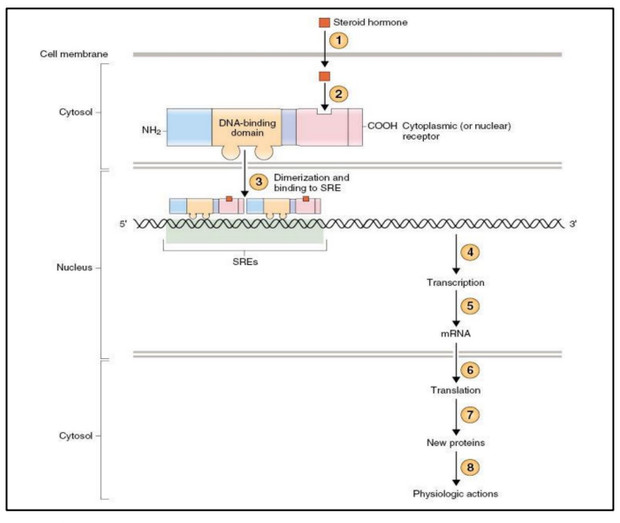



**Figure 1-17**

## FOOTNOTES

1. Tyrosine-derived hormones include catecholamines, they resemble peptide hormones as they are dissolved in plasma and act via cell surface receptors. Similarly, thyroid hormones are transported via plasma proteins and act intracellularly, but through nuclear receptors rather than cytoplasmic.

| Adenylyl Cyclase Mechanism (cAMP) | Phospholipase C Mechanism ($IP_3/Ca^{2+}$) | Steroid Hormone Mechanism | Tyrosine Kinase Mechanism |
|---|---|---|---|
| ACTH | GnRH | Glucocorticoids | Insulin |
| LH | TRH | Estrogen | IGF-1 |
| FSH | GHRH | Progesterone | |
| TSH | Angiotensin II | Testosterone | |
| ADH ($V_2$ receptor) | ADH ($V_1$ receptor) | Aldosterone | |
| HCG | Oxytocin | 1,25-Dihydroxycholecalciferol | |
| MSH | $\alpha_1$ Receptors | Thyroid hormones | |
| CRH | | | |
| Calcitonin | | | |
| PTH | | | |
| Glucagon | | | |
| $\beta_1$ and $\beta_2$ receptors | | | |

**Figure 1-18**

Summary of mechanism of actions.

## Regulation of Hormones and Their 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[1]
- Decrease synthesis, increased degradation, or Inactivation of receptors. Example: triiodothyronine **(T3)**

**Upregulation**

- The hormone induces greater than normal formation of a receptor or intracellular signaling proteins.
- Increase synthesis, decreased degradation, receptor activation. Example: prolactin.

## Receptor Regulation

- **Dose-response relationship:** Describes how the concentration of a particular hormone relates to its physiological effect.
- **Sensitivity:** Refers to the responsiveness of a particular cells to a hormonal stimulus due to the presence of receptors.
- **Number:** Numbers of receptors on a particular cell that responds to a specific hormone.
- **Affinity:** Refers to the affinity of a receptor to its particular ligand (hormone).

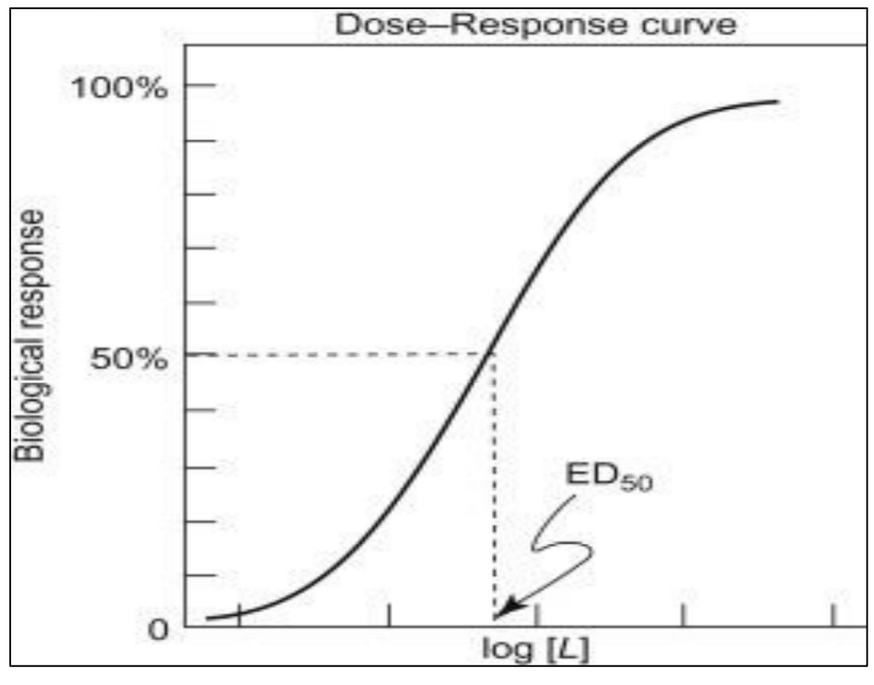



**Figure 1-19**

## Interaction of Hormones at Target Cells

**Permissiveness:** One hormone allows another hormone to have its full effect. (Especially during growth)(this occurs through upregulation of the receptors or the intracellular enzymes required for the action of another hormone)

- Thyroid hormone have permissive effect on growth hormone action.
- Deficiency of thyroid hormone in infants leads to dwarfism.
- Thyroid hormone have permissive effect on epinephrine through upregulation of beta-2 receptors, partially why hyperthyroidism causes excessive sympathetic stimulation.

**Synergism:** Combined action of hormones is more than just additive (the combined effects are greater than if the effects of the individual hormones are measured separately)

- Glucagon, cortisol and epinephrine

**Antagonism:** Antagonistic hormones have opposing physiological actions

- Hormone B diminishes the effect of hormone A
- (Glucagon, insulin)(Calcitonin, parathyroid hormone)

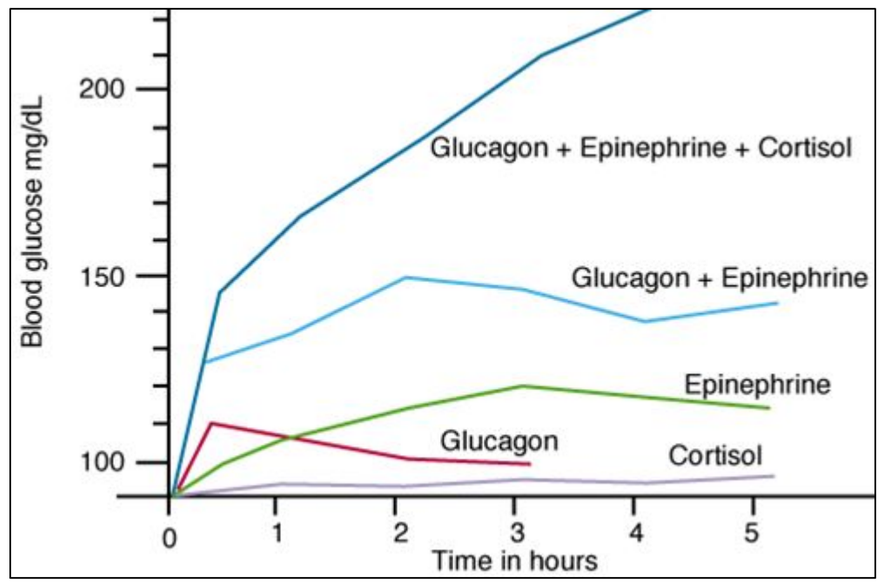



**Figure 1-20**

## Clearance of Hormones

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

- The rate of its secretion
- The rate of its removal and inactivation (metabolic clearance)

**Hormones are cleared by:**

- Metabolic destruction by tissues through enzymes
- Excretion by the liver into bile
- Excretion by the kidney into urine
- Binding with tissues

Clearance of protein- bound hormones is slower than clearance of peptide hormones (dissolved hormones).

## FOOTNOTES

1. Meaning that the hormonal secretion varies at different times during a 24 hour cycle.For example, growth hormone secretion increases during the early hours of sleep then decreases later on. In fact, as much as 75% of GH secretion occurs during sleep.

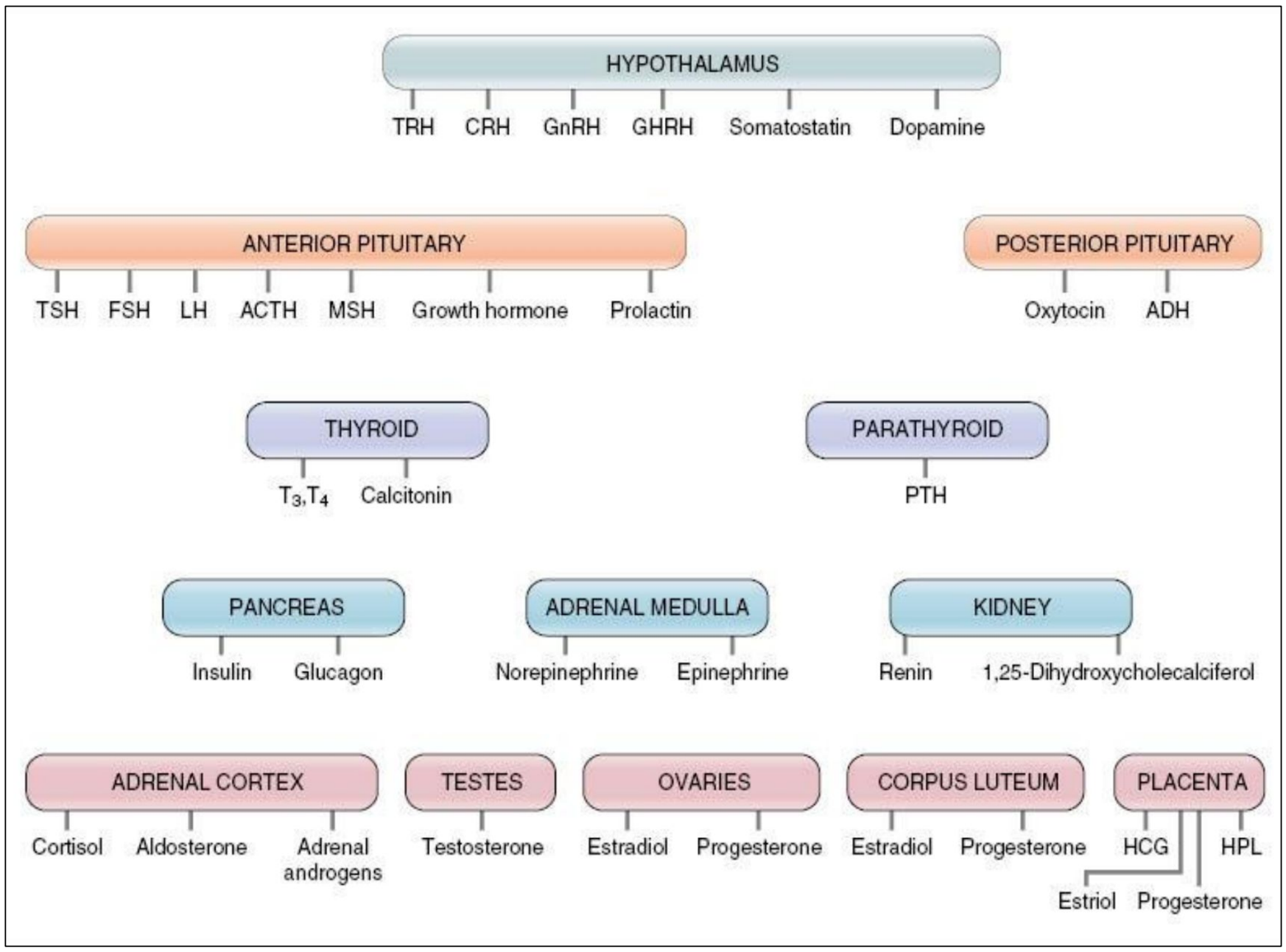



**Figure 1-21** For upcoming lectures.

# QUIZ

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1. A relationship in which one hormone augments the effects of another hormone, primarily by upregulating receptors:

A) Synergism
B) Permissiveness
C) Antagonism
D) Co-agonist synergy

2. The removal of the docking peptide of preprohormones occurs during:

A) Uptake by endoplasmic reticulum
B) Golgi apparatus
C) In the mitochondria
D) Ribosomes

3. The term “neuroendocrine” refers to:

A) A neuron secreting chemical substances across a synaptic cleft
B) A neuron secreting chemical substances into the bloodstream
C) A gland secreting its hormones across into the bloodstream
D) Chemical substances secreted by neurons that act on the same neurons producing them.

4. Insulin is an example of:

A) A steroid hormone
B) Protein hormone
C) Amine hormone
D) Tyrosine-derived hormone

5. In Phospholipase C-IP3/DAG, the protein that cleaves phospholipase is:

A) G protein
B) G protein-linked receptor
C) DAG
D) Protease C

ANSWER KEY: B, A, B, B, A

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## REFERENCES


- Guyton and Hall Textbook of Medical Physiology
- Ganong's Review of Medical Physiology