Secretions and Glands

Paracrine – secretion that signals to the neighboring/adjacent cell
  - Neuron to neuron (synaptic cleft)
  - Neuromuscular junctions
  - Localized communication

Autocrine – secretion that signals to the same cell
  - Feedback
  - Localized communication

Exocrine – secretion to the external environment through ducts
  - Salivary, alimentary, lacrimal

Endocrine – secretions from glands into the blood stream that signal to distant cells
  - Wide-spread/systemic
  - Long-lasting effects

Endocrine System

- Features organs that secrete hormones into the blood
- Exist as a series of organs that signal to each other in sequence
  - Referred to as an axis
  - Signal from brain to the pituitary to an organ → hypothalamic-pituitary-adrenal axis
- All signals originally come from the hypothalamus in the brain
- Hormones secreted interact with distant cells that express the corresponding hormone receptor
- Receptors may reside on the plasma membranes, in the cytoplasm or in the nucleus

Mechanisms of Intercellular Communication

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Transmission</th>
<th>Chemical Mediators</th>
<th>Distribution of Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct communication</td>
<td>Through-gap junctions</td>
<td>ions, small molecules, lipid derivatives</td>
<td>Usually limited to adjacent cells of the same type that are interconnected by continuities</td>
</tr>
<tr>
<td>Paracrine communication</td>
<td>Through extracellular fluid</td>
<td>Paracrine factors</td>
<td>Primarily limited to the locators, where paracrine factor concentrations are relatively high, target cells must have appropriate receptors</td>
</tr>
<tr>
<td>Endocrine communication</td>
<td>Through the bloodstream</td>
<td>Hormones</td>
<td>Target cells are primarily in other tissues or organs and must have appropriate receptors</td>
</tr>
<tr>
<td>Synaptic communication</td>
<td>Across synaptic clefts</td>
<td>Neurotransmitters</td>
<td>Limited to very specific axon-target cell interactions with appropriate receptors</td>
</tr>
</tbody>
</table>

Classes of Hormones

Peptide/protein
- Amino acid chains
- Can be complex proteins with carbohydrate modification
- Multiple peptides might arise from a single protein
- Some pro-hormones processed into multiple hormones

Lipid
- Eicosanoids – signaling molecules derived from fatty acid chains
- Steroids – derived from cholesterol

Monoamine
- Derived from amino acids
- Modified by a decarboxylase enzyme
- Neurotransmitters like dopamine, norepinephrine

The three types of hormones and paracrine factors in the body

Amino Acid Derivatives

Peptide Hormones

Lipid Derivatives

The diagram illustrates the actions of amino acid derivatives, peptide hormones, and lipid derivatives on various cellular processes and functions in the body.
Hormones and receptors

- To be sensitive to a hormone, a target cell must have the appropriate protein receptor.
- Without the receptor, the circulating hormone has no effect.
- Cells have receptors for many different hormones.
- Different combinations of receptors produce differential effects on specific tissues.
- Two possible receptor locations on target cells:
  1) Receptor in plasma membrane
     - Water-soluble hormones cannot cross plasma membrane.
     - Act as first messenger, relaying message to an intracellular intermediary (second messenger).
     - Second messenger then affects enzyme activity and changes cellular metabolic reactions.
  2) Receptor in cytoplasm or nucleus
     - Lipid-soluble hormones diffuse through plasma membrane.
     - Steroids affect DNA transcription rate and protein synthesis.
     - Change synthesis of enzyme and structural proteins affecting cell’s metabolic activity and structure.
     - Thyroid hormones:
       - Bind to receptors on mitochondria, affecting energy production.
       - Bind to receptors in nucleus, affecting cell’s metabolic activity and structure.

G-Protein Coupled Receptor

- Referred to as metabotropic receptors.
- Modulate the cell directly.
- Signal transferred to the interior of the cell setting forth metabolic changes.
  - Cascade of events that amplify the message through second messengers.
  - cAMP (cyclic AMP)
  - Ca²⁺
  - Activation of protein kinases (phosphorylates proteins).
  - Phosphorylation activates/deactivates proteins by changing conformation.
  - Signal can be long-term if affecting transcription factors.

The actions of second messengers for hormones that bind to receptors in the plasma membrane.

Effects on cAMP Levels

- Many G proteins, once activated, exert their effects by changing the concentration of cyclic AMP, which acts as the second messenger within the cell.

Effects on Ca²⁺ Levels

- Upon hormone stimulation, Ca²⁺ ions enter the cell, allowing the release of stored Ca²⁺ from intracellular stores.
- Ca²⁺ ions then activate enzymes.

The events associated with the binding of a steroid hormone to receptors in the cytoplasm or nucleus.

- Binding of hormone-receptor complex to DNA.
- Gene activation.
- Transcription and mRNA production.
- Translation and protein synthesis.
- Alteration of cellular structure or activity.

The events associated with the binding of a thyroid hormone to receptors on mitochondria and within the nucleus.

- Binding of hormone-receptor complex to DNA.
- Gene activation.
- Transcription and mRNA production.
- Translation and protein synthesis.
- Alteration of cellular structure or activity.
Hypothalamus provides highest level of endocrine function through three mechanisms
- Has neurons that secrete two hormones released from posterior pituitary
  - Antidiuretic hormone (from supraoptic nucleus) aka Vasopressin
  - Oxytocin (from paraventricular nucleus)
- Secretes regulatory hormones or tropic hormones that control anterior pituitary gland endocrine cells
  - Released from median eminence of infundibulum
- Hypophysial portal system (hypophysis, pituitary gland) fenestrated capillaries that transport tropic hormones to pituitary
- Two regulatory hormone types
  1) Releasing hormones (stimulate hormone release)
  2) Inhibiting hormones (prevent hormone release)
- Contains autonomic (sympathetic) neurons that stimulate release of hormones from adrenal medulla — direct innervation
Once within the anterior lobe, these vessels form a second capillary network that branches among the endocrine cells. The vessels between the median eminence and the anterior lobe carry blood from one capillary network to another. Blood vessels that link two capillary networks are called portal vessels; in this case, they have the histological structure of veins, so they are called portal veins.

The capillary networks in the median eminence are supplied by the superior hypophyseal artery. Before leaving the hypothalamus, the capillary networks unite to form a series of larger vessels that spiral around the infundibulum to reach the anterior lobe.

Hypophyseal Portal System

Control of the production of anterior pituitary hormones by hypothalamic regulatory hormones

Neurons of these structures manufacture antidiuretic hormone and oxytocin, respectively, which are released by synaptic terminals at capillaries in the posterior lobe of the pituitary gland.

It all starts in the brain

- The brain regulates the major functions of the body
- The hypothalamus is the portion of the brain that regulates all endocrine systems
- The hypothalamus sends signals to the pituitary gland

Pituitary Gland

- Referred to as the hypophysis
- Composed of the anterior and posterior lobes
- Anterior ➔ adenohypophysis (7 hormones)
- Posterior ➔ neurohypophysis (2 hormones)
- Hormones secreted into portal vessels

Gonadotropins (regulate gonadal activities)

1) Follicle-stimulating hormone (FSH)
   - Females: promotes ovarian follicle development and (in concert with LH) stimulates secretion of estrogens
   - Males: promotes maturation of sperm
   - Inhibited by inhibin (peptide released by gonads)

2) Luteinizing hormone (LH)
   - Females: induces ovulation, promotes secretion of estrogen and progestins (e.g., progesterone)
   - Males: stimulates production of sex hormones (androgens), primarily testosterone

Anterior pituitary hormones

Thyroid-stimulating hormone (TSH)

- Stimulates release of thyroid hormones
- Released in response to thyrotropin-releasing hormone (TRH) from hypothalamus
- Decreased release when thyroid hormone levels rise (negative feedback)
- Composed of 2 peptide chains

- α chain of TSH, LH and FSH are identical

- Often called “Master Gland”
- Sits in sella turcica (Turkish saddle)
- Adenohypophysis is own gland
- Neurohypophysis is derived from axon terminals from the hypothalamus
- Tropic hormones
  - Hormones that act on other endocrine glands
  - From hypothalamus
  - Therefore, hypothalamus is the real master gland
Melanocyte-stimulating hormone (MSH)
- From pars intermedia of anterior lobe
- Stimulates melanocytes of skin to increase melanin production
- In adults, almost none produced

Adrenocorticotropic hormone (ACTH)
- Stimulates release of steroid hormones from adrenal cortex
  - Specifically those that affect glucose metabolism
- Released in response to corticotropin-releasing hormone (CRH) from hypothalamus

β-endorphin
- "Endogenous morphine"

Proopiomelanocortin (POMC)
- Precursor protein that is proteolytically processed
- Yields MSH, ACTH and β-endorphin
- POMC, LSH and Gonadotropin cells are basophilic histologically labeling the lysosomes

Prolactin (PRL; pro- before + lac, milk)
- Works with other hormones to stimulate mammary gland development and milk production
- Released in response to several prolactin-releasing factors
- Inhibited by prolactin-inhibiting hormone (PIH)

Hyperprolactinemia
- Is the presence of abnormally-high levels of prolactin in the blood
- Results in disruption of menstrual cycle
- Results in lactation (even in men)

Growth hormone (GH)
- Also called somatotropin
- Stimulates cell growth and reproduction by stimulating rate of protein synthesis
- Released in response to growth hormone-releasing hormone (GH–RH) and growth hormone–inhibiting hormone (GH–IH)

Antidiuretic hormone (ADH)
- Also known as arginine vasopressin (AVP)
- Released in response to a variety of stimuli
- Primarily increases solute concentration of blood (vasopressin receptors), or a decrease in blood pressure or volume
- Inhibited by increase in extracellular fluid volume
- Also inhibited by alcohol
- Primary function is to decrease water lost from kidney
- Also causes vasoconstriction

Oxytocin (OXT; oktytokos, swift birth)
- Increased release in response to:
  - Childbirth
  - Nursing
  - Sexual arousal (function unknown)
  - Sensory input (neuroendocrine reflex)
  - Stimulates contraction of:
    - Smooth muscle walls of uterus
    - Mammary gland myoepithelial cells releasing milk
    - Related to social bonding and interactions and maternal behavior
Posterior Pituitary Hormones

**ADH**
- Antidiuretic hormone is most notably released in response to a rise in the solute concentration in the blood or a fall in blood volume or blood pressure. The primary function of ADH is to decrease the amount of water lost at the kidneys. ADH also causes vasoconstriction, which helps elevate blood pressure. ADH release is inhibited by alcohol.

**OXT**
- In women, oxytocin stimulates smooth muscle contraction in the wall of the uterus, promoting labor and delivery, and after labor it stimulates the contraction of myoepithelial cells around the secretory alveoli and the ducts of the mammary glands, promoting the ejection of milk. Circulating concentrations of oxytocin rise during sexual arousal and peak at orgasm in both sexes.

Feedback loops

The control of hypothalamic and pituitary hormone secretion by negative feedback

**Thyroid**
- **Pinealocytes**
  - Neurosecretory cells
  - Produce melatonin
  - Inhibits reproductive functions (may control human sexual maturation)
  - Protects tissues from free radicals
  - Maintains daily physiological changes (circadian rhythms)
  - Coordinated by collaterals of visual pathway to coordinate with day–night cycle

The location of the pineal gland

"principal seat of the soul" - René Descartes → the point of connection between the intellect and the body

Pineal – The Third Eye

Thyroid

Thyroglobulin in colloidal (C) (clear) cells (produce calcitonin)

Cuboidal epithelium of follicle

Thyroid follicle

Section of thyroid gland LM x 260

Right lobe of thyroid gland

Common carotid artery

Trachea

Outline of sternum

Thyroid cartilage

Internal jugular vein

Left lobe of thyroid gland

Isthmus of thyroid gland

Thyroid
Thyroid

- Contains large numbers of follicles (hollow spheres lined with follicular cells of simple cuboidal epithelium)
- Follicular cells secrete thyroglobulin (molecule containing building block amino acid tyrosine) into colloid within follicles
  1) Iodide ions from diet delivered to thyroid gland and taken up by follicular cells
  2) Enzymes activate iodide and attach to tyrosine portions of thyroglobulin molecule
  3) $T_4$ (Thyroxine, 4 iodide molecules) and $T_3$ (3 iodide molecules) are produced and stored in thyroglobulin
  4) Follicle cells remove thyroglobulin from follicle via endocytosis
  5) Enzymes break down thyroglobulin, releasing thyroid hormones into cytoplasm
  6) $T_4$ (90% of thyroid secretions) and $T_3$ (<10%) diffuse across basement membrane and enter bloodstream
  7) 75% of thyroid hormones travel in the blood attached to transport proteins (thyroid-binding globulins)

- C (clear) cells in between follicular cells (aka Parafollicular Cells)
  - Secrete hormone calcitonin
    - Lowers blood $Ca^{2+}$
    - Inhibits intestinal absorption of $Ca^{2+}$

Hypothyroidism

- weight gain, depression, mania, sensitivity to heat and cold, paresthesia, fatigue, panic attacks, Bradycardia, tachycardia, high cholesterol, reactive hypoglycemia, constipation, migraines, muscle weakness, cramps, memory loss, infertility and hair loss
- Cretinism - severely stunted physical and mental growth due to untreated congenital deficiency of thyroid hormones and from severe iodine deficiency
- Hashimoto's disease - autoimmune disease in which the thyroid gland is attacked by a variety of cell- and antibody-mediated immune processes
  - Thyroiditis from attack of the thyroid by immune system

Hyperthyroidism

- nervousness, irritability, increased perspiration, heart racing, hand tremors, anxiety, difficulty sleeping, thinning of the skin, fine brittle hair, and muscular weakness
- Weight loss, sometimes significant, may occur despite a good appetite, vomiting may occur, and, for women, menstrual flow may lighten and menstrual periods may occur less often
- Graves Disease
  - insomnia, hand tremor, hyperactivity, hair loss, excessive sweating, heat intolerance, weight loss despite increased appetite, diarrhea, frequent defecation, palpitations, muscle weakness and skin being warm as well as moist
  - Autoimmune disease where thyroid autoantibodies (TSHR-Ab) that activate the TSH-receptor (TSHR), thereby stimulating thyroid hormone synthesis and secretion, and thyroid growth (causing a diffusely enlarged goiter)
**Parathyroid**

- Oxiphyl cells (no known function)
- Parathyroid chief cells → Parathyroid Hormone (PTH)
  - Mobilizes calcium from bone
  - Inhibit osteoblast deposition
  - Activate osteoclast production
  - Erosion of bone
- Enhances Kidney absorption of Ca²⁺
- Stimulates kidney release of calcitriol
- Increases Ca²⁺ and PO₄³⁻ absorption in intestine

**Adrenal Gland - Cortex**

- Zona glomerulosa
  - Mineralocorticoids (primarily aldosterone)
    - Increases renal reabsorption of Na⁺ and water
    - Especially in presence of ADH
    - Accelerates renal loss of K⁺
- Zona fasciculata (fasciculus, little bundle)
  - Glucocorticoids (primarily cortisol and corticosterone)
    - Increase rates of liver glucose and glycogen formation
    - Stimulate release of:
      - Amino acids from skeletal muscles
      - Lipids from adipose tissue
    - Promote lipid metabolism
    - Can have anti-inflammatory effect and immune suppressant
- Zona reticularis (reticulum, network)
  - Androgens (small amounts)
    - Stimulate pubic hair before puberty
    - Androstenedione and DHEA

**Calcium Homeostasis**

- PTH and calcitonin from thyroid gland have opposing effects
- In healthy adults, PTH (along with calcitriol) is primary regulator of circulating Ca²⁺ concentrations
- Removal of thyroid gland has no effect on Ca²⁺
- Calcitonin can be administered clinically in metabolic disorders with excessive calcium

**Adrenal Androgens**

- Addison's Disease
  - Deficiency of adrenal cortex steroid production (hyposecretion)
  - a fatigue, lightheadedness upon standing or while upright, muscle weakness, fever, weight loss, difficulty in standing up, anxiety, nausea, vomiting, diarrhea, headache, sweating, changes in mood and personality, and joint and muscle pains
  - Some have marked cravings for salt or salty foods due to the urinary losses of sodium
  - Treated with steroids
  - Many Addison's patients suffer from hyperpigmentation
  - Hyponatremia (low sodium level in the blood)
  - Hyperkalemia (elevated potassium level in the blood)
  - Hypercalcemia (elevated calcium level in the blood)

**Adrenal Cortex diseases**

- Adrenal capsule (thin, outer connective tissue)
- Adrenal cortex
  - Produces >24 steroid hormones collectively known as adrenocortical steroids or corticosteroids
- Adrenal medulla
  - Produces epinephrine and norepinephrine
  - Developmentally neural in origin

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Adrenal Cortex diseases

Cushing’s syndrome
- Excessive (hypersecretion) exposure to glucocorticoids
- Weight gain → in trunk and face
- Dilution of facial capillaries → blushing appearance
- Profuse sweating
- Hypertension
- Insulin resistance → diabetes

Adrenal Medulla

- Epinephrine and norepinephrine
  - Derived from neural tissue
  - Receives direct innervation from the sympathetic nervous system
  - Adrenaline and Noradrenaline

Pancreas

- Islets of Langerhans → Pancreatic Islets
  - Alpha cells
    - Glucagon
    - Raises blood glucose by increasing liver glycogen breakdown
  - Beta cells
    - Insulin
    - lowers blood glucose by increasing glucose uptake and utilization by cells
    - increasing glycogen production in liver, skeletal muscles
    - Decreased lipolysis
  - Delta cells
    - Peptide hormone identical to growth hormone–inhibiting hormone (GH–IH)
    - Suppresses release of glucagon and insulin
  - F cells
    - Pancreatic polypeptide (PP)
    - Inhibits gallbladder contraction and reduces digestive activity of pancreas and digestive tract

Pancreas

- Exocrine pancreas (99% of volume)
  - Cells (pancreatic acini) forming glands and ducts that secrete pancreatic fluid and enzymes with digestive function

- Endocrine pancreas (1%)
  - Small groups of cells scattered in clusters (pancreatic islets) that secrete hormones

Glucose homeostasis
- Insulin and glucagon are primary hormones controlling blood glucose levels
- Have opposing effects
- As blood glucose rises, beta cells secrete insulin bringing glucose into target cells
- As blood glucose declines, alpha cells secrete glucagon causing liver breakdown of glycogen and glucose release
Diabetes mellitus (mellitus, honey)
- Characterized by glucose concentrations high enough to overwhelm kidney reabsorption
- Hyperglycemia – high glucose levels in blood
- Glycosuria – glucose in urine → sweet urine
- Polyuria - excessive urine production (diabetes)

**Type 1 (insulin dependent) diabetes**
- Inadequate insulin production from beta cells
- Individuals must receive exogenous insulin daily
- Only 5%–10% of all diabetes cases
- Characterized by glucose concentrations high enough to overwhelm kidney reabsorption
- Can be treated with diet, exercise, and drugs
- Often develops in childhood (Juvenile Diabetes)
- Associated with obesity
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Reproductive Control - Female

- **Follicular Phase**
  - GnRH signals follicle development
  - GnRH → FSH
  - Developing follicles secrete estrogens (estradiol)
    - Inhibits LH secretion
    - Endometrial growth
    - Contributes to fat deposition

- **Luteal phase**
  - After ovulation
  - LH surge
  - Completion of primary oocyte meiosis I
  - Forceful rupture of follicular wall
  - Formation of corpus luteum
  - Corpus luteum produces progesterone
  - Maintains the thick endometrium

**Reproductive Control - Female**

- Without implantation, endometrium sheds → menses
- If implantation → embryo/fetus produces chorionic gonadotropin
- **Human Chorionic Gonadotropin (hCG)**
- Replaces the LH signal to maintain corpus luteum
- Maintains progesterone output to maintain endometrium

- **RU-486/Mifiprestone**
  - Abortifacent glucocorticoid analog
  - Blocks progesterone receptor to terminate pregnancy

**Control of Growth**

- The effects of various hormones on normal growth
- **Insulin Parathyroid Hormone and Calcitriol**
  - Growing cells need adequate supplies of energy and nutrients. Without insulin, the passage of glucose and amino acids across plasma membranes is drastically reduced or eliminated.
  - Parathyroid hormone (PTH) and calcitriol promote the absorption of calcium salts for subsequent deposition in bone. Without adequate levels of both hormones, bones can still enlarge, but they will be poorly mineralized, weak, and flexible.
- **Thyroid Hormones**
  - Normal growth requires appropriate levels of thyroid hormones. If these hormones are absent during fetal development or the first year of life, the nervous system will not develop normally, and mental retardation will result. If T4 concentrations decline before puberty, normal skeletal development will not continue.
  - The activity of osteoblasts in key locations and the growth of specific cell populations are affected by the presence or absence of reproductive hormones (androgens in males, estrogens in females). These sex hormones stimulate cell growth and differentiation in their target tissues. The targets differ for androgens and estrogens, and the differential growth induced by each accounts for gender-related differences in skeletal proportions and secondary sex characteristics.
- **Growth Hormone**
  - In children, growth hormone supports muscular and skeletal development.
  - In adults, growth hormone assists in the maintenance of normal blood glucose concentrations and in the mobilization of lipid reserves stored in adipose tissue. It is not the primary hormone involved, however, and an adult with a GH deficiency but normal levels of thyroxine (T4), insulin, and glucocorticoids will have no physiological problems.
- **Reproductive Hormones**
  - The growth and differentiation of certain tissues and organs are controlled by specific reproductive hormones.

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