Chapter 45 - Hormones and the Endocrine System

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 from its target cells—such as a change in metabolism—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 chemical signals bind to target receptors, triggering specific response pathways.

- Hormones and other chemical signals trigger responses by binding to specific receptor proteins in or on target cells.
  - Only cells with receptors for a particular signal are target cells; other cells are unresponsive to that signal.

- Signals are often classified by the type of secreting cell and the route taken by the signal in reaching its target.

- Endocrine signals, or hormones, are secreted into extracellular fluids and reach target cells via the bloodstream or hemolymph.

- Some endocrine cells are found in organs and tissues that are part of other organ systems.
  - For example, the stomach and kidney both contain endocrine cells.

- Other endocrine cells are grouped in ductless organs called **endocrine glands**.
  - Like isolated endocrine cells, 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.

- Hormones serve a range of functions in the body.
  - Hormones maintain steady-state conditions; mediate responses to environmental stimuli; and regulate growth, development, and reproduction.
  - Hormones coordinate responses to stress, dehydration, and low blood glucose levels.

    - They also control the appearance of characteristics that distinguish juveniles from adults.

- **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.

- Chemical signals play a critical role in the transmission of information by neurons.
- Neurons communicate with target cells in other neurons and muscles at specialized junctions known as synapses.
- At many synapses, neurons secrete chemical signals called **neurotransmitters,** which diffuse a very short distance to bind receptors on the target cell.

- *Neurosecretory cells*, specialized neurons in the brain, 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 marking trails leading to food sources, warning of predators, and attracting potential mates.

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

- Polypeptides and many amine hormones are water-soluble.
- Because they are insoluble in lipids, these hormones cannot pass through cell membranes.

- Steroid hormones, as well as other largely nonpolar hormones such as thyroxine, are lipid-soluble and can pass through cell membranes readily.

- Whether or not a hormone is able to cross cell membranes influences the location of receptors in target cells.

- Evidence for intracellular receptors for steroid hormones was discovered in the 1960s.
- Researchers demonstrated that estrogen and progesterone accumulate within the nuclei of cells in the reproductive tract of female rats but not in the nuclei of cells in tissues that do not respond to estrogen.

- These observations led to the hypothesis that cells sensitive to steroid hormones contain internal receptor molecules that bind the hormones.
- Researchers have since identified the intracellular protein receptors for other steroid hormones and lipid-soluble hormones such as thyroxine.

- Studies that show binding of radioactive water-soluble hormones to isolated cell membranes support the hypothesis that receptors for such hormones are located on the cell membrane.

- John Horowitz and his colleagues investigated the location of receptors for the water-soluble hormone melanocyte-stimulating hormone (MSH).
    - In frogs, MSH controls the location of pigment granules in skin cells.

    - The investigators microinjected tiny amounts of MSH into skin cells or surrounding fluid.
    - MSH triggered a response only if it was allowed to bind to cell-surface receptors.

- There are several differences in the response pathways of water-soluble and lipid-soluble hormones.

- 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 and travel in the bloodstream bound to transport proteins.
    - Upon diffusing into target cells, lipid-soluble hormones bind to 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 on and inside 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 signal, or *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.

- For lipid-soluble hormones, intracellular receptors 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 interacts with DNA or with a DNA-binding protein, stimulating the transcription of specific genes.

- Estradiol is a form of estrogen that has a specific receptor in the liver of female birds and frogs.
- 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, 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 act through protein kinase A to regulate 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 express an α-type epinephrine receptor.
  - The α-type receptor triggers a distinct signaling pathway involving a different G protein and a different enzyme, resulting in smooth muscle contraction and restricted blood flow.

- 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.

- A given hormone may have different effects in different *species*.

  - For example, 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.

Local regulators are signals that link neighboring cells or provide feedback to 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 neighboring 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 interfering with the breakdown of NO.

- Local regulators called **prostaglandins (PGs)** are modified fatty acids, first discovered in prostate-gland secretions.
    - Released by most 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.

Concept 45.2 Negative feedback and antagonistic hormone pairs are common features of the endocrine system.

- Endocrine cells secrete hormones in response to internal or environmental stimuli.
- The hormone travels in the bloodstream and binds to its specific receptor in or on its target cells.
- Signal transduction within target cells brings about a physiological response, which reduces the stimulus and causes the pathway to shut off.
- Finally, the response reduces the stimulus and the pathway shuts off.

- 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.

- The response pathway for secretin (and many other 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.

- Simple hormone pathways are widespread among animals.
- 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.
    - Metabolic balance is crucial for bioenergetics and homeostasis because 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 lowers the concentration.
- When the blood glucose concentration falls below the set point, **glucagon** is released and its effects increase the

concentration.

- Each hormone operates in a simple endocrine pathway regulated by negative feedback.

- The **pancreas** has both endocrine and exocrine functions.
    - Its exocrine function is the secretion of bicarbonate ions and digestive enzymes, which are released into small ducts and carried to the small intestine via the pancreatic duct.
    - Tissues and glands that discharge secretions into ducts are described as *exocrine*.

- Glucagon and insulin are produced in the pancreas.
- Clusters of endocrine cells, the **islets of Langerhans**, are scattered throughout the pancreas.
- Each islet has a population of *alpha cells,* which produce the hormone glucagon, and a population of *beta cells,* which produce the hormone 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.
    - The liver is a key fuel-processing center because only liver cells are sensitive to glucagon.

- When glucose levels decrease to below the set point, glucagon signals the 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 approximately 90 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.

- **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.

- The high level of glucose in the blood exceeds 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.

Concept 45.3 The endocrine and nervous systems act individually and together to regulate an animal's physiology.

Invertebrate endocrine and nervous systems are integrated in the control of reproduction and development.

- In the mollusc *Aplysia*, specialized nerve cells secrete egg-laying hormone, which stimulates the laying of thousands of eggs and inhibits feeding and locomotion, activities that interfere with reproduction.

- Hormones control the metamorphosis of the caterpillar (a larva) into the adult butterfly but also regulate the development of the newly hatched egg into the fully grown caterpillar.
    - During its development, the larva grows in stages.
    - The larva must periodically molt, shedding the old exoskeleton and secreting a new one.

- The hormonal control of insect development is well understood.

- Neurosecretory cells in the brain produce *prothoracicotropic hormone (PTTH),* a peptide neurohormone.
- In response to PTTH, the prothoracic glands, a pair of endocrine glands just behind the brain, release **ecdysone**.
    - Ecdysone promotes molting and the development of adult characteristics.

- A pair of small endocrine glands behind the brain, the corpora allata, secretes a third signal, **juvenile hormone**.
    - As the name suggests, juvenile hormone promotes the retention of larval (juvenile) characteristics.

- Juvenile hormone influences development indirectly by modifying the activity of ecdysone.

    - In the presence of a high level of juvenile hormone, ecdysone stimulates molting, but the product is simply a larger larva.
    - When the level of juvenile hormone decreases, ecdysone-induced molting produces a pupa.
    - Within the pupa, metamorphosis produces the adult form.

- Synthetic juvenile hormone is used as an insecticide to prevent insects from maturing to reproductive adults.

Animals have two systems of internal communication and regulation: the nervous system and the endocrine system.

- The **hypothalamus** integrates vertebrate endocrine and nervous functions.
- This region of the lower brain receives information from nerves throughout the body and from other parts of the brain, and initiates endocrine signals appropriate to environmental conditions.

- Signals from the hypothalamus travel to the **pituitary gland** located at its base.

- The **posterior pituitary**, or *neurohypophysis*, stores and secretes two hormones made by the hypothalamus.

- The **anterior pituitary**, or *adenohypophysis***,** develops from a fold of tissue at the roof of the embryonic mouth.
    - This tissue grows upward toward the brain and eventually loses its connection to the mouth.

- Hormones released by the hypothalamus regulate the secretion of hormones by the anterior pituitary.
    - Several of these hormones have other endocrine glands as their targets.

- The posterior pituitary releases two hormones: oxytocin and antidiuretic hormone (ADH).
- Synthesized in the hypothalamus, these hormones travel along the long axons of neurosecretory cells to the posterior pituitary, where they are stored and released as needed.

- **Oxytocin** regulates the release of milk during nursing, a function mediated by a simple neurohormone pathway.
    - In a neurohormone pathway, a stimulus received by a sensory neuron stimulates a neurosecretory cell, which then secretes a neurohormone.
    - The neurohormone diffuses into the bloodstream and travels to target cells.

- Stimulation of sensory nerve cells in the mother's nipples by a baby's suckling generates nervous signals that eventually reach the hypothalamus.
- A nerve impulse from the hypothalamus then triggers the release of oxytocin from the posterior pituitary gland.
- In response to circulating oxytocin, the mammary glands secrete milk.

- Oxytocin signaling exhibits **positive feedback**.
- Unlike negative feedback, which dampens a stimulus, positive feedback reinforces a stimulus, leading to an even greater response.
    - Oxytocin stimulates the release of milk, which leads to more suckling and more stimulation.
    - Activation of the pathway is sustained until the baby stops suckling.

- Oxytocin has several additional roles related to reproduction.

- During birthing in mammals, oxytocin induces target cells in the uterine muscles to contract.
    - This pathway has positive feedback regulation, driving birthing to completion.

- Oxytocin also functions in regulating mood and sexual arousal in both males and females.

- **Antidiuretic hormone (ADH)**, or *vasopressin*, regulates the osmolarity of the blood.
- ADH acts on the kidneys to increase their water retention, thus decreasing urine volume.

- The anterior pituitary synthesizes and secretes many different hormones and is regulated by the hypothalamus.

- Each hypothalamic hormone is considered 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.
    - *Thyrotropin-releasing hormone (TRH)* is a product of the hypothalamus that stimulates the anterior pituitary to secrete thyrotropin, or *thyroid-stimulating hormone (TSH)*.
    - Every anterior pituitary hormone is controlled by at least one releasing hormone.
    - Some anterior pituitary hormones 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 TRH.
    - TRH targets the anterior pituitary, which responds by secreting 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.

- TSH functions as a *tropic hormone*, regulating the function of endocrine cells or glands.

- Three other tropic hormones are secreted by the anterior pituitary: **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.
    - ACTH stimulates the production and secretion of steroid hormones by the adrenal cortex.

- Two nontropic hormones are produced by the anterior pituitary: prolactin and melanocyte-stimulating hormone (MSH).

- **Prolactin (PRL)** 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 some fishes, amphibians, and reptiles.
- In mammals, MSH acts on neurons in the brain, inhibiting hunger.

- **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 metabolism, homeostasis, development, and behavior.

In vertebrates, thyroid hormone regulates both homeostasis and development.

- In mammals, thyroid hormone regulates bioenergetics; helps maintain normal blood pressure, heart rate, and muscle tone; and regulates digestive and reproductive functions.

- The **thyroid gland** of mammals consists of two lobes located on the ventral surface of the trachea.
- The term *thyroid hormone* refers to two 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 thyroid secretes mainly T_4, but target cells convert most of it to T_3 by removing one iodine atom.
  - The same receptor molecule in the cell nucleus binds both hormones.

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

- 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.

- An insufficient amount of thyroid hormones is known as hypothyroidism, producing symptoms such as weight gain, lethargy, and intolerance to cold in adults.

- Proper thyroid function requires dietary iodine, readily obtained from seafood or iodized salt.
  - 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.

- In vertebrates, thyroid hormones play a variety of roles in development and maturation.

  - Thyroid hormones control the metamorphosis of a tadpole into a frog, with major reorganization of many different tissues.

- 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.

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

- In addition to cells that produce T_3 and T_4, the mammalian thyroid gland produces **calcitonin.**

- Calcitonin acts in conjunction with parathyroid hormone to maintain calcium homeostasis.

- 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, 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 thyroid gland can also contribute 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 some vertebrates, calcitonin makes a significant contribution to 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 the neural crest 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.

- The adrenal medulla hormones act 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 is a homeostatic mechanism that 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.

- All the steroid hormones are synthesized from cholesterol, and their structures differ in minor ways.
    - These small differences 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.
    - Among other effects, anabolic steroids have a negative feedback effect on testosterone production, causing 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).

The pineal gland is involved in biorhythms.

- The **pineal gland** is a small mass of tissue near the center of the mammalian brain.
- The pineal gland synthesizes and secretes the hormone **melatonin**, a modified amino acid.

- Depending on the species, the pineal gland contains light-sensitive cells or has nervous connections from the eyes that control its secretory activity.
- The primary functions of melatonin are related to biological rhythms associated with reproduction.

- Melatonin secretion is regulated by light/dark cycles.
    - Melatonin is secreted at night, and the amount secreted depends on the length of the night.
    - Thus, melatonin production is a link between a biological clock and daily or seasonal activities such as reproduction.
    - Recent evidence suggests that the main target cells of melatonin are the part of the brain called the suprachiasmatic nucleus (SCN), which functions as a biological clock.
    - Melatonin seems to decrease the activity of neurons in the SCN, and this may be related to its role in mediating rhythms.

- Much remains to be learned about the precise role of melatonin and about biological clocks in general.