Chapter 15
Endocrine System

Overview of the Endocrine System

- Body’s 2nd great controlling system which influences metabolic activities of cells by means of hormones, which are produced by endocrine glands
  - Endocrine glands: pituitary, thyroid, parathyroid, adrenal, pineal, and thymus
  - Pancreas & gonads produce both hormones and exocrine products
  - Hypothalamus has both neural functions & releases hormones
  - Other tissues & organs that produce hormones: adipose cells, pockets of cells in walls of small intestine, stomach, kidneys, and heart

Functions of Endocrine System

1. Metabolism and tissue maturation
2. Ion regulation
3. Water Balance
4. Immune system regulation
5. Heart rate & blood pressure regulation
6. Control of blood glucose & other nutrients
7. Control of reproductive function
8. Uterine contractions and milk release

Overview of the Endocrine System

- Both endocrine system and nervous system regulate activities of structures in body, but they do so in different ways
  1. Endocrine system is amplitude-modulated (a), whereas nervous system is frequency-modulated (b)
  2. Response of target tissues to hormones is usually slower and of longer duration than that of neurons

Hormones

- Chemical substances secreted by cells into interstitial fluid & diffuse into blood
- Act on specific tissues, called target tissues
- Have lag times ranging from seconds to hours
- Tend to have prolonged effects
- Are chemically categorized as belonging to
  - Protein group
    - Proteins, glycoproteins, polypeptides, and amino acid derivatives
  - Lipid group
    - Steroids and fatty acid derivatives
Control of Secretion Rate

- **Negative-feedback** mechanisms, which maintain homeostasis, control secretion of most hormones
- Hormone secretion from endocrine tissue is regulated by 1 or more of these three mechanisms:
  1. Changes in extracellular concentration of a non-hormone substance
  2. Stimulation by nervous system
  3. Stimulation by a hormone from another endocrine tissue

Hormonal Regulation of Hormone Secretion

- Hormones dissolved in plasma or bind to plasma proteins
- **Water-soluble hormones**
  - Proteins, epinephrine, & norepinephrine
  - Do not bind to plasma proteins or readily diffuse out of blood
  - Quickly broken down by enzymes or are taken up by tissues
  - Regulate activities that have a rapid onset & a short duration
- **Lipid-soluble hormones and thyroid hormones**
  - Not quickly removed from blood
  - Produce a prolonged effect
- Hormones leave blood to reach target tissues or are excreted by kidneys or liver

Hormone Transport and Excretion

Classes of Receptors

- Target tissues have receptor molecules specific for particular hormone
- Only cells with receptor for hormone respond to the hormone

Classes of Receptors

- **Membrane-bound receptors**
  - Span plasma membrane
  - Bind to water-soluble or large-molecular-weight hormones
- **Intracellular (nuclear) receptors**
  - In cell cytoplasm or nucleus
  - Bind to lipid-soluble hormones
Classes of Receptors

- Many membrane-bound receptors produce responses through action of G proteins
  - G proteins consist of 3 subunits
    - Alpha (α)
    - Beta (β)
    - Gamma (γ)
  - Inactive state: GDP bound to α subunit
  - Active state: GTP bound to α subunit

- Hormones that activate G proteins
  - Luteinizing hormone
  - Follicle-stimulating hormone
  - Thyroid-stimulating hormone
  - Adrenocorticotropic hormone
  - Oxytocin
  - Antidiuretic hormone
  - Calcitonin
  - Parathyroid hormone
  - Glucagon
  - Epinephrine

G Proteins and Ion Channels

1. The α subunit, with GTP bound to it, combines with the Ca²⁺ channel and causes it to open.
2. The Ca²⁺ diffuses into the cell and combines with calmodulin. This combination of Ca²⁺ with calmodulin produces the cell’s response to the hormone.
G Proteins and Enzymes

Classes of Receptors

- A hormone binding to a membrane-bound receptor can directly activate intracellular enzymes
  - Those enzymes in turn can either
    - Synthesize intracellular mediators, such as cGMP
    - Add phosphate groups to intracellular enzymes, which alters their activity

Membrane-Bound Receptor That Directly Activates Enzymes

1. The hormone binds with its receptor.
2. At the inner surface of the plasma membrane, the receptor is activated to produce cGMP from GTP.
3. Cyclic GMP is an intracellular mediator that alters the activity of other intracellular enzymes to produce the response of the cell.
4. Phosphodiesterase is an enzyme that converts cGMP to inactive GMP.

Membrane-Bound Receptors That Phosphorylate Intracellular Proteins

1. The hormone binds to its receptor.
2. The hormone-activates the intracellular receptor.
3. The activated receptor then phosphorylates specific enzymes, altering them. The phosphorylated enzymes activate the intracellular proteins, producing the cell's response.
4. Phosphodiesterase enzymes are activated by converting cGMP to GMP.
Cascade Effect

- Intracellular mediator mechanisms (as previously mentioned) are act rapidly because they work on already existing enzymes & produce a cascade effect.

Intracellular Receptors

- Lipid-soluble hormones bind with intracellular receptors
  - receptor-hormone complex diffuses into nucleus where it activates genes
    - mRNA is produced
    - mRNA initiates production of certain proteins (enzymes) that produce response of target cell to hormone

- Intracellular receptor mechanisms are slow-acting because time is required to produce mRNA and protein
Pituitary Gland and Hypothalamus

- Pituitary gland secretes at least 9 hormones that regulate numerous body functions & other endocrine glands.
- Hypothalamus regulates pituitary gland activity through hormones & action potentials.

**Pituitary Gland**

- Posterior pituitary
  - Neurohypophysis
  - Develops from floor of brain & connects to hypothalamus by infundibulum
- Anterior pituitary
  - Adenohypophysis
  - Develops from roof of mouth

**Hypothalamic Regulation of the Anterior Pituitary**

Tab. 15.1

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Structure</th>
<th>Target Tissue</th>
<th>Response</th>
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<tbody>
<tr>
<td>Growth hormone-releasing hormone (GHRH)</td>
<td>Peptide</td>
<td>Anterior pituitary cells that secrete growth hormone</td>
<td></td>
</tr>
<tr>
<td>Growth hormone-inhibiting hormone (GHIH)</td>
<td>Small peptide</td>
<td>Anterior pituitary cells that secrete growth hormone</td>
<td></td>
</tr>
<tr>
<td>Thyrotropin-releasing hormone (TRH)</td>
<td>Small peptide</td>
<td>Anterior pituitary cells that secrete thyroid-stimulating hormone</td>
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<tr>
<td>Corticotropin-releasing hormone (CRH)</td>
<td>Peptide</td>
<td>Anterior pituitary cells that secrete adrenocorticotropic hormone</td>
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</tr>
<tr>
<td>Somatostatin-releasing hormone (SRH)</td>
<td>Small peptide</td>
<td>Anterior pituitary cells that secrete somatostatin</td>
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<tr>
<td>Prolactin-releasing hormone (PH)</td>
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<td>Anterior pituitary cells that secrete prolactin</td>
<td>Increased prolactin secretion</td>
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<tr>
<td>Proopiomelanocortin (POMC)</td>
<td>Unknown</td>
<td>Anterior pituitary cells that secrete prolactin</td>
<td>Increased prolactin secretion</td>
</tr>
</tbody>
</table>

**Pituitary Gland**

- Hypothalamohypophyseal portal system connects hypothalamus & anterior pituitary.
  - Hormones produced in hypothalamic neurons
  - Through portal system, hormones inhibit or stimulate hormone production in anterior pituitary
- Hypothalamohypophyseal tract connects hypothalamus and posterior pituitary.
  - Hormones produced in hypothalamic neurons
  - The hormones move down axons of tract & are secreted from posterior pituitary

Fig. 15.14

Fig. 15.15
Hormones of the Pituitary Gland

- **Anterior Pituitary**
  - Table 15.2
  - Growth Hormone (GH)
  - Thyroid-stimulating hormone (TSH)
  - Adrenocorticotropic hormone (ACTH)
  - Melanocyte-stimulating hormone (MSH)
  - Luteinizing hormone (LH)
  - Follicle-stimulating hormone (FSH)
  - Prolactin

Growth Hormone (GH)

- GH stimulates growth in most tissues and is a regulator of metabolism
  - GH stimulates
    - uptake of amino acids & conversion into proteins
    - breakdown of fats & synthesis of glucose
    - production of somatomedins (with GH they promote bone and cartilage growth)
  - GH secretion increases in response to low blood glucose, stress, & an increase in certain amino acids
  - GH is regulated by two hypothalamic hormones
    - Growth hormone-releasing hormone (GHRH)
    - Growth hormone-inhibiting hormone (GHIH)

Control of Growth Hormone (GH) Secretion

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Thyroid Gland

- **largest endocrine gland**
- Located in anterior neck
- 2 lateral lobes connected by a median tissue mass called isthmus
- Composed of follicles that produce glycoprotein thyroglobulin
- Other endocrine cells, parafollicular cells, produce hormone calcitonin

Thyroid Hormones

- Consist of 2 related iodine-containing compounds
  - Triiodothyronine (T<sub>3</sub>): has two tyrosines with three bound iodine atoms (10%)
  - Tetraiodothyronine (thyroxine or T<sub>4</sub>): has two tyrosine molecules plus four bound iodine atoms (90%)

Synthesis of Thyroid Hormones

- Iodides (I⁻) are actively taken into cell, oxidized to iodine (I₂), & released into lumen
- Thyroglobulin is synthesized & discharged into lumen
- Iodine attaches to tyrosine
  - Mediated by peroxidase enzymes
  - Forming T₁ (moniodotyrosine, or MIT) & T₂ (diiodotyrosine, or DIT)
- Iodinated tyrosines link together to form T<sub>3</sub> and T<sub>4</sub>
- Large amounts of T₁ & T₂ are stored within thyroid follicles as part of thyroglobulin (~2-4 month supply)
- Thyroglobulin (with T₁ & T₂ attached) is then brought in by endocytosis
  - Combined with a lysosome
  - T₁ & T₂ are cleaved & diffuse into bloodstream
Effects of Thyroid Hormones

- $T_3$ and $T_4$
  - Increase rate of glucose, fat, & protein metabolism in many tissues
  - Increase body temperature
- $T_3$ and $T_4$ play a role in
  - Maintaining blood pressure
  - Regulating tissue growth
  - Developing skeletal & nervous systems
  - Maturation & reproductive capabilities

Regulation of Thyroid Hormone Secretion

- Thyrotropin-releasing hormone (TRH) & thyroid-stimulating hormone (TSH) regulate $T_3$ & $T_4$ secretion
  - TRH from hypothalamus increases TSH secretion
    - Increases as a result of chronic exposure to cold
    - Decreases as a result of food deprivation, injury, and infection
  - Increased TSH from anterior pituitary increases $T_3$ & $T_4$ secretion
  - $T_3$ & $T_4$ inhibit TSH & TRH secretion (negative feedback)

Calcitonin

- Parafollicular cells secrete calcitonin
- Directly regulated by blood $Ca^{2+}$ levels
  - Blood $Ca^{2+}$ levels drop = calcitonin levels drop
  - Blood $Ca^{2+}$ levels rise = calcitonin levels rise
- Calcitonin targets the skeleton to
  - Inhibit osteoclast activity & release of calcium from bone matrix
  - Stimulate calcium uptake & incorporation into bone matrix

Negative Feedback!

Parathyroid Glands

- Tiny glands embedded in posterior aspect of thyroid
- Secrete polypeptide hormone: parathyroid hormone (PTH)
  - essential in regulating calcium balance in blood (much more important than calcitonin)
- PTH increases release of $Ca^{2+}$ from bones into blood by increasing # of osteoclasts
Parathyroid Glands

• PTH also
  - Promotes Ca\(^{2+}\) reabsorption by kidneys & formation of active vitamin D by kidneys
  - Active vitamin D increases calcium absorption by intestine
• A decrease in blood Ca\(^{2+}\) levels stimulates PTH secretion

Adrenal Glands

• Paired, pyramid-shaped organs, sit on top of kidneys
• Divided into 2 parts
  - Adrenal medulla (inner area)
    • Arises from same cells that give rise to postganglionic sympathetic neurons
  - Adrenal cortex (outer area)
    • Glandular tissue derived from embryonic mesoderm
    • Composed of 3 layers
      — Zona glomerulosa
      — Zona fasciculata
      — Zona reticularis
• Structurally & functionally, 4 glands in one

Hormones of the Adrenal Medulla

• Approximately 80% of the hormones released is epinephrine (adrenaline) and 20% is norepinephrine
• Secretion of these hormones prepares body for physical activity by:
  - Increasing blood glucose levels
  - Increasing the use of glycogen and glucose by skeletal muscle
  - Increasing heart rate and force of contraction
  - Causes vasoconstriction in skin and viscera
  - Causes vasodilation in skeletal and cardiac muscle
• Released by sympathetic division of the ANS in response to
  - Emotions
  - Injury
  - Stress
  - Low blood glucose levels

Regulation of Adrenal Medullary Secretions

1. Stress, physical activity, and low blood glucose levels stimulate the sympathetic nervous system to increase epinephrine release.
2. Increased frequency of neuronal firing causes norepinephrine release from sympathetic nerve endings.
3. Norepinephrine stimulates beta-adrenergic receptors on chromaffin cells, leading to epinephrine release.
Hormones of the Adrenal Cortex

• Synthesizes and releases steroid hormones called corticosteroids
• Different corticosteroids are produced in each of 3 layers
  – Zona glomerulosa: mineralocorticoids (chiefly aldosterone)
  – Zona fasciculata: glucocorticoids (chiefly cortisol)
  – Zona reticularis: gonadocorticoids (chiefly androgens)

Zona Glomerulosa

• Mineralocorticoids
  – Regulate electrolytes in extracellular fluids
    – Aldosterone: most important mineralocorticoid
      • Maintains Na\(^+\) balance by reducing excretion of sodium from body
      • Stimulates reabsorption of Na\(^+\) by kidneys
      • Decreases K\(^-\) and H\(^+\) levels in blood
  – Aldosterone secretion is stimulated by:
    • Rising blood levels of K\(^-\)
    • Low blood Na\(^-\)
    • Decreasing blood volume or pressure

Zona Fasciculata

• Glucocorticoids (especially cortisol)
  – Help the body resist stress by
    • Keeping blood sugar levels relatively constant
    • Maintaining blood volume and preventing water shift into tissue
  – Cortisol provokes
    • Gluconeogenesis (formation of glucose from non-carbohydrates)
    • Rises in blood glucose, fatty acids, and amino acids
  – Excessive levels of glucocorticoids
    • Depress cartilage and bone formation
    • Inhibit inflammation
    • Depress the immune system
    • Promote changes in cardiovascular, neural, and gastrointestinal function

Zona Reticularis

• Gonadocorticoids (Sex Hormones)
  – Most gonadocorticoids secreted are androgens (male sex hormones)
  – most important is testosterone
  – Androgens contribute to:
    • The onset of puberty
    • The appearance of secondary sex characteristics
    • Sex drive in females
  – Androgens can be converted into estrogens after menopause

Regulation of Cortisol Secretion

1. Corticotropin releasing hormone (CRH) from the hypothalamus causes the anterior pituitary to secrete ACTH.
2. ACTH stimulates the secretion of adrenocortical hormones (cortisol) from the anterior pituitary.
3. ACTH stimulates the synthesis of cortisol from the adrenal cortex.
4. Cortisol acts on target tissues, leading to increases in blood glucose, fatty acids, and amino acids.
5. Cortisol has a negative feedback effect because it inhibits CRH release from the hypothalamus and ACTH secretion from the anterior pituitary.
6. Cortisol has a negative feedback effect because it inhibits CRH release from the hypothalamus and ACTH secretion from the anterior pituitary.

Fig. 15.24
Pancreas

- A triangular gland, which has both exocrine and endocrine cells, located behind stomach
- Acinar cells produce an enzyme-rich juice used for digestion (exocrine product)
- Pancreatic islets (islets of Langerhans) produce hormones (endocrine products)
- The islets contain two major cell types:
  - Alpha (α) cells that produce glucagon
  - Beta (β) cells that produce insulin

Insulin

- Target tissues
  - Liver
  - Adipose tissue
  - Muscle
  - Satiation center in the hypothalamus
- Nervous system relies on blood glucose levels maintained by insulin
- Increases uptake of glucose and amino acids by cells
  - Glucose
    - Is used for energy
    - Stored as glycogen
    - Converted into fats
  - Amino acids are used to synthesize proteins
- Low levels of insulin promote the formation of ketone bodies by the liver

Glucagon

- Target tissue is mainly the liver
- Causes breakdown of glycogen to glucose
- Stimulates synthesis of glucose from amino acids
- Liver releases glucose into blood

Regulation of Pancreatic Hormone Secretion

- Insulin
  - Increases because
    - Elevated blood glucose levels
    - Increase in some amino acids
    - Parasympathetic stimulation
    - Gastrointestinal hormones
  - Sympathetic stimulation decreases insulin secretion
- Glucagon
  - Secretion is stimulated by
    - Low blood glucose levels
    - Certain amino acids
    - Sympathetic stimulation
  - Somatostatin inhibits insulin and glucagon secretion

Summary of Insulin Secretion Regulation
Hormonal Regulation of Nutrients

• **After a meal**, the following events take place
  – High glucose levels stimulate insulin secretion but inhibit glucagon, cortisol, GH, and epinephrine secretion
  – Insulin increases the uptake of glucose, amino acids, and fats, which are used for energy or are stored
  – Sometime after the meal, blood glucose levels drop
    • Insulin levels decrease and glucagon, GH, cortisol, and epinephrine levels increase
    • Glucose is released from tissues
  – Liver releases glucose into blood, and use of glucose by most tissues, other than nervous tissue, decreases
  – Adipose tissue releases fatty acids and ketones, which most tissues use for energy

• **During exercise**, the following events occur
  – Sympathetic activity increases epinephrine and glucagon secretion, causing a release of glucose from the liver into the blood
  – Low blood sugar levels, caused by uptake of glucose by skeletal muscles, stimulate epinephrine, glucagon, GH, and cortisol secretion
    • Causes an increase in fatty acids and ketones in the blood, all of which are used for energy

Testes and Ovaries

• **Testes**
  – Secrete testosterone
    • Initiates maturation of male reproductive organs
    • Causes appearance of secondary sexual characteristics and sex drive
    • Is necessary for sperm production
    • Maintains sex organs in their functional state

• **Ovaries**
  – Secrete estrogens and progesterone
    • Maturation of the reproductive organs
    • Appearance of secondary sexual characteristics
    • Breast development and cyclic changes in the uterine mucosa

Pineal Body

• Small, pinecone-shaped structure located superior and posterior to the thalamus
• Secretory product is melatonin
• Melatonin
  – Can inhibit reproductive maturation
  – May regulate sleep-wake cycles

Regulation of Melatonin Secretion from the Pineal Body

Fig. 15.27
Thymus

- Lobulated gland located deep to the sternum
- Major hormonal products are thymopoietins and thymosins
- These hormones are essential for the development of T lymphocytes (T cells) of immune system

Other Endocrine Organs

- Gastrointestinal tract
  - Produces gastrin, secretin, and cholecystokinin, which regulate digestive functions
- Kidneys
  - Produce erythropoietin, which stimulates red blood cell production
- Placenta
  - Secretes human chorionic gonadotropin, which is essential for the maintenance of pregnancy

Hormonelike Substances

- Autocrine agents
  - Chemical signals that locally affect cells of same type as cell producing the autocrine agent
  - Prostaglandins, thromboxanes, prostacyclins, and leukotrienes
- Paracrine agents
  - Chemical signals that locally affect cells of a different type than cell producing the paracrine agent
  - Growth factors, clotting factors, and histamine
- Autocrine and paracrine chemical signals differ from hormones in that
  - They are not secreted from discrete endocrine glands
  - They have local effects rather than systemic effects
  - They have functions that are not understood in all cases

Effects of Aging on the Endocrine System

- There is a gradual decrease in the secretion rate of most, but not all, hormones
- Some decreases are secondary to gradual decreases in physical activity