Chapter 18
The Endocrine System

- Endocrine and nervous systems work together
- Endocrine system
  - hormones released into the bloodstream travel throughout the body
  - results may take hours, but last longer
- Nervous system
  - certain parts release hormones into blood
  - rest releases neurotransmitters excite or inhibit nerve, muscle & gland cells
  - results in milliseconds, brief duration of effects
General Functions of Hormones

- Regulation:
  - extracellular fluid
  - metabolism
  - biological clock
  - contraction of cardiac & smooth muscle
  - glandular secretion
  - some immune functions
- Growth & development
- Reproduction
Endocrine Glands Defined

- **Exocrine glands**
  - secrete products into ducts which empty into body cavities or body surface
  - sweat, oil, mucous, & digestive glands

- **Endocrine glands**
  - secrete products (hormones) into bloodstream
  - pituitary, thyroid, parathyroid, adrenal, pineal
  - other organs secrete hormones as a 2nd function
    - hypothalamus, thymus, pancreas, ovaries, testes, kidneys, stomach, liver, small intestine, skin, heart & placenta
Hormone Receptors

- Hormones only affect target cells with specific membrane proteins called receptors
Role of Hormone Receptors

- Constantly being synthesized & broken down
- A range of 2000-100,000 receptors / target cell
- Down-regulation
  - excess hormone, produces a decrease in number of receptors
    - receptors undergo endocytosis and are degraded
  - decreases sensitivity of target cell to hormone
- Up-regulation
  - deficiency of hormone, produces an increase in the number of receptors
  - target tissue more sensitive to the hormone
Blocking Hormone Receptors

- Synthetic hormones that block receptors for naturally occurring hormones
  - RU486 (mifepristone) binds to the receptors for progesterone preventing it from maintaining the uterus in a pregnant woman
    - used to induce abortion
    - brings on menstrual cycle
- Hormone is prevented from interacting with its receptors and can not perform its normal functions
Circulating & Local Hormones

- Circulating hormones
  - act on distant targets
  - travel in blood

- Local hormones
  - paracrine act on neighboring cells
  - autocrines act on same cell that secreted them
Hormone Transport in Blood

- Protein hormones circulate in free form in blood
- Steroid (lipid) & thyroid hormones must attach to transport proteins synthesized by liver
  - improve transport by making them water-soluble
  - slow loss of hormone by filtration within kidney
  - create reserve of hormone
    - only .1 to 10% of hormone is not bound to transport protein = free fraction
General Mechanisms of Hormone Action

- Hormone binds to cell surface or receptor inside target cell
- Cell may then
  - synthesize new molecules
  - change permeability of membrane
  - alter rates of reactions
- Each target cell responds to hormone differently
  - liver cells---insulin stimulates glycogen synthesis
  - adipose---insulin stimulates triglyceride synthesis
**Action of Lipid-Soluble Hormones**

- Hormone diffuses through phospholipid bilayer & into cell
- Binds to receptor turning on/off specific genes
- New mRNA is formed & directs synthesis of new proteins
- New protein alters cell’s activity
Action of Water-Soluble Hormones

- Can not diffuse through plasma membrane
- Hormone receptors are integral membrane proteins
  - act as first messenger
- Receptor protein activates $G$-protein in membrane
- $G$-protein activates adenylate cyclase to convert ATP to cAMP in the cytosol
- Cyclic AMP is the 2nd messenger
- Activates kinases in the cytosol to speed up/slow down physiological responses
- Phosphodiesterase inactivates cAMP quickly
- Cell response is turned off unless new hormone molecules arrive
Second Messengers

- Some hormones exert their influence by increasing the synthesis of cAMP
  - ADH, TSH, ACTH, glucagon and epinephrine
- Some exert their influence by decreasing the level of cAMP
  - growth hormone inhibiting hormone
- Other substances can act as 2nd messengers
  - calcium ions
  - cGMP
- Same hormone may use different 2nd messengers in different target cells
Amplification of Hormone Effects

- Single molecule of hormone binds to receptor
- Activates 100 G-proteins
- Each activates an adenylate cyclase molecule which then produces 1000 cAMP
- Each cAMP activates a protein kinase, which may act upon 1000’s of substrate molecules
- One molecule of epinephrine may result in breakdown of millions of glycogen molecules into glucose molecules
Hormonal Interactions

- Permissive effect
  - a second hormone, strengthens the effects of the first
  - thyroid strengthens epinephrine’s effect upon lipolysis

- Synergistic effect
  - two hormones acting together for greater effect
  - estrogen & LH are both needed for oocyte production

- Antagonistic effects
  - two hormones with opposite effects
  - insulin promotes glycogen formation & glucagon stimulates glycogen breakdown
Control of Hormone Secretion

- Regulated by signals from nervous system, chemical changes in the blood or by other hormones
- **Negative feedback** control (most common)
  - decrease/increase in blood level is reversed
- **Positive feedback** control
  - the change produced by the hormone causes more hormone to be released
- Disorders involve either hyposecretion or hypersecretion of a hormone
Negative Feedback Systems

- Decrease in blood levels
- Receptors in hypothalamus & thyroid
- Cells activated to secrete more TSH or more T₃ & T₄
- Blood levels increase
Positive Feedback

- Oxytocin stimulates uterine contractions
- Uterine contractions stimulate oxytocin release
Hypothalamus and Pituitary Gland

- Both are master endocrine glands since their hormones control other endocrine glands
- Hypothalamus is a section of brain above where pituitary gland is suspended from stalk
- Hypothalamus receives input from cortex, thalamus, limbic system & internal organs
- Hypothalamus controls pituitary gland with 9 different releasing & inhibiting hormones
Flow of Blood to Anterior Pituitary

- Controlling hormones enter blood
- Travel through portal veins
- Enter anterior pituitary at capillaries
Human Growth Hormone

- Produced by somatotrophs
- Within target cells increases synthesis of *insulinlike growth factors* that act locally or enter bloodstream
  - common target cells are liver, skeletal muscle, cartilage and bone
- increases cell growth & cell division by increasing their uptake of amino acids & synthesis of proteins
- stimulate lipolysis in adipose so fatty acids used for ATP
- retard use of glucose for ATP production so blood glucose levels remain high enough to supply brain
Regulation of hGH

- Low blood sugar stimulates release of GNRH from hypothalamus
  - anterior pituitary releases more hGH, more glycogen broken down into glucose by liver cells

- High blood sugar stimulates release of GHIH from hypothalamus
  - less hGH from anterior pituitary, glycogen does not breakdown into glucose
Diabetogenic Effect of Human Growth Hormone

- Excess of growth hormone
  - raises blood glucose concentration
  - pancreas releases insulin continually
  - beta-cell burnout
- Diabetogenic effect
  - causes diabetes mellitus if no insulin activity can occur eventually
Thyroid Stimulating Hormone (TSH)

- Hypothalamus regulates thyrotroph cells
- Thyrotroph cells produce TSH
- TSH stimulates the synthesis & secretion of T₃ and T₄
- Metabolic rate stimulated
Follicle Stimulating Hormone (FSH)

- Releasing hormone from hypothalamus controls gonadotrophs
- Gonadotrophs release follicle stimulating hormone
- FSH functions
  - initiates the formation of follicles within the ovary
  - stimulates follicle cells to secrete estrogen
  - stimulates sperm production in testes
Luteinizing Hormone (LH)

- Releasing hormones from hypothalamus stimulate gonadotrophs
- Gonadotrophs produce LH
- In females, LH stimulates
  - secretion of estrogen
  - ovulation of 2nd oocyte from ovary
  - formation of corpus luteum
  - secretion of progesterone
- In males, stimulates interstitial cells to secrete testosterone
Prolactin (PRL)

- Hypothalamus regulates lactotroph cells
- Lactotrophs produce prolactin
- Under right conditions, prolactin causes milk production
- Suckling reduces levels of hypothalamic inhibition and prolactin levels rise along with milk production
- Nursing ceases & milk production slows
Adrenocorticotropic Hormone

- Hypothalamus releasing hormones stimulate corticotrophs
- Corticotrophs secrete ACTH & MSH
- ACTH stimulates cells of the adrenal cortex that produce glucocorticoids
Melanocyte-Stimulating Hormone

- Secreted by corticotroph cells
- Releasing hormone from hypothalamus increases its release from the anterior pituitary
- Function not certain in humans (increase skin pigmentation in frogs)
Posterior Pituitary Gland (Neurohypophysis)

- Does not synthesize hormones
- Consists of axon terminals of hypothalamic neurons
- Neurons release two neurotransmitters that enter capillaries
  - antidiuretic hormone
  - oxytocin
Oxytocin

- Two target tissues both involved in neuroendocrine reflexes

- During delivery
  - baby’s head stretches cervix
  - hormone release enhances muscle contraction
  - baby & placenta are delivered

- After delivery
  - suckling & hearing baby’s cry stimulates milk ejection
  - hormone causes muscle contraction & milk ejection
Oxytocin during Labor

- Stimulation of uterus by baby
- Hormone release from posterior pituitary
- Uterine smooth muscle contracts until birth of baby
- Baby pushed into cervix, increase hormone release
- More muscle contraction occurs
- When baby is born, positive feedback ceases
Antidiuretic Hormone (ADH)

- Known as vasopressin
- Functions
  - decrease urine production
  - decrease sweating
  - increase BP
Regulation of ADH

- Dehydration
  - ADH released
- Overhydration
  - ADH inhibited
Thyroid Gland

- On each side of trachea is lobe of thyroid
- Weighs 1 oz & has rich blood supply
Histology of Thyroid Gland

- Follicle = sac of stored hormone (colloid) surrounded by follicle cells that produced it
  - T3 & T4
- Inactive cells are short
- In between cells called parafollicular cells
  - produce calcitonin
Photomicrograph of Thyroid Gland

- Basement membrane
- Follicular cell
- Thyroid follicle
- Thyroglobulin (TGB)
- Parafollicular (C) cell
Formation of Thyroid Hormone

- Iodide trapping by follicular cells
- Synthesis of thyroglobulin (TGB)
- Release of TGB into colloid
- Iodination of tyrosine in colloid
- Formation of T3 & T4 by combining T1 and T2 together
- Uptake & digestion of TGB by follicle cells
- Secretion of T3 & T4 into blood
**Actions of Thyroid Hormones**

- **T₃ (triiodothyronine) and T₄ (thyroxine) or thyroid hormones from follicular cells**
  - **T₃ & T₄** = thyroid hormones responsible for our metabolic rate, synthesis of protein, breakdown of fats, use of glucose for ATP production

- **Calcitonin (CT) from parafollicular cells**
  - **Calcitonin** = responsible for building of bone & stops reabsorption of bone (lower blood levels of Calcium)
Control of T3 & T4 Secretion

- Negative feedback system
- Low blood levels of hormones stimulate hypothalamus
- It stimulates pituitary to release TSH
- TSH stimulates gland to raise blood levels

Key:
TRH = Thyrotropin releasing hormone
TSH = Thyroid-stimulating hormone
T₃ = Triiodothyronine
T₄ = Thyroxine (Tetraiodothyronine)
Parathyroid Glands

- 4 pea-sized glands found on back of thyroid gland
Histology of Parathyroid Gland

- Principal cells produce parathyroid hormone (PTH)
- Oxyphil cell function is unknown
Parathyroid Hormone

- Raise blood calcium levels
  - increase activity of osteoclasts
  - increases reabsorption of Ca+2 by kidney
  - inhibits reabsorption of phosphate (HPO₄)²⁻
  - promote formation of calcitriol (vitamin D₃) by kidney which increases absorption of Ca+2 and Mg+2 by intestinal tract
- Opposite function of calcitonin
High or low blood levels of Ca+2 stimulate the release of different hormones --- PTH or CT
Adrenal Glands

- One on top of each kidney
- $3 \times 3 \times 1$ cm in size and weighs 5 grams
- Cortex produces 3 different types of hormones from 3 zones of cortex
- Medulla produces epinephrine & norepinephrine
Structure of Adrenal Gland

- Cortex derived from mesoderm
- Medulla derived from ectoderm
Histology of Adrenal Gland

- **Cortex**
  - 3 zones
- **Medulla**

- Capsule
- Zona glomerulosa secretes mineralocorticoids, mainly aldosterone
- Zona fasciculata secretes glucocorticoids, mainly cortisol
- Zona reticularis secretes androgens, mainly dehydroepiandrosterone (DHEA)
- Adrenal medulla chromaffin cells secrete epinephrine and norepinephrine (NE)
Mineralocorticoids

- 95% of hormonal activity due to aldosterone

Functions
- increase reabsorption of Na+ with Cl-, bicarbonate and water following it
- promotes excretion of K+ and H+

Hypersecretion = tumor producing aldosteronism
- high blood pressure caused by retention of Na+ and water in blood
Regulation of Aldosterone
Glucocorticoids

- 95% of hormonal activity is due to cortisol
- Functions = help regulate metabolism
  - increase rate of protein catabolism & lipolysis
  - conversion of amino acids to glucose
  - stimulate lipolysis
  - provide resistance to stress by making nutrients available for ATP production
  - raise BP by vasoconstriction
  - anti-inflammatory effects reduced (skin cream)
    - reduce release of histamine from mast cells
    - decrease capillary permeability
    - depress phagocytosis
Regulation of Glucocorticoids

- Negative feedback
Androgens from Zona Reticularis

- Small amount of male hormone produced
  - insignificant in males
  - may contribute to sex drive in females
  - is converted to estrogen in postmenopausal females
Adrenal Medulla

- Chromaffin cells receive direct innervation from sympathetic nervous system
  - develop from same tissue as postganglionic neurons
- Produce **epinephrine & norepinephrine**
- Hormones are sympathomimetic
  - effects mimic those of sympathetic NS
  - cause fight-flight behavior
- Acetylcholine increase hormone secretion by adrenal medulla
Anatomy of Pancreas

- Organ (5 inches) consists of head, body & tail
- Cells (99%) in acini produce digestive enzymes
- Endocrine cells in pancreatic islets produce hormones
Cell Organization in Pancreas

- Exocrine acinar cells surround a small duct
- Endocrine cells secrete near a capillary
Histology of the Pancreas

- 1 to 2 million pancreatic islets
- Contains 4 types of endocrine cells
Cell Types in the Pancreatic Islets

- Alpha cells (20%) produce glucagon
- Beta cells (70%) produce insulin
- Delta cells (5%) produce somatostatin
- F cells produce pancreatic polypeptide
Regulation of Glucagon & Insulin Secretion

- **Low blood glucose stimulates release of glucagon**
- **High blood glucose stimulates secretion of insulin**

1. Low blood glucose (hypoglycemia) stimulates release of GLUCAGON by alpha cells
2. Glucagon acts on hepatocytes (liver cells) to:
   - convert glycogen into glucose (glycogenolysis)
   - form glucose from lactic acid and certain amino acids (gluconeogenesis)
3. Glucose released by hepatocytes raises blood glucose level to normal
4. If blood glucose continues to rise, hyperglycemia inhibits release of glucagon
5. High blood glucose (hyperglycemia) stimulates release of INSULIN by beta cells
6. Insulin acts on various body cells to:
   - accelerate facilitated diffusion of glucose into cells
   - speed conversion of glucose into glycogen (glycogenesis)
   - increase uptake of amino acids and increase protein synthesis
   - speed synthesis of fatty acids (lipogenesis)
   - slow glycogenolysis
   - slow gluconeogenesis
7. Blood glucose level falls
8. If blood glucose continues to fall, hypoglycemia inhibits release of insulin
Ovaries and Testes

- **Ovaries**
  - estrogen, progesterone, relaxin & inhibin
  - regulate reproductive cycle, maintain pregnancy & prepare mammary glands for lactation

- **Testes**
  - produce testosterone
  - regulate sperm production & 2nd sexual characteristics
Pineal Gland

- Small gland attached to 3rd ventricle of brain
- Consists of pinealocytes & neuroglia
- Melatonin responsible for setting of biological clock
- Jet lag & SAD treatment is bright light
Melatonin secretion producing sleepiness occurs during darkness due to lack of stimulation from sympathetic ganglion.
Seasonal Affective Disorder and Jet Lag

- Depression that occurs during winter months when day length is short
- Due to overproduction of melatonin
- Therapy
  - exposure to several hours per day of artificial light as bright as sunlight
  - speeds recovery from jet lag
Thymus Gland

- Important role in maturation of T cells
- Hormones produced by gland promote the proliferation & maturation of T cells
  - thymosin
  - thymic humoral factor
  - thymic factor
  - thymopoietin
Miscellaneous Hormones

Eicosanoids

- Local hormones released by all body cells
- Leukotrienes influence WBCs & inflammation
- Prostaglandins alter
  - smooth muscle contraction, glandular secretion, blood flow, platelet function, nerve transmission, metabolism etc.
- Ibuprofen & other nonsteroidal anti-inflammatory drugs treat pain, fever & inflammation by inhibiting prostaglandin synthesis
Nonsteroidal Anti-inflammatory Drugs

- Answer to how aspirin or ibuprofen works was discovered in 1971
  - inhibit a key enzyme in prostaglandin synthesis without affecting the synthesis of leukotrienes
- Treat a variety of inflammatory disorders
  - rheumatoid arthritis
- Usefulness of aspirin to treat fever & pain implies prostaglandins are responsible for those symptoms
Growth Factors

- Substances with mitogenic qualities
  - cause cell growth from cell division
- Many act locally as autocrines or paracrines
- Selected list of growth factors (Table 18.12)
  - epidermal growth factor
  - platelet-derived growth factor
  - fibroblast growth factor
  - nerve growth factor
  - tumor angiogenesis factors
  - transforming growth factors
Stress & General Adaptation Syndrome

- Stress response is set of bodily changes called general adaptation syndrome (GAS)
- Any stimulus that produces a stress response is called a stressor
- Stress resets the body to meet an emergency
  - eustress is productive stress & helps us prepare for certain challenges
  - distress type levels of stress are harmful
    - lower our resistance to infection
General Adaptation Syndrome
Alarm Reaction (Fight-or-Flight)

- Initiated by hypothalamic stimulation of sympathetic portion of the ANS & adrenal medulla
- Dog attack
  - increases circulation
  - promotes ATP synthesis
  - nonessential body functions are inhibited
    - digestive, urinary & reproductive
Resistance Reaction

- Initiated by hypothalamic releasing hormones (long-term reaction to stress)
  - corticotropin, growth hormone & thyrotropin releasing hormones
- Results
  - increased secretion of aldosterone acts to conserve Na+ (increases blood pressure) and eliminate H+
  - increased secretion of cortisol so protein catabolism is increased & other sources of glucose are found
  - increase thyroid hormone to increase metabolism
- Allow body to continue to fight a stressor
Exhaustion

- Resources of the body have become depleted
- Resistance stage can not be maintained
- Prolonged exposure to resistance reaction hormones
  - wasting of muscle
  - suppression of immune system
  - ulceration of the GI tract
  - failure of the pancreatic beta cells
Stress and Disease

- Stress can lead to disease by inhibiting the immune system
  - hypertension, asthma, migraine, gastritis, colitis, and depression
- Interleukin - 1 is secreted by macrophages
  - link between stress and immunity
  - stimulates production of immune substances
  - feedback control since immune substance suppress the formation of interleukin-1
Aging and the Endocrine System

- Production of human growth hormone decreases
  - muscle atrophy
- Production of TSH increase with age to try and stimulate thyroid
  - decrease in metabolic rate, increase in body fat & hypothyroidism
- Thymus after puberty is replaced with adipose
- Adrenal glands produce less cortisol & aldosterone
- Receptor sensitivity to glucose declines
- Ovaries no longer respond to gonadotropins
  - decreased output of estrogen (osteoporosis & atherosclerosis)
Pituitary Gland Disorders

- Hyposecretion during childhood = pituitary dwarfism (proportional, childlike body)
- Hypersecretion during childhood = giantism
  - very tall, normal proportions
- Hypersecretion as adult = acromegaly
  - growth of hands, feet, facial features & thickening of skin
Thyroid Gland Disorders

- Hyposecretion during infancy results in dwarfism & retardation called cretinism.
- Hypothyroidism in adult produces sensitivity to cold, low body temp. weight gain & mental dullness.
- Hyperthyroidism (Grave’s disease)
  - weight loss, nervousness, tremor & exophthalmos (edema behind eyes)
- Goiter = enlarged thyroid (dietary)
Cushing’s Syndrome

- Hypersecretion of glucocorticoids
- Redistribution of fat, spindly arms & legs due to muscle loss
- Wound healing is poor, bruise easily
Diabetes Mellitus & Hyperinsulinism

- Diabetes mellitus marked by hyperglycemia
  - excessive urine production (polyuria)
  - excessive thirst (polydipsia)
  - excessive eating (polyphagia)
- Type I----deficiency of insulin (under 20)
- Type II---adult onset
  - drug stimulates secretion of insulin by beta cells
  - cells may be less sensitive to hormone