

2I. Endocrine System

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Focus Questions—to Guide Your Reading of This Chapter

1. How is the endocrine system different from the nervous system?
2. How do endocrine gland structure and complexity change through the evolution of vertebrates?
3. What are the main hormones secreted by each major endocrine gland? What are each hormone's main functions, and how do they differ across vertebrate taxa?
4. What endocrine glands and hormones are part of the following hormonal axes: (a) hypothalamic-pituitary-thyroid (HPT) axis, (b) hypothalamic-pituitary-adrenal (HPA) axis, and (c) hypothalamic-pituitary-gonadal (HPG) axis?

2I.1 Introduction

There are two major control systems in the body: the nervous system (covered in detail in [Chapters 19](#) and [20](#)) and the endocrine system. These two systems frequently work together to coordinate

organ activity and maintain **homeostasis** or a stable internal physiological state.

The endocrine system is composed of a series of **endocrine glands** that are spread throughout the body (Figure 21.1). Unlike **exocrine glands** (e.g., sweat glands, sebaceous glands; see [Chapter 6](#)), which deposit their products on the body's surface or into organs through ducts and act only in the immediate vicinity of the gland, endocrine glands produce chemical messengers known as **hormones**, which can affect the function of body parts far removed from the gland's location. Such far-reaching effects are possible because endocrine glands deposit hormones into circulating body fluids (typically the bloodstream but also occasionally the lymph or cerebrospinal fluid). The hormones are then transported throughout the body to act on their target tissues. Target tissues must express **receptors** specific to that hormone for it to affect the function of the target.

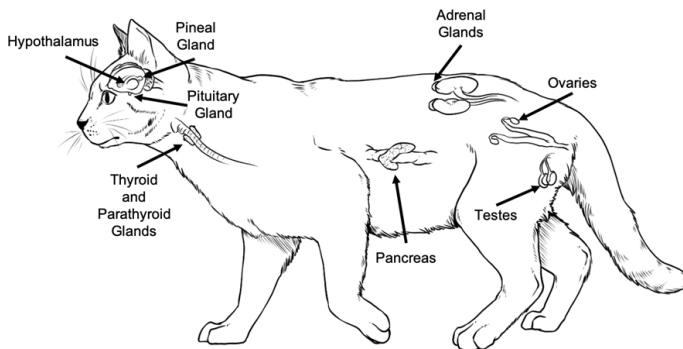


Figure 21.1—Overview of the major endocrine glands evolutionarily conserved across vertebrates.

We know at this point that form and function go hand in hand, so it should come as no surprise that endocrine glands and exocrine glands have some basic structural differences related to

their different functions. The primary structural difference between these two gland types is the presence or absence of a duct through which products are released. Exocrine glands contain ducts that may be simple (i.e., a singular duct) or compound (i.e., a branched duct), and their products are released into these ducts for transport to the epithelial surface they act on (Figure 21.2). Again, because the products of exocrine glands are released at a specific site, they can only act locally and within the general vicinity of the gland itself. Endocrine glands, in contrast, lack ducts entirely. Instead, these glands tend to be highly vascularized, so their products can diffuse directly into the capillary beds and then be transported throughout the body via the bloodstream (Figure 21.2). Because endocrine products can be transported throughout the body via the bloodstream, these glands can act globally (i.e., impact areas of the body beyond the immediate vicinity of the gland).

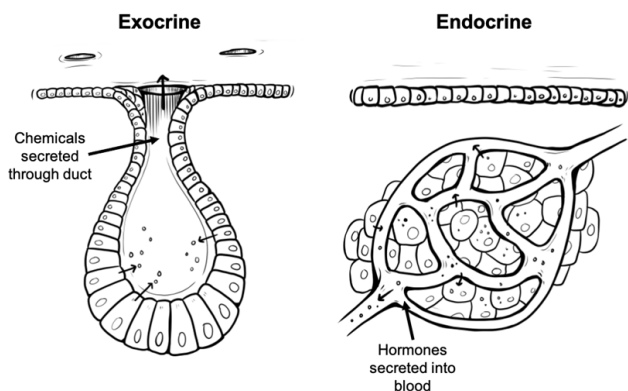


Figure 21.2—Structural differences between exocrine and endocrine glands.

The effects of hormones on target tissues can be categorized as activational or organizational depending on the stage of development or age of the organism at the time of hormone exposure. **Activational effects** of hormones are temporary and

reversible changes in the organism's physiology and/or behavior. These activational effects occur when hormones secreted at certain levels or times of the year in the bloodstream act on target tissues to regulate their function. For example, increased testosterone secretion in adult testes-bearing songbirds during the breeding season can lead to increased aggression, territory defense, and courtship behavior; however, testosterone levels decrease in the nonbreeding season and these behaviors are not expressed as intensely or frequently. **Organizational effects** of hormones occur during critical periods of development (i.e., prenatal or early postnatal stages) and permanently shape anatomical, physiological, and/or behavioral traits. For example, exposure to certain sex steroid hormones (e.g., androgens and estrogens) during fetal development can permanently influence the sexual differentiation of the brain and reproductive organs (e.g., gonads). Thus, it is important to consider the age and stage of development of the vertebrate in question at the time of hormone exposure when discussing the functions of hormones.

Hormones can be classified as **protein hormones** (water-soluble; Figure 21.3A) or **steroid hormones** (lipid-soluble; Figure 21.3B). The chemical properties associated with each class of hormone determine how they are produced and stored in endocrine cells in addition to their mode of action (i.e., which types of receptors they bind to on target cells). Protein hormones are made of amino acids that form hydrophilic (i.e., attracted to or soluble in water) polypeptides. Depending on their size (i.e., number of amino acids), these hydrophilic hormones can be categorized as amines, peptides, or proteins. Glycoproteins are another class of hydrophilic hormone, which are proteins with oligosaccharide chains (glycans) bonded covalently to the amino acids. Steroid hormones are derived from cholesterol, creating hydrophobic (i.e., repelled by water or insoluble in water) molecules. Protein hormones are synthesized in the endoplasmic reticulum of endocrine cells where they undergo posttranslational modifications and are stored in secretory vesicles (i.e., membrane-bound organelles that carry proteins, peptides, or

neurotransmitters to the exterior of a cell). Because they can be stored in advance (i.e., require active transport out of cell membranes), protein hormones generally elicit rapid responses by binding to membrane-bound receptors on the outside of the target cell. Due to their lipophilic (i.e., attracted to or soluble in fats and oils) structure, steroid hormones can easily diffuse out of the cell membrane; therefore, the effects of steroid hormones are slower and more prolonged, as they cannot be stored in advance. Steroid hormones typically bind to intracellular receptors on the nucleus, but some do bind extracellular membrane-bound receptors. Last, protein hormones circulate through the bloodstream in their unbound form because they can dissolve in the blood, whereas steroid hormones require carrier proteins for transport in the bloodstream.

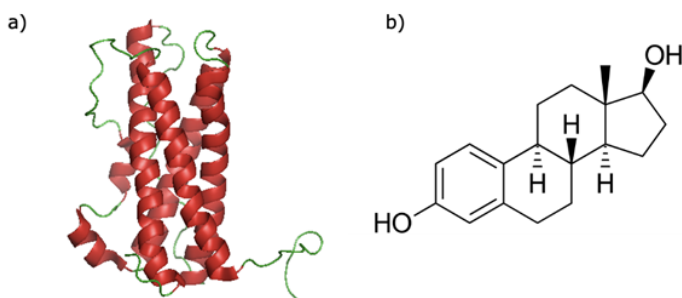


Figure 21.3—Protein versus steroid hormones including (a) prolactin (protein hormone) and (b) estradiol (steroid hormone).

How does the body naturally keep hormone levels within a specified range? Positive and negative feedback are two mechanisms by which the endocrine system promotes or inhibits hormone secretion, respectively. In **negative feedback**, increasing levels of a hormone initiate physiological responses that eventually inhibit the secretion of that hormone. Once circulating hormones rise to a certain threshold, the binding of the hormone to receptors

on various endocrine glands signals to those glands to shut off production of the target hormone or other hormones in a hormonal axis. For example, the adrenal glands secrete glucocorticoid hormones in response to stressful stimuli (Figure 21.4). Once glucocorticoid levels pass a threshold concentration in the blood, glucocorticoids bind to receptors on the adrenal gland to shut off their own production but also bind to receptors on the pituitary gland and hypothalamus that each secrete other hormones that stimulate glucocorticoid secretion from the adrenal glands. We will cover this topic in more detail when we discuss the hypothalamic-pituitary-adrenal (HPA) axis. In **positive feedback**, increasing levels of a hormone continue to promote secretion of that hormone. For example, as labor progresses in humans, oxytocin is released from the pituitary gland in response to uterine contractions. Oxytocin stimulates further contractions, leading to more oxytocin release. This positive feedback loop continues until childbirth is completed.

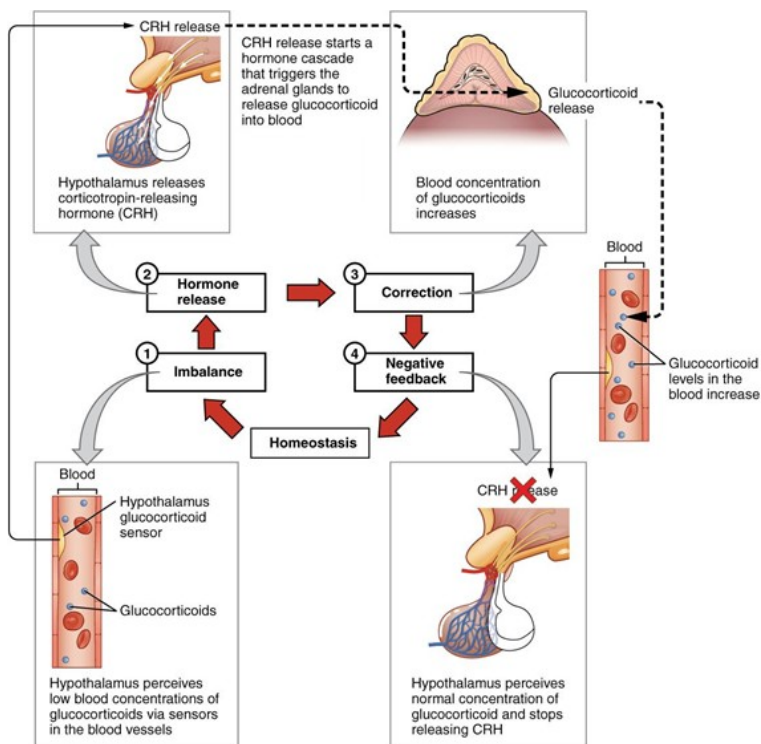


Figure 21.4—Negative feedback loop for glucocorticoid hormones.

In this chapter, we will survey the major endocrine glands of the vertebrate body, looking at their structures, development, and evolution. Because these glands are tightly integrated with other systems, we will link back to other chapters in this textbook for details related to function.

21.2 Hypothalamus and Pituitary Gland

Structure and Function

The **hypothalamus** and **pituitary gland** are considered the masters of the endocrine system because they coordinate numerous homeostatic processes throughout vertebrates (Figure 21.5).

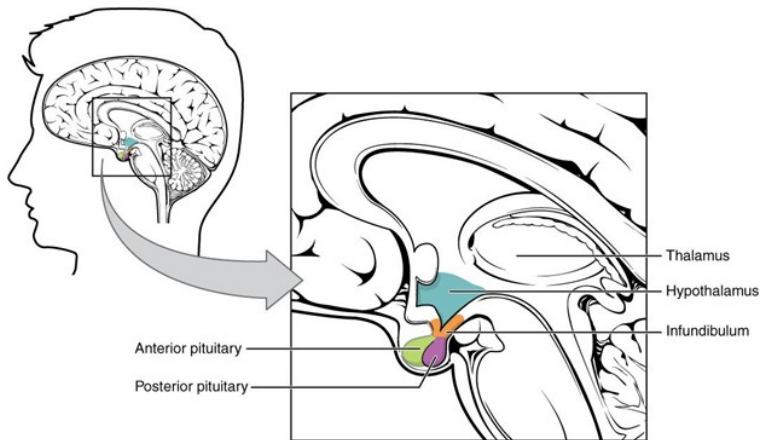


Figure 21.5—Location of the hypothalamus and pituitary gland in a human.

Together they form **hypothalamus-pituitary (HP) axes** that control the functions of other peripheral endocrine glands such as the thyroid gland (**hypothalamic-pituitary-thyroid [HPT] axis**), adrenal gland (**hypothalamic-pituitary-adrenal [HPA] axis**), and gonads (**hypothalamic-pituitary-gonadal [HPG] axis**). **Neurosecretory neurons** (i.e., neurons that secrete neurohormones into the blood) in the hypothalamus secrete **hypothalamic releasing** or **inhibiting hormones**, which regulate secretion of **tropic hormones** (i.e., hormones that have other endocrine glands as their targets) from the pituitary gland. These hypothalamic hormones travel to the pituitary via two routes: (1) release into the **median eminence** at the base of the hypothalamus, which contains a portal capillary system that vascularizes the anterior pituitary; or (2) direct axon innervation into the posterior pituitary. The tropic hormones are released from the pituitary into the bloodstream where they

travel to peripheral endocrine glands (Figure 21.6). The peripheral endocrine glands will release their hormones into the blood to target other endocrine or nonendocrine tissues with corresponding target receptors.

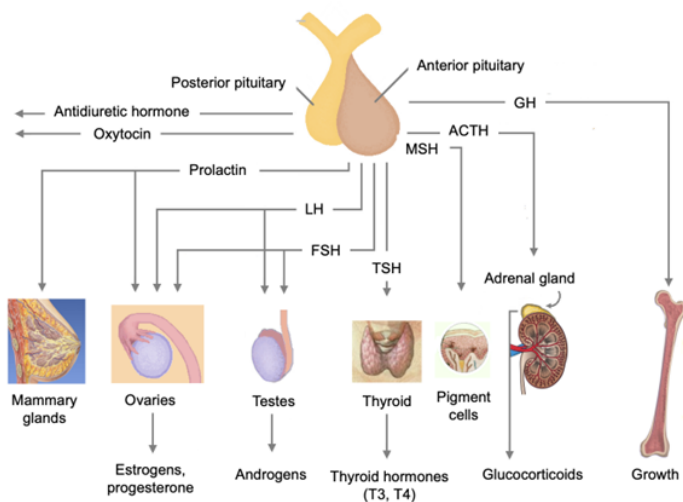


Figure 21.6—Tropic hormones from the pituitary gland and their target peripheral endocrine glands. Abbreviations for hormones are provided in the text.

Hormones from other endocrine glands can induce positive or negative feedback at the level of the pituitary and/or hypothalamus. However, the class of the hormone (i.e., protein vs. steroid) determines whether it can reach receptors within the hypothalamus, as it is protected by the **blood-brain barrier**. The blood-brain barrier is a selectively permeable membrane that regulates the passage of ions and molecules from the blood into the brain, maintaining ionic homeostasis and protecting the brain from neurotoxins found in the blood. The blood-brain barrier is formed by microvascular endothelial cells lining the cerebral capillaries that penetrate the brain and spinal cord of most mammals and other

organisms with a well-developed central nervous system. Endothelial cell tight junctions limit the passage of hydrophilic molecules across the blood-brain barrier. Hydrophilic molecules including protein hormones can only pass through the barrier via carrier- or receptor-mediated active transport. In contrast, lipophilic molecules such as steroid hormones can passively diffuse across the membrane barrier. The pituitary gland is not protected by the blood-brain barrier, allowing protein tropic hormones to freely circulate to the rest of the body through the bloodstream.

Hypothalamus

The hypothalamus evolved before the vertebrate brain (see Lemaire et al., 2021). The structure of the hypothalamus is highly conserved across vertebrates due to its integral function in regulating fundamental aspects of physiological homeostasis. It is located at the most ventral position in the forebrain (see [Chapter 19](#)). The mammalian hypothalamus contains bilateral neurosecretory nuclei (i.e., groupings of neurons based on proximity and shared function) such as the preoptic nucleus (PON) or paraventricular nucleus (PVN), among others. The axons of the hypothalamic neurosecretory cells extend directly into the posterior pituitary or into the median eminence where neurohormones travel to the anterior pituitary. These neurohormones are categorized as releasing hormones or inhibiting hormones depending on whether they stimulate or prevent tropic hormone release from the pituitary. All hypothalamic releasing hormones are protein hormones ranging in size (i.e., number of amino acids). These hormones are synthesized in the cell bodies of the hypothalamus and stored in secretory vesicles. Each hypothalamic regulatory hormone is named after the first tropic hormone it was discovered to control in addition to whether its primary action is stimulatory or inhibitory. We outline the functions of each one here.

1. **Corticotropin-releasing hormone (CRH)** is a peptide hormone that stimulates the synthesis and the secretion of adrenocorticotrophic hormone (ACTH) by corticotroph cells of the anterior pituitary gland. It is the first hormone in the HPA axis, which coordinates the vertebrate hormonal stress response.
2. **Thyrotropin-releasing hormone (TRH)** is a peptide hormone that stimulates the synthesis and secretion of thyrotropin (thyroid-stimulating hormone) by thyrotroph cells of the anterior pituitary gland. It is the first hormone in the HPT axis, which regulates internal body temperature and metabolism.
3. **Gonadotropin-releasing hormone (GnRH)** is a peptide hormone that stimulates the synthesis and secretion of the two gonadotropin hormones including Luteinizing Hormone (LH) and follicle-stimulating hormone (FSH) by gonadotroph cells of the anterior pituitary. It is the first hormone in the HPG axis, which coordinates reproduction and expression of primary and secondary sex characteristics.
4. **Gonadotropin-inhibitory hormone (GnIH)** is a peptide hormone that suppresses gonadotroph function, preventing the release of LH and FSH from the anterior pituitary.
5. **Growth hormone-releasing hormone (GHRH)** or somatocrinin is a peptide hormone that stimulates synthesis and release of growth hormone (GH, somatotropin) by somatotroph cells of the anterior pituitary.
6. **Growth hormone-inhibiting hormone (GHIH)** or somatostatin is a peptide hormone that inhibits a variety of physiological functions in the gastrointestinal tract, such as gastrointestinal motility and gastric acid production. It also inhibits the secretion of pancreatic and intestinal hormones such as insulin and glucagon.

Pituitary Gland

The pituitary gland is also called the **hypophysis** due to its location below the hypothalamus where it is attached to the brain via a stalk. In adult mammals, it is located ventral to the brain and posterior to the optic chiasm. The term *pituitary* is derived from the Latin word for phlegm (*pituita*) due to its assumed function of channeling mucus from the brain into the nasal cavity. The pituitary is divided into two lobes including the **adenohypophysis** (anterior pituitary; Figure 21.7) and **neurohypophysis** (posterior pituitary; Figure 21.7). The anterior pituitary or adenohypophysis is made of different endocrine cell types (e.g., somatotrophs, lactotrophs, gonadotrophs, thyrotrophs, corticotrophs) that synthesize and secrete a wide array of tropic hormones (see below). The anterior pituitary further divides into three regions: *pars distalis*, *pars intermedia*, and *pars tuberalis*. The *pars distalis* comprises the majority of the anterior pituitary across vertebrates. The *pars tuberalis* is located anterior to the *pars distalis* but is only found in tetrapods. The *pars intermedia* lies between the anterior pituitary and posterior pituitary, physically connecting them. The posterior pituitary or neurohypophysis consists of neurosecretory neurons that project down from the hypothalamus. These neurosecretory neurons release neurohormones into capillaries within the median eminence. The posterior pituitary further divides into two regions: the *pars nervosa* and median eminence. The *pars nervosa* has a separate blood supply from the body than that of the anterior pituitary.

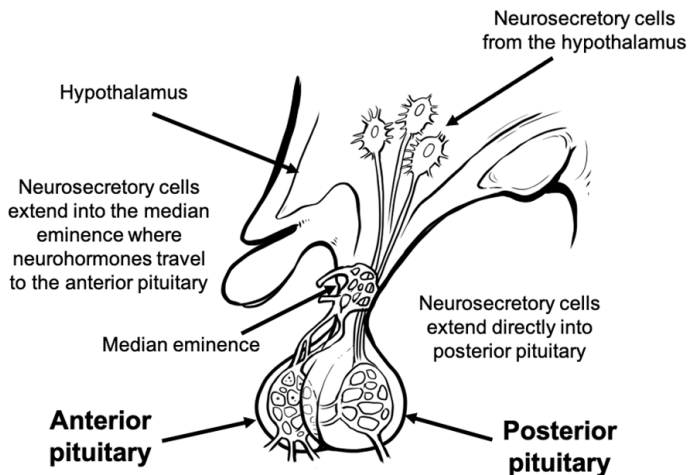


Figure 21.7—The two lobes of the pituitary including the anterior pituitary (adenohypophysis) and posterior pituitary (neurohypophysis).

Anterior Pituitary (Adenohypophysis) Tropic Hormones

1. **Thyroid-stimulating hormone (TSH)** or thyrotropin is a glycoprotein hormone synthesized and secreted by thyrotrophs of the anterior pituitary. It is the secondary hormone in the HPT axis that is released in response to thyrotropin-releasing hormone (TRH). TSH stimulates follicular cells within the thyroid gland to release thyroid hormones.
2. **Adrenocorticotrophic hormone (ACTH)** is a peptide hormone synthesized and secreted by corticotrophs of the anterior pituitary. It is the secondary hormone in the HPA axis that is

released in response to corticotropin-releasing hormone (CRH). ACTH stimulates the adrenal cortex to release glucocorticoid and androgen hormones.

3. **Luteinizing hormone (LH)** is a glycoprotein hormone that is synthesized and co-secreted along with follicle-stimulating hormone (FSH) by gonadotroph cells of the anterior pituitary. It is one of the secondary hormones in the HPG axis, triggered by gonadotropin-releasing hormone (GnRH). LH stimulates the Leydig cells of the testes to produce testosterone. LH triggers the secretion of steroid hormones from the ovaries and release of progesterone after ovulation from the corpus luteum (i.e., a temporary mass of cells that forms during the mammalian menstrual cycle inside an ovary). Additionally, LH helps regulate the length and order of the menstrual cycle by playing roles in both ovulation and implantation of an egg in the uterus (see Box 21.3).
4. **Follicle-stimulating hormone (FSH)** is a glycoprotein hormone that is synthesized and co-secreted along with LH by gonadotroph cells of the anterior pituitary. It is one of the secondary hormones in the HPG axis, triggered by GnRH. FSH promotes follicle development in ovaries and spermatogenesis in testes.
5. **Prolactin (PRL)** is a polypeptide hormone that is synthesized and secreted by lactotroph cells in the anterior pituitary. PRL promotes milk production and the development of mammary glands within breast tissues in mammals. It can stimulate crop milk production (i.e., nutrient-rich substance secreted from the lining of the crop) in some bird species including pigeons (Figure 21.8). PRL also promotes parental care behavior in some vertebrates.



Figure 21.8—An adult common wood pigeon (*Columba palumbus*) feeds its offspring.

6. **Growth hormone (GH)** is a protein hormone synthesized and secreted by acidophilic and somatotroph cells of the anterior pituitary. GH promotes cartilage and bone growth in addition to increased production of insulin-like growth factor-1.
7. **Melanocyte-stimulating hormone (MSH)** is a protein hormone that is synthesized and secreted by melanocytes or melanophores of the anterior pituitary. MSH promotes the development of pigmentation in skin, hair, and feathers by depositing the pigment melanin. It has also been shown to suppress appetite.

Posterior Pituitary (Neurohypophysis) Tropic Hormones

1. **Oxytocin (OXY)** is a nonapeptide hormone that is synthesized by neurosecretory cells in the hypothalamus and then stored

and released by the posterior pituitary. It promotes uterine contractions via positive feedback during birth in mammals and promotes social behavior (e.g., pair bonding between mates) in certain animals.

2. **Antidiuretic hormone (ADH)** is also known as arginine vasopressin (AVP) or vasopressin. AVP is a nonapeptide hormone that is synthesized by neurosecretory cells in the hypothalamus and then stored and released by the posterior pituitary. AVP regulates blood volume and osmolarity of the body by promoting water reabsorption by the kidneys.

Development

The hypothalamus arises from the ventral portion of the diencephalon. The pituitary develops from two sources including a ventral outgrowth of the diencephalon called the infundibulum and an invagination off the anterior roof of the stomodeum (i.e., invagination of the ectoderm that turns into the mouth) called Rathke's pouch. The infundibulum maintains a connection to the brain forming the posterior pituitary, whereas the connection between the stomodeum and Rathke's pouch is severed forming the anterior pituitary. The secretory cells of the anterior pituitary and neurosecretory cells of the hypothalamus arise from the neuroectoderm (neural ridge). The embryonic origins of the pituitary gland are the same across all vertebrates with the exception of hagfishes. The anterior pituitary of the hagfish originates from endoderm rather than stomodeal ectoderm.

Evolution

The evolution of the vertebrate brain is covered in detail in [Chapter](#)

18, but we will highlight differences in the neurovascular connection between the hypothalamus and pituitary. Releasing hormones from the hypothalamus exert control over tropic hormone release from the pituitary via vascular connection through the median eminence. The neurovascular connection between the hypothalamus and pituitary is found across all vertebrates with a few exceptions. Hagfishes do not have vascular or neural connections between the brain and anterior pituitary. However, a primitive neurohemal area has been described in the Pacific hagfish similar to a median eminence. In chondrosteian fishes, the median eminence is separated from the pars distalis by connective tissue so that no neurons penetrate the pars distalis but a portal system is present. Teleost fishes also do not possess vascular connections between the hypothalamus and anterior pituitary but the axons of the hypothalamus directly feed into the pituitary.

The organization and location of the pituitary gland differs across vertebrates (Figure 21.9).

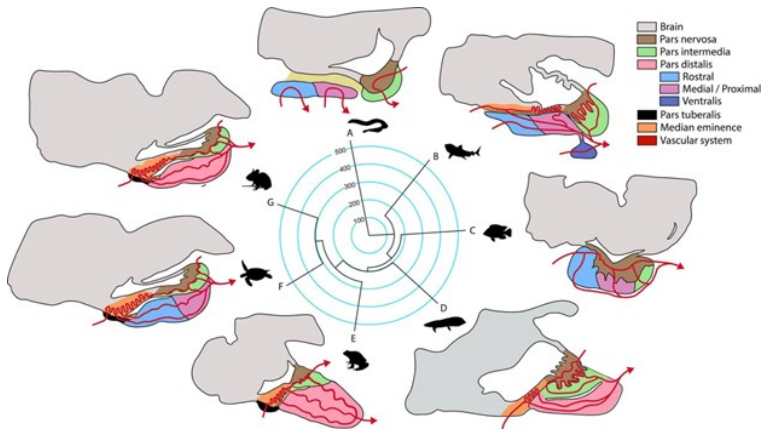


Figure 21.9—Anatomical pituitary organization across vertebrates. From Santiago-Andres, Golan, and Fiordelisi (2021).

The hagfish anterior pituitary arises from a different embryonic source than other vertebrates. The hagfish anterior

pituitary consists of patches of cells in the connective tissue with no differentiated regions. The hagfish posterior pituitary consists of the pars nervosa in the shape of a long sac that extends from the diencephalon with no median eminence. In lamprey, the anterior pituitary consists of a pars intermedia and a pars distalis that is divided into rostral and proximal subregions. The lamprey posterior pituitary does not have a median eminence. It extends from the ventral region of the brain and is in contact with the anterior pituitary. The anterior pituitary of gnathostome fish contains a pars distalis and pars intermedia, and the posterior pituitary is made of a pars nervosa and median eminence.

In the elasmobranch anterior pituitary, there is a projection from the pars distalis called the ventral lobe or pars ventralis. Though the function is unknown, it is thought to be homologous to the pars tuberalis of tetrapods. The elasmobranch pars distalis is subdivided into rostral and proximal regions like lampreys. There is a vascular portal system between the pars distalis of the anterior pituitary and the median eminence of the posterior pituitary. Above the elasmobranch posterior pituitary, there is a structure derived from the hypothalamus called the saccus vasculosus, which senses seasonal changes in day length.

The pars tuberalis first appears in amphibians and persists through the majority of later vertebrates. In most tetrapods, the anterior pituitary consists of a pars distalis, pars tuberalis, and pars intermedia, whereas the posterior pituitary consists of the pars nervosa and median eminence. The amphibian pars distalis has no distinct regions and no known functions. In reptiles, the pars distalis has cephalic and caudal lobes. The reptilian pars tuberalis is absent in snakes. In birds, there is no pars intermedia in the anterior pituitary but the remaining structure is similar to the typical tetrapod pituitary. The avian pars distalis has cephalic and caudal lobes like reptiles. Though size and structure vary, the mammalian pituitary follows the typical pattern of the anterior pituitary consisting of a pars distalis, pars tuberalis, and pars intermedia, and

the posterior pituitary consisting of the pars nervosa and median eminence.

21.3 Pineal Gland

Structure and Function

The **pineal gland** or **epiphysis** is an unpaired gland located behind the third ventricle in the brain midline (Figure 21.10). The term *pineal* comes from the Latin word *pinea* due to the pine cone shape of the gland. The pineal gland and the adjacent **parapineal organ** make up the **epiphysial complex** in mammals. The pineal gland is not protected by the blood-brain barrier. The main hormone synthesized, stored, and secreted by the pineal gland is **melatonin** (protein hormone). In the 1900s, the pineal gland was originally thought to only affect pigmentation. Pineal extracts caused lightening of the skin in amphibian larvae by concentrating melatonin levels within melanophores. We know now that pineal gland secretions of melatonin also coordinate circadian rhythms (i.e., a pattern of an organism that follows a 24-hour period) in most higher vertebrates. The parapineal organ is an adjacent structure that may convey photosensory information to the pineal gland in lower vertebrates.

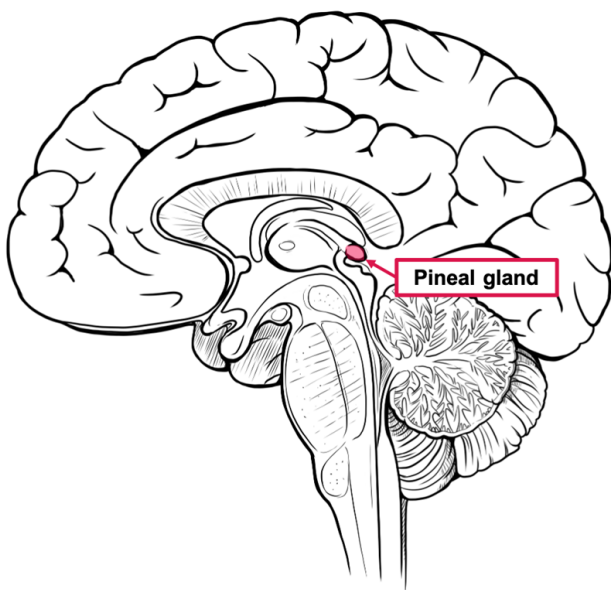


Figure 21.10—Location of human pineal gland.

In mammals, melatonin regulates endogenous rhythms including the suppression of thyroid function and reproductive activity. Circulating melatonin levels are higher at night than during the day. The retina of the eyes detects changes in photoperiod (i.e., day length) and entrains the **suprachiasmatic nucleus (SCN)** of the hypothalamus to the timing of light/dark cycles. Changes in photoperiod detected by the retina sends neural signals to the SCN via the **retinohypothalamic pathway** that controls melatonin synthesis and release from pinealocytes (Figure 21.11). Light suppresses melatonin production by reducing sympathetic input signals to the pineal gland. In photoperiodic species (i.e., seasonally breeding species that coordinate reproductive cycles based on photoperiod), melatonin suppresses reproductive hormones such as luteinizing hormone (LH) during the nonbreeding season (i.e., short

day/photoperiod). As days become longer (i.e., longer photoperiod), light suppresses melatonin production, leading to an increase in LH during the breeding season. During gestation in mammals, maternal melatonin provides the fetus with information on photoperiod until the fetal pineal gland is formed. The pineal gland also impacts melanophore expression in the skin of lower vertebrates such as fish and amphibians.

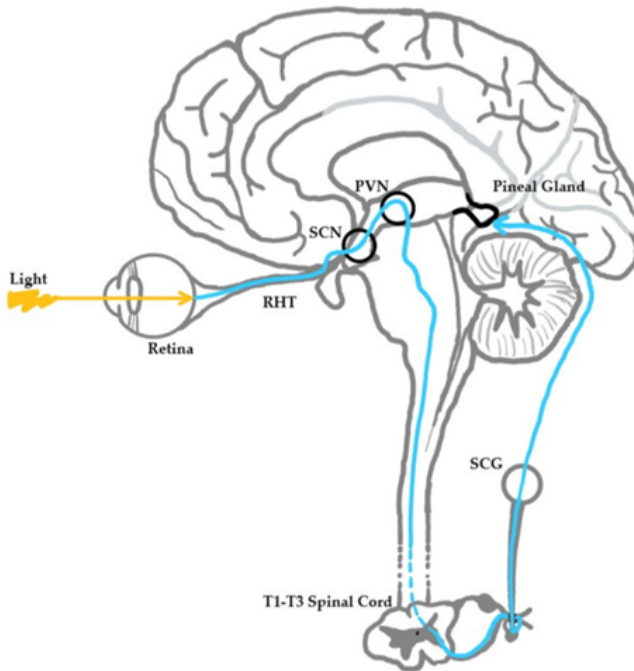


Figure 21.11—Neuroanatomical pathway of light stimulus to the pineal gland depicting the retinohypothalamic tract (RHT) to suprachiasmatic nucleus (SCN) to paraventricular nucleus (PVN) to the brain stem to the spinal cord to the superior cervical ganglion (SCG) to the pineal gland. From Vasey, McBride, and Penta (2021).

Development

The pineal gland is derived from the roof of the diencephalon of the brain called the epithalamus. During development, evaginations of the epithalamus differentiate into multiple secretory structures including the epiphyseal complex (pineal and parapineal organs), paraphysis, and dorsal sac. The paraphysis develops from the telencephalon as the anterior most evagination of the epiphysial complex. The paraphysis may function like the choroid plexus, a branching network of cells found in each ventricle of the brain that secretes cerebrospinal fluid. The dorsal sac develops as an evagination anterior to the epiphyseal complex and posterior to the paraphysis. The dorsal sac contributes to the formation of the choroid plexus in most vertebrates. It is hypothesized that the organs of the epiphyseal complex arose in primitive fishes as a pair of diverticula and then continued to differentiate into the structures we see today.

Evolution

Through vertebrate evolution, there has been a shift from the pineal gland acting as its own photoreceptor to a heavy reliance on the SCN-pineal pathway to coordinate photoperiod detection and melatonin secretion. Almost all vertebrates possess a pineal gland and a parapineal organ that compose the epiphyseal complex. In cyclostomes, the epiphyseal complex consists of a pineal organ and a parapineal gland that are both potentially photosensory. In Chondrichthyes, the pineal organ is photosensitive but we do not know how functionally important it is. There is no documented existence of a parapineal organ in chondrichthyans.

In teleost fishes, the epiphyseal complex consists of a pineal organ but a reduced parapineal organ is only found in some

species. There are no generalized patterns of melatonin secretion across teleost fish species with peaks occurring regardless of photoperiod. Melatonin has been shown to influence melanophore function in several teleost species. Melatonin is also produced in the retinas of teleost fishes where increased melatonin levels could cause the concentration of pigment in retinal melanophores to increase light sensitivity of retinal cells. Some teleost species also exhibit neural connections to the SCN similar to the mammalian retinohypothalamic pathway. The strength of phototaxis (i.e., an organism alters its movement in response to light stimuli) expressed by a teleost species depends on the opaqueness and thickness of the skull covering their pineal spot.

In amphibians, the epiphyseal complex contains a pineal organ and parapineal organ. There is no documented retinohypothalamic pathway in amphibians; though melatonin expresses a typical diurnal rhythm. Some anuran species have a parapineal end vesicle known as the frontal organ or stirnorgan. The parapineal organ penetrates the skull and possesses photosensory cells (Figure 21.12). It is referred to as the **parietal eye** (i.e., due to the opening in the parietal bones of the skull) or the “third eye” (i.e., due to its ability to transmit photosensory information to the pineal organ). The pineal organ has been thought to evolve in a single direction by losing photosensory capacity and augmenting secretory function in the transitions from amphibians and reptiles to birds and mammals. New evidence reveals that a “fourth eye” reevolved from the pineal organ at least once within reptiles, specifically in an extinct monitor lizard (*Saniwa ensidens*) in which the pineal and parapineal penetrated the skull simultaneously.



Figure 21.12—Parietal eye of an anole (*Anolis carolinensis*).

The arrangement of the epiphyseal complex is variable across reptiles. Crocodylians do not possess a pineal or parapineal organ but do have blood levels of melatonin from the retina. Similar to amphibians, lizards have a parapineal organ that penetrates the skull (i.e., parietal eye) that can communicate with the photoreceptive pineal organ. Turtles and snakes only have the glandular portion of the pineal organ, suggesting that they may coordinate photoperiod and melatonin secretion via the retinohypothalamic pathway.

In birds, the pineal organ only possesses the glandular basal portion making it the pineal gland. The pineal gland does not possess photoreceptive cells, and there is no parapineal organ in birds. The pineal gland is innervated with sympathetic fibers, suggesting a retinohypothalamic pathway as in mammals as described above. Mammals possess the typical epithalamus

structure with a pineal gland and parapineal organ, relying on the retinohypothalamic pathway to coordinate melatonin secretion.

21.4 Thyroid and Parathyroid Glands

Structure and Function

The **thyroid gland** or glandula thyroidea is named after the Greek word for shield due to its shield-shaped appearance at the base of the neck in humans. The thyroid gland is responsible for regulating metabolism, growth, body temperature, and reproduction. Across all vertebrates, the thyroid gland secretes two main hormones: **thyroxine (T4)** and **triiodothyronine (T3)**. Both hormones are protein hormones composed of large quantities of iodine. T3 and T4 are the end products of the HPT axis (Figure 21.13). The hypothalamus releases TRH, which travels to the anterior pituitary, which then secretes TSH. TSH stimulates the release of T3 and T4 from the thyroid gland. T4 is considered inactive but makes up about 90% of circulating thyroid hormone levels. T3 is the bioactive form, which makes up the other 10% of circulating thyroid hormone. T4 is converted to T3 by deiodinases (i.e., enzymes involved in the activation or deactivation of thyroid hormones) in tissues with high blood flow such as the liver and kidneys. Both thyroid hormones (T3 is more effective than T4) can initiate negative feedback on TRH at the level of the hypothalamus and on the thyrotropes of the anterior pituitary, decreasing TSH secretion.

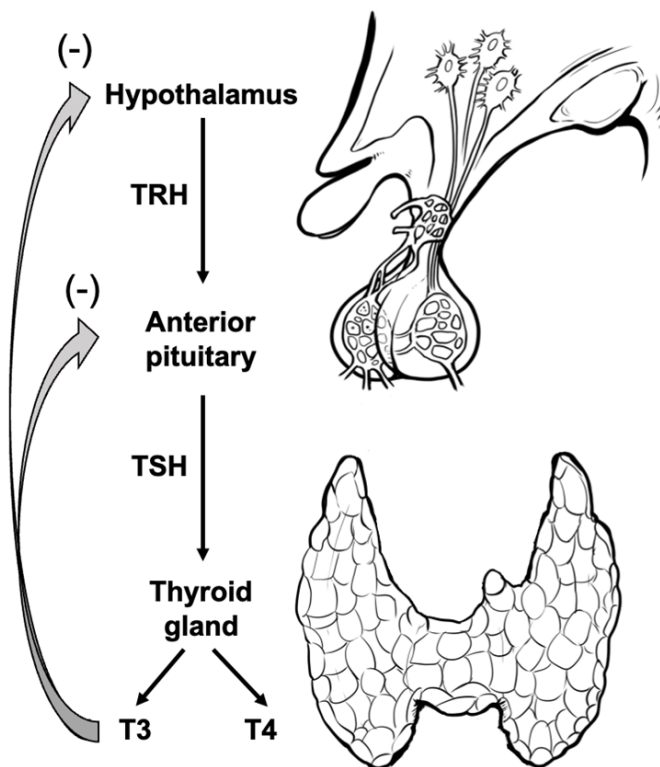


Figure 21.13—Hypothalamic-pituitary-thyroid (HPT) axis. Gray arrows denote negative feedback. TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine.

The parathyroid glands are positioned posterior to the thyroid gland in tetrapods and humans, which normally possess four parathyroid glands (Figure 21.14). Within the thyroid gland, there are follicles made of follicular cells that synthesize and secrete thyroid hormones. **Follicular cells** also secrete a glycoprotein-rich colloid called **thyroglobulin** that stores the secreted thyroid

hormones in the space between the follicular cells (inside the thyroid follicles). In between these thyroid follicles or within the wall of the thyroid follicles, there are **parafollicular cells** or **C cells** that produce **calcitonin**, a peptide hormone that regulates calcium levels in blood. Calcitonin is hypocalcemic, meaning it lowers levels of calcium in the blood. When calcium levels are too high, the parathyroid gland secretes **parathyroid hormone (PTH)**. PTH is hypercalcemic, meaning it increases blood calcium levels. Calcitonin and PTH work antagonistically to each other via a negative feedback loop to maintain calcium homeostasis in the blood (Box 21.1).

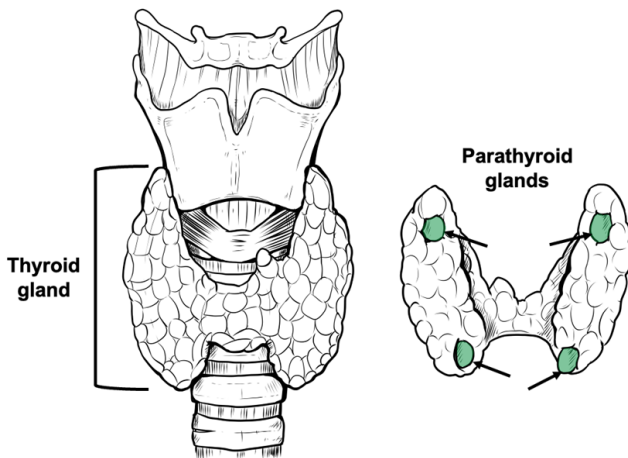


Figure 21.14—Location of the human thyroid and parathyroid glands.

Box 21.1—Calcium Ion Homeostasis

PTH and calcitonin, primarily secreted by the parathyroid glands and thyroid gland, respectively, are key players in calcium ion regulation. PTH raises blood calcium levels by stimulating bone resorption, which releases calcium into the bloodstream. PTH also enhances calcium reabsorption in the kidneys, which reduces urinary calcium excretion. Calcitonin acts antagonistically to PTH to decrease calcium levels in the blood. Calcitonin inhibits bone resorption and promotes calcium deposition in bones.

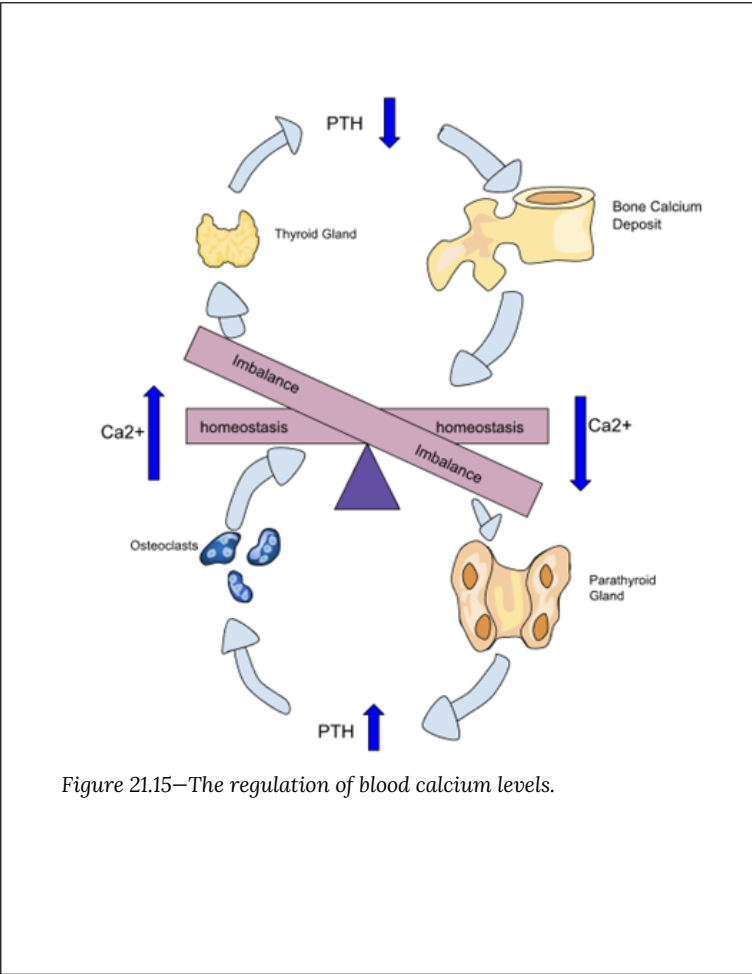


Figure 21.15—The regulation of blood calcium levels.

Thyroid hormones regulate metabolism and can help generate body heat by increased oxidation of glucose. Basal metabolic rate is linked to thyroid hormone concentrations in birds and mammals. Thyroid hormones also promote growth through a permissive effect on growth hormone (GH) release from the anterior pituitary. Finally, thyroid hormones can also promote reproduction through a permissive effect on gonadotropins (e.g., LH and FSH) from the pituitary that stimulate gonad growth and sex steroid

hormone release. Thyroid hormones are also involved in metamorphosis of lower vertebrates such as fishes and amphibians. Thyroid hormones also regulate proximodistal patterning in fin rays of many teleost fish species.

Development

Across vertebrates, the thyroid gland initially develops as an outgrowth from the floor of the embryonic pharynx. The gland will eventually separate from the pharynx, but the mature gland looks different across vertebrates. The thyroid gland is derived from a ventral bud in the floor of the embryonic pharynx or endoderm between the first and second pharyngeal pouches. There is an initial differentiation into cellular cords, which separate into cell clusters and form thyroid follicles. Unlike the endodermal origin of thyroid gland follicular cells, the thyroid parafollicular cells have a neural crest origin and then migrate into the embryonic glands. Parafollicular cells (C cells) that occur adjacent to or between the follicles arise from the ultimobranchial body, another pharyngeal derivative. The ultimobranchial body originates from neural crest embryonic primordia from the pharyngeal pouches of embryos. The parathyroid gland originates from the ventral edges of the embryonic pharyngeal pouches, but like parafollicular cells, the secretory cells of the parathyroid gland are also of neural crest origin and migrate to the gland later in embryonic development.

Evolution

In adult cyclostomes, the thyroid consists of scattered follicles, and T₃ and T₄ are stored intracellularly. Cyclostomes also do not possess pituitary thyrotropes or TSH. In most teleost fishes, the

thyroid gland consists of clumps of follicles that are spread across the pharyngeal region, and the follicles contain colloid that stores the hormones extracellularly. In other types of fish and tetrapods, the thyroid gland is a discrete single- or double-lobed gland located at the base of the throat anterior to the heart. Though not present in cyclostomes, the ultimobranchial bodies are located in the neck as paired cell masses in fishes, amphibians, reptiles, and birds during development. In nonplacental mammals, the ultimobranchial body fuses with the thyroid gland. Derived from the ultimobranchial bodies, the parafollicular cells (C cells) are interspersed among the thyroid follicles.

The location of the mature parathyroid gland varies across vertebrates. The parathyroid is completely absent in fishes and does not appear in amphibians until after the gills are lost during metamorphosis. After maturation, the parathyroid gland(s) are either located on the thyroid or interspersed throughout the neck veins in amphibians, reptiles, and birds. In mammals, the glands are either within the thyroid gland or adjacent to it. The parathyroid gland is made of **chief cells**, which secrete PTH. In some mammalian species including humans, there are also oxyphil cells present in the parathyroid gland. We do not know the function of these cells, but they only appear at the onset of sexual maturity, whereas chief cells are present at birth.

21.5 Pancreatic Islets

Structure and Function

The **pancreas** is made of exocrine and endocrine cells that play essential roles in digestion and metabolism (Figure 21.16). The exocrine component includes **acini**, which are made of **acinar cells**

that secrete digestive enzymes into ducts. These enzymes include trypsin and chymotrypsin to digest proteins, amylase for the digestion of carbohydrates, and lipase to break down fats. However, we will focus on the endocrine component of the pancreas in this chapter.

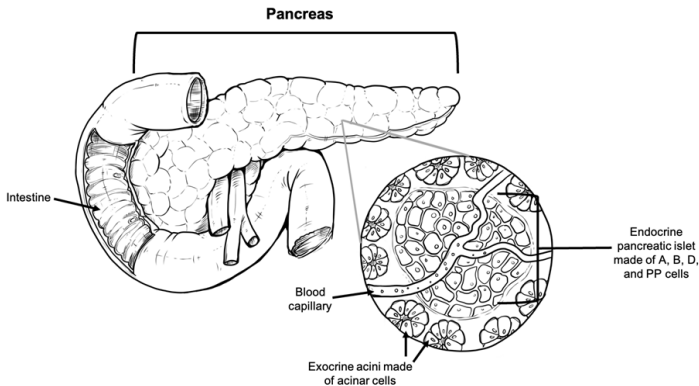


Figure 21.16—Location of the human pancreas depicting endocrine pancreatic islets versus exocrine acini.

Pancreatic islets (otherwise known as **islets of Langerhans**) are masses of different endocrine cell types that secrete hormones with varying metabolic functions. Within the islets, **A cells** produce **glucagon**, a hormone that promotes the conversion of glycogen to glucose in the liver. This hyperglycemic protein hormone serves to increase blood glucose levels. Within the islets, **B cells** secrete **insulin**, which serves to decrease blood glucose levels in an antagonist role to the function of glucagon. This hypoglycemic protein hormone triggers intracellular absorption of glucose from the bloodstream. Insulin and glucagon regulate blood glucose levels via a negative feedback loop (Figure 21.17).

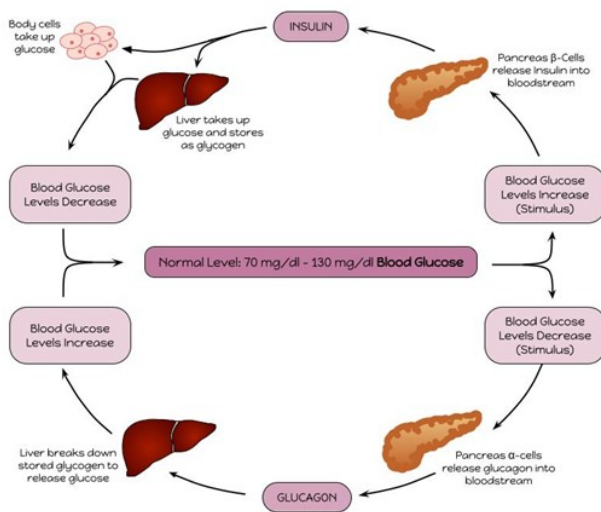


Figure 21.17—Hormonal control of blood glucose levels by insulin and glucagon in humans.

D cells secrete **somatostatin** or **growth hormone-inhibiting hormone**, which inhibits the secretion of insulin and glucagon in certain contexts. The final cell type, **PP cells**, secrete **pancreatic polypeptide**, which promotes the release of hydrochloric acid into the stomach immediately following a meal.

Development

Across vertebrates, the pancreas arises from a diverticulum that grows from the endodermal lining of the embryonic gut through surrounding mesenchyme. A dorsal bud from the intestine fuses with one or two ventral buds to form the pancreas. The exocrine tissue forms small ductules that merge into larger ducts that

eventually become a large duct connecting the exocrine part of the pancreas to the small intestine. The pancreatic islets develop as small buds from the ductules; however, the true embryonic origin of the endocrine cells remains unclear. There are hypotheses that they may originate from mesoderm, neuroectodermal neural crest cells, or gut endoderm.

Evolution

In cyclostomes, acini and endocrine islets form separate groups of tissue but are close to each other. In hagfishes, the islets occur at the base of the common bile duct. In lampreys, islets occur within the mucosal wall of the intestine and the liver. Cyclostomes have B and D cells but lack A and PP cells. In chondrichthyans, the islets are located around the ducts of the exocrine portion of the pancreas. Chondrichthyans have A, B, D, and PP cells. In most bony fishes, islets are clumped together in **Brockmann bodies** that occur along the gallbladder, bile ducts, liver, and surface of the intestines (Figure 21.18). In a few bony fish species, islet tissue occurs in the exocrine portion of the pancreas. These Brockmann bodies contain B, A, and D cells but PP cells occur only in pyloric Brockmann bodies. In most tetrapods, the islets are distributed into clumps within a discrete, extraintestinal gland. In many birds and in the toad *Bufo*, islets form lobes embedded in the exocrine component of the pancreas and contain all four cell types. In mammals, the pancreatic islets consist of small masses of endocrine cells among the acinar tissue. In addition to A, B, D, and PP cells, another cell type called amphophils are found in the islets of mammals, sharks, teleost fishes, amphibians, and reptiles with no known function.



Figure 21.18—Brockmann body (BB) of a freshly dissected Pacific jellynose fish (*Ateleopus japonicus*). Modified from Chanet et al. (2023).

21.6 Adrenal Glands

Structure and Function

Adrenal glands are named for their location superior to the kidneys in humans (ad-renal). Each adrenal gland consists of an inner **adrenal medulla** consisting of **chromaffin cells** and an outer **adrenal cortex** made of steroidogenic **adrenocortical cells** (Figure 21.19). The adrenal medulla coordinates the fight-or-flight response by secreting catecholamine neurotransmitters (e.g., epinephrine and norepinephrine) within seconds of a stressful stimulus. Minutes later, a region within the adrenal cortex will secrete **glucocorticoid hormones** (steroids) that coordinate physiological and behavioral responses to stressors. At low levels, glucocorticoids mediate basic metabolic processes, but when elevated in response to a stressor, glucocorticoids cause shifts in energy usage to counteract acute and chronic stressors. Another region of the adrenal cortex secretes mineralocorticoids when stimulated by the **renin-angiotensin**

system that regulates ions (potassium K^+ and sodium Na^+) and water balance in the body (Box 21.2). In addition to chromaffin cells and adrenocortical cells, a novel cell type was recently discovered in the adrenal gland of the monogamous oldfield mouse (*Peromyscus polionotus*) that expresses an enzyme that converts progesterone into 20α -hydroxyprogesterone and induces monogamous-typical parental behavior.

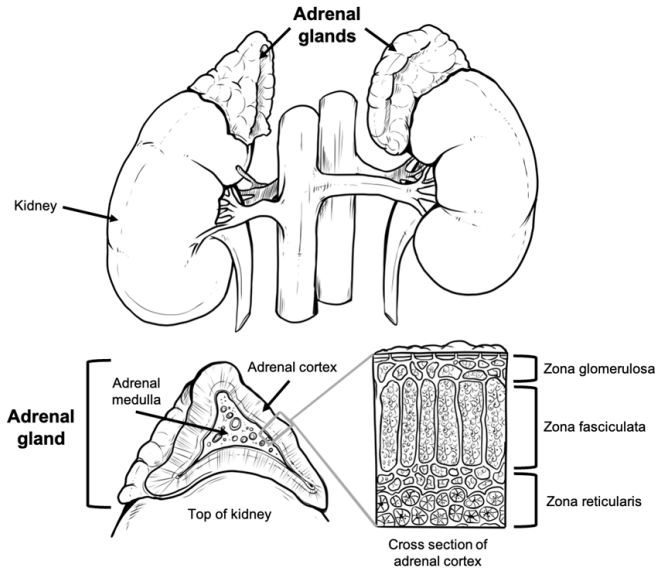


Figure 21.19—Location of the human adrenal gland depicting zonation of the adrenal cortex.

In mammals, there are distinct zones of the adrenal cortex that each secrete different hormones. The outermost **zona glomerulosa** releases mineralocorticoids to regulate water balance in the kidneys. This zone contains receptors for angiotensin II (described below as part of the renin-angiotensin system), which triggers the endocrine glands to release aldosterone, the primary mammalian mineralocorticoid hormone. The middle region **zona**

fasciculata is responsible for secreting glucocorticoids, which mediate the hormonal stress response. This zone is involved in the **HPA axis** (Figure 21.20). A stressful stimulus is perceived by the hypothalamus, which secretes CRH to the anterior pituitary. The pituitary releases ACTH, which attaches to receptors in the zona fasciculata that trigger the release of glucocorticoids (e.g., cortisol or corticosterone). Glucocorticoids can initiate negative feedback on the HPA axis at the level of the hypothalamus and anterior pituitary, suppressing CRH and ACTH, respectively. The innermost **zona reticularis** secretes androgens and other glucocorticoids. This zone contains receptors for ACTH, LH, and human chorionic gonadotropin (hCG), which trigger the release of DHEA, DHEA-S, and androstenedione.

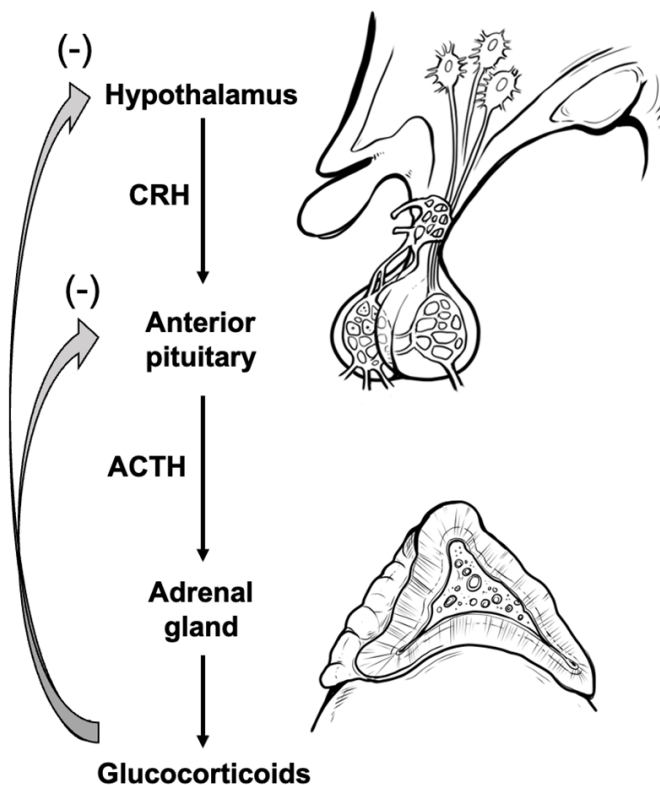


Figure 21.20—Hypothalamic-pituitary-adrenal (HPA) axis. Gray arrows denote negative feedback. CRH = corticotropin-releasing hormone; ACTH = adrenocorticotropic hormone.

The adrenal medulla does not possess the zonation patterns found in the cortex of mammals. The medulla has direct communication with the nervous system via synapses of preganglionic sympathetic neurons. Any signals from these neurons trigger the release of catecholamine neurotransmitters **epinephrine (adrenaline)** and **norepinephrine (noradrenaline)**. Known as the “fight-or-flight” response, catecholamines are

released as the first wave of the stress response during a perceived challenge. The adrenal cortex and medulla are supplied with blood directly from the connective tissue capsule, but the medulla receives a secondary blood source from the cortical sinuses.

In addition to coordinating the vertebrate stress response, the adrenal glands are also essential in regulating sodium and potassium ion balance in the body but also controlling extracellular fluid volume. When blood pressure is low, the kidneys release an enzyme called **renin** that transforms the protein **angiotensinogen** into **angiotensin I** in the bloodstream. The inactive angiotensin I is converted to a more active form called **angiotensin II** by the angiotensin-converting enzyme. Angiotensin II causes the walls of arterioles to constrict, which raises blood pressure. Angiotensin II also triggers the release of aldosterone from the adrenal cortex, which stimulates the kidneys to retain sodium and excrete potassium. Increased sodium concentrations retain water, increasing blood pressure and volume.

Box 21.2—Blood Pressure Regulation

The renin-angiotensin-aldosterone system is the central player in blood pressure regulation in vertebrates. Renin is an enzyme released by the kidneys in response to low blood pressure or decreased sodium levels. Renin converts angiotensinogen to angiotensin II, which constricts blood vessels to elevate blood pressure. Angiotensin II also stimulates the release of aldosterone from the cortex of the adrenal gland. Aldosterone promotes sodium reabsorption in the kidneys, which leads to water retention and blood pressure elevation. Another hormone involved in blood pressure regulation is **atrial natriuretic peptide (ANP)**.

ANP works antagonistically to the renin-angiotensin-aldosterone system. ANP is released by the atria of the heart in response to increased blood volume and pressure. ANP acts to lower blood pressure by promoting vasodilation, increasing urinary sodium excretion, and inhibiting renin and aldosterone secretion.

Development

The adrenal gland is composed of two tissue types that each develop from a different source. Interrenal or adrenocortical tissue is derived from splanchnic mesoderm adjacent to the urogenital ridge. This tissue is responsible for secreting mineralocorticoids and glucocorticoids. Chromaffin tissue arises from neural crest cells and is responsible for releasing catecholamines. In some mammal species (e.g., human and nonhuman primates), the adrenal cortex is dominated by the fetal zone prior to birth. The fetal zone produces steroid hormones that serve as precursors of the estrogens secreted by the placenta. At birth, the fetal zone will stop functioning and decline in size throughout postnatal development.

Evolution

Across vertebrates, the adrenocortical or interrenal tissue and chromaffin tissue occur in different arrangements. In adult cyclostomes and teleost fishes, the two tissue types are separated. In cyclostomes, clusters of chromaffin cells are not in contact with

the adrenocortical tissue, which is found in clumps above the pronephric funnels in the kidney and dispersed along the posterior cardinal veins above the pronephros. There is no evidence that the adrenocortical cells in lampreys can produce cortisol or corticosterone but there is circulating 11-deoxycortisol and 11-deoxycorticosterone in sea lampreys. In elasmobranchs, chromaffin tissue remains separate as cell clusters along the border of the kidneys. Some elasmobranch species have one large unpaired adrenal gland that is entirely adrenocortical tissue located posterior to the kidneys. Elasmobranchs secrete a unique corticosteroid called 1 α -hydroxycorticosterone in addition to 11-deoxycorticosterone.

As stated in [Chapter 16](#), bony fish kidneys vary in their function and structure across species, so we will consider actinopterygian kidneys for most of this section. In some teleost fishes, adrenocortical tissue is found inside the pronephros in clusters or in a strip around the posterior cardinal veins. Teleost adrenocortical tissue is located in the most anterior portion of the kidney known as the “head kidney” that has lost its renal function ([Figures 16.11](#) and 21.20). Adrenocortical tissue of some species without a head kidney are not associated with kidney elements and surround the posterior cardinal veins. Chromaffin tissue occurs in clumps near the adrenocortical tissue in teleosts. The main glucocorticoid in teleost fishes is cortisol; however, the teleost HPA differs from that of other vertebrates. The hypothalamic neurosecretory cells directly innervate the pars distalis of the pituitary. Amphibian adrenocortical cells are extrarenal and vary in their location. In anurans, adrenocortical tissue occurs in clumps loosely organized into a pair of interrenal glands on the ventral side of the kidneys. Anuran chromaffin cells occur near adrenocortical cells in clumps. The main hormones secreted by the amphibian adrenal gland are aldosterone and corticosterone, though cortisol is found in amphibian species.

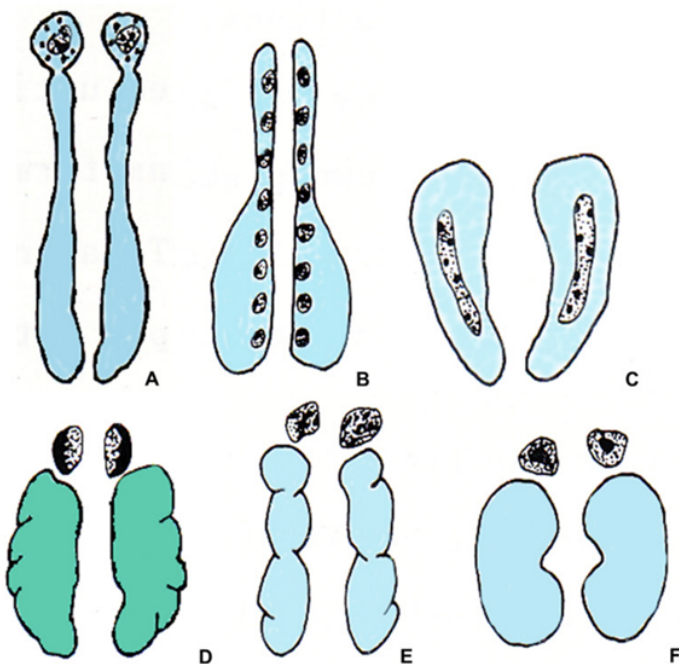


Figure 21.21—Different arrangements of steroidogenic tissue (gray), chromaffin tissue (black), kidneys (light blue), and gonads (green) across vertebrates including (A) teleost, (B) urodele amphibian, (C) anuran amphibian, (D) lacertilian reptile, (E) bird, and (F) mammal. From Capaldo (2023).

In reptiles, the arrangement and positioning of the adrenal glands differs by group. Crocodylians and most snakes have paired suprarenal adrenal glands with cords of chromaffin cells within the adrenocortical cells. In lizards and some snakes, the adrenocortical cells are partially encapsulated by chromaffin cells similar to the mammalian medulla. The reptilian adrenal gland evolved the first independent vascular supply and venous drainage in vertebrates. Reptiles produce aldosterone and corticosterone. Similar to crocodylians and most snakes, the two tissue types of the avian adrenal gland occur together forming distinct glands on or near

the kidneys. Birds also secrete aldosterone and corticosterone as the main hormones from their adrenal glands. In mammals, adrenocortical tissue forms the adrenal cortex, and chromaffin tissue forms the medulla. As described above, the mammalian adrenal cortex exhibits distinct zonation including zona glomerulosa, zona fasciculata, and zona reticularis. There is also zonation of the cortex in anurans, reptiles, and birds, but it is less distinct.

21.7 Gonads

Structure and Function

In addition to gamete production (see [Chapter 17](#)—Reproduction), **gonads** (i.e., testes and ovaries) are responsible for production of **sex steroid hormones** (e.g., androgens and estrogens) that coordinate onset of sexual maturity in juveniles and reproductive processes in adult vertebrates. In **testes**, **Leydig** or **interstitial cells** produce **androgens** and are located between the seminiferous tubules (i.e., tubes within the testes that produce, maintain, and store sperm; Figure 21.22). Testes also consist of **Sertoli cells** that are responsible for spermatogenesis or sperm development (covered in [Chapter 17](#)). In ovaries, **ovarian follicles** consist of the oocyte surrounded by a layer of **granulosa cells** and then a layer of **theca cells** (Figure 21.22). The theca cells produce androgens in response to LH as well as progesterone in the preovulatory follicles. The granulosa cells produce estrogen in response to FSH. Granulosa cells in the preovulatory follicle also respond to LH and produce progesterone. The **corpus luteum** (i.e., temporary mass of cells that forms in the ovary after ovulation) also produces progesterone. Egg

development (covered in detail in [Chapter 17—Reproduction](#)) is regulated by gonadotropins released from the anterior pituitary.

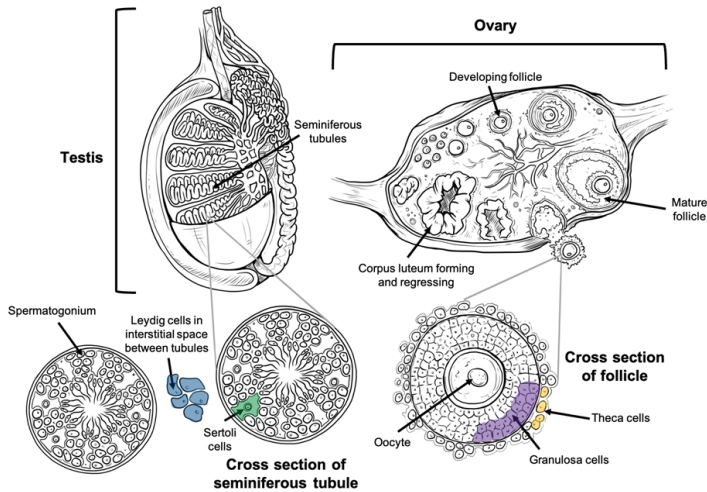


Figure 21.22—Cross section of seminiferous tubules inside a human testis depicting Leydig cells (blue) and Sertoli cells (green) and a cross section of a follicle inside a human ovary depicting theca cells (yellow) and granulosa cells (purple).

Sex steroids also induce the expression of **secondary sex characteristics** (i.e., phenotypic traits that emerge at sexual maturity) in vertebrates such as changes in body size/mass, ornamentations, hair or feather colors, and behaviors that are used to either attract mates or compete with others for access to mates (Figure 21.23). This can result in sexual dimorphism or phenotypic distinctions between sexes within a species.

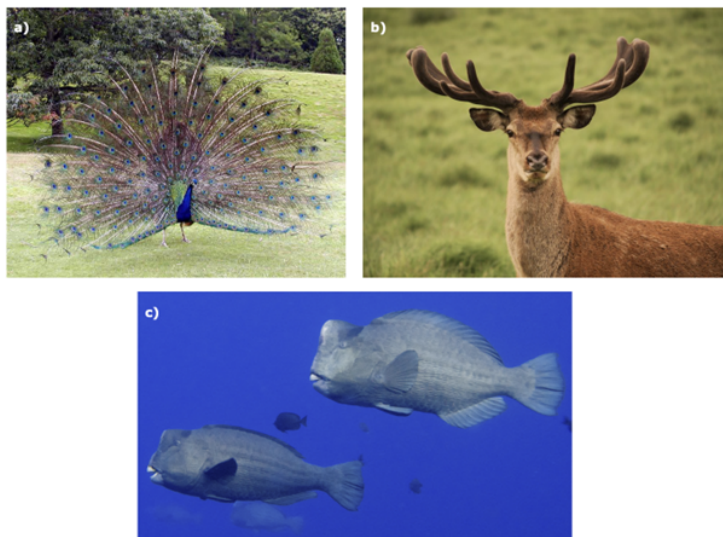


Figure 21.23—Examples of secondary sex characteristics including (a) feathers of a testes-bearing Indian peafowl (*Pavo cristatus*), (b) antlers of a testes-bearing red deer (*Cervus elaphus*), and (c) sexual dimorphism in green humphead parrotfish (*Bolbometopon muricatum*).

The **hypothalamic-pituitary-gonadal axis (HPG)** has been identified in all vertebrates (though the specific hormones involved may differ; Figure 21.24). The hypothalamus releases GnRH, which travels to the anterior pituitary via the portal system. The anterior pituitary releases gonadotropins including FSH and LH. Most vertebrates have two separate gonadotropins similar to mammalian FSH and LH. Teleost fishes, amphibians, birds, and most reptiles have separate FSH- and LH-like hormones. Squamate reptiles are an exception that only require an FSH-like hormone for reproduction. LH controls spermiation (i.e., mature sperm are released from the Sertoli cells into the lumen of the seminiferous tubules) in testes and ovulation in ovaries. FSH controls spermatogenesis or sperm development in testes (see [Figure 17.7](#)) and follicular development in ovaries (Box 21.3).

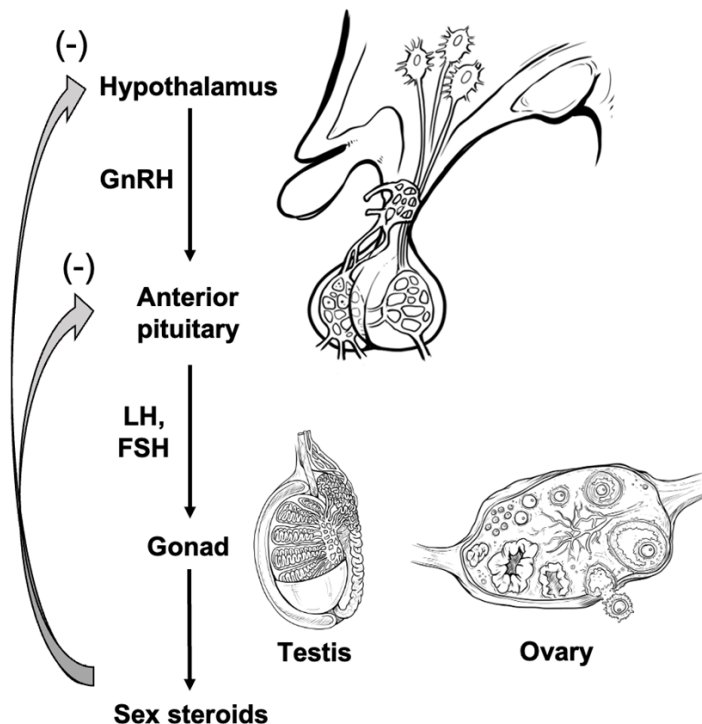


Figure 21.24—Hypothalamic–pituitary–gonadal axis (HPG axis). Gray arrows denote negative feedback. GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; FSH = follicle-stimulating hormone.

The gonadotropins travel to the gonads (either testes or ovaries), which triggers the release of sex steroids (e.g., androgens and estrogens depending on the type of gonad). The main circulating estrogen produced from ovaries is **estradiol**, whereas testes produce different androgens including **testosterone**, 5 α -dihydrotestosterone (DHT), and 11-ketotestosterone (11-KT). Relative levels of androgens to estrogens are not always characteristic or predictable across sexes as both testes and ovaries produce

androgens and estrogens. For example, testosterone is converted to estradiol by the enzyme **aromatase**. Once circulating levels reach a certain threshold, gonadal steroids initiate negative feedback at the level of the hypothalamus and pituitary.

Box 21.3—Reproductive Hormones: Hormonal Contraception

The most common types of hormonal contraception (birth control) include pills, patches, injections, and hormonal intrauterine devices (IUDs). These methods typically contain combinations of synthetic steroid hormones including estrogen and progestin. These hormones work together to prevent pregnancy by inhibiting ovulation (i.e., the release of an egg from the ovary) during the fertile period.

Using the human menstrual cycle as an example, FSH stimulates the growth of follicles during the follicular phase. As the follicle matures, estrogen production begins to thicken the endometrium (i.e., the lining of the uterus). Increased estrogen production triggers a surge of LH, which initiates ovulation. After releasing the ovum, the ruptured follicle is transformed into the corpus luteum (i.e., a temporary mass of cells that produces progesterone) during the luteal phase. Progesterone helps maintain the uterine lining in preparation for implantation of a fertilized egg. If there is no fertilization of the ovum by sperm, the corpus luteum deteriorates and production of progesterone stops, causing the uterine lining to shed (i.e., menstruation). The continued delivery of estrogen and

progesterin maintains the suppression of FSH and LH via negative feedback.

The synthetic estrogen and progesterin found in birth control harness the power of negative feedback of the HPG axis. The estrogen suppresses production of FSH in the pituitary gland, preventing follicle maturation. Constant low levels of progesterin that bind to receptors on the hypothalamus and pituitary prevent the LH surge that would otherwise trigger ovulation. The constant level of progesterin also makes the lining of the uterus inhospitable to implantation of an embryo.

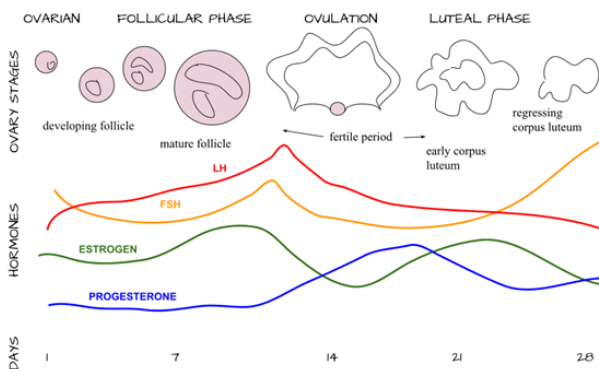


Figure 21.25—The cycling of reproductive hormones and their relationship to follicle development.

Development

Here, we discuss the development of the testes and ovaries. Development of gametes (i.e., oogenesis and spermatogenesis) and reproductive accessory organs such as ducts are covered in [Chapter 17—Urogenital System: Reproduction](#). In cyclostomes, there is fusion of paired primordia early in development. The gonad arises from the embryonic cortex and subsequently differentiates into a testis or an ovary. In hagfishes, there is a single ovary because one primordium fails to develop. In lampreys, the indifferent gonad will undergo one of two pathways to form a testis or ovary. To form a testis, the posterior portion develops into testicular tissue, but the anterior portion degenerates. To form an ovary, the anterior gonad develops into the ovary and the posterior portion degenerates. In elasmobranchs, the ovary is covered by germinal epithelium and may contain a cavity derived from large lymph spaces within the stroma. In teleost fishes, the gonad develops from a cortical primordium.

In most amphibians, the gonads develop from a bipotential gonad that differentiates into a testis or ovary early in development. However, there are a few species that undergo semidifferentiated gonadal development during which the gonads first develop as ovaries regardless of genetic sex followed by further differentiation into testes. Bufonid toads have rudimentary ovaries called Bidder's organs that develop from cortical remnants of embryonic genital ridge prior to gonadal differentiation. Amphibian ovaries are derived from the embryonic cortex and covered by germinal epithelium.

Reptilian gonads also start as bipotential and then differentiate into testes or ovaries. Granulosa cells are derived from germinal epithelium. In birds, the gonads develop from a pair of undifferentiated primordia associated with the embryonic nephrotome. Primordial germ cells migrate through the blood to the gonads where they develop into germinal epithelium. To form an avian ovary, the cortical tissue of the bipotential gonad

differentiates while the medullary tissue is suppressed. To form an avian testis, the medullary tissue of the bipotential gonad differentiates while the cortical tissue is suppressed. As outlined below, most avian species only develop the left ovary while the right regresses whereby more germ cells migrate to the left ovary during development. Both testes usually develop but the left is usually larger than the right in adults.

In mammals, the gonads begin as paired primordia from the mesoderm as a genital ridge on either side of the midline in close association with the transitory mesonephric kidney. Each primordium consists of an outer cortex derived from peritoneum and an inner medulla that differentiates into primary sex cords. To form a mammalian testis, the primary sex cords differentiate into seminiferous cords and the cortex regresses. Germ cells migrate from the yolk sac endoderm to the medulla where Sertoli and interstitial or Leydig cells form. Interstitial cells arise from the medulla surrounding the primary sex cords. To form a mammalian ovary, the primary sex cords degenerate, and secondary sex cords arise from the cortical tissue. Germ cells migrate from the yolk sac endoderm to the cortex where oogonia develop (eventually become primary oocytes) surrounded by follicular cells.

Evolution

Amniote testes exhibit a tubular pattern of seminiferous elements interspersed with clumps of interstitial cells. In vertebrates that are not amniotes, the testes exhibit a cystic organization. The testes of elasmobranchs and cyclostomes have isolated cellular cysts. The testes of bony fishes and amphibians consist of lobes or lobules composed of large cellular cysts. In anamniotes, Leydig cells are present between testicular cysts or in the periphery of or adjacent to the testis. In amniotes, Leydig cells develop between the tubules in the interstitial region.

In lampreys, there is either a single ovary or a single lobular testis with cystic organization. Interstitial cell masses are located between the lobules in the testis. Lamprey gonads secrete 15 α -hydroxylated steroids that are not secreted by other vertebrates. In hagfishes, there is also a single gonad that differentiates into an ovary or testis when hagfishes reach 20 cm in length. Hagfish testes do not appear to have interstitial cells, but they secrete testosterone. Egg-producing Atlantic hagfish (*Myxine glutinosa*) also possess a functional corpus luteum (plural: corpora lutea) that can produce progesterone.

Elasmobranchs have paired testes with Sertoli cells that secrete androgens and estrogens. Leydig cells are present between testicular cysts in a few species but are not a significant source of androgens. Testosterone, 11-KT, and DHT have been documented in some elasmobranch species. Testes also produce estradiol and progesterone. Elasmobranch ovaries are hollow and contain follicles similar to mammals where most estrogen production occurs in mature follicles with well-developed granulosa. Granulosa cells are the major source of testosterone and estrogens in atretic follicles and corpora lutea. Ovaries of viviparous sharks (see [Chapter 17](#) for definition of viviparous) also secrete relaxin (i.e., a similar hormone called raylaxin has been found in rays and skates), which prevents premature uterine contractions in sharks. Elasmobranchs are the only other vertebrate group besides mammals that produces relaxin.

Teleost fishes can be **gonochoristic** (i.e., individuals have only ovaries or testes) or **ambisexual** (i.e., simultaneous or sequential hermaphrodites). Simultaneous hermaphroditic fishes contain both functional ovaries and testes within the same individual, but sequential hermaphrodites start with one functional gonad type and then shift to the other type later in life. The testes of teleost fish (cystic organization) produce 11-KT and testosterone from Leydig cells. The ovary of most teleost fishes is hollow, but a few species have solid ovaries. There are masses of follicles embedded in stroma and the ovarian cavity is lined with epithelial

tissue. Theca cells produce androgens (testosterone), and granulosa cells produce estrogens.

In amphibians, adults typically only possess ovaries or testes but there are cases of juvenile hermaphroditism in certain species. Fat bodies lie adjacent to the gonads of amphibians and can secrete steroid hormones. The testes of anurans and urodeles secrete both testosterone and DHT in response to LH (urodeles also produce 11-KT). The testes of urodeles are of cystic organization consisting of one or more lobes. The testes of anurans are also of cystic organization with Leydig cells that resemble those of mammals. The ovaries of anurans and urodeles are hollow, sac-like structures. Granulosa cells are the major producer of estrogens, but theca cells also produce them. Amphibian ovaries produce progesterone, estradiol, estrone, testosterone, androstenedione and DHT.

In reptiles, the testes consist of convoluted seminiferous tubules each surrounded by the connective sheath tunica propria. Leydig cells and Sertoli cells are both steroidogenic. Reptilian ovaries are paired hollow structures with little stromal tissue. Granulosa cells in most species are the major source of follicular estrogen, but skinks produce estrogen from the theca cells instead. Crocodylians and turtles possess LH and FSH, but squamate reptiles only have one FSH-like hormone.

In birds, GnRH stimulates gonadotropin release from the anterior pituitary, whereas GnRH inhibits their secretion. Testes are paired masses of convoluted seminiferous tubules lined with germinal epithelium surrounded by connective tissue. There are steroidogenic interstitial cells between the seminiferous tubules as in reptiles and mammals. LH stimulates Leydig cells to secrete androgens, whereas FSH stimulates spermatogenesis and local androgen release from Sertoli cells. There are two ovaries during development but typically the left ovary will reach maturity while the right regresses, which is interpreted as an adaptation for flight (i.e., lighter body mass). The avian ovary consists of follicles containing oocytes surrounded by a layer of granulosa cells and

then another layer of theca cells, both of which are steroidogenic. FSH stimulates follicular development, whereas both LH and FSH stimulate estrogen synthesis.

Photoperiod (i.e., day length) tightly regulates gonad size and function in birds. Melatonin secreted from the pineal gland suppresses sex steroid release from the gonads during short days. As spring approaches and day length increases, an increase in LH and FSH release from the adenohypophysis leads to increased synthesis of spermatogenesis and androgen secretion of interstitial cells. Gonads will regress in size during the nonbreeding season and/or migration. Prolactin can inhibit gonadotropins from the pituitary but stimulates the formation of a brood patch (i.e., a patch of featherless, highly vascularized skin that forms in incubating adult birds to provide direct skin to egg contact) and secretion of crop milk in some species.

In mammals, the testes and ovaries are paired. Testes are composed of Sertoli cells (i.e., sperm production) and Leydig cells (i.e., androgen production) between the seminiferous tubules. Ovaries contain follicles that consist of follicular cells as depicted in Figure 21.22. Mammalian sex steroid release follows the typical HPG axis pattern described in Figure 21.24 whereby GnRH from the hypothalamus stimulates the release of LH and FSH from the anterior pituitary. FSH controls gametogenesis and estrogen synthesis, whereas LH controls androgen synthesis and gamete release. The role of reproductive hormones in mammalian menstruation are described in Box 21.3. The brains of egg-producing mammals contain a surge center that controls the LH surge in response to increased estrogen. The other notable endocrine organ of eutherian mammals is the placenta, which secretes estrogens and progesterone in addition to various polypeptide hormones (e.g., chorionic gonadotropins) during pregnancy. Finally, lactogenesis (i.e., milk production) in the mammary gland is controlled by prolactin release from the anterior pituitary, whereas lactation (i.e., milk ejection) is triggered by oxytocin release from the posterior pituitary.

21.8 Summary

This chapter highlights the myriad functions of vertebrate hormones due to their ability to travel long distances in the bloodstream to target tissues throughout the body. Hormones can be classified as either proteins or steroids and exert their effects on target tissues by binding to corresponding receptors, which can initiate positive or negative feedback. Across vertebrates, the hypothalamus and pituitary (hypothalamic-pituitary axes) control the function of other endocrine glands. The hypothalamus synthesizes and secretes releasing or inhibiting hormones, whereas the pituitary releases hormones that travel to other endocrine and nonendocrine target tissues. Hypothalamic neurohormones and pituitary tropic hormones are the first and second steps in many hormonal axes including the HPT, HPA, and HPG axes. Endocrine glands differ in developmental pathways, location, shape, and function across vertebrates. The photosensitive pineal gland secretes melatonin, which coordinates endogenous rhythms in higher vertebrates and pigmentation in lower vertebrates. The thyroid gland regulates metabolism and growth in addition to working with the parathyroid gland to regulate blood calcium levels. Pancreatic islets regulate blood glucose levels via a negative feedback loop with insulin and glucagon. The adrenal glands secrete glucocorticoids, which regulate the physiological and behavioral responses to stressors, in addition to secreting mineralocorticoids, which help regulate ion and water balance in the kidneys. Last, the gonads (i.e., testes and ovaries) secrete androgens and estrogens that regulate reproductive timing and activity across vertebrates. Throughout this chapter, we have highlighted the fact that hormones control nearly every function in the vertebrate body. The feedback between form and function has led to the evolution of diverse endocrine glands that influence the physiology, behavior, and fitness of nearly all vertebrates.

Application Questions

1. How can knowledge of comparative vertebrate endocrinology inform veterinary medicine?
2. What are the potential implications for human health based on insights from comparative vertebrate endocrinology studies?
3. How does the class of hormone (protein vs. steroid) affect its mode and speed of action at target cells?
4. What is positive versus negative feedback in terms of endocrine function?
5. What are the structural and functional differences between endocrine glands vs. exocrine glands?
6. What is an activational versus organizational effect of a hormone?

21.9 Further Reading

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