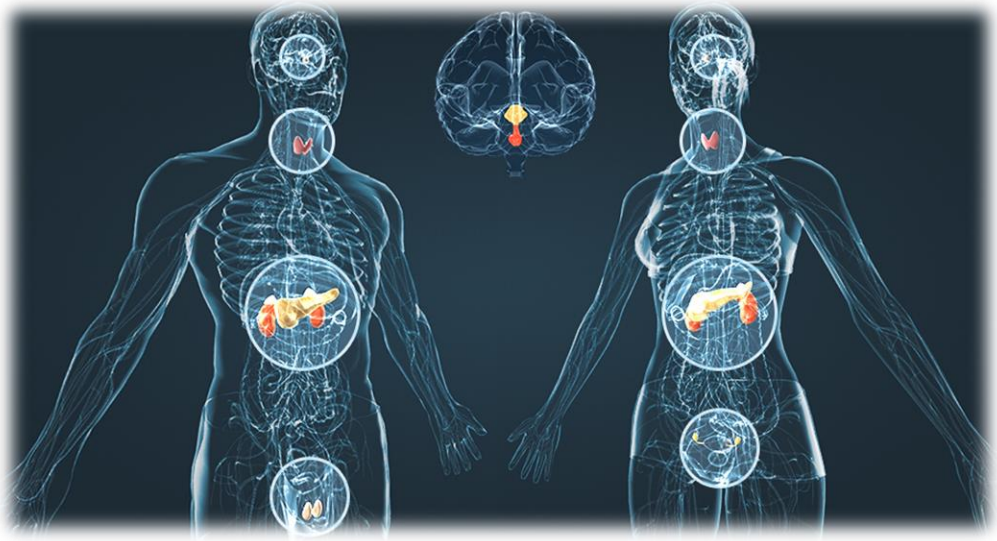

Introduction to Endocrine System Physiology-I

Endocrine System and Disorders (MED321)
Year 3-Semester 1

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Lecture Outline

- ✓Physiological functions and components of endocrine system
- ✓Hormone chemistry and mechanisms of action
- ✓Cellular effects of hormones
- ✓Hormone receptors and signal trasduction
- ✓Control of hormone release

Endocrine system

Classical description:

A chemical messenger or hormone produced by an organ is released into the circulation to produce an effect on a distant target organ.

Current description:

An integrated network of multiple organs derived from different embriologic origins that release hormones ranging from small peptides to glycoproteins, which exert their effects either in neighboring or distant target cells.

The function of the endocrine system

To **coordinate** and **integrate** cellular activity within the whole body by **regulating** cellular and organ function throughout life and **maintaining homeostasis**.

Some of the key functions of the endocrine system

Regulation of sodium and water balance and control of blood volume and pressure

Regulation of calcium and phosphate balance to preserve extracellular fluid concentrations required for cell membrane integrity and intracellular signaling

Regulation of energy balance and control of fuel mobilization, utilization, and storage to ensure that cellular metabolic demands are met

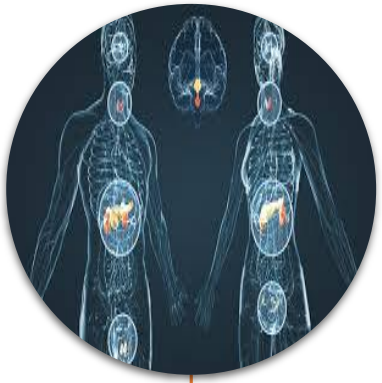
Coordination of the host hemodynamic and metabolic counterregulatory responses to stress

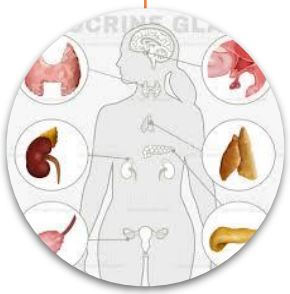
Regulation of reproduction, development, growth, and senescence

Endocrine network of organs and mediators;

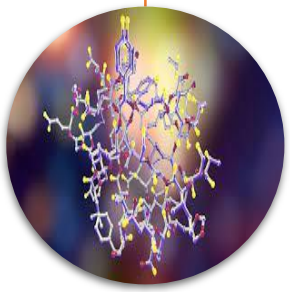
- ✓ **does not** work in isolation
- ✓ is closely integrated with the **central** and **peripheral nervous** systems (neuroendocrine system) as well as with the **immune system** (neuroendocrine-immune)

Endocrine System

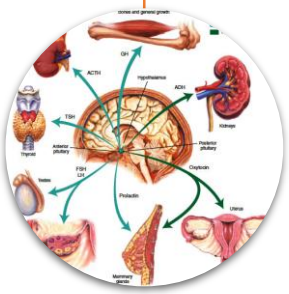




Endocrine Glands



Hormones



Target organ

Endocrine glands

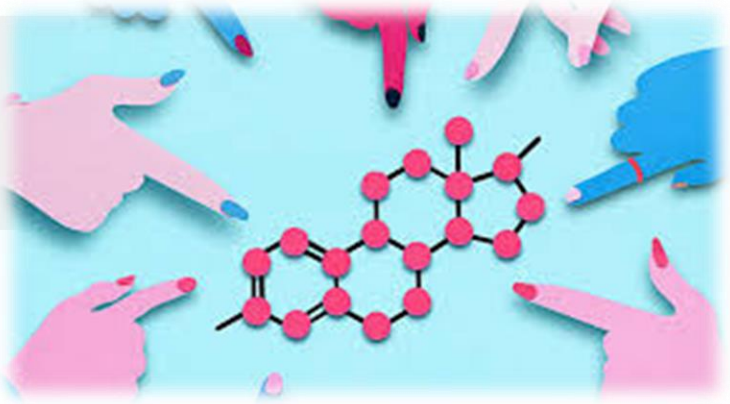
- Ductless

- Secrete their chemical products (hormones) into the interstitial space from where they reach the circulation

Endocrine glands

- Unlike the cardiovascular, renal, and digestive systems, the endocrine glands **are not anatomically connected** and are scattered throughout the body.
- They **do form a system in the functional sense**.
- Communication among the different organs is ensured through the release of hormones and neurotransmitters.

Hormones



- Chemical products, released in very small amounts
- Exert a biologic action on a target cell
- Secreted from: Endocrine glands, Brain, Other organs (heart, liver, adipose tissue)

Target Organ

- Contains cells that express hormone-specific receptors
- Respond to hormone binding by a demonstrable biologic response

HORMONE CHEMISTRY AND MECHANISMS OF ACTION

Hormones

- Peptides and Proteins
- Amino acid derivatives (amines)
  - Cell surface receptors
  - An exception: Thyroid hormone → Nuclear receptor

- Steroids
  - Intracellular receptors

Hormone structure influences the half-life of the hormone

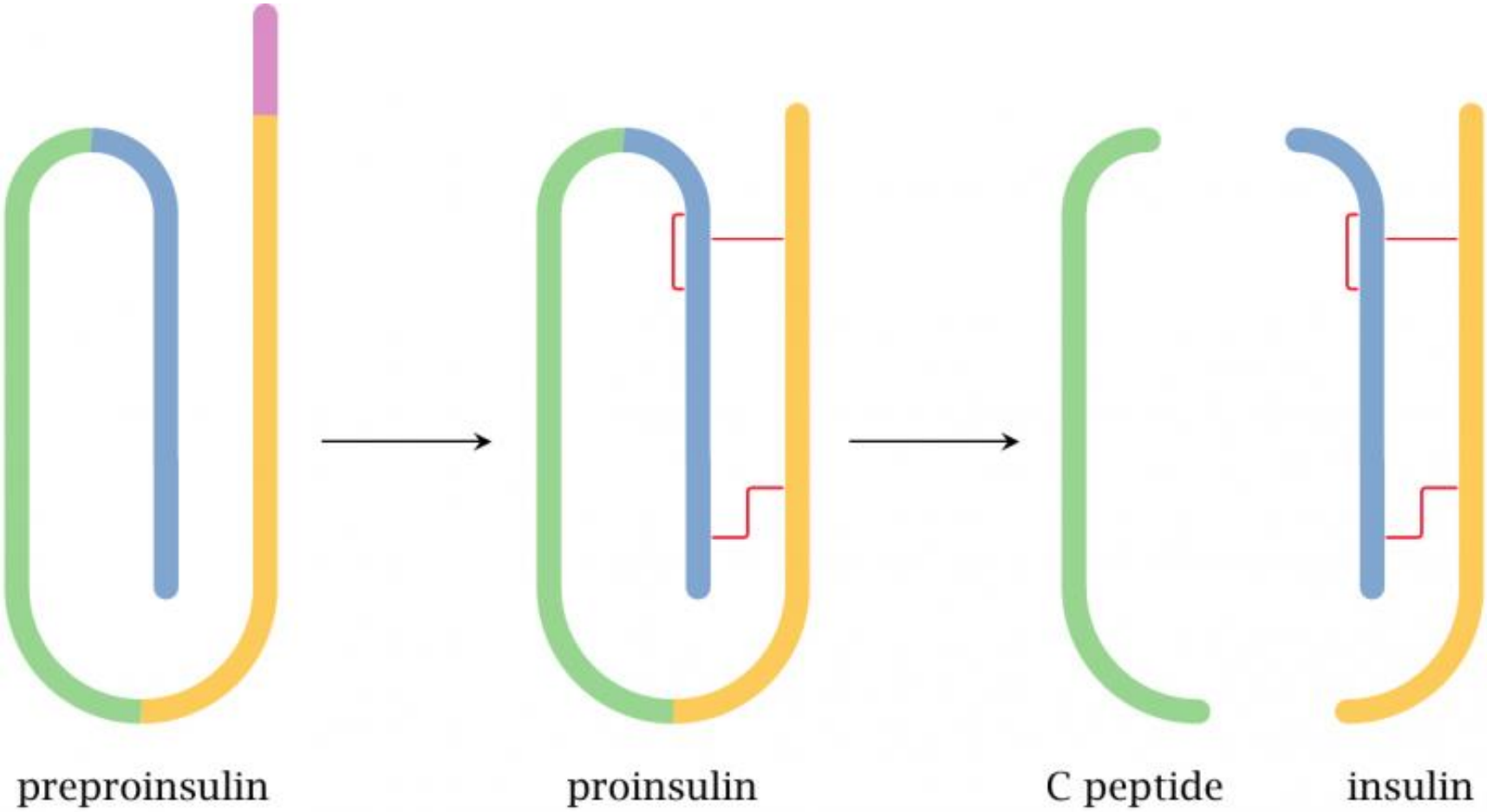
- Amines (2-3 min)
- Polypeptides (4-40 min)
- Steroids and proteins (0.75 days-6.7 days)

Protein or Peptide Hormones

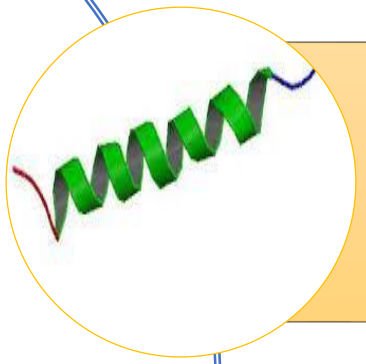
- Constitute the majority of hormones
- 3-200 amino acid residues
- Synthesized as **preprohormones**
- Cleaved to **prohormones** by proteolytic enzymes in the rough endoplasmic reticulum
- Undergo post-translational processing (Active hormone)
- Stored in secretory granules
- Secreted by exocytosis

Preprohormone → Prohormone → Active hormone

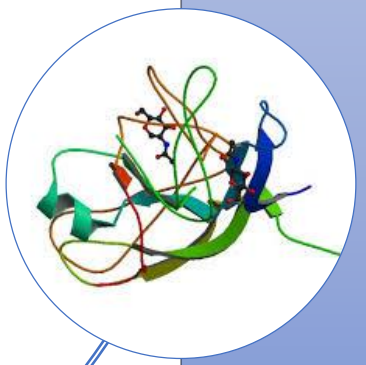
Example: Synthesis of insulin in the pancreas



Protein or Peptide Hormones



Insulin, glucagon, and ACTH



Gonadotropic hormone, Luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone, and human chorionic gonadotropin: **Glycoproteins**

- Carbohydrate moieties play important roles in determining the biologic activities and circulating clearance rates of glycoprotein hormones

Steroid Hormones

- Derived from **cholesterol**
- Synthesized in the **adrenal cortex**, **gonads**, and **placenta**
- Lipid soluble
- Circuate bound to binding proteins in plasma
- Cross the plasma membrane to bind to intracellular cytosolic or nuclear receptors
- Vitamin D and its derivatives are also considered steroid hormones

Amino Acid-Derived Hormones

- Synthesized from amino acid **Thyrosine**
- **Catecholamines**: Norepinephrin, epinephrine, dopamine
  - Norepinephrine and epinephrine: Adrenal medulla
  - Dopamine: Hypothalamus
- **Thyroid hormones**
  - Thyroid gland

Hormone Effects

Depending on where the biologic effect of a hormone is elicited in relation to where the hormone was released, its effects can be classified in 1 of 3 ways

- ✓Autocrine
- ✓Paracrine
- ✓Endocrine

Autocrine: The hormone affects the cell that secretes it.

Paracrine: After being secreted, the hormone diffuses and acts on nearby cells.

Endocrine: Hormones act on target cells over long distances through the bloodstream.

Hormone Transport

- Hormones released into the circulation can circulate either

  - **Freely**: Dissolved in the plasma
    - Catecholamines, most peptide and protein hormones
    - Hydrophilic

  - **Bound** to carrier plasma proteins (binding proteins)
    - Thyroid hormones
    - Vitamin D
    - Lipophilic

Binding proteins serve as a reservoir for the hormone and **prolong the hormone's half-life.**

Half-life: the time during which the concentration of a hormone decreases to 50% of its initial concentration

They **slow the clearance** of hormones from plasma

- **Free** / Unbound **hormone** is the **active form** of the hormone, which binds to the specific hormone receptor.

- **Hormone binding to its carrier protein** serves to **regulate the activity** of the hormone by determining how much hormone is free to exert a biologic action.

- **Most carrier proteins** are **globulins** and are synthesized in the liver.

- ✓Some of the binding proteins are specific for a given protein (e.g. cotisol-binding proteins)

- ✓Proteins such as globulins and albumin are known to bind hormones as well.

- ✓Since the most part of these proteins are synthesized in the liver, **alterations in hepatic function may indirectly affect total hormone levels**.

Chemical Class	Major Form in Plasma	Location of Receptors	Most Common Signaling Mechanisms*	Rate of Excretion/Metabolism
Peptides and catecholamines	Free (unbound)	Plasma membrane	1. Second messengers (e.g., cAMP, Ca^{2+}, IP_3) 2. Enzyme activation by receptor (e.g., JAK) 3. Intrinsic enzymatic activity of receptor (e.g., tyrosine autophosphorylation)	Fast (minutes)
Steroids and thyroid hormone	Protein-bound	Intracellular	Intracellular receptors directly alter gene transcription	Slow (hours to days)

HORMONE METABOLISM AND EXCRETION

Once a hormone has been synthesized and secreted into the blood, has acted on a target tissue, and its increased activity is no longer required, the concentration of the hormone in the blood usually returns to normal.

This is necessary to prevent excessive, possibly harmful effects from the prolonged exposure of target cells to hormones.

Hormone concetration in the plasma

Rate of **secretion** by the endocrine gland

Rate of **removal** from the blood (**Clearance**)

1. Excretion
2. Metabolic transformation

The **liver** and the **kidneys** are the major organs that metabolize or excrete hormones

- Once hormones are released into the circulation, they can
  - Bind to their specific receptor in a target organ
  - Undergo metabolic transformation by the liver
  - Undergo urinary excretion
- Removal of the hormones from the circulation is known as **metabolic clearance rate**

  i.e. The volume of plasma cleared of the hormone per unit of time.

Target cell uptake

- The liver and kidneys are not the only routes for eliminating hormones.
- Sometimes a hormone is metabolized by the cells upon which it acts.
- Receptor-mediated **endocytosis** of hormone–receptor complexes.
- The receptors are then often recycled to the plasma membrane.
- Only a very small fraction of total hormone production is excreted intact in the urine and feces.

Metabolic degradation/inactivation

In the liver;

Hormones can be inactivated through **Phase I** (hydroxylation or oxidation) and/or **Phase II** (glucuronidation, sulfation, or reduction with glutathione) **reactions**

Then **excreted by the liver** through the bile or **by the kidney** through urine.

Enzymes in the blood and tissues rapidly break down **catecholamine and peptide hormones**.

These hormones therefore tend to remain in the bloodstream for only brief periods—**minutes to an hour**.

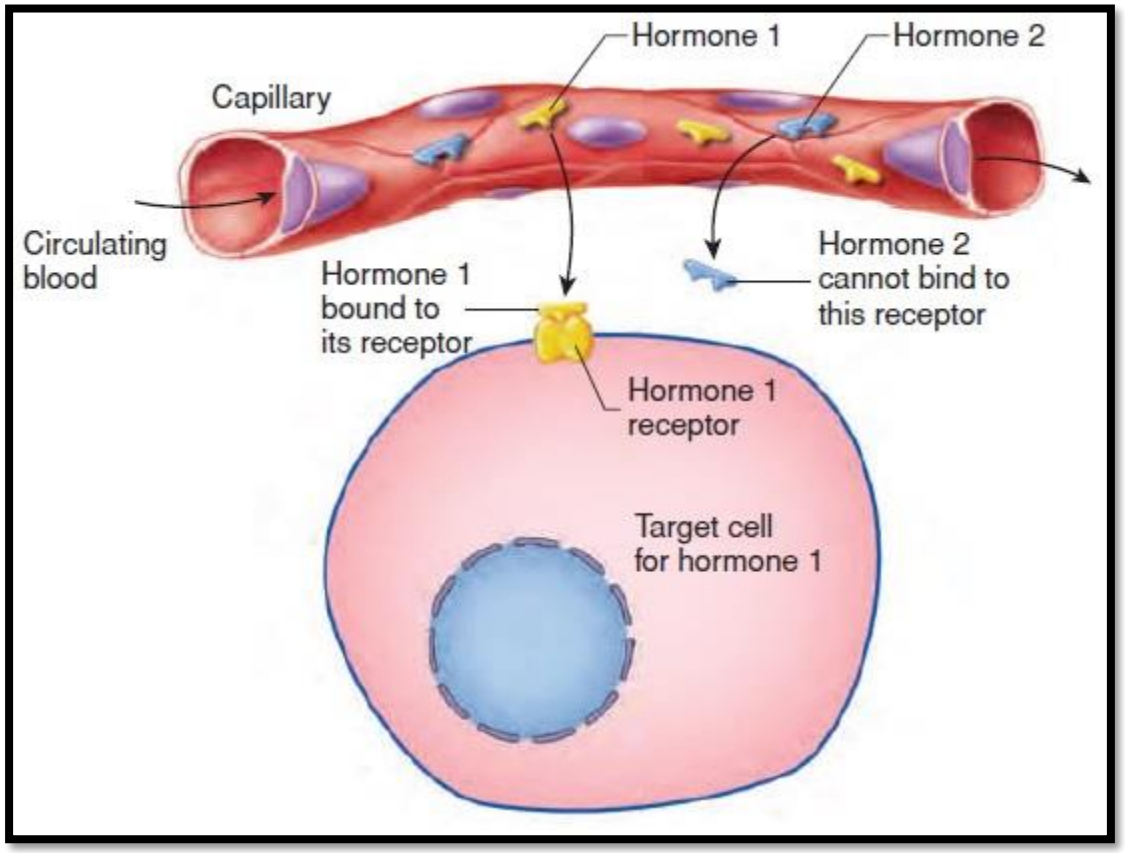
In contrast, protein-bound hormones are protected from excretion or metabolism by enzymes as long as they remain bound.

Therefore, removal of the **circulating steroid and thyroid hormones** generally takes longer, often **several hours to days**.

- In some cases, **metabolism** of a hormone ***activates*** the hormone rather than inactivates it.
- In other words, the secreted hormone may be relatively inactive until metabolism transforms it.
- T4 produced by the thyroid gland, which is converted to the much more active hormone T3 inside the target cell.

MECHANISMS OF HORMONE ACTION

- Because hormones are transported in the blood, they can **reach all tissues**.
- Yet, the **response** to a hormone is **highly specific**, involving only the target cells for that hormone.
- The biologic response to hormones is elicited through binding to **hormone-specific receptors** at the **target organ**.
- Hormones circulate in **very low concentrations** (**10^{-7}-10^{-12} M**)
- The receptor must have **high affinity and specificity** for the hormone to produce a biologic response



- **Affinity** is determined by the rates of dissociation and association for the hormone-receptor complex under equilibrium conditions.

- The equilibrium dissociation constant (Kd): the hormone concentration required for binding 50% of the receptor sites.

- ***The lower the Kd, the higher the affininty of binding***.

- The **affinity** is a reflection of **how tight** the hormone-receptor interation is

- **Specificity** is the **ability of** a hormone-receptor to **discriminate** among hormones with related structures.

The binding of hormones to their receptors is saturable, with a finite number of hormone receptors to which a hormone.

Most target cells, the maximal biologic response to a hormone can be achieved without reaching 100% hormone-receptor occupancy.

- The receptors that are not occupied are called **spare receptors**

Frequently, the hormone-receptor occupancy needed to produce a biologic response in a given target cell is very low.

- A decrease in the number of receptors in target tissues may not necessarily lead to an immediate impairment in hormone action.