HISTOLOGY 2024-2025

Endocrine Glands Part I/III

Hormones are the signaling molecules that are produced by secretory cells of the endocrine glands directly into the capillaries for distribution throughout the body. Endocrine glands have no ducts like exocrine glands. Endocrine cells are typically epithelial, at least in origin, and arranged as cords or clusters intervened by fenestrated capillaries. Other organs have specialized functions other than endocrine but containing various endocrine cells, such as the heart, thymus, gut, kidneys, testis and ovaries.

Distribution by the circulation allows hormones to act on target cells with receptors for those hormones at a distance from the site of their secretion. However, endocrine cells may involve:

- **Autocrine secretion**: when cells produce molecules that act on themselves or on cells of the same type (such as insulin-like growth factor IGF produced my several cells that act on the same cells).
- **Juxtracrine secretion**: the signaling molecule remains on the surface of the secreting cell or adjacent extracellular matrix and affects target cells.
- **Paracrine secretion**: with localized distribution of hormones in interstitial fluid or through short loops of blood vessels (as when gastrin made by pyloric G cells reaches target cells in the fundic glands).

Hormones, like neurotransmitters, are frequently hydrophilic molecules such as proteins, glycoproteins, peptides or modified amino acids with their receptors on the surface of the target cells (either G protein-linked receptors of catalytic receptors). On the other hand, steroid-based hormones & thyroid hormones are hydrophobic and must circulate on transport proteins but can diffuse through cell membrane and activate cytoplasmic or nuclear receptors in target cells.

PITUITARY GLAND (HYPOPHYSIS)

Pituitary gland is 10x13x6 mm in dimensions, it weighs about 0.5 g in adults and located below the brain in the sella turcica of the sphenoid bone. The pituitary gland is developed from two embryonic origins, partly from the developing brain, known as **neurohypophysis** that remains attached to the median eminence of the hypothalamus by a stalk (infundibulum), it composed of two parts; pars nervosa and the infundibulum (stalk). And partly from the roof of the primitive mouth as outpouching of ectoderm that grows cranially (Rathke's pouch), known as **adenohypophysis** that consists of three parts: pars distalis, pars tuberalis and pars intermedia.

Hypophyseal portal system

The hypophyseal blood supply derives from two groups of blood vessels from internal carotid artery and drained by hypophyseal vein.

The superior hypophyseal arteries supply the median eminence and the infundibular stalk, which further divides into primary plexus of capillaries that irrigate the stalk and median eminence. These capillaries rejoin to form venules (**hypophyseal portal veins**) that branch again to form larger secondary plexus in the adenohypophysis that ultimately form a hypophyseal vein into systemic circulation. This portal circulation is of great importance as it carries neuropeptides from the median eminence the short distance to the adenohypophysis where they either stimulate or inhibit hormone release by the endocrine cells there.

The inferior hypophyseal arteries supply the pars nervosa of the neurohypophysis and drained via hypophyseal vein after irrigating the pars nervosa.

The hypothalamic-hypophyseal tract

The neurohypophysis is part of the brain so its structure is basically an extension from the hypothalamus as bundle of neuronal axons extends from two important hypothalamic nuclei (supraoptic & paraventricular nuclei) where the site of large neurosecretory neurons secreting peptides antidiuretic hormones ADH and oxytocin, respectively. These hormones undergo axonal transport from the nuclei to the pars nervosa though the stalk and accumulate temporarily in the axons of the hypothalamic-hypophyseal tract before their release into the circulation.

Adenohypophysis (Anterior pituitary)

Pars distalis

It comprises 75% of the adenohypophysis and has a thin fibrous capsule. The main components are cords of well-stained endocrine cells and intervened by fenestrated capillaries and supporting reticular connective tissue. Staining with H&E shows two groups of cells in pars distalis:

Chromophobes (afraid of staining) stain weakly with few or no secretory granules, and also include variable group of stem & undifferentiated progenitor cells as well as degranulated cells.

Chromophils (love staining) are secretory cells in which hormones are stored in cytoplasmic granules. There are two subtypes of chromophils based on their affinities into acidophils and basophils. Subtypes of basophilic and acidophilic cells are identified by their granular morphology in the TEM or more easily by immunohistochemistry. The cells are named according to their hormones' target cells.

Acidophils: which have an acidophilic cytoplasmic granule. They secrete either:

1. Growth hormone (somatotropin); these cells called ***somatotrophs***, they comprise 50% of cells.
2. Prolactin: these cells are called ***lactotrophs***, they comprise 15-20%.

Basophils: which have a basophilic cytoplasmic granules. They secrete either:

1. Pro-opiomelanocortin POMC (that is cleaved into adrenocorticotrophic hormone ACTH and β-lipotropin LPH); these cells called ***corticotrophs***. They comprise 15-20%.
2. Gonadotrophins (luteinizing hormone LH (in male called interstitial cell stimulating hormone ICSH) and follicular stimulating hormone FSH), these cells called ***gonadotrophs*** and comprise 10% of cells
3. Thyroid stimulating hormone (TSH), these cells called ***thyrotrophs*** and comprise 5% of total cells.

Cell Type	% of Total Cells	Hormone Produced	Major Function
Somatotrophs	50	Somatotropin (growth hormone, GH), a 22-kDa protein	Stimulates growth in epiphyseal plates of long bones via insulin-like growth factors (IGFs) produced in liver
Lactotrophs (or mammotrophs)	15-20	Prolactin (PRL), a 22.5-kDa protein	Promotes milk secretion
Gonadotrophs	10	Follicle-stimulating hormone (FSH) and luteinizing hormone (LH; interstitial cell-stimulating hormone [ICSH] in men), both 28-kDa glycoprotein dimers, secreted from the same cell type	FSH promotes ovarian follicle development and estrogen secretion in women and spermatogenesis in men; LH promotes ovarian follicle maturation and progesterone secretion in women and interstitial cell androgen secretion in men
Thyrotrophs	5	Thyrotropin (TSH), a 28-kDa glycoprotein dimer	Stimulates thyroid hormone synthesis, storage, and liberation
Corticotrophs	15-20	Adrenal corticotropin (ACTH), a 4-kDa polypeptide	Stimulates secretion of adrenal cortex hormones
		Lipotropin (LPH)	Helps regulate lipid metabolism

Pars tuberalis

It is a smaller funnel-shaped region surrounding the infundibulum of the neurohypophysis. Most of the cells of the pars tuberalis are gonadotrophs.

Pars intermedia

A narrow zone lying between the pars distalis and the pars nervosa, the pars intermedia contains basophils (corticotrophs), chromophobes and small colloid-filled cysts derived from the lumen of the embryonic hypophyseal pouch (remnant of Rathke pouch). Corticotrophs of the pars intermedia synthesize POMC that is cleaved differently than those of pars distalis, it is being cleaved into two hormones melanocyte-stimulating hormone MSH, β-endorphin.

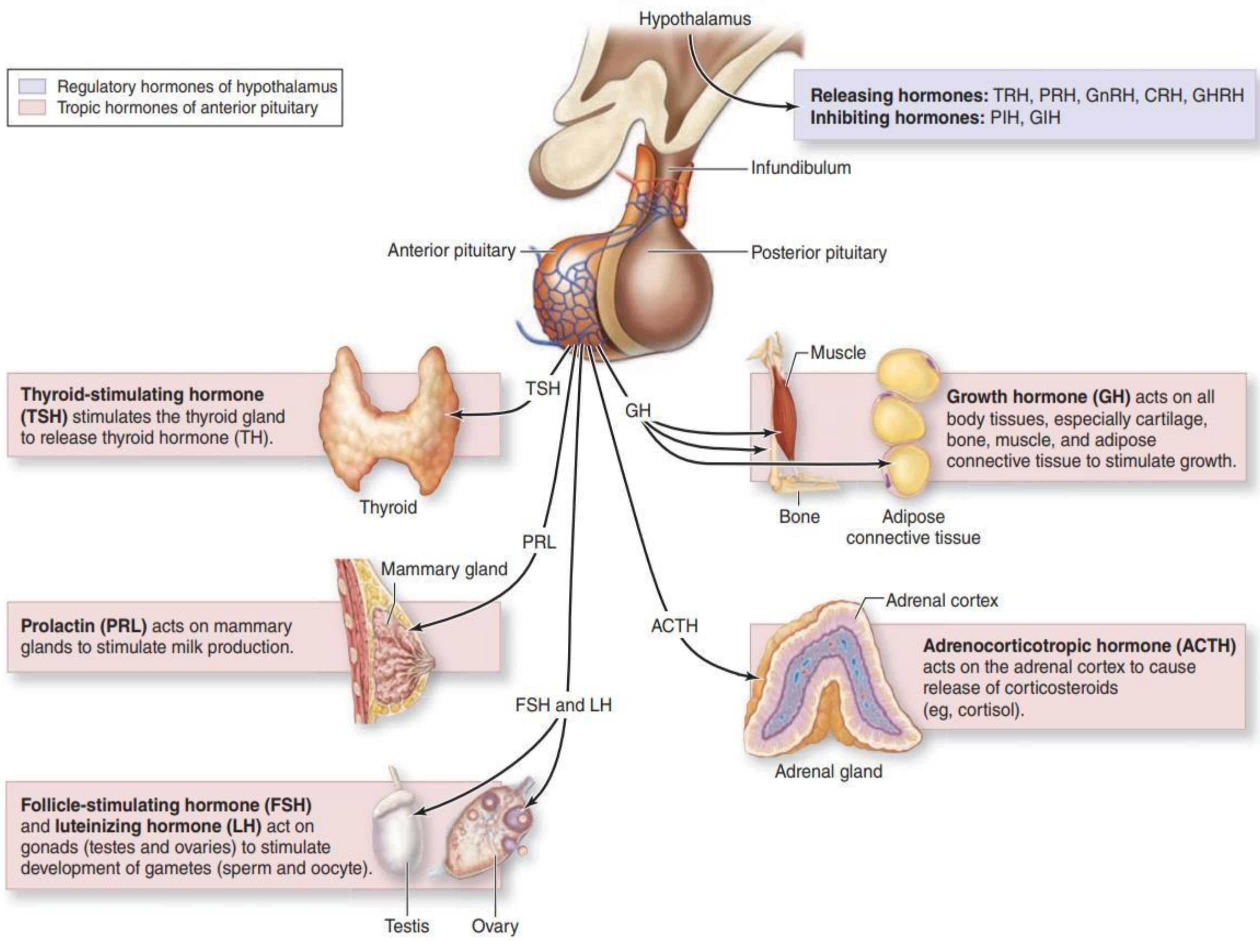

Figure 1. Hormones of the pars distalis and their targets

Control of hormone secretion in the adenohypophysis

The activities of the cells of the adenohypophysis are regulated primarily by peptide-related hypothalamic hormones produced by small neurons near the third ventricle, released from axons in the median eminence and transported by capillaries of the portal system into the anterior pituitary. Most of the hormones are releasing hormones that stimulate secretion by corresponding pituitary cells. However, only two of the hypothalamic factors are inhibitory hormones which block hormone secretion in the corresponding pituitary cells. (see below table 2)

Table 2	Hypothalamic hormones regulating cells of the anterior pituitary.	
Hormone	**Chemical Form**	**Functions**
Thyrotropin-releasing hormone (TRH)	3-amino acid peptide	Stimulates release of thyrotropin (TSH)
Gonadotropin-releasing hormone (GnRH)	10-amino acid peptide	Stimulates the release of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH)
Somatostatin	14-amino acid peptide	Inhibits release of both somatotropin (GH) and TSH
Growth hormone-releasing hormone (GHRH)	40- or 44-amino acid polypeptides (2 forms)	Stimulates release of GH
Dopamine	Modified amino acid	Inhibits release of prolactin (PRL)
Corticotropin-releasing hormone (CRH)	41-amino acid polypeptide	Stimulates synthesis of pro-opiomelanocortin (POMC) and release of both β-lipotropic hormone (β-LPH) and corticotropin (ACTH)

Another mechanism regulating activity of anterior pituitary cells is negative feedback by hormones from the target organs on secretion of both the hypothalamic hormones and on pituitary hormones as well. Such as thyroid gland (see below figure 2).

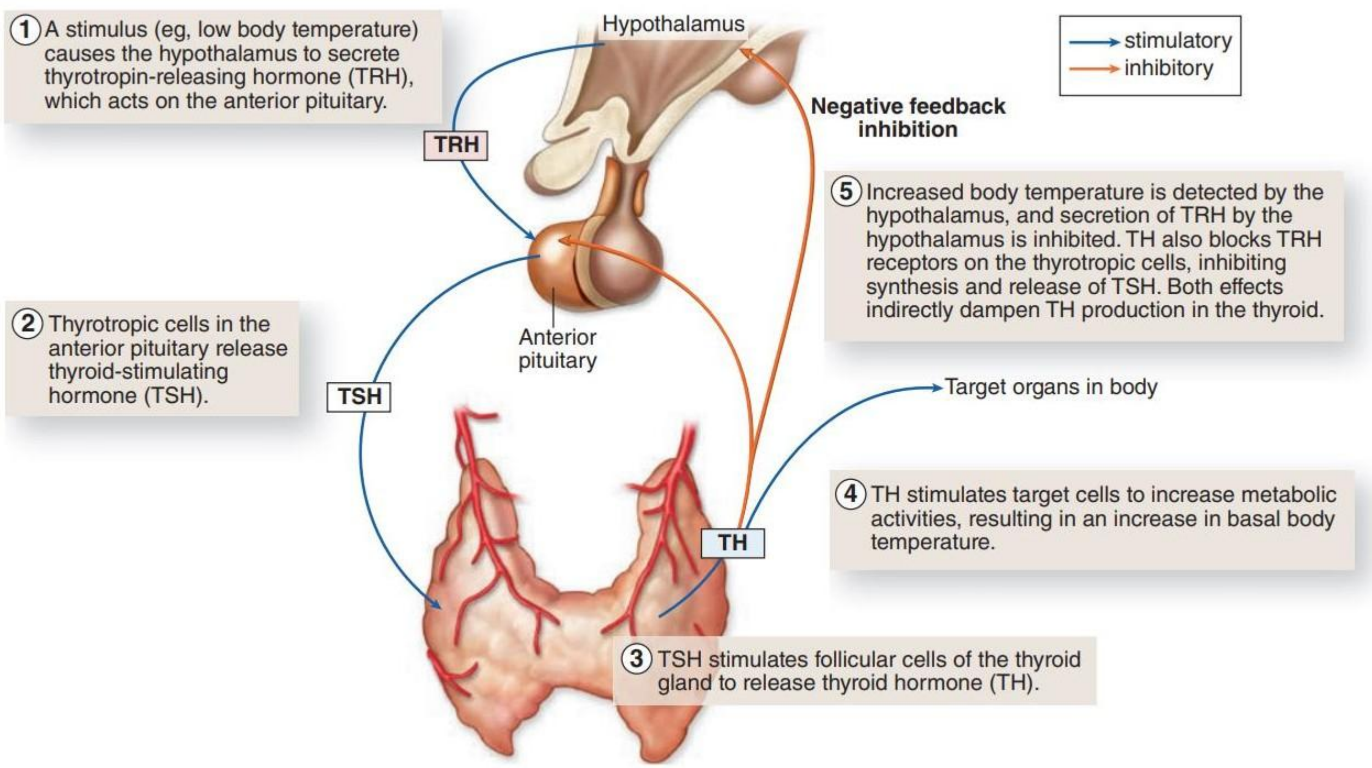

Figure 2. Negative feedback loops affecting anterior pituitary secretion

Neurohypophysis (posterior pituitary)

The neurohypophysis consists of the pars nervosa and the infundibular stalk. It does not contain true endocrine cells that synthesize its two hormones (ADH & oxytocin). It is composed of neural tissue, containing some 100,000 unmyelinated axons of large secretory neurons with cell bodies in the supraoptic and paraventricular nuclei of the hypothalamus. Also present are highly branched glial cells called **pituicytes** that resemble astrocytes and are the most abundant cell type in the posterior pituitary.The secretory neurons have all the characteristics of typical neurons, including the ability to conduct an action potential, but have larger-diameter axons and well-developed synthetic components related to the productionof the 9-amino acid peptide hormones antidiuretic hormone ADH (also called arginine vasopressin) and oxytocin and transported axonally into the pars nervosa and accumulate in axonal dilatations called **neurosecretory (Herring) bodies**. Herring bodies appear as lightly-stained acidophilic bodies contain membrane-bound granuleswith either ADH or oxytocin, those hormones are bound into a carrier proteins called neurophysin I and II.

ADH is released in response to increased blood osmolarity, sensed by osmoreceptor cells in the hypothalamus, which then stimulate ADH synthesis in supraoptic neurons. ADH increases the permeability of the renal collecting ducts to water. Oxytocin stimulates contraction of uterine smooth muscle during childbirth and the myoepithelial cells in the mammary gland during infant nursing. Oxytocin also produces psychological effects, such as promotion of pair bonding behavior.

Benign pituitary adenomas often produce excessive numbers of functional acidophils or basophils. Adenomas involving somatotropic cells can cause gigantism if occurring in children before closure of the long bones' epiphyseal plates or acromegaly in adults, with musculoskeletal, neurologic, and other medical consequences.

Loss of ADH secretion for whatever the reason resulting in loss of ability to concentrate the urine with excessive urination & drinking water with an inability to maintain normal plasma osmolarity this condition known as diabetes insipidus.

THYROID GLAND

The thyroid gland, located anterior and inferior to the larynx, consists of two lobes united by an isthmus. It originates during embryonic life from the foregut endoderm near the base of the tongue. It produces thyroid hormones thyroxine (tetra-iodothyronine or T4) and tri-iodothyronine (T3) which help control the basal metabolic rate throughout the body, as well as the polypeptide hormone calcitonin.

The thyroid gland is covered by a fibrous capsule from which septa extend into the parenchyma, dividing it into lobules and carrying blood vessels, nerves, and lymphatics.

The parenchyma of the thyroid is composed of millions of rounded epithelial thyroid follicles of variable diameter. Follicles are densely packed together, separated from one another only by sparse reticular connective tissue, each with simple epithelium and a central lumen densely filled with gelatinous acidophilic colloid. The thyroid is the only endocrine gland in which a large quantity of secretory product is stored. Moreover, storage is outside the cells, in the colloid of the follicle lumen, which is also unusual. There is sufficient hormone in follicles to supply the body for up to 3 months with no additional synthesis. Thyroid colloid contains iodinated large glycoprotein thyroglobulin (660 kDa), the precursor for the active thyroid hormones.

The follicular cells, or ***thyrocytes***, range in shape from squamous to low columnar, their size and other features varying with their activity, which is controlled by thyroid-stimulating hormone (TSH) from the anterior pituitary. Active glands have more follicles of low columnar epithelium; glands with mostly squamous follicular cells are hypoactive.

Thyrocytes have apical junctional complexes and rest on a basal lamina. The cells exhibit organelles indicating active protein synthesis and secretion, as well as phagocytosis and digestion. The nucleus is generally round and central. Basally the cells are rich in rough ER and apically, facing the follicular lumen, are Golgi complexes, secretory granules, numerous phagosomes and lysosomes, and microvilli.

Another endocrine cell type, the **parafollicular cell** or **C cell**, is also found inside the basal lamina of the follicular epithelium or as isolated clusters between follicles. Derived from the neural crest, parafollicular cells are usually somewhat larger than follicular cells and stain less intensely. They have a smaller amount of rough ER, large Golgi complexes, and numerous small (100-180 nm in diameter) granules containing calcitonin. Secretion of calcitonin is triggered by elevated blood Ca2+ levels, and it inhibits osteoclast activity, but this function in humans is less important than the roles of parathyroid hormone and vitamin D in the regulation of normal calcium homeostasis.

Production of Thyroid Hormone & Its Control

1. The production of thyroglobulin, which is similar to that in other glycoprotein-exporting cells in the rough ER and glycosylation in the Golgi apparatus. Thyroglobulin has no hormonal activity but it is critical for thyroid hormone synthesis. The glycoprotein is released as an exocrine product from apical vesicles of thyrocytes into the follicular lumen.
2. Iodide uptake from blood by Na/I symporters (NIS) in the basolateral cell membranes, which allows for 30-fold concentration of iodide in thyroid tissue relative to plasma. An apical iodide/chloride transporter (aka pendrin) pumps I- into colloid.
3. Oxidation of iodide into iodine by thyroid peroxidase enzyme and iodination of tyrosyl residues in thyroglobulin with either one or two.
4. Formation of T3 and T4 (thyroxine) occurs as two iodinated tyrosines still part of colloidal thyroglobulin get coupled to form thyroid hormones.
5. Endocytosis of iodinated thyroglobulin by the thyrocytes where the endocytic vesicles fuse with lysosomes, and the thyroglobulin is degraded by lysosomal proteases freeing active thyroid hormones as both T3 and T4.
6. Secretion of T4 and T3 at the basolateral domain and immediately taken by capillaries.

The major regulator of the anatomic and functional state of thyroid follicles is TSH (thyrotropin) from the anterior pituitary. With TSH receptors abundant on the basal cell membrane of thyrocytes, this tropic hormoneincreases cell height in the follicular epithelium and stimulates all stages of thyroid hormone production and release. Thyroid hormones inhibit the release of TSH, maintaining levels of circulating T4 and T3 within the normal range.

***Graves disease** is an autoimmune disorder in which antibodies produce chronic stimulation of the follicular cells and release of thyroid hormones (hyperthyroidism), which causes a hypermetabolic state marked by weight loss, nervousness, sweating, heat intolerance, and other features. Hypothyroidism, with reduced thyroid hormone levels, can be caused by local inflammation (**Hashimoto's thyroiditis**) or inadequate secretion of TSH by the anterior pituitary gland and is often manifested by tiredness, weight gain, intolerance of cold, and decreased ability to concentrate.*