Chapter 45

Hormones and the Endocrine System

Lecture Outline

Overview: The Body's Long-Distance Regulators

- An animal **hormone** is a chemical signal that is secreted into the extracellular fluid, circulates in the blood or hemolymph, and communicates regulatory messages within the body.
  - A hormone may reach all parts of the body, but only specific target cells have the receptors that enable a response.
  - A given hormone traveling in the bloodstream elicits specific responses—such as a change in metabolism—only from *its target cells* while other cells are unaffected.
- Chemical signaling by hormones is the function of the **endocrine system**, one of two basic systems for communication and regulation throughout the body.
  - Hormones secreted by endocrine cells regulate reproduction, development, energy metabolism, growth, and behavior.
- The other major communication and control system is the **nervous system**, a network of specialized cells called neurons that transmit signals along dedicated pathways.
  - These signals in turn regulate other cells, including neurons, muscle cells, and endocrine cells.
- Because signaling by neurons can regulate the release of hormones, the nervous and endocrine systems often overlap in function.

Concept 45.1 Hormones and other signaling molecules bind to target receptors, triggering specific response pathways.

- Endocrine signaling is one of several ways information is transmitted between animal cells.
  - The ways that signals are transmitted between animal cells are often classified by the type of secreting cell and the route taken by the signal in reaching its target.
- Hormones are secreted into extracellular fluids and reach target cells via the bloodstream or hemolymph.
- Endocrine signaling maintains homeostasis, mediates responses to environmental stimuli, and regulates growth and development.
  - Hormones coordinate responses to stress, dehydration, and low blood glucose levels.
  - They trigger behavioral and physical changes that underlie sexual maturity and reproduction.
- **Local regulators** are chemical signals that act over short distances, reaching their target cells by diffusion.

- For example, immune cells communicate with each other by local regulators called cytokines.
- Local regulators function in many other processes, including blood pressure regulation, nervous system function, and reproduction.

- Local regulators are divided into paracrine and autocrine signals.
    - **Paracrine** signals act on cells near the secreting cell.
    - **Autocrine** signals are secreted regulators that act on the secreting cell itself.
    - Some signals have both paracrine and autocrine activity.
- Secreted molecules are crucial for two types of signaling by neurons.
- In *synaptic signaling*, neurons form specialized junctions called synapses with target cells, such as other neurons and muscle cells.
    - At synapses, neurons secrete molecules called **neurotransmitters**, which diffuse a very short distance to bind to receptors on the target cell.
- In *neuroendocrine signaling,* specialized neurons called neurosecretory cells secrete chemical signals that diffuse from nerve cell endings into the bloodstream.
    - These signals are a class of hormones called **neurohormones**.
    - One example is ADH (antidiuretic hormone, or vasopressin), a hormone critical to kidney function and water balance.
- Members of the same animal species may communicate with **pheromones**, chemical signals released into the external environment.
    - Pheromones serve many functions, including defining territories, marking trails leading to food sources, warning of predators, and attracting potential mates.
- Some endocrine cells are found in organs and tissues that are part of other organ systems.
    - For example, the stomach contains endocrine cells.
- Other endocrine cells are grouped in ductless organs called **endocrine glands**.
    - Endocrine glands secrete hormones directly into the surrounding fluid.
    - In contrast, *exocrine glands*, such as salivary glands, have ducts that secrete substances onto body surfaces or into body cavities.

There are three groups of hormones: polypeptides, amines, and steroids.

- The polypeptide hormone insulin is made up of two polypeptide chains, formed by cleavage of a longer protein chain.
- Epinephrine and thyroxine are amine hormones, which are synthesized from a single amino acid, either tyrosine or tryptophan.
- Steroid hormones, such as cortisol and ecdysteroid, are lipids that contain four fused carbon rings. All are derived from the steroid cholesterol.
- Polypeptides and most amine hormones are water-soluble.
    - Because they are insoluble in lipids, these hormones cannot pass through cell membranes.
    - Instead, they bind to cell-surface receptors that relay information to the nucleus through intracellular pathways.
- Steroid hormones, as well as other largely nonpolar hormones such as thyroxine, are lipid-soluble and can pass through cell membranes readily.
    - Receptors for lipid-soluble hormones typically reside in the cytoplasm or nucleus.

- There are several differences in the response pathways of water-soluble and lipid-soluble hormones. One difference is the location of the target cells' signal receptors.
- Water-soluble hormones are secreted by exocytosis, travel freely in the bloodstream, and bind to cell-surface receptors.
  - Binding of water-soluble hormones to receptors induces changes in cytoplasmic molecules and may alter gene transcription.
- Lipid-soluble hormones diffuse out across the membranes of endocrine cells.
  - Outside the cell, they bind to transport proteins that keep them soluble in the aqueous environment of the bloodstream.
  - Upon leaving the bloodstream, they diffuse into target cells, bind to intracellular signal receptors, and trigger changes in gene transcription.

Epinephrine is an example of a water-soluble hormone.

- A water-soluble hormone binds to a receptor protein, triggering events at the plasma membrane that result in a cellular response such as enzyme activation, uptake or secretion of a molecule, or cytoskeletal rearrangement.
  - Cell-surface receptors may cause cytoplasmic proteins to move into the nucleus and alter the transcription of specific genes.
- The series of changes in cellular proteins that converts the extracellular chemical signal to a specific intracellular response is called **signal transduction**.
  - Signal transduction pathways involve multiple steps with specific molecular interactions.
- In response to a stressful situation, the adrenal gland secretes **epinephrine**.
- When epinephrine reaches liver cells, it binds to a G-protein-linked receptor on the plasma membrane.
  - This triggers a cascade of events involving the synthesis of cyclic AMP (cAMP) as a short-lived *second messenger*.
- cAMP activates protein kinase A, leading to activation of an enzyme required for glycogen breakdown and inactivation of an enzyme necessary for glycogen synthesis.
  - The liver releases glucose into the bloodstream, providing the fuel needed to deal with the stressful situation.

Estradiol is an example of a lipid-soluble hormone.

- Intracellular receptors for lipid-soluble hormones perform the entire task of transducing a signal within a target cell.
- Binding of a steroid hormone to its cytoplasmic receptor forms a hormone-receptor complex that moves into the nucleus.
- In the nucleus, the receptor portion of the complex alters transcription of particular genes by interacting with a specific DNA-binding protein or response element in the DNA.
- Estradiol is a form of estrogen that has a specific receptor in liver cell.
- Estradiol binds to its receptor, activating the transcription of the vitellogenin gene.
  - Following translation, vitellogenin protein is transported in the blood to the ovary, where it is used to produce egg yolk.

- Thyroxine, vitamin D, and other lipid-soluble hormones that are not steroid hormones diffuse from the bloodstream across both the plasma membrane and the nuclear membrane, binding with receptors located in the nucleus.
    - The receptor then binds to specific sites in the cell's DNA and stimulates the transcription of specific genes.
- Recent experiments indicate that lipid-soluble hormones can sometimes trigger responses at the cell surface without first entering the nucleus. How and when these responses arise are currently the subjects of active investigation.

Many hormones have multiple effects.

- Many hormones elicit many different responses in the body, depending on the target cell.
- Target cells may differ in the molecules that receive, transduce, or act upon the hormone signal.
    - For example, epinephrine simultaneously triggers glycogen breakdown in the liver, decreased blood flow to the digestive tract, and increased blood flow to major skeletal muscles.
    - All of these effects enhance the rapid reactions of the body in emergencies.
- Responding tissues vary in their expression of receptors or signal transduction pathways.
    - Target cell recognition of epinephrine involves G-protein-linked receptors.
    - β-type epinephrine receptors of liver cells activate protein kinase A, which regulates enzymes in glycogen metabolism.
    - In blood vessels supplying skeletal muscle, the same kinase activated by the same epinephrine receptor *inactivates* a muscle-specific enzyme, resulting in smooth muscle relaxation and increased blood flow.
    - Intestinal blood vessels have an α-type epinephrine receptor, which triggers a distinct signaling pathway involving a different G protein and a different enzyme.
    - The result is smooth muscle contraction and restricted blood flow to the intestines.
- Lipid-soluble hormones often exert different effects on different target cells as well.
    - The estrogen that stimulates a bird's liver to synthesize the yolk protein vitellogenin also stimulates its reproductive system to synthesize proteins that form the egg white.

Local regulators are signals that link neighboring cells or directly regulate the secreting cell.

- Local regulators can act on their target cells within seconds or milliseconds, eliciting responses more quickly than hormones can.
- Binding of local regulators to their receptors triggers events within target cells similar to those elicited by hormones.
- Several types of chemical compounds function as local regulators.
- Polypeptide local regulators include **cytokines**, which play a role in immune responses, and most **growth factors**, which stimulate cell proliferation and differentiation.
- Another important local regulator is the gas **nitric oxide (NO)**, which serves as a neurotransmitter and local regulator.
    - When the blood oxygen level falls, endothelial cells synthesize and release NO.
    - NO activates an enzyme that relaxes surrounding smooth muscle cells, dilating the walls of blood vessels and improving blood flow to tissues.

- NO plays a role in male sexual function, increasing blood flow to the penis to produce an erection.
    - Highly reactive and potentially toxic, NO usually triggers changes in the target cell within a few seconds of contact and then breaks down.
    - Viagra (sildenafil citrate) sustains an erection by prolonging activity of the NO response pathway.
- Local regulators called **prostaglandins (PGs)** are modified fatty acids, first discovered in prostate-gland secretions.
- Released by many types of cells into interstitial fluids, PGs regulate nearby cells in various ways, depending on the tissue.
    - In semen that reaches the female reproductive tract, PGs trigger the contraction of the smooth muscles of the uterine wall, helping sperm to reach the egg.
    - PGs secreted by the placenta cause the uterine muscles to become more excitable, helping to induce uterine contractions during childbirth.
    - In the immune system, PGs promote fever and inflammation and also intensify the sensation of pain. These responses contribute to the body's defense.
    - The anti-inflammatory effects of aspirin and ibuprofen are due to the drugs' inhibition of PG synthesis.
    - PGs also help regulate the aggregation of platelets, one step in the formation of blood clots. This is why people at risk for a heart attack may take daily low doses of aspirin.
    - PGs also help maintain a protective lining in the stomach, and long-term aspirin therapy can cause debilitating stomach irritation.

The endocrine and nervous systems act coordinately to control reproduction and development.

- Consider the life cycle of a butterfly.
- A butterfly larva grows in stages and periodically molts, shedding the old exoskeleton and secreting a new one.
- The signals that direct molting originate in the brain.
    - Neurosecretory cells produce *prothoracicotropic hormone* (PTTH), a polypeptide neurohormone.
    - In response to PTTH, a pair of endocrine glands behind the brain release ecdyteroid, which triggers each successive molt as well as the metamorphosis of larva into butterfly during the final molt.
- Since ecdysteroid triggers both molting and metamorphosis, what determines when metamorphosis takes place?
    - The answer is a third molecule, *juvenile hormone,* secreted by a pair of endocrine glands just behind the brain.
- Juvenile hormone modulates the activity of ecdysteroid.
    - As long as the level of juvenile hormone is high, ecdysteroid stimulates larval molting.
    - When the juvenile hormone level drops, ecdysteroid-induced molting instead produces the pupal form, within which metamorphosis occurs.
- Knowledge of endocrine signaling in insects has important applications for agricultural pest control.
    - Synthetic chemicals that bind to the ecdysteroid receptor cause insect larvae to molt prematurely and die.

Concept 45.2 Feedback regulation and antagonistic hormone pairs are common in endocrine systems.

- In a *simple endocrine pathway*, endocrine cells respond directly to an internal or environmental stimulus by secreting a particular hormone.
  - The hormone travels in the bloodstream to target cells where it interacts with its specific receptors.
- Signal transduction within target cells brings about a physiological response, which reduces the stimulus and causes the pathway to shut off.
  - Signal transduction within target cells brings about a physiological response.
- For example, the low pH of stomach contents entering the duodenum stimulates S cells, endocrine cells in the duodenum, to secrete the hormone *secretin*.
  - Secretin travels via blood vessels to target cells in the **pancreas**, causing the release of bicarbonate, which raises the pH in the duodenum.
- In a *simple neuroendocrine pathway*, the stimulus is received by a sensory neuron, which stimulates a neurosecretory cell.
  - The neurosecretory cell secretes a neurohormone, which diffuses into the bloodstream and travels to target cells.
- Such a pathway regulates milk release during nursing in mammals.
  - Suckling by an infant stimulates sensory neurons in the nipples, generating signals in the nervous system, which reach the hypothalamus.
  - Nerve impulses from the hypothalamus trigger the release of the neurohormone oxytocin from the posterior pituitary gland.
  - In response to circulating oxytocin, the mammary glands secrete milk.

A feedback loop connecting the response to the initial stimulus is characteristic of control pathways.

- The response pathway for many hormones involves **negative feedback**, a loop in which the response reduces the initial stimulus.
  - By decreasing or abolishing hormone signaling, negative feedback regulation prevents excessive pathway activity.
  - Negative feedback loops are an essential part of many hormone pathways, especially those involved in maintaining homeostasis.
- Unlike negative feedback, which dampens a stimulus, **positive feedback** reinforces a stimulus, leading to an even greater response.
- Positive feedback is important in oxytocin pathways.
  - In response to circulating oxytocin, the mammary glands secrete milk. Milk released in response to oxytocin leads to more suckling and therefore more stimulation. Activation of the pathway is sustained until the baby stops suckling.
  - When mammals give birth, oxytocin induces target cells in the uterine muscles to contract. This pathway, too, is characterized by positive-feedback regulation, such that it drives the birth process to completion.
- While positive feedback amplifies both stimulus and response, negative feedback helps restore a preexisting state.

    - The hormone pathways involved in homeostasis typically involve negative rather than positive feedback.

Homeostatic control systems may rely on pairs of negatively regulated hormone pathways, each counterbalancing the other.

- Sets of simple hormone pathways with coordinated activities form homeostatic control systems.
    - Often pathways are paired, with each providing a counterbalance for the other.
    - Regulation of blood glucose levels provides an example of such a control system.
- Metabolic balance in humans depends on maintaining blood glucose concentrations near a set point of about 90 mg/100 mL.
    - Glucose is a major fuel for cellular respiration and a key source of carbon skeletons for the synthesis of other organic compounds.
- Insulin and glucagon are antagonistic hormones that regulate the concentration of glucose in the blood.
    - When the blood glucose concentration exceeds the set point, **insulin** is released and triggers uptake of glucose from the blood into body cells, decreasing blood glucose.
    - When the blood glucose concentration falls below the set point, **glucagon** is released and promotes release of glucose into blood from liver glycogen, increasing blood glucose.
- Each hormone operates in a simple endocrine pathway regulated by negative feedback.
- Glucagon and insulin are produced in the pancreas, an organ with both endocrine and exocrine functions.
- Clusters of endocrine cells called pancreatic islets are scattered throughout the pancreas.
    - Each pancreatic islet has a population of *alpha cells*, which make glucagon, and a population of *beta cells*, which make insulin.
    - Both hormones are secreted into the extracellular fluid and enter the circulatory system.
- Hormone-secreting endocrine cells make up only 1–2% of the mass of the pancreas.
    - The pancreas is also an exocrine gland, releasing digestive enzymes and bicarbonate ions into the small intestine via the pancreatic duct.
- Insulin lowers blood glucose levels by stimulating all body cells (except brain cells) to take up glucose from the blood.
    - Brain cells can take up glucose without insulin, and have access to circulating fuel at all times.
- Insulin also decreases blood glucose levels by slowing glycogen breakdown in the liver and inhibiting the conversion of amino acids and glycerol to glucose.
- Glucagon influences blood glucose levels through its effects on target cells in the liver.
    - The liver, skeletal muscles, and adipose tissues store large amounts of fuel.
    - The liver and muscles store sugar as glycogen, whereas adipose tissue cells convert sugars to fats.
- When glucose levels decrease to below the set point, a primary effect of glucagon is to signal liver cells to increase glycogen hydrolysis, convert amino acids and glycerol to glucose, and release glucose into the circulation.
    - The net effect is to restore the blood glucose concentration to the set point, 70-110 mg/100 mL.

- The antagonistic effects of glucagon and insulin are vital to glucose homeostasis and the regulation of fuel storage and fuel consumption by body cells.
- The liver's ability to perform its vital roles in glucose homeostasis results from the metabolic versatility of its cells and its access to absorbed nutrients via the hepatic portal vein.
- A number of disorders can disrupt glucose homeostasis with potentially serious consequences, especially for the heart, blood vessels, eyes, and kidneys.
- **Diabetes mellitus** is caused by a deficiency of insulin or a decreased response to insulin in target tissues.
    - In people who have diabetes, blood glucose levels rise, but cells are unable to take up enough glucose to meet their metabolic needs.
    - Without sufficient glucose to meet the needs of most body cells, fat becomes the main substrate for cellular respiration.
    - In severe cases of diabetes, acidic metabolites formed during fat breakdown accumulate in the blood, threatening life by lowering blood pH and depleting sodium and potassium ions.
- In people with diabetes mellitus, the level of glucose in the blood may exceed the capacity of the kidneys to reabsorb it.
    - Glucose remains in the filtrate and is reabsorbed.
    - As glucose is concentrated in the urine, more water is excreted with it, resulting in excessive volumes of urine and persistent thirst.
- *Type 1 diabetes* (insulin-dependent diabetes) is an autoimmune disorder in which the immune system destroys the beta cells of the pancreas.
    - Type I diabetes usually appears in childhood and destroys the person's ability to produce insulin.
- The treatment is insulin injections, usually several times a day.
    - Human insulin is available from genetically engineered bacteria.
    - Stem cell research may someday offer a cure, introducing functional beta cells into the body.
- *Type 2 diabetes* (non-insulin-dependent diabetes) is characterized by decreased responsiveness to insulin in target cells because of some change in insulin receptors.
    - This form of diabetes occurs after age 40, and the risk increases with age.
    - Although heredity can play a role in type 2 diabetes, excess body weight and lack of exercise significantly increase the risk.
    - Type 2 diabetes accounts for more than 90% of diabetes cases.
- Many people with type 2 diabetes can manage their blood glucose level with regular exercise and a healthy diet, although some require insulin injections.
- Type 2 diabetes is the seventh most common cause of death in the United States and a growing public health problem worldwide.
- The resistance to insulin signaling in type 2 diabetes may be due to a genetic defect in the insulin receptor or the insulin response pathway.
    - In many cases, events in target cells suppress activity of an otherwise functional response pathway.
    - One source of this suppression appears to be inflammatory signals generated by the innate immune system.

- How obesity and inactivity relate to this suppression is being studied in both humans and laboratory animals.

Concept 45.3 The hypothalamus and pituitary are central to endocrine regulation.

- In vertebrates, the **hypothalamus** integrates vertebrate endocrine and nervous functions.
  - One of several endocrine glands located in the brain, the hypothalamus receives information from nerves throughout the body and brain.
  - In response, it initiates endocrine signals appropriate to environmental conditions.
- Signals from the hypothalamus travel to the **pituitary gland** located at its base.
- The **posterior pituitary** is an extension of the hypothalamus.
  - Hypothalamic axons that extend into the posterior pituitary secrete neurohormones synthesized in the hypothalamus.
- The **anterior pituitary** is an endocrine gland that synthesizes and secretes hormones.
  - Secretion of each hormone by the anterior pituitary is regulated by one or more signals from the hypothalamus.
- Neurosecretory cells of the hypothalamus synthesize two hormones: oxytocin and antidiuretic hormone (ADH).
  - These hormones travel along the long axons of neurosecretory cells to the posterior pituitary, where they are stored and released in response to nerve impulses transmitted by the hypothalamus.
- Oxytocin regulates milk secretion by the mammary glands and contractions of the uterus during birthing.
  - Oxytocin also influences behaviors related to maternal care, pair bonding, and sexual activity.
- **Antidiuretic hormone (ADH)**, or *vasopressin*, also regulates both physiology and behavior.
  - ADH acts on the kidneys to increase their water retention, thus decreasing urine volume and regulating blood osmolarity.
  - It also plays an important role in social behavior.
- Endocrine signals generated by the hypothalamus regulate hormone secretion by the anterior pituitary.
- Each hypothalamic hormone is either a *releasing hormone* or an *inhibiting hormone*, reflecting its role in promoting or inhibiting the release of one or more specific hormones by the anterior pituitary.
  - *Prolactin-releasing hormone* is a hypothalamic hormone that stimulates the anterior pituitary to secrete **prolactin (PRL)**, which stimulates milk production.
- Every anterior pituitary hormone is controlled by at least one releasing hormone.
  - Some (such as prolactin) have both a releasing hormone and an inhibiting hormone.
- Hypothalamic releasing and inhibiting hormones are secreted near capillaries at the base of the hypothalamus.
  - The capillaries drain into short portal vessels, which subdivide into a second capillary bed within the anterior pituitary.
  - Releasing and inhibiting hormones thus have direct access to the gland they control.

Hormones from the hypothalamus, anterior pituitary, and a target endocrine gland are often organized into a hormone cascade pathway.

- Signals to the brain stimulate the hypothalamus to secrete a hormone that stimulates or inhibits the release of a particular anterior pituitary hormone.
- The anterior pituitary hormone acts on a target endocrine tissue, stimulating the secretion of yet another hormone that exerts systemic metabolic or developmental effects.
- As an example of a *hormone cascade pathway*, consider the activation of the thyroid gland upon exposure of an infant to cold temperatures.
  - When the infant's body temperature drops, the hypothalamus secretes *thyrotropin-releasing hormone (TRH).*
  - TRH stimulates the anterior pituitary to secrete thyrotropin, or *thyroid-stimulating hormone (TSH)*.
  - TSH acts on the **thyroid gland** to stimulate the release of *thyroid hormone*.
  - Thyroid hormone increases the metabolic rate, raising body temperature.
- Like simple hormone pathways, hormone cascade pathways typically involve negative feedback.
  - In the thyroid hormone pathway, thyroid hormone itself carries out negative feedback.
  - Thyroid hormone blocks TSH release from the anterior pituitary and TRH release from the hypothalamus, preventing overproduction of thyroid hormone.
  - The hormone cascade pathway links the original stimulus to a self-limiting response in the target cells.

Too much or too little thyroid hormone can cause serious metabolic disorders.

- An insufficient amount of thyroid hormones is known as hypothyroidism, producing symptoms such as weight gain, lethargy, and intolerance to cold in adults.
- Hyperthyroidism is the excessive secretion of thyroid hormones, leading to high body temperature, profuse sweating, weight loss, irritability, and high blood pressure.
  - The most common form of hyperthyroidism is Graves' disease.
  - In this autoimmune disorder, the immune system produces antibodies that bind to the receptor for TSH, activating sustained thyroid hormone production.
  - Protruding eyes, caused by fluid accumulation behind the eyes, are a typical symptom.
- Malnutrition can also alter thyroid hormone production.
- The term *thyroid hormone* refers to a pair of very similar hormones derived from the amino acid tyrosine: **triiodothyronine (T_3)**, which contains three iodine atoms, and tetraiodothyronine or **thyroxin (T_4)**, which contains four iodine atoms.
  - In mammals, the same receptor molecule in the cell nucleus binds both hormones.
- The thyroid gland secretes mainly T_4, but target cells convert most of it to T_3 by removing one iodine atom.
- Although iodine is readily available from seafood or iodized salt, people in many parts of the world suffer from inadequate dietary iodine.
  - Without sufficient iodine, the thyroid gland cannot synthesize adequate amounts of T_3 and T_4.
  - The resulting low blood levels of these hormones cannot exert negative feedback on the hypothalamus and anterior pituitary.

- The pituitary continues to secrete TSH, elevating TSH levels and enlarging the thyroid into a goiter, a characteristic swelling of the neck.

- All vertebrates require thyroid hormones for normal functioning of bone-forming cells and branching of nerve cells during embryonic brain development.
  - In humans, congenital hypothyroidism, an inherited condition of thyroid deficiency, results in retarded skeletal growth and poor mental development.
  - These problems can often be remedied by treatment with thyroid hormones early in life.
  - Iodine deficiency in childhood is fully preventable if iodized salt is used in food preparation.
- A given hormone may have different effects in different species.
- Thyroxine regulates metabolism in frogs, humans, and other vertebrates.
  - In frogs, thyroxine stimulates resorption of the tadpole's tail in its metamorphosis into an adult.
- Prolactin stimulates mammary gland growth and milk production and secretion in mammals.
  - PRL also regulates fat metabolism and reproduction in birds, delays metamorphosis in amphibians, and regulates salt and water balance in freshwater fishes.
  - These varied roles suggest that prolactin is an ancient hormone whose functions have diversified during the evolution of vertebrate groups.
- **Melanocyte-stimulating hormone (MSH)** regulates the activity of pigment-containing cells in the skin of fishes, amphibians, and reptiles.
  - In mammals, MSH also acts on neurons in the brain, inhibiting hunger.
- The specialized action of MSH in the mammalian brain is of medical importance.
  - Patients with late-stage cancer, AIDS, tuberculosis, and certain aging disorders frequently suffer from a devastating wasting condition called *cachexia*.
  - Characterized by weight loss, muscle atrophy, and loss of appetite, cachexia is only poorly responsive to existing therapies.
- Activation of one brain receptor for MSH stimulates metabolism of fat and severely decreases appetite, changes also seen in cachexia.
  - This fact led scientists to hypothesize that activation of this MSH receptor causes cachexia.
  - When mice with cancerous tumors causing cachexia were treated with drugs that inhibit the brain MSH receptor, cachexia did not develop.
  - Whether such drugs can be used to treat cachexia in humans is an area of active study.

Tropic hormones regulate the function of endocrine cells or glands.

- Several tropic hormones are secreted by the anterior pituitary: thyroid-stimulating hormone (TSH), **follicle-stimulating hormone (FSH)**, **luteinizing hormone (LH)**, and **adrenocorticotropic hormone (ACTH)**.
  - FSH and LH are also called *gonadotropins* because they stimulate the activities of the gonads. Their hypothalamic regulator is called *gonadotropin-releasing hormone* (*GnRH*).
  - ACTH stimulates the production and secretion of steroid hormones by the adrenal cortex.
- **Growth hormone (GH)**, which is secreted by the anterior pituitary, acts on a wide variety of target tissues with both tropic and nontropic effects.

- The major tropic action of GH is to signal the liver to release *insulin-like growth factors (IGFs)*, which circulate in the blood and directly stimulate bone and cartilage growth.
- In the absence of GH, the skeleton of an immature animal stops growing.
- GH also exerts diverse metabolic effects that raise blood glucose levels, opposing the effects of insulin.

- Abnormal production of GH can produce several disorders.
  - Gigantism is caused by hypersecretion (excessive GH production) during development.
  - Acromegaly is caused by GH hypersecretion during adulthood, resulting in an overgrowth of the adult target cells in the face, hands, and feet.
  - Pituitary dwarfism is caused by childhood GH hyposecretion and can be treated successfully by genetically engineered GH.

Concept 45.4 Endocrine glands respond to diverse stimuli in regulating homeostasis, development, and behavior.

- The regulation of calcium ion concentration in the circulatory system is another example of a simple hormone pathway.

Parathyroid hormone, vitamin D, and calcitonin balance blood calcium.

- Rigorous homeostatic control of blood calcium levels is critical because calcium ions (Ca^{2+}) are essential to the normal functioning of all cells.
  - If the blood Ca^{2+} level falls substantially, skeletal muscles begin to contract convulsively, a potentially fatal condition called tetany.
  - If the blood Ca^{2+} level rises substantially, precipitates of calcium phosphate can form in body tissues, leading to widespread organ damage.
- In mammals, the **parathyroid glands**, a set of four small glands embedded on the surface of the thyroid, play a major role in blood Ca^{2+} regulation near a set point of about 10 mg/100 mL.
- When the blood Ca^{2+} concentration falls below the set point, the glands release **parathyroid hormone (PTH)**.
- PTH raises the level of blood Ca^{2+} by direct and indirect effects.
  - PTH causes the mineralized matrix of bone to decompose, releasing Ca^{2+} into the blood.
  - In the kidneys, PTH directly stimulates reabsorption of Ca^{2+} through the renal tubules.
- PTH also has an indirect effect on the kidneys, promoting the conversion of vitamin D, a steroid-derived molecule, to an active hormone.
  - An inactive form of vitamin D is obtained from food or synthesized in the skin.
  - Activation of vitamin D begins in the liver and is completed in the kidneys, a process stimulated by PTH.
  - The active form of vitamin D acts directly on the intestines, stimulating the uptake of Ca^{2+} from food and augmenting the effect of PTH.
- As the blood Ca^{2+} level rises, a negative feedback loop inhibits further release of PTH from the parathyroid glands.
- The thyoid gland also contributes to calcium homeostasis.

- If the blood Ca^{2+} level rises above the set point, the thyroid gland releases **calcitonin**, a hormone that inhibits bone resorption and enhances Ca^{2+} release by the kidney.
- In rodents and fishes, calcitonin is required for Ca^{2+} homeostasis.
- In humans, however, calcitonin is apparently required only during the extensive bone growth of childhood.

Adrenal hormones coordinate the response to stress.

- The **adrenal glands** are located adjacent to the kidneys.
  - In mammals, each adrenal gland is actually made up of two glands with different cell types, functions, and embryonic origins.
  - The *adrenal cortex* is the outer portion, and the *adrenal medulla* is the central portion.
- Like the pituitary, the adrenal gland is a fused endocrine and neuroendocrine gland.
  - The adrenal cortex consists of true endocrine cells, whereas the secretory cells of the adrenal medulla derive from neural tissue during embryonic development.
- The adrenal medulla produces two hormones: epinephrine (adrenaline) and **norepinephrine** (noradrenaline).
  - These hormones are members of a class of hormones, the **catecholamines**, amines that are synthesized from the amino acid tyrosine.
  - Both hormones are also neurotransmitters in the nervous system.
- Either positive or negative stress stimulates the secretion of epinephrine and norepinephrine from the adrenal medulla.
- These hormones act directly on several target tissues to give the body a rapid bioenergetic boost.
  - They increase the rate of glycogen breakdown in the liver and skeletal muscles, promote glucose release into the blood by liver cells, and stimulate the release of fatty acids from fat cells.
  - The released glucose and fatty acids circulate in the blood and can be used by the body as fuel.
- Epinephrine and norepinephrine also exert profound effects on the cardiovascular and respiratory systems.
  - These hormones increase heart rate and the stroke volume of the heartbeat and dilate the bronchioles in the lungs to increase the rate of oxygen delivery to body cells.
  - Physicians sometimes prescribe epinephrine as a heart stimulant or to open the airway during an asthma attack.
  - Catecholamines also act to shunt blood away from the skin, digestive organs, and kidneys and to increase the blood supply to the heart, brain, and skeletal muscles.
- Epinephrine generally has a stronger effect on heart and metabolic rates, while the primary role of norepinephrine is in modulating blood pressure.
- Secretion of these hormones by the adrenal medulla is stimulated by nerve signals carried from the brain via involuntary (autonomic) neurons.
  - Acting on target tissues, epinephrine and norepinephrine each function in a simple neurohormone pathway.
- Hormones from the adrenal cortex also function in the body’s response to stress.

- In contrast to the adrenal medulla, which reacts to nervous input, the adrenal cortex responds to endocrine signals.

- Stressful stimuli cause the hypothalamus to secrete a releasing hormone that stimulates the anterior pituitary to release the tropic hormone ACTH.
- When ACTH reaches the adrenal cortex via the bloodstream, it stimulates the endocrine cells to synthesize and secrete a family of steroids called **corticosteroids**.
- The two main types of corticosteroids in humans are *glucocorticoids* and *mineralocorticoids*.
- Both hormones help maintain homeostasis when stress is experienced over a long period of time.
- The primary effect of **glucocorticoids** is on bioenergetics, specifically on glucose metabolism.
    - Glucocorticoids make more glucose available as fuel.
    - Glucocorticoids, such as cortisol, act on skeletal muscle, causing a breakdown of muscle proteins.
    - The resulting amino acids are transported to the liver and kidneys, where they are converted to glucose and released into the blood.
    - The synthesis of glucose from muscle proteins provides circulating fuel when body activities require more than the liver can metabolize from its metabolic stores.
- Cortisol and other glucocorticoids also suppress certain components of the body's immune system.
    - Because of their anti-inflammatory effect, glucocorticoids have been used to treat inflammatory diseases such as arthritis.
    - However, long-term use of these hormones can have serious side effects due to their metabolic actions and can also increase susceptibility to infection.
    - Nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin or ibuprofen, generally are preferred for treating chronic inflammatory conditions.
- **Mineralocorticoids** act principally on salt and water balance.
    - For example, *aldosterone* functions in ion and water homeostasis of the blood.
    - Low blood volume or pressure leads to the production of angiotensin II, which stimulates the secretion of aldosterone.
    - Aldosterone stimulates cells in the kidneys to reabsorb sodium ions and water from filtrate, thus raising blood pressure and volume.
    - When an individual is under severe stress, the resulting rise in blood ACTH levels can increase the rate at which the adrenal cortex secretes aldosterone as well as glucocorticoids.

Sex hormones regulate growth, development, reproductive cycles, and sexual behavior.

- The hormone products of the adrenal cortex include small amounts of the steroid hormones that function as sex hormones.
- Small structural differences between steroid hormones are associated with major differences in effect.
- The sex hormones produced by the adrenal cortex are mainly "male" hormones (androgens), with small amounts of "female" hormones (estrogens and progestins)
    - Androgens secreted by the adrenal cortex may account for the female sex drive.

- The gonads are the primary source of the sex hormones, producing and secreting three major categories of steroid hormones: androgens, estrogens, and progestins.
    - All three types are found in both males and females but in different proportions.
- The testes primarily synthesize **androgens**, the main one being **testosterone**.
    - Androgens promote the development and maintenance of male sex characteristics.
    - Androgens produced early in development determine whether a fetus develops as a male or a female.
    - At puberty, high levels of androgens are responsible for the development of male secondary sex characteristics, including male patterns of hair growth, a low voice, and increased muscle mass and bone mass typical of males.
- The muscle-building action of testosterone and other anabolic steroids has led some athletes to take them as supplements.
    - Abuse of these hormones carries many health risks, and they are banned in most competitive sports.
    - Anabolic steroids can cause severe acne, liver damage, and significant decreases in sperm count and testicular size.
- **Estrogens**, the most important being **estradiol**, are responsible for the development and maintenance of the female reproductive system and the development of female secondary sex characteristics.
- In mammals, **progestins**, which include **progesterone**, promote the growth of the uterine lining, which supports the growth and development of an embryo.
- Estrogens, progestins, and androgens are components of hormone cascade pathways.
    - Their secretion is controlled by gonadotropins (FSH and LH) from the anterior pituitary gland.
    - FSH and LH production is controlled by a releasing hormone from the hypothalamus, GnRH (gonadotropin-releasing hormone).
- Between 1938 and 1971, some pregnant women at risk for complications were prescribed a synthetic estrogen called diethylstilbestrol (DES). This hormone can alter reproductive system development in the fetus.
    - Daughters of women who took DES are at risk of a number of reproductive abnormalities, including a form of vaginal and cervical cancer, structural changes in the reproductive organs, and increased risk of miscarriage (spontaneous abortion).
    - DES is an *endocrine disruptor*, a foreign molecule that interrupts the normal function of a hormone pathway.
- In recent years, it has been hypothesized that molecules in the environment also act as endocrine disruptors.
    - Some estrogen-like molecules, such as those present in soybeans and other edible plant products, may lower breast cancer risk.
    - Others, such as bisphenol A, a chemical used in making some plastics, may interfere with normal reproduction and development.

The pineal gland is involved in biorhythms.

- The **pineal gland** is a small mass of tissue near the center of the mammalian brain that is a primary source of the hormone **melatonin**, a modified amino acid.

- The primary functions of melatonin are related to biological rhythms associated with reproduction and activity.
- Melatonin secretion is regulated by light/dark cycles.
    - Melatonin is secreted at night, and the amount secreted depends on the length of the night.
    - In winter, when days are short and nights are long, more melatonin is secreted.
- Nightly increases in the levels of melatonin also play a significant role in promoting sleep.
- Pineal gland release of melatonin is controlled by a group of neurons in the hypothalamus called the suprachiasmatic nucleus (SCN), which functions as a biological clock.
    - The SCN receives input from specialized light-sensitive neurons in the retina of the eye.
    - Although the SCN regulates melatonin production during the 24-hour light-dark cycle, melatonin also influences SCN activity.
- Much remains to be learned about the precise role of melatonin and about biological clocks in general.