Chapter 11 Outline

- Endocrine Glands and Hormones
- Mechanisms of Hormone Action
- Pituitary Gland
- Adrenal Glands
- Thyroid and Parathyroid Hormones
- Pancreas and Other Endocrine Glands
- Autocrine and Paracrine Regulation
Endocrine Glands

- Are ductless and secrete hormones into bloodstream
- Hormones travel to target cells that contain receptor proteins for it
- Neurohormones are secreted into blood by specialized neurons
- Hormones affect metabolism of targets

Chemical Classification of Hormones

- **Amine** hormones are derived from tyrosine or tryptophan
  - Include NE, Epi, thyroxine, melatonin
- **Peptide hormones**
  - Polypeptide and protein hormones are chains of amino acids
    - Include ADH, GH, insulin, oxytocin, glucagon, ACTH, PTH
  - Glycoproteins include LH, FSH, TSH
- **Steroids** are lipids derived from cholesterol
  - Include testosterone, estrogen, progesterone, aldosterone and cortisol
Hormonal Actions and Interactions

Common Aspects of Neural and Endocrine Regulation
- Both NS and endocrine system use chemicals to communicate
- Difference between NTs and hormones is transport in blood and more diversity of effects in hormone targets
- Some chemicals are used as hormones and NTs
- Targets for both NTs and hormones must have specific receptor proteins
- Must be a way to rapidly inactivate both

Hormone Interactions
- A tissue usually responds to various of hormones
- 2 hormones are synergistic if work together to produce an effect (additive or complementry)
  - Produce a larger effect together than individual effects added together
- A hormone has permissive effect if it enhances responsiveness of a target organ to 2nd hormone
- If action of 1 hormone inhibits effect of another, it is antagonistic
Hormone Levels and Tissue Responses

- **Half-life** is time required for blood level to be reduced by half
- Ranges from mins to hrs for most (days for thyroid hormones)
- Normal tissue responses are produced only when hormones are in physiological range
- High ([pharmacological](#)) doses can cause a number of side effects
  - Probably by binding to receptors of different but closely related other hormones

- **Priming effect (upregulation)** occurs when a hormone induces more of its own receptors in target cells
  - Results in greater response in target cell
- **Desensitization (downregulation)** occurs after long exposure to high levels of hormone
  - Subsequent exposure to this hormone produces a lesser response
  - Due to decrease in number of receptors on targets
- Most peptide hormones have [pulsatile secretion](#) which prevents downregulation

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Mechanisms of Hormone Action
Mechanisms of Hormone Action

- Target cell receptors show **specificity, high affinity, and low capacity** for a hormone.
- Lipophilic hormones have receptors in target's cytoplasm and/or nucleus because they can diffuse through plasma membrane.
  - Their target is the nucleus where they affect transcription.
  - Called **genomic action** and takes at least 30 mins.
- Hydrophilic hormones have receptors on the surface of the target cell.
  - These act through 2nd messengers; effects are quick.
  - Some steroids also act on cell surface receptors.
  - Called **nongenomic action**.

Hormone Effects on Gene Activity

Hormones That Bind to Nuclear Receptor Proteins

- Lipid hormones travel in blood attached to carrier proteins.
  - They dissociate from carriers to pass through the plasma membrane of the target.
  - Receptors are called **nuclear hormone receptors**.
Nuclear Hormone Receptors

- Serve as transcription factors when bound to hormone ligands
- Activate transcription
- Constitute a "superfamily" composed of steroid family and thyroid hormone family (which includes vitamin D and retinoic acid)

Nuclear Hormone Receptors

- Have ligand (hormone)-binding and DNA-binding domains
- Binds hormone and translocates to nucleus
- Binds to hormone-response element (HRE) on DNA located adjacent to target gene

Mechanisms of Steroid Hormones

- HRE consists of 2 half-sites
- 2 ligand-bound receptors have to bind to each HRE (dimerization)
- This stimulates transcription of target gene
Mechanism of Thyroid Hormone Action

- Thyroid secretes 90% T₄ (thyroxine) and 10% T₃
- 99.96% of T₄ in blood is bound to carrier protein (thyroid binding globulin - TBG)
- Only free thyroxine and T₃ can enter cells
- Protein bound thyroxine serves as a reservoir
- T₄ converted to T₃ inside target cell
  - T₃ binds to receptor protein located in nucleus

Mechanism of Thyroid Hormone Action

The receptor for T₃:
- T₃ and receptor bind to 1 half-site
- Other half-site binds retinoic acid
- Two partners form heterodimer that activates HRE
  - Stimulates transcription of target gene
Hormones That Use 2nd Messengers

- Water soluble hormones use cell surface receptors because cannot pass through plasma membrane
- Actions are mediated by 2nd messengers
- Hormone is extracellular signal; 2nd messenger carries signal from receptor to inside of cell

Adenylate Cyclase-cAMP

- cAMP mediates effects of many polypeptide and glycoprotein hormones
- Hormone binds to receptor causing dissociation of a G-protein subunit

Adenylate Cyclase-cAMP

- G-protein subunit binds to and activates adenylate cyclase
- Which converts ATP into cAMP
- cAMP attaches to inhibitory subunit of protein kinase
Adenylate Cyclase-cAMP
- Inhibitory subunit dissociates, activating protein kinase
- Which phosphorylates enzymes that produce hormone's effects
- cAMP inactivated by phosphodiesterase

Phospholipase-C-Ca²⁺
- Serves as 2nd messenger system for some hormones
- Hormone binds to surface receptor, activates G-protein, which activates phospholipase C
- Phospholipase C splits a membrane phospholipid into 2nd messengers IP₃ and DAG
  - IP₃ diffuses through cytoplasm to ER
  - Ca²⁺ channels open

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Phospholipase-C-Ca\(^{2+}\)

- Ca\(^{2+}\) diffuses into cytoplasm and binds to and activates calmodulin
- Ca\(^{2+}\)-Calmodulin activates protein kinases which phosphorylate enzymes that produce hormone's effects

Epinephrine Can Act Via Two 2\(^{nd}\) Messengers

Tyrosine Kinase 2nd Messenger System

- Is used by insulin and many growth factors to cause cellular effects
- Surface receptor is tyrosine kinase
- Consists of 2 units that form active dimer when insulin binds
Tyrosine Kinase 2nd Messenger System

- Activated tyrosine kinase phosphorylates signaling molecules that induce hormone/growth factor effects.

Insulin Action

- Insulin stimulates glucose uptake by means of GLUT-4 carrier proteins.
- 2nd messengers cause vesicles containing GLUT4 transporters to be inserted into plasma membrane.

Pituitary Gland
Pituitary Gland

- Pituitary gland is located beneath hypothalamus at base of forebrain
- Is structurally and functionally divided into anterior and posterior lobes
- Hangs below hypothalamus by **infundibulum**
- Anterior produces own hormones
  - Controlled by hypothalamus
- Posterior stores and releases hormones made in hypothalamus

Posterior Pituitary

- Stores and releases the hormones **vasopressin (ADH)** and **oxytocin** that are made in the hypothalamus
Anterior Pituitary

- Secretes 6 **trophic** hormones that maintain size of targets
- **High blood levels** cause target to hypertrophy
- **Low blood levels** cause atrophy

**Growth hormone (GH)** promotes growth, protein synthesis, and movement of amino acids into cells

**Thyroid stimulating hormone (TSH)** stimulates thyroid to produce and secrete T<sub>4</sub> and T<sub>3</sub>

**Adrenocorticotrophic hormone (ACTH)** stimulates adrenal cortex to secrete cortisol, aldosterone

**Follicle stimulating hormone (FSH)** stimulates growth of ovarian follicles and sperm production

**Luteinizing hormone (LH)** causes ovulation and secretion of testosterone in testes

**Prolactin (PRL)** stimulates milk production by mammary glands
Anterior Pituitary

- Release of Anterior Pituitary hormones is controlled by hypothalamic
  - releasing factors
  - inhibiting factors
  - feedback from levels of target gland hormones

Table 1.7: Hypothalamic Hormones Involved in the Control of the Anterior Pituitary

<table>
<thead>
<tr>
<th>Hypothalamic Hormone</th>
<th>Structure</th>
<th>Effect on Anterior Pituitary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotropin-releasing hormone (CRH)</td>
<td>31 amino acids</td>
<td>Stimulates secretion of adrenocorticotropic hormone (ACTH)</td>
</tr>
<tr>
<td>Somatostatin-releasing hormone (SRH)</td>
<td>18 amino acids</td>
<td>Stimulates secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH)</td>
</tr>
<tr>
<td>Pro-opiomelanocortin (POMC)</td>
<td>Dopamine</td>
<td>Inhibits prolactin secretion</td>
</tr>
<tr>
<td>Neurotensin</td>
<td>14 amino acids</td>
<td>Stimulates secretion of growth hormone</td>
</tr>
<tr>
<td>Hypothalamic-releasing hormone (HRH)</td>
<td>39 amino acids</td>
<td>Stimulates secretion of luteinizing hormone (LH)</td>
</tr>
<tr>
<td>Somatostatin-releasing hormone (SRH)</td>
<td>13 amino acids</td>
<td>Stimulates growth hormone secretion</td>
</tr>
</tbody>
</table>

Anterior Pituitary

- Releasing and inhibiting hormones from hypothalamus are released from axon endings into capillary bed in median eminence.
- Carried by hypothalamo-hypophyseal portal system directly to another capillary bed in A. Pit.
- Diffuse into A. Pit. and regulate secretion of its hormones.
Feedback Control of Anterior Pituitary

- The hypothalamic-pituitary-gonad axis (control system)
- Involves short feedback loop in which retrograde flow of blood and hormones from A. Pit. to hypothalamus inhibits secretion of releasing hormone
- Involves negative feedback of target gland hormones
- And during menstrual cycle, estrogen stimulates "LH surge" by positive feedback

Sex and Reproductive Hormones

- **Gonads** *(testes and ovaries)* secrete steroid hormones testosterone, estrogen, and progesterone
- **Placenta** secretes estrogen, progesterone, hCG, and somatomammotropin

The Ovarian Cycle – 3 phases

- **Follicular Phase** - first ½ of ovarian cycle
  - Follicle development
- **Ovulation** – Midpoint of ovarian cycle
  - Oocyte exits from one ovary
    - Enters the peritoneal cavity
    - Is swept into the uterine tube
- **Luteal Phase** – second ½ of ovarian cycle
  - Remaining follicle becomes a corpus luteum
  - Secretes progesterone
  - Acts to prepare for implantation of an embryo
**Ovarian Cycle Summary**

The Uterine Cycle
- Series of cyclic phases of the endometrium
- Phases coordinate with the ovarian cycle
- Endometrial phases directed by FSH and LH
- Phases of uterine cycle – 3 phases
  - **Menstrual phase** – days 1-5
    - Stratum functionalis is shed
  - **Proliferative phase** – days 6-14
  - **Secretory phase** – days 15-28

**The Uterine Cycle**

Menstrual and Ovarian Cycles
Higher Brain Function and Anterior Pituitary Secretion

- Hypothalamus receives input from higher brain centers that can affect Anterior Pituitary secretion
  - e.g. emotional states and psychological stress can affect circadian rhythms, menstrual cycle, and adrenal hormones

Posterior Pituitary

- Stores and releases 2 hormones produced in hypothalamus:
  - **Antidiuretic hormone (ADH/vasopressin)**
    - Promotes H$_2$O conservation by kidneys
  - **Oxytocin**
    - Stimulates contractions of uterus during parturition
    - Stimulates contractions of mammary gland alveoli for milk-ejection reflex

Hypothalamic Control of Posterior Pituitary

- **Supraoptic nuclei** of hypothalamus produce ADH
- **Paraventricular nuclei** produce oxytocin
- Both transported along hypothalamo-hypophyseal tract to posterior pituitary
- Release controlled in hypothalamus by neuroendocrine reflexes
Adrenal Gland

Adrenal Glands
- Sit on top of kidneys
- Each consists of outer cortex and inner medulla
- Which arise differently during development

Adrenal Glands
- Medulla synthesizes and secretes 80% Epinephrine and 20% Norepinephrine
  - Controlled by sympathetic division of ANS
- Cortex is controlled by ACTH and secretes:
  - **Cortisol** which inhibits glucose utilization and stimulates gluconeogenesis
  - **Aldosterone** which stimulate kidneys to reabsorb Na⁺ and secrete K⁺
  - And some supplementary **sex steroids**
Adrenal Medulla
- Hormonal effects of Epinephrine last 10X longer than Norepinephrine
- Innervated by preganglionic Sympathetic fibers
- Activated during "fight or flight" response
  - Causes:
    - Increased respiratory rate
    - Increased HR and cardiac output
    - General vasoconstriction which increases venous return
    - Glycogenolysis and lipolysis

Stress and the Adrenal Gland
- Stress induces a non-specific response called general adaptation syndrome (GAS)
- Causes ACTH and cortisol release

Stress and the Adrenal Gland
- Chronic stress can induce high levels of cortisol that cause a number of negative effects:
  - atrophy of hippocampus (involved in memory)
  - reduced sensitivity of tissues to insulin (insulin resistance)
  - inhibition of vagus nerve activity
  - suppression of growth hormone, thyroid hormone, and gonadotropins
Thyroid Gland

- Is located just below the larynx
- Secretes T4 and T3 which set **Base Metabolic Rate** (BMR) and are needed for growth, development
- A scan of the thyroid 24 hrs. after intake of radioactive iodine (b)

Thyroid Gland

- Consists of microscopic **thymus follicles**
  - Outer layer is **follicle cells** that synthesize T4
  - Interior filled with **colloid**, a protein-rich fluid
Production of Thyroid Hormones

- Iodide (I⁻) in blood is actively transported into follicles and secreted into colloid
- Where it is oxidized to iodine (I₂) and attached to tyrosines of thyroglobulin
- A large storage molecule for T₄ and T₃
- TSH stimulates hydrolysis of T₄ and T₃ from thyroglobulin and then secretion

Diseases of the Thyroid - Goiter

- In absence of sufficient dietary iodide, T₄ and T₃ cannot be made and levels are low
- Low T₄ and T₃ don’t provide negative feedback and TSH levels go up
- Because TSH is a trophic hormone, thyroid gland grows
- Resulting in a goiter
Diseases of the Thyroid

- **Hypothyroid** - People with inadequate T₄ and T₃ levels
  - Have low BMR, weight gain, lethargy, cold intolerance
- **Hyperthyroid** - People with increased T₄ and T₃ levels.
  - Characterized by weight loss, heat intolerance, irritability, high BMR, exophthalmos.

Diseases of the Thyroid

- **Goiter** – Enlargement of thyroid gland due to iodine deficiency
- **Grave’s disease**
  - Autoimmune disease where antibodies act like TSH and stimulate thyroid gland to grow and oversecrete.

Parathyroid Glands

- Are 4 glands embedded in lateral lobes of posterior side of thyroid gland
- Secrete **Parathyroid hormone (PTH)**
- Most important hormone for control of blood Ca²⁺ levels
Parathyroid Hormone

- Release stimulated by decreased blood Ca²⁺
- Acts on bones, kidney, and intestines to increase blood Ca²⁺ levels

Islets of Langerhans

- Are scattered clusters of endocrine cells in pancreas
- Contain alpha and beta cells
Islets of Langerhans

- Alpha cells secrete glucagon in response to low blood glucose
  - Stimulates glycogenolysis and lipolysis
  - Increases blood glucose

Islets of Langerhans

- Beta cells secrete insulin in response to high blood glucose
  - Promotes entry of glucose into cells
  - And conversion of glucose into glycogen and fat
  - Decreases blood glucose