An Introduction to the Endocrine System

Chapter 17
Overview of Cell Communications

- Internal communication between cells is necessary to coordination cellular activities.
- four principal mechanisms of communication exist between cells
  - **gap junctions**
    - pores in cell membrane allow signaling molecules, nutrients, and electrolytes to move from cell to cell
  - **neurotransmitters**
    - released from neurons to travel across synaptic cleft to second cell
  - **paracrine (local) hormones**
    - secreted into tissue fluids to affect nearby cells
  - **hormones**
    - chemical messengers that travel in the bloodstream to other tissues and organs
    - the endocrine system
• **endocrine system** - glands, tissues, and cells that secrete hormones

• **endocrine glands** – organs that are traditional sources of hormones

• **hormones**
  chemical messengers that are transported by the bloodstream and stimulate physiological responses in cells of another tissue or organ, often a considerable distance away

• **endocrinology** – the study of this system and the diagnosis and treatment of its disorders

**Key Steps:**

1. Hormone synthesized by tissue.
2. Hormone released into blood.
3. Hormone circulates within cardiovascular system
4. Hormone leaves blood, diffuse to target tissue’s receptor.
5. Hormone binds to receptor.
6. Hormone changes metabolism of target tissue.
Comparison of Endocrine and Exocrine Glands

- **exocrine glands**
  - have ducts carry secretion to an epithelial surface or the mucosa of the digestive tract – ‘external secretions’
  - extracellular effects (food digestion)

- **endocrine glands**
  - no ducts
  - contain dense, fenestrated capillary networks which allows easy uptake of hormones into bloodstream
  - ‘internal secretions’
  - intracellular effects such as altering target cell metabolism

- **Pancreas**
  - Exocrine – digestive enzymes
  - Endocrine – insulin / glucagon

- **Hepatocytes** (liver cells) defy rigid classification
  - releases hormones
  - releases bile into ducts
  - releases albumin and blood-clotting factors into blood (not hormones)
Comparison of Nervous and Endocrine Systems
(Differences)

- both serve for internal communication
  - nervous - both electrical and chemical
  - endocrine - only chemical

- **speed and persistence of response**
  - nervous - reacts quickly (1-10 msec), stops quickly
  - endocrine - reacts slowly (hormone release in seconds or days), effect may continue for weeks

- **adaptation to long-term stimuli**
  - nervous - response declines (adapts quickly)
  - endocrine - response persists (adapts slowly)

- **area of effect**
  - nervous - targeted and specific (one organ)
  - endocrine - general, widespread effects (many organs)
Comparison of Nervous and Endocrine Systems
(Similarities)

• several chemicals function as both hormones and neurotransmitters
  – norepinephrine, cholecystokinin, thyrotropin-releasing hormone, dopamine and antidiuretic hormone

• some hormones secreted by neuroendocrine cells (neurons) that release their secretion into the bloodstream
  – oxytocin and catecholamines

• both systems with overlapping effects on same target cells
  – norepinephrine and glucagon cause glycogen hydrolysis in liver

• systems regulate each other
  – neurons trigger hormone secretion
  – hormones stimulate or inhibit neurons

• target organs or cells – those organs or cells that have receptors for a hormone and can respond to it.
Communication by the Nervous and Endocrine Systems

(a) Nervous system

(b) Endocrine system
Major Endocrine Organs

organs of endocrine system
<table>
<thead>
<tr>
<th>Source</th>
<th>Hormone</th>
<th>Target Organs and Tissues</th>
<th>Principal Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic islets</td>
<td>Glucagon</td>
<td>Primarily liver</td>
<td>Stimulates amino acid absorption, gluconeogenesis, glycogen and fat breakdown; raises blood glucose and fatty acid levels</td>
</tr>
<tr>
<td></td>
<td>Insulin</td>
<td>Most tissues</td>
<td>Stimulates glucose and amino acid uptake; lowers blood glucose level; promotes glycogen, fat, and protein synthesis</td>
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<tr>
<td></td>
<td>Somatostatin</td>
<td>Stomach, intestines, pancreatic islet cells</td>
<td>Modulates digestion, nutrient absorption, and glucagon and insulin secretion</td>
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<tr>
<td></td>
<td>Pancreatic polypeptide</td>
<td>Pancreas, gallbladder</td>
<td>Inhibits release of bile and digestive enzymes</td>
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<tr>
<td></td>
<td>Gastrin</td>
<td>Stomach</td>
<td>Stimulates acid secretion and gastric motility</td>
</tr>
<tr>
<td>Ovaries</td>
<td>Estradiol</td>
<td>Many tissues</td>
<td>Stimulates female reproductive development and adolescent growth; regulates menstrual cycle and pregnancy; prepares mammary glands for lactation</td>
</tr>
<tr>
<td></td>
<td>Progesterone</td>
<td>Uterus, mammary glands</td>
<td>Regulates menstrual cycle and pregnancy; prepares mammary glands for lactation</td>
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<tr>
<td></td>
<td>Inhibin</td>
<td>Anterior pituitary</td>
<td>Inhibits FSH secretion</td>
</tr>
<tr>
<td>Testes</td>
<td>Testosterone</td>
<td>Many tissues</td>
<td>Stimulates fetal and adolescent reproductive development, musculoskeletal growth, sperm production, and libido</td>
</tr>
<tr>
<td></td>
<td>Inhibin</td>
<td>Anterior pituitary</td>
<td>Inhibits FSH secretion</td>
</tr>
<tr>
<td>Skin</td>
<td>Cholecalciferol</td>
<td>—</td>
<td>Precursor of calcitriol (see kidneys)</td>
</tr>
<tr>
<td>Liver</td>
<td>Calcidiol</td>
<td>—</td>
<td>Precursor of calcitriol (see kidneys)</td>
</tr>
<tr>
<td></td>
<td>Angiotensinogen</td>
<td>—</td>
<td>Precursor of angiotensin II (see kidneys)</td>
</tr>
<tr>
<td></td>
<td>Erythropoietin</td>
<td>Red bone marrow</td>
<td>Promotes red blood cell production, increases oxygen-carrying capacity of blood</td>
</tr>
<tr>
<td></td>
<td>Hepcidin</td>
<td>Small intestine, liver</td>
<td>Promotes iron absorption and mobilization</td>
</tr>
<tr>
<td></td>
<td>Insulin-like growth factor I</td>
<td>Many tissues</td>
<td>Prolongs and mediates action of growth hormone</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Angiotensin I</td>
<td>—</td>
<td>Precursor of angiotensin II, a vasoconstrictor</td>
</tr>
<tr>
<td></td>
<td>Calcitriol</td>
<td>Small intestine</td>
<td>Increases blood calcium level mainly by promoting intestinal absorption of Ca^{2+}</td>
</tr>
<tr>
<td></td>
<td>Erythropoietin</td>
<td>Red bone marrow</td>
<td>Promotes red blood cell production, increases oxygen-carrying capacity of blood</td>
</tr>
<tr>
<td>Heart</td>
<td>Atrial natriuretic peptide and</td>
<td>Kidney</td>
<td>Lower blood volume and pressure by promoting Na^{+} and water loss</td>
</tr>
<tr>
<td></td>
<td>brain natriuretic peptide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach and small</td>
<td>Cholecystokinin</td>
<td>Gallbladder, brain</td>
<td>Bile release; appetite suppression</td>
</tr>
<tr>
<td>intestine</td>
<td>Gastrin</td>
<td>Stomach</td>
<td>Stimulates acid secretion</td>
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<tr>
<td></td>
<td>Ghrelin</td>
<td>Brain</td>
<td>Stimulates hunger, initiates feeding</td>
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<tr>
<td></td>
<td>Peptide YY</td>
<td>Brain</td>
<td>Produces sense of satiety, terminates feeding</td>
</tr>
<tr>
<td></td>
<td>Other enteric hormones</td>
<td>Stomach, intestines</td>
<td>Coordinate secretion and motility in different regions of digestive tract</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>Leptin</td>
<td>Brain</td>
<td>Limits appetite over long term</td>
</tr>
<tr>
<td>Osseous tissue</td>
<td>Osteocalcin</td>
<td>Pancreas, adipose tissue</td>
<td>Stimulates pancreatic beta cells to multiply, increases insulin secretion, enhances insulin sensitivity of various tissues, and reduces fat deposition</td>
</tr>
<tr>
<td>Placenta</td>
<td>Estrogen, progesterone</td>
<td>Many tissues of mother and fetus</td>
<td>Stimulate fetal development and maternal bodily adaptations to pregnancy; prepare mammary glands for lactation</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Name</td>
<td>Source</td>
<td></td>
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<tr>
<td>--------------</td>
<td>-----------------------------------------------------</td>
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<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone (corticotropin)</td>
<td>Anterior pituitary</td>
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<tr>
<td>ADH</td>
<td>Antidiuretic hormone (arginine vasopressin)</td>
<td>Posterior pituitary</td>
<td></td>
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<tr>
<td>ANP</td>
<td>Atrial natriuretic peptide</td>
<td>Heart</td>
<td></td>
</tr>
<tr>
<td>CRH</td>
<td>Corticotropin-releasing hormone</td>
<td>Hypothalamus</td>
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<tr>
<td>DHEA</td>
<td>Dehydroepiandrosterone</td>
<td>Adrenal cortex</td>
<td></td>
</tr>
<tr>
<td>EPO</td>
<td>Erythropoietin</td>
<td>Kidney, liver</td>
<td></td>
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<tr>
<td>FSH</td>
<td>Follicle-stimulating hormone</td>
<td>Anterior pituitary</td>
<td></td>
</tr>
<tr>
<td>GH</td>
<td>Growth hormone (somatotropin)</td>
<td>Anterior pituitary</td>
<td></td>
</tr>
<tr>
<td>GHRH</td>
<td>Growth hormone–releasing hormone</td>
<td>Hypothalamus</td>
<td></td>
</tr>
<tr>
<td>GnRH</td>
<td>Gonadotropin-releasing hormone</td>
<td>Hypothalamus</td>
<td></td>
</tr>
<tr>
<td>IGFs</td>
<td>Insulin-like growth factors (somatomedins)</td>
<td>Liver, other tissues</td>
<td></td>
</tr>
<tr>
<td>LH</td>
<td>Luteinizing hormone</td>
<td>Anterior pituitary</td>
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</tr>
<tr>
<td>NE</td>
<td>Norepinephrine</td>
<td>Adrenal medulla</td>
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<tr>
<td>OT</td>
<td>Oxytocin</td>
<td>Posterior pituitary</td>
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<tr>
<td>PIH</td>
<td>Prolactin-inhibiting hormone (dopamine)</td>
<td>Hypothalamus</td>
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<tr>
<td>PRL</td>
<td>Prolactin</td>
<td>Anterior pituitary</td>
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<tr>
<td>PTH</td>
<td>Parathyroid hormone (parathormone)</td>
<td>Parathyroids</td>
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<tr>
<td>T₃</td>
<td>Triiodothyronine</td>
<td>Thyroid</td>
<td></td>
</tr>
<tr>
<td>T₄</td>
<td>Thyroxine (tetraiodothyronine)</td>
<td>Thyroid</td>
<td></td>
</tr>
<tr>
<td>TH</td>
<td>Thyroid hormone (T₃ and T₄)</td>
<td>Thyroid</td>
<td></td>
</tr>
<tr>
<td>TRH</td>
<td>Thyrotropin-releasing hormone</td>
<td>Hypothalamus</td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid-stimulating hormone (thyrotropin)</td>
<td>Anterior pituitary</td>
<td></td>
</tr>
</tbody>
</table>
• Next, we will continue our discussion of the endocrine system by looking at the hormone chemistry.
Three Chemical Classes

- **steroids**
  - derived from cholesterol
  - secreted by gonads and adrenal glands
  - estrogens, progesterone, testosterone, cortisol, corticosterone, aldosterone, DHEA, and calcitriol

- **peptides (and glycoproteins)**
  - created from chains of amino acids
  - secreted by pituitary and hypothalamus
  - oxytocin, antidiuretic hormone, releasing and inhibiting hormones, and anterior pituitary hormones

- **monoamines (biogenic amines)**
  - derived from amino acids
  - secreted by adrenal, pineal, and thyroid glands
  - epinephrine, norepinephrine, melatonin, and thyroid hormone

Note: all hormones are made from either cholesterol or amino acids with carbohydrate added to make glycoproteins.
Hormone Synthesis: Steroid Hormones

- synthesized from cholesterol – differs in functional groups attached to 4-ringed steroid backbone
Peptides

- synthesized in same way as any protein
- at first is an inactive **pre-prohormone**
- first several amino acids is a signal peptide that guides it into cisterna of rough endoplasmic reticulum
- signal peptide removed to form **prohormone**
- Golgi does final transformation to **hormone** packaged for secretion
Hormone Synthesis: Insulin

- begins as **pre-proinsulin**, then becomes **proinsulin**

- when **connecting peptide** is removed, two polypeptide chains are formed that make up insulin
Monoamines

- **Synthesized from amino acid**

- **melatonin** is synthesized from amino acid **tryptophan**

- **thyroid hormone** is composed of 2 tyrosines
**Thyroid Hormone Synthesis**

1. **Iodide absorption and oxidation**
2. **Thyroglobulin synthesis and secretion**
3. **Iodine added to tyrosines of thyroglobulin**
4. **Thyroglobulin uptake and hydrolysis**
5. **Release of T₄ and a small amount of T₃ into the blood**
T₃ and T₄ Synthesis

- **follicular cells**
  - absorb **iodide (I⁻) ions** from blood and store in lumen as a reactive form of iodine
  - synthesize **thyroglobulin** and store in lumen
    - forms colloid
    - contains lots of tyrosine
  - tyrosine and iodine combine to form thyroxine (T₄) bound to thyroglobulin
  - stored in follicle
- **TSH**
  - stimulates follicular cells to remove T₄ from thyroglobulin for release into plasma
  - most T₃ is produced in liver or by target cells removing an iodine from circulating T₄
  - 95% T₄ and 5% T₃
Chemistry of Thyroid Hormone

MIT contains one iodine atom, DIT has two

\[ T_3 \] - combination of MIT plus DIT

\[ T_4 \] - combination of two DITs
Hormone Transport

- **most monoamines and peptides** are **hydrophilic**
  - mix easily with blood plasma

- **steroids and thyroid hormone** are **hydrophobic**
  - bind to **transport proteins** (albumins and globulins synthesized by the liver)
  - these hormones are "**bound hormones**"
    - have longer half-life
    - protected from liver enzymes and kidney filtration
    - transport proteins protect circulating hormones
    - being broken down by enzymes in the plasma and liver
    - being filtered out of the blood by the kidneys
  - only **unbound hormone** leaves capillaries to reach target cell

- **thyroid hormone** binds to three transport proteins in the plasma
  - **albumin**, **thyretin** and **TGB (thyroxine-binding globulin)**
  - more than 99% of circulating TH is protein bound

- **steroid hormones** bind to **globulins**
  - transcortin – the transport protein for cortisol

- **aldosterone** - short half-life
  - 85% unbound
  - 15% binds weakly to albumin and others
Hormone Receptors

- Hormones stimulate only those cells that have receptors for them.
- **Receptors** are protein or glycoprotein molecules:
  - on plasma membrane, in the cytoplasm, or in the nucleus.
- **Receptors** act like switches turning on metabolic pathways when hormone binds to them.
- Usually each target cell has a few thousand receptors for a given hormone.
- Receptor-hormone interactions exhibit *specificity* and *saturation*:
  - Specific receptor for each hormone.
  - Saturated when all receptor molecules are occupied by hormone molecules.
Hormone Mode of Action

- **hydrophobic hormones**
  - penetrate plasma membrane and enter nucleus
  - act directly on the genes changing target cell physiology
  - estrogen, progesterone, thyroid hormone act on nuclear receptors
  - take several hours to days to show effect due to lag for protein synthesis

- **hydrophilic hormones**
  - cannot penetrate into target cell
  - must stimulate physiology indirectly
Thyroid Hormone

- thyroid hormone enters target cell by diffusion – mostly as $T_4$ with little metabolic effect

- within target cell, $T_4$ is converted to more potent $T_3$

- $T_3$ enters target cells and binds to receptors in chromatin

- activates genes
  - make a muscle protein (myosin) enhancing cardiac muscle response to sympathetic stimulation
  - strengthening heartbeat
**Peptides and Catecholamines: Hydrophilic**

- hormone binds to cell-surface receptor
- receptor linked to second messenger system on other side of the membrane
- activates G protein which
- activates adenylate cyclase
- produces cAMP
- activates or inhibits enzymes
- possible metabolic reactions:
  - synthesis
  - secretion
  - change membrane potentials
Other Second Messengers

- diacylglycerol (diglyceride) second-messenger system
- inositol triphosphate second-messenger system
- act on cell metabolism in a variety of ways
Enzyme Amplification

- Hormones are extraordinarily potent chemicals.
- One hormone molecule can trigger the synthesis of many enzyme molecules.
- Very small stimulus can produce very large effect.
- Circulating concentrations very low.

Diagram:
- Small stimulus
- Hormone
- cAMP and protein kinase
- Activated enzymes
- Metabolic product
- Great effect
- Reaction cascade (time)
Modulation of Target Cell Sensitivity

- target cell sensitivity adjusted by changing the number of receptors
  - **up-regulation** means number of receptors is increased
    - sensitivity is increased
  - **down-regulation** reduces number of receptors
    - cell less sensitive to hormone
    - happens with long-term exposure to high hormone concentrations
      - bind to other receptors
      - converted to different hormone
Hormone Interactions

• **most cells** sensitive to more than one hormone and exhibit interactive effects

• **synergistic effects**
  – multiple hormones act together for greater effect
    • synergism between FSH and testosterone on sperm production

• **permissive effects**
  – one hormone enhances the target organ’s response to a second later hormone
    • estrogen prepares uterus for action of progesterone

• **antagonistic effects**
  – one hormone opposes the action of another
    • insulin lowers blood glucose and glycogen raises it
Hormone Clearance

- hormone signals **must be turned off** when they have served their purpose

- most hormones are **taken up and degraded by liver and kidney**
  - excreted in bile or urine

- **metabolic clearance rate (MCR)**
  - rate of hormone removal from the blood
  - **half-life** - time required to clear 50% of hormone from the blood
  - faster the MCF, the shorter is the half-life