Endocrine System
I. Background:
A. There are two types of glands:
1. Endocrine
   a. Ductless
   b. Secrete hormones into surrounding tissue fluid
   c. Vascular or lymphatic drainage receive hormones
   d. Examples of endocrine glands:
      i. Pituitary
      ii. Thyroid
      iii. Parathyroid
      iv. Adrenal
      v. Pineal
      vi. Thymus
   e. Some organs also have discrete areas of endocrine tissue as well as exocrine tissue
      i. Pancreas
      ii. Gonads
      iii. Hypothalamus
2. Exocrine
   a. Have ducts
   b. Nonhormonal products are directed to membrane surfaces

II. Hormones—chemical substances secreted by cells into extracellular fluids, that regulate metabolic function of other cells in the body
A. Chemistry
1. Classification
   a. Amino acid-based hormones
      i. Most hormones
   b. Steroid hormones
      i. Gonadal and adrenocortical hormones
B. Mechanism of action—increase or decrease rates of normal cellular activity
1. Hormonal effects
   a. Alter plasma membrane permeability
   b. Alter protein or regulatory molecule synthesis
   c. Activate or inactivate enzyme
   d. Induction of secretory activity
   e. Stimulate mitosis
2. Mechanisms that transduce hormonal signal into an intracellular change
   a. G-protein linked receptor activation of intracellular second messengers
      i. Amino acid-based hormones
   b. Direct gene activation
      i. Steroid hormones
3. Overview of second-messenger systems

- a. Hormone binds plasma membrane receptor
- b. G-protein signals effector to produce an intracellular message (i.e., second messenger)
- c. Second messenger mediates cellular response to hormone
  - i. Signaling cascades
  - ii. Protein kinases

4. Examples of signaling mechanisms
- a. cAMP (slide)
- b. PIP-Calciu signal mechanism (slide)
5. Direct gene activation

a. Steroid hormones are lipid soluble
   i. Pass through plasma membrane
b. Once inside, hormone binds to intracellular receptor
   i. Activated complex is formed
c. Activated complex passes into nucleus and binds to specific DNA sequences
d. Association with DNA sequence turns on gene
   i. Gene sequence is transcribed

C. Target cell specificity
1. Mediated by specific protein receptors
   a. Receptors are localized to cells that are influenced by a given hormone
   b. Hormones act as molecular triggers
2. Factors affecting target cell activation
   a. Hormonal levels
   b. Number of receptors on target cell
   c. Receptor affinity
      i. Can be up or down regulated based on microenvironmental conditions

D. Hormonal activity—half-life, onset and duration
1. Half-life—measure of hormonal persistence in blood stream
   a. Depends on rate of synthesis and release
   b. Speed of removal or degradation
2. Onset of effect is dependent on hormone type
   a. Steroid
      i. Hours to days
3. Duration is generally short (e.g., 20 minutes) although depends on hormone type
E. Control of hormone release

1. Typically negative feedback
   a. Hormone secretion is triggered in response to a stimulus
   b. As hormone level increases, target organ is affected
c. Further hormone release is inhibited

2. Types of stimuli
   a. Humoral
      i. Endocrine glands release hormones in direct response to changing levels of ions or nutrients
      ii. E.g., PTH release in response to changes in calcium levels
   b. Neural
      i. Nerve fibers stimulate hormonal release
      ii. E.g., sympathetic activated release of catecholamines from adrenal medulla
   c. Hormonal
      i. Glands release hormones in response to other hormones
      ii. E.g., hypothalamic releasing and inhibiting factors
III. Major Endocrine Organs

- Pineal gland
- Hypothalamus
- Pituitary gland
- Thyroid gland
- Parathyroid glands (on dorsal aspect of thyroid gland)
- Thymus
- Adrenal glands
- Pancreas
- Testes (male)
- Gonads
- Ovaries (female)
A. Pituitary (hypophysis)
1. General characteristics

a. Connected to the superiorly lying hypothalamus
   i. Infundibulum—stalk-like connection
   ii. Hypothalamus is part of the brain
      iia. Connection between brain and endocrine system

b. Two major lobes
   i. Posterior
   ii. Anterior

c. Posterior lobe + infundibulum = neurohypophysis

d. Anterior lobe (adenohyophysis) is comprised of glandular tissue

e. Highly vascular

2. Connections between posterior pituitary and hypothalamus

a. Posterior is an outgrowth of the brain and maintains its neural connections
b. Neurons in the supraoptic and paraventricular nuclei of the hypothalamus give rise to the hypothalamic-hypophyseal tract
   i. Hormones are synthesized in the secretory cells of the hypothalamus
   ii. Oxytocin and antidiuretic hormone

   c. When neurons fire, hormones are released into capillary bed in post. pituitary
3. Connections between anterior pituitary and hypothalamus
   a. Anterior lobe is derived from epithelial tissue
   b. No direct connection between post. pituitary or hypothalamus
   c. Vascular connection
      i. Hypophyseal portal veins
   d. Releasing and inhibiting hormones secreted by hypothalamus are carried by portal system to anterior pituitary
      i. Regulate the activity of secretory cells in ant. pituitary

B. Anterior pituitary hormones
1. Anterior pituitary is referred to as the Master gland
2. 6 hormones as well as a number of other active molecules
3. Tropic hormones (4/6)
   a. Regulate secretory activity of other endocrine glands
   b. TSH—thyroid-stimulating hormone
   c. ACTH—adrenocorticotropic hormone
   d. FSH—follicle-stimulating hormone
   e. LH—lutenizing hormone
4. Other hormones (2/6)
   a. Have neuroendocrine targets
   b. PRL—Prolactin
   c. GH—growth hormone
5. Growth hormone
a. Produced by somatotropic cells
b. Stimulates most cells in the body to grow and divide
c. Major targets are bones and muscles
d. Anabolic hormone
   i. Promotes metabolism
e. Growth-promoting effects are mediated indirectly
   i. IGF’s—insulin-like growth factors
   ii. Produced by liver and other tissues
f. Effects of growth hormone
   i. Stimulates uptake of amino acids from blood and their incorporation into proteins
   ii. Stimulates sulfur uptake
   iii. Mobilizes fats from fat deposits
   iv. Decreases rate of glucose uptake and metabolism
      i. Diabetogenic effect—elevation of blood glucose
g. Regulation by hypothalamic hormones (negative feedback)
   i. GHRH—growth hormone releasing hormone (somatocrinin)
   ii. GHIH—growth hormone inhibiting hormone (somatostatin)

6. Thyroid-stimulating hormone (TSH)
   a. Stimulates normal growth and activity of the thyroid gland
   b. Tropic hormone
c. Controlled by hypothalamus
   i. TRH—thyroid releasing hormone
   ii. Feedback inhibition
   iii. GHIH also inhibits

7. Adrenocorticotropic hormone (ACTH)
   a. ACTH stimulates adrenal cortex to release corticosteroid hormones
      i. Glucocorticoids—offset effects of stress
   b. ACTH release is controlled by CRH
      i. Corticotropin-releasing hormone (CRH) is a hypothalamic hormone
      ii. CRH has a diurnal rhythm
   c. Feedback inhibition: rising glucocorticoids inhibit CRH secretion

8. Gonadotropins: FSH and LH
   a. Regulate gonads
   b. FSH stimulates gamete production
   c. LH promotes production of gonadal hormones
   d. FSH and LH work in concert to cause follicle to mature
      i. LH causes egg to be extruded from follicle
   e. In males, LH stimulates interstitial cells of the testes to produce testosterone
   f. LH and FSH release is controlled by the hypothalamus
      i. GnRH—gonadotropin-releasing hormone
   g. Negative feedback inhibition regulates FSH and LH release

9. Prolaction
   a. Stimulates milk production
   b. PRH and PIH
      i. Serotonin and dopamine
   c. Levels parallel those of estrogen
C. Posterior pituitary hormones

1. General characteristics
   a. ADH and oxytocin are comprised of 9 amino acids
      i. Differ only in the identity of 2 residues
   b. Released in response to neural signals from hypothalamus

2. Oxytocin
   a. Stimulates smooth muscle contraction
   b. Muscle response depends on number of oxytocin receptors
      i. Uterus and breast
      ii. Number of receptors increases during pregnancy
      iii. Afferent impulses as uterus stretches during pregnancy signals release of oxytocin during late stages of pregnancy
   c. Hormonal trigger for milk ejection
   d. Positive feedback mechanism

3. ADH—antidiuretic hormone
   a. Inhibits or prevents urine production
   b. In response to increases in solute concentration, ADH is released from hypothalamus
      i. Hypothalamus has osmoreceptors
   c. ADH causes kidney tubules to reabsorb more water
   d. At high doses, ADH causes vasoconstriction
      i. Causes increases systolic BP
   e. Diabetes insipidus (tasteless)
      i. Deficiency in ADH secretion
      ii. Output of huge amounts of urine and thirst
C. Thyroid gland

1. Structure
   a. Two lobes connected by isthmus
   b. Follicles
      i. Follicle cells produce thyroglobin
      ii. Lumen stores colloid—thyroglobin in association with iodine
   c. Thyroid hormone is derived from iodinated thyroglobin
   d. Parafollicular cells produce calcitonin
2. Thyroid hormone (TH)

a. Two metabolically active iodine-containing hormones
   i. Thyroxine (T₄)
   ii. Triiodothyronine (T₃)

b. Thyroxine (T₄) is produced by thyroid gland

c. Triiodothyronine (T₃) is formed at target tissue
   i. T₄ is converted into T₃

d. Increases metabolism in most tissues by stimulating glucose oxidation

e. Increases adrenergic receptors in blood vessels

f. Regulates tissue growth and development

g. T₄ is bound to plasma proteins (TBG—thyroxine-binding globulin) and transported to target tissues
   i. Bind target tissue receptors
   ii. T₃ is bound more readily

h. Regulation
   i. Falling levels trigger TSH release
   ii. Rising levels of thyroxine inhibits TSH release
   iii. Conditions in which there is increased energy requirements causes TRH release from hypothalamus

3. Metabolic disturbances associated with thyroid gland activity
   a. Myxsedea—hypothyroid disorder
      i. If from lack of iodine, condition is called endemic (colloidal) goiter
      ii. Colloid is made but cannot be iodinated to make functional hormone
      iii. TSH secretion increase to stimulate TH production
      iv. Follicles accumulate more useless colloid

b. Cretinism—hypothyroidism in infants
   i. Thyroid hormone replacement therapy prevents but cannot reverse effects

c. Graves' disease—hyperthyroid pathology
   i. Autoimmune disease
   ii. Abnormal antibodies that mimic TSH
   iii. Exophthalmus
4. Calcitonin
   a. Lowers blood calcium levels
   b. Antagonist to the effect of parathyroid hormone
      i. Inhibits calcium release from bones by osteoclast activity
      ii. Stimulates calcium uptake and incorporation
      iii. Calcium acts as a humoral signal for calcitonin release

D. Parathyroid glands

1. Two pairs of glands in the posterior aspect of the thyroid gland
2. Chief cells (principal cells) secrete PTH—parathyroid hormone
3. Parathyroid hormone
a. Controls calcium balance
b. Released in response to falling blood calcium levels
c. PTH stimulates osteoclast activity
   i. Digest bone matrix and releases calcium
d. Enhances reabsorption by kidney tubules
e. Increases calcium absorption by intestine
   i. Stimulates conversion of vitamin D into active form
1. Two endocrine glands
   a. Adrenal medulla
      i. Acts as part of the sympathetic NS
   b. Adrenal cortex
2. Involved in response to stressful conditions
3. Adrenal cortex
   a. Corticosteroids
      i. Steroids
      ii. More than two dozen
      iii. Synthesized from cholesterol
   b. Mineralocorticoids (type of corticosteroid)
      i. Regulate electrolyte concentrations in extracellular fluid
      ii. Aldosterone is most abundant
      iii. Aldosterone reduces excretion of sodium from the body
      iv. Stimulates reabsorption of sodium in the distal tubule of kidney
c. Mechanisms controlling aldosterone secretion (4)

i. Renin-angiotensin mechanism: JGA releases renin in response to blood pressure decrease, initiates cascade forming angiotensin II formation, angiotensin II stimulates aldosterone release from adrenal cortex

ii. Direct stimulation by plasma sodium and potassium ions

iii. ACTH: at very high levels of ACTH, aldosterone secretion is increased

iv. ANP—atrial natriuretic peptide: when blood pressure is high, heart release ANP to inhibit renin and aldosterone secretion
d. Glucocorticoids (type of corticosteroid)
   i. Influence metabolism and mediate response to stress
   ii. Cortisol, cortisone, corticosterone
   iii. Only cortisol is secreted in significant amounts
   iv. Non-stress: CRH, ACTH, cortisol release, negative feedback
   v. Stress: Sympathetic NS overrides inhibitory effects of elevated cortisol levels and triggers CRH release
   vi. Gluconeogenesis: primary effect of cortisol; conversion of fats into glucose

e. Gonadocorticoids (Sex hormones): primarily androgens
   i. Androstenedione converted to testosterone and dihydrotestosterone
   ii. Small amounts of estrogens
   iii. Adrenal cortex secretion of sex hormones is only a fraction of gonadal sources
   iv. Possible role in onset of puberty (levels rise during years preceding onset)

4. Adrenal medulla

   a. Chromaffin cells
      i. Modified postganglionic sympathetic neurons
      ii. Secrete epinephrine and norepinephrine

   b. Initial response to stress is mediated by sympathetic NS

   c. Activation of adrenal medulla and associated release of EPI and NE prolong sympathetic response
      i. Elevated BP and heart rate
      ii. Mobilization of glucose
      iii. Shunt blood from GI
F. Pancreas
1. Contains both exocrine (GI enzymes) and endocrine cells
2. Pancreatic islets (islets of Langerhans)
   a. Two populations
      i. Alpha cells—produce glucagons
      ii. Beta cells—produce insulin

3. Effects
   a. Insulin: hypoglycemic hormone
   b. Glucagon: hyperglycemic hormone
4. Glucagon effects
   a. Breakdown of glycogen to glucose (glyconeogenesis)
   b. Synthesis of glucose from lactic acid, fatty acids and amino acids
   c. Release of glucose from liver
5. Regulation of glycogen
   a. Humoral response to decreased circulating glucose
6. Insulin effects
   a. Lower blood glucose
      i. Enhances membrane transport of glucose into body cells
   b. Alter protein and fat metabolism
   c. Inhibits breakdown of glycogen
   d. Triggers enzymatic activity
      i. Oxidation of glucose for ATP production
      ii. Synthesis and storage of glycogen
      iii. Conversion of glucose to fat and its storage
7. Regulation of insulin
   a. Humoral response to increased circulating glucose
G. Gonads
1. Same sex hormones as those produced by adrenal cortex
2. Ovaries produce estrogens and progesterone
   a. Sexual maturation and menstrual cycle
3. Testes produce testosterone
   a. Sexual maturation
   b. Sex drive
4. Release of gonadal hormones is regulated by gonadotropins

H. Pineal gland
1. Floor of third ventricle within diencephalons
2. Primary secretory product is melatonin
3. Pineal gland receives indirect inputs from visual system
4. SCN has melatonin receptors

I. Thymus
1. Large in children, decreases with age
2. Hormonal products important for T cell maturation
   a. Thymopoietins
   b. Thymosins