Chapter 16. Endocrine System

Overview
- Endocrine system functions
- Endocrine vs. neural control
- Types of hormones and their receptors
- Hypothalamic – pituitary regulation
- Anterior pituitary
- Specific endocrine organs
- Endocrine diseases

Two types of glands in the body
- **Exocrine** – secrete products through a duct onto epithelial surface, e.g. sweat, oil, salivary glands
- **Endocrine** - release hormones into the blood or lymph often to travel throughout the body, e.g. pituitary, pancreas, thyroid

Endocrine System
- Cells release chemicals called **hormones** that enter the bloodstream
- Influences metabolism of specific targets cells/organisms (how is this accomplished?)
- Regulated by negative feedback
- Goal is to preserve homeostasis

Endocrine System Functions
- Provides long-term regulation and adjustments of homeostatic mechanisms:
  - fluid and electrolyte balance
  - cell and tissue metabolism
  - growth and development
  - reproductive functions
  - assists nervous system response to stressful stimuli through general adaptation syndrome
Endocrine and Nervous Systems

- Are similarly organized:
  - rely on release of chemicals that bind to receptors
  - share many chemical messengers
  - are regulated primarily by negative feedback
  - share a common goal: to preserve homeostasis

Endocrine vs. Nervous System

- Nervous system handles crisis management but its effects are short lived. Also, not possible to innervate every cell of the body
- Endocrine system handles longer term changes in physiology and behavior and coordinates cellular activity on a large scale but is unable to handle split-second responses

Nervous System Modulation

- The nervous system can override normal endocrine controls
  - For example, control of blood glucose levels
    - Normally the endocrine system maintains blood glucose
    - Under stress, the body needs more glucose
    - The hypothalamus and the sympathetic nervous system are activated to supply ample glucose

Intercellular Communication – types

- **Direct** – gap junctions (rare). E.g. epithelial cell cilia coordination
- **Synaptic** – neurotransmitters across small gap- fast action, good for quick responses
- **Paracrine** – chemical signals transfer information from cell to cell locally, within a single tissue (most common). E.g. prostaglandins
- **Endocrine** – specialized cells release chemicals called hormones into bloodstream, alters metabolic activities of many tissues and organs simultaneously

Hormones and the Endocrine System

- **Hormones**: chemicals secreted by cells into extracellular fluid that regulate metabolic functions of other cells (tissues) in the body
- **Endocrine System** includes all endocrine cells and body tissues that produce hormones or paracrine factors
- **Endocrine cells**: glandular secretory cells that release their secretions into extracellular fluids (blood, lymph, etc.)
### Target Cells

- How do cells “know” whether to respond to a hormone or not?
- Vast differences exist in the specificity of hormones

### Hormone Effects

- Stimulate synthesis of enzymes or structural proteins
- Increase or decrease rate of enzyme synthesis
- Turn an existing enzyme or membrane channel “on” or “off”
- Tend to have prolonged effects

### Types of hormones

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acid/Peptide derived</td>
<td>Amino acid derivatives: from tyrosine or tryptophan: thyroid hormones (T₃ and T₄), epinephrine (E), norepinephrine (NE), dopamine, melatonin</td>
</tr>
<tr>
<td></td>
<td>Peptide hormones: chains of amino acids, synthesized as prohormones</td>
</tr>
<tr>
<td>Lipid derived</td>
<td>Steroids derived from cholesterol (sex hormones: androgens by testes, estrogens, and progestins by ovaries and adrenal cortex hormones) corticosteroids and mineralcorticoids; also calcitriol (kidneys)</td>
</tr>
<tr>
<td></td>
<td>Eicosanoids (local factors: leukotrienes from WBCs, prostaglandins from most tissues)</td>
</tr>
</tbody>
</table>

### Peptide Hormones

- All hormones from the hypothalamus
- All hormones from the anterior and posterior pituitary gland
- Many smaller peptides include all the hormones secreted by:
  - heart
  - thymus
  - digestive tract
  - pancreas

### Hormones bind to receptors on target cells

- Protein hormones (peptide/amino acids)
  - Where are their receptors?
- Lipid hormones
  - Where are their receptors?
- The signal needs to get inside the cell to have effects (on enzymes, the nucleus)
- Easy for steroid hormones, not so much for peptides

### 2 Mechanisms of Hormone Action

- Hormones that bind to receptors on the cell membrane (protein based)
  - Act as FIRST messengers by binding to receptor
  - Activate a SECOND messenger system involving a G protein
- Steroid hormones
  - Cross cell membrane easily
  - Bind to receptors in the cytoplasm or nucleus, then directly activate or inactivate specific genes
- Thyroid hormones
G Proteins and Hormone Activity

Second messengers: Amplification
- The binding of a small number of hormone molecules to membrane receptors leads to thousands of second messengers in cell
- Magnifies the effect of hormone on target cell

Steroid Hormones
- Alter rate of DNA transcription in nucleus:
  - Changes patterns of protein synthesis
- Affect metabolic activity and structure of target cell

Special Case: Thyroid Hormones
- Cross cell membrane:
  - Primarily by transport mechanism
- Bind to receptors in nucleus and on mitochondria:
  - Activating specific genes
  - Changing rate of transcription
- Free vs bound hormone:
  - Hormones are removed from the blood by: degrading enzymes, the kidneys, or liver enzymes
  - Free protein hormones may last awhile but free steroid and thyroid hormones remain functional for less than 1 hour
  - Thus steroids and thyroid hormones are bound to plasma proteins in the blood while all others are free
  - Bound hormones: Remain in circulation much longer
  - More than 99% of steroid and thyroid hormones become attached to special transport proteins.
  - Why the difference?
Autoregulation

- **Down-regulation**: Continued presence of a hormone triggers decrease in number of hormone receptors. High levels of a particular hormone cause cells to become less sensitive to it.
- **Up-regulation**: Absence of a hormone triggers increase in number of hormone receptors, cells become more sensitive.

Hormone effects

- The effects of a hormone binding to its receptor are a lot like the effects of the modulatory neurotransmitters (the ones that bind to indirect/G protein receptors)... effects take some time, but they are usually more profound (like changes in gene expression) and longer lasting.

**KEY CONCEPT**

- Hormones coordinate cell, tissue, and organ activities
- They circulate in extracellular fluid and bind to specific receptors
- Hormones modify cellular activities by:
  - altering membrane permeability
  - activating or inactivating key enzymes
  - changing genetic activity

Control of Hormone Secretion

- **Endocrine Reflexes**:  
  - Functional counterparts of neural reflexes  
  - In most cases, controlled by **negative feedback** mechanisms

Endocrine Reflexes cause changes in hormone release

- Three main ways to change hormone release
  - **Humoral stimuli**:  
    - changes in composition of extracellular fluid (e.g. increased Calcium levels cause PTH release)
  - **Hormonal stimuli**:  
    - arrival or removal of specific hormone (e.g. TSH hormone causes the release of thyroid hormone)
  - **Neural stimuli**:  
    - arrival of neurotransmitters at neuroglandular junctions (Symp NS neurons cause adrenal medulla to release E, NE)
Hypothalamus

Integrates activities of nervous and endocrine systems in 3 ways:
1. Secretes regulatory hormones that control endocrine cells in pituitary gland
2. Acts as an endocrine organ itself
3. Contains autonomic centers that exert direct neural control over endocrine cells of adrenal medullae (sympathetic NS) = neuroendocrine reflex

Hormone release and target cell response

- Pulses: some hypothalamic and pituitary hormones are released in sudden bursts and the frequency of these results in different target cell responses.
- Concentration: unlike neurotransmitters, more hormone does not necessarily mean a bigger target cell response (thresholds, inverse effects).

Pituitary (Hypophysis) is the Master Endocrine Gland

- Pea size gland sits in sella turcica, hangs off hypothalamus (hypophysis = to grow beneath)
- Secretes 9 major peptide hormones
- Two lobes:
  - posterior (neurohypophysis): neural
  - anterior (adenohypophysis): glandular

Pituitary and Hypothalamus

- Makes and secretes seven peptide hormones
- Three regions:
  - Pars distalis (largest; TSH, ACTH, FSH, LH, PRL, GH)
  - Pars tuberalis
  - Pars intermedia (MSH)
Hypothalamic – Pituitary system

- Hypothalamus secretes Regulatory Hormones (releasing hormones)
- Causes anterior pituitary to release stimulating hormone (tropic hormones)
- Tropic hormones stimulate target cells to respond, either directly, or by releasing hormones of their own with widespread activity

Hypothalamic Regulatory Hormones
These are released by the hypothalamus and affect the anterior pituitary
- PRF – prolactin-releasing factor
- TRH – thyrotropin-releasing hormone
- CRH – corticotropin-releasing hormone
- GnRH – gonadotropin-releasing hormone
- GH-RH – growth hormone-releasing hormones

Hypothalamic – Pituitary system

- Hypothalamic Releasing Hormones don’t have to go too far (only a few mm)
- A special system ensures that Releasing Hormones reach intended target cells in anterior pituitary before entering general circulation: the hypophyseal portal system
Hypophyseal Portal System

- A unique system of two capillary beds linked together by veins known as a portal system.
- Median eminence contains a capillary bed with fenestrated capillaries.
- Arterial blood enters median eminence, picks up releasing hormone, then...

Portal veins connect the capillary bed in the median eminence with a second capillary bed in the anterior pituitary.
- Releasing hormones diffuse out of blood in the anterior pituitary, causing release of stimulating (tropic) hormones
- Stimulating hormones are released into venous circulation → heart → target organs

Anterior Pituitary

- AP releases tropic hormones, which have an endocrine gland as the target
  - Thyroid-stimulating hormone (TSH)
  - Adrenocorticotropic hormone (ACTH)
  - Follicle-stimulating hormone (FSH)
  - Luteinizing hormone (LH)
- Other anterior pituitary hormones have direct effects on cells
  - Growth hormone (GH)
  - Prolactin (PRL)

6 A.P. pars distalis stimulating hormones

- 1. Thyroid-Stimulating Hormone (TSH)
  - Also called thyrotropin
  - Triggers release of thyroid hormones
  - Stimulated by?
- 2. Adrenocorticotropic Hormone (ACTH)
  - Stimulates release of glucocorticoids
  - Steroid hormones by adrenal cortex
  - Stimulated by?
Gonadotropins: LH and FSH

3. FSH:
- Stimulates follicle development and estrogen secretion in females
- Stimulates sustentacular cells in males, promotes physical maturation of sperm
- Production inhibited by inhibin, a peptide hormone released by testes and ovaries

4. LH:
- Causes ovulation and progestin production in females (ovaries)
- Causes androgen production in males (testes)

FSH and LH Production

- Both are stimulated by gonadotropin-releasing hormone (GnRH) from hypothalamus
- Negative feedback: GnRH production inhibited by estrogens, progestins, and androgens (all of which are indirectly stimulated by GnRH)

5. Prolactin (PRL)

- Stimulates development of mammary glands (exocrine) and milk production
- PRL production is inhibited by prolactin-inhibiting hormone (PIH) from hypothalamus, which is actually dopamine
- Negative feedback:
  - PRL Stimulates PIH release
  - PRL Inhibits secretion of prolactin-releasing factors (PRF) from hypothalamus

6. Growth Hormone (GH)

- Also called somatotropin
- Stimulates cell growth and replication throughout the body, promote protein synthesis
- Causes liver to release somatomedins, which act on many cells too and mediate the majority of GH effects
- Production regulated by 2 hypothalamic hormones:
  - growth hormone–releasing hormone (GH–RH)
  - growth hormone–inhibiting hormone (GH–IH) also called somatostatin
Ant. Pit. pars intermedia:
Melanocyte-Stimulating Hormone (MSH)
- Stimulates melanocytes to produce melanin
- Inhibited by dopamine
- Secreted during:
  - fetal development
  - early childhood
  - pregnancy
  - certain diseases

KEY CONCEPT
- Hypothalamus produces regulatory factors that adjust activities of anterior lobe of pituitary gland, which produces 7 hormones
- Most hormones control other endocrine organs, including thyroid gland, adrenal gland, and gonads

Posterior Pituitary (neurohypophysis)
- It’s really just a releasing station for two hormones manufactured in the hypothalamus
- Contains terminals of unmyelinated axons from two hypothalamic nuclei which manufacture:
  - antidiuretic hormone (ADH)
  - oxytocin (OT)

Antidiuretic Hormone (ADH)
- Decreases amount of water lost at kidneys
- Promotes thirst
- Special hypothalamic neurons monitor the blood concentration
- Elevates blood volume and pressure
- Release inhibited by alcohol

Diabetes Insipidus
- Inadequate amounts of ADH released from posterior lobe
- Impairs water conservation at kidneys
Oxytocin

- Stimulates smooth muscles in uterus during labor and delivery (positive f/b); also in prostate gland
- Stimulates contractile cells in mammary glands ("milking let-down"). Secretion and milk ejection are part of neuroendocrine reflex: suckling → hypothalamus → OT release → milk let down
- May be involved in empathic feelings

**Summary:** The Hormones of the Pituitary Gland

Thyroid Gland

- Largest endocrine gland
- Lies anterior to thyroid cartilage of larynx
- Consists of 2 lobes connected by narrow isthmus
- Composed of thyroid Follicles: hollow spheres lined by cuboidal epithelium, follicle cavity contains viscous colloid containing the protein thyroglobulin
- Other endocrine cells, the parafollicular cells, produce the hormone calcitonin

Thyroglobulin

- Globular protein synthesized by follicle cells and secreted into colloid of thyroid follicles
- Basically, it’s the storage form of the thyroid hormones thyroxine (T₄) and triiodothyronine (T₃)
Thyroid Follicles

Thyroid-Stimulating Hormone (TSH)

- Absence causes thyroid follicles to become inactive:
  - neither synthesis nor secretion occur
- Binds to membrane receptors in thyroid
  - Stimulates iodide transport into cells
  - Stimulates thyroglobulin production
  - Stimulates release of T<sub>3</sub> and T<sub>4</sub>
  - Major factor in the rate of Thyroid hormone release is TSH concentration in circulating blood

Thyroid hormones

- Two types:
  - Thyroxine (T<sub>4</sub>): tetraiodothyronine contains 4 iodide ions
  - Triiodothyronine (T<sub>3</sub>) has 3 iodide ions
- Most is released as T<sub>4</sub> but it gets converted to T<sub>3</sub> in the tissues (which is 10x more active)
- 99.5% of thyroid hormones in blood are bound
- Bind to intracellular receptors in most all cells

Thyroid hormones

- Control "background" rate of cell metabolism
- Exert greatest effects on metabolically active tissue
- Calorigenic Effect: cell consumes more energy resulting in increased heat generation
- Responsible for strong, immediate, and short-lived increase in rate of cellular metabolism

C (Clear) Cells

- Produce calcitonin (CT):
  - lowers blood Ca<sup>2+</sup> levels in children

Parathyroid Glands

- Four, embedded in the posterior aspect of the thyroid gland
- Produce parathyroid hormone (PTH)
- Two cell types
  - Chief (principal) cells secrete PTH which increases calcium in the blood
  - Oxyphil cells
Parathyroid Glands

- Chief cells – produce PTH
- Oxyphils – function unknown

PTH and Calcitonin regulate calcium levels

Adrenal Glands

- Lie along superior border of each kidney
- Subdivided into superficial adrenal cortex (glandular) and an inner adrenal medulla (neural)

Figure 18–14

Adrenal Cortex

- Stores lipids, especially cholesterol and fatty acids
- Manufactures steroid hormones:
  - adrenocortical steroids (corticosteroids)
- Subdivided into 3 regions:
  1. zona glomerulosa - mineralcorticoids
  2. zona fasciculata - glucocorticoids
  3. zona reticularis – androgens + estrogens

Mineralcorticoids: Aldosterone

- Stimulates:
  - conservation of sodium ions and water
  - elimination of potassium ions
  - does this at kidneys, sweat glands, salivary glands, pancreas
- Increases sensitivity of salt receptors in taste buds
- Secreted in response to:
  - drop in blood Na⁺, blood volume, or blood pressure or rise in blood K⁺ concentration
  - Renin-angiotensin mechanism – kidneys release renin, which is converted into angiotensin II that in turn stimulates aldosterone release
  - ACTH – causes small increases of aldosterone during stress

Zona Fasciculata

- Endocrine cells are larger and contain more lipids than zona glomerulosa
- Produces glucocorticoids: cortisol (hydrocortisone) and corticosterone
  - liver converts cortisol to cortisone
Glucocorticoids

- Help you manage stress
- Function is glucose sparing: causes adipocytes to release fatty acids that other cells can use instead of glucose
- Anti-inflammatory effects
- Negative feedback: Glucocorticoids have an inhibitory effect on both of the hormones that stimulate their release:
  - corticotropin-releasing hormone (CRH) in hypothalamus causes release of...
  - ACTH in anterior pituitary, which causes GC release

Adrenal Cortex

<table>
<thead>
<tr>
<th>Type of Hormone</th>
<th>Hormone Released</th>
<th>Major Target</th>
<th>Major Effect</th>
<th>Regulatory System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>Ketosteroids</td>
<td>Metabolism</td>
<td>Hormone</td>
<td>Steroidogenesis</td>
</tr>
<tr>
<td>Steroids</td>
<td>Glucocorticoids</td>
<td>Adipocytes</td>
<td>Fatty Acids</td>
<td>Adipogenesis</td>
</tr>
<tr>
<td>Steroids</td>
<td>Androgens</td>
<td>Testes</td>
<td>Steroid</td>
<td>Androgenesis</td>
</tr>
<tr>
<td>Steroids</td>
<td>Estrogens</td>
<td>Ovaries</td>
<td>Steroid</td>
<td>Estrogenesis</td>
</tr>
<tr>
<td>Steroids</td>
<td>Mineralocorticoids</td>
<td>Kidneys</td>
<td>Hormone</td>
<td>Renin-angiotensin system</td>
</tr>
</tbody>
</table>

Adrenal Medulla

- Remember this one?
- What hormones are produced?
- What triggers the release?
- Epinephrine is the more potent stimulator of the heart and metabolic activities
- Norepinephrine is more influential on peripheral vasoconstriction and blood pressure

Pineal gland

- Secretes melatonin in inverse proportion to sunlight
- Regulates circadian rhythms

Pancreas

- A unique gland with both exocrine and endocrine functions
  - Exocrine: acinar cells produce enzymes for digestion
  - Endocrine: islet cells produce hormones for blood glucose regulation
- Lies between inferior border of stomach and proximal portion of small intestine
Endocrine Functions of Pancreatic Islets

Cells form clusters called pancreatic islets, or islets of Langerhans

- **Alpha cells:**
  - produce glucagon
- **Beta cells:**
  - secrete insulin

Blood Glucose Levels

- When levels rise:
  - beta cells secrete insulin, stimulates transport of glucose across all cell membranes and use by all tissues
- When levels decline:
  - alpha cells secrete glucagon, stimulates glycogen breakdown and release by liver, switch to other methods of nutrition in most tissues

5 Effects of Insulin

1. Accelerates glucose uptake (all cells)
2. Accelerates glucose utilization and enhanced ATP production
3. Stimulates glycogen formation
4. Stimulates amino acid absorption and protein synthesis
5. Stimulates triglyceride formation in adipose tissue

3 Effects of Glucagons

1. Stimulates breakdown of glycogen to glucose in skeletal muscle and liver cells
2. Stimulates breakdown of triglycerides in adipose tissue
3. Stimulates liver production and release of glucose from absorbed amino acids (**gluconeogenesis**)
Hormones Produced by Specific Organs

Other Organs with Endocrine Functions

- **Intestines**: produce hormones important to coordination of digestive activities – discussed later
- **Kidneys**: produce the hormones calcitriol (from vit D), erythropoietin, and renin

### Kidneys

- **Erythropoietin (EPO)**: Stimulates red blood cell production by bone marrow, more RBCs elevate blood volume
- **Renin** converts angiotensinogen to angiotensin I which is then converted to angiotensin II at the lungs

### Angiotensin II

1. Stimulates adrenal production of aldosterone (function?)
2. Stimulates pituitary release of ADH
3. Promotes thirst
4. Elevates blood pressure and volume

### Heart

- Produces natriuretic peptides (ANP and BNP) when blood volume becomes excessive
- Oppose renin-angiotensin system by reducing blood volume and blood pressure
Thymus

- Produces thymosin hormones:
  - that helps develop and maintain normal immune defenses

Testes

- Produce androgens in interstitial cells:
  - testosterone:
    - is most important male hormone
  - Secrete inhibin in sustentacular cells:
    - support differentiation and physical maturation of sperm

Ovaries

- Produce estrogens:
  - principle estrogen is estradiol
- After ovulation, follicle cells:
  - reorganize into corpus luteum
  - release estrogens and progestins, especially progesterone

General Adaptation Syndrome (GAS)

- Also called stress response
- How bodies respond to stress-causing factors

General Adaptation Syndrome (GAS)

GAS divided into 3 phases:
- alarm phase
  - immediate response to stress directed by ANS
  - Dominant hormone is epinephrine (“Fight or Flight”)
  - Energy reserves mobilized (glucose)
- resistance phase
  - Entered if stress lasts longer than few hours
  - Dominant hormones are glucocorticoids
  - Energy demands remain high
  - Glycogen reserves nearly exhausted after several hours of stress
- exhaustion phase
  - homeostatic regulation breaks down
  - Mineral imbalance
  - Failure of one or more organ systems will prove fatal

Endocrine System Disorders
### Diseases of Endocrine System

- **Primary Disorders**: problems within the endocrine organ itself because of:
  - metabolic factor (can't make hormone)
  - physical damage
  - congenital problems
- **Secondary Disorders**: Problems in other organs or target tissues
  - Often involve hypothalamus or pituitary gland

### Endocrine disorders

- Which gland is involved?
- Is it hyposecretion or hypersecretion?
- Primary or secondary disorder?
- Treatment?

### Symptoms

- Low metabolic rate
- Myxedema: subcutaneous swelling, dry skin, hair loss, low body temperatures and cold-intolerance, muscle weakness, slowed reflexes
- Gland? Hyper or hypo?

### Hypothyroidism

- Often causes enlarged throat (goiter)
- Inadequate TSH (from?) 1° or 2°?
- Inadequate TRH (from?) 1° or 2°?

### Hyperthyroidism

- Excess production of thyroid hormones
- Symptoms?
Hyperthyroidism

- Rapid heart rate, skin flushing, increased blood pressure, restlessness, excitability, easily fatigued
- Grave’s Disease: autoimmunity, exophthalmos
- Treatment?

Hyperthyroidism

- Excessive TSH or TRH production (rarely, due to pituitary tumors) or Graves disease
- So usually 1° or 2°?

Parathyroid gland

- Hyperparathyroidism – too much PTH
- Hypoparathyroidism – too little PTH
- Symptoms?
- Primary or secondary?
- Treatments?

Adrenal cortex – zona glomerulosa

- Hypoaldosteronism
- Hyperaldosteronism
- Symptoms?
- What could cause primary disorder?
- What could cause secondary disorder?
- What other problems might this cause?

Adrenal cortex – zona fasciculata

- Cushing’s disease:
  - Overproduction of glucocorticoids
- Addison’s disease
  - Underproduction of glucocorticoids (and often mineralcorticoids)
- One causes: weakness, weight loss, stress intolerance, low blood pressure, skin coloration changes
- The other causes: reduced glucose metabolism, lipids + amino acids mobilize, buildup of fat around belly, cheeks, base of neck, hypertension, reduced muscle mass
- Which is which?

Adrenal cortex – zona fasciculata

- Addison’s:
  - Primary or secondary?
  - Treatment?
- Cushing’s:
  - Primary or secondary?
  - Treatment?

Note: ACTH affects glucocorticoid release more than mineralcorticoids. Aldosterone is primarily regulated by…
• Acromegaly – excessive bone and cartilage growth, facial abnormalities, large hands and feet
  • Organ?
  • Hormone?
  • Treatments?

---

Growth Hormone

• Pituitary growth failure (children)
• Treatment?

---

Diabetes mellitus

• Type I – primary or secondary?
• Type II – primary or secondary?

---

Summary

• Endocrine system functions
• Endocrine vs. neural control
• Types of hormones and their receptors
• Hypothalamic – pituitary regulation
• Anterior pituitary
• Specific endocrine organs
• Endocrine diseases