Histology of the Endocrine glands

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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:

- **Paracrine secretion**: with localized distribution of hormones in interstitial fluid of through short loops of blood vessels (as when gastrin made by pyloric G cells reaches target cells in the fundic glands).
- **Juxtracrine secretion**: the signaling molecule remains on the surface of the secreting cell or adjacent extracellular matrix and affects target cells.
- **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).

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. 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 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 pouch), known as **adenohypophysis** that consists of three part: pars distalis, pars tuberalis and pars intermedia.

Hypophyseal portal system

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

The superior hypophyseal arteries supply the median eminence and the infandibular 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 with 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 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.

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.

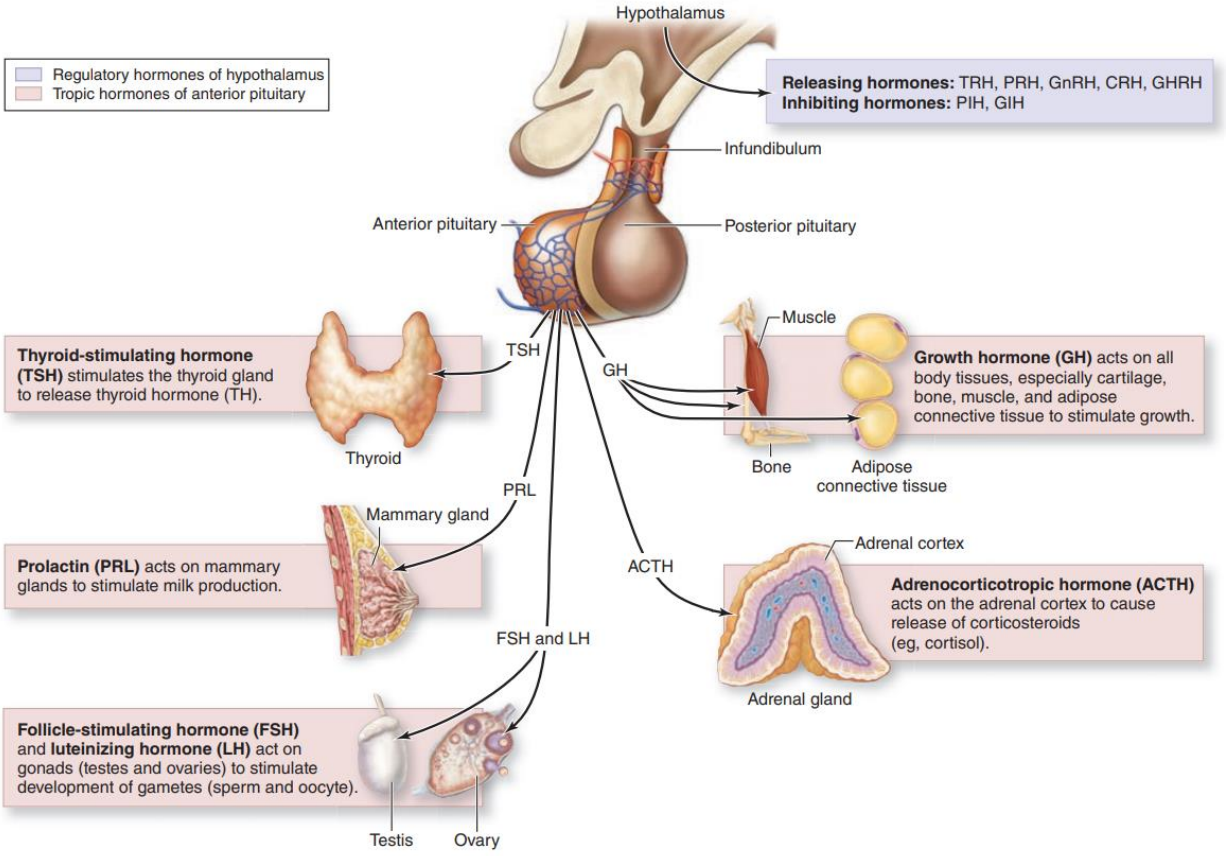

Figure 1. Hormones of the pars distalis and their targets

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 1)

Table 1 **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).

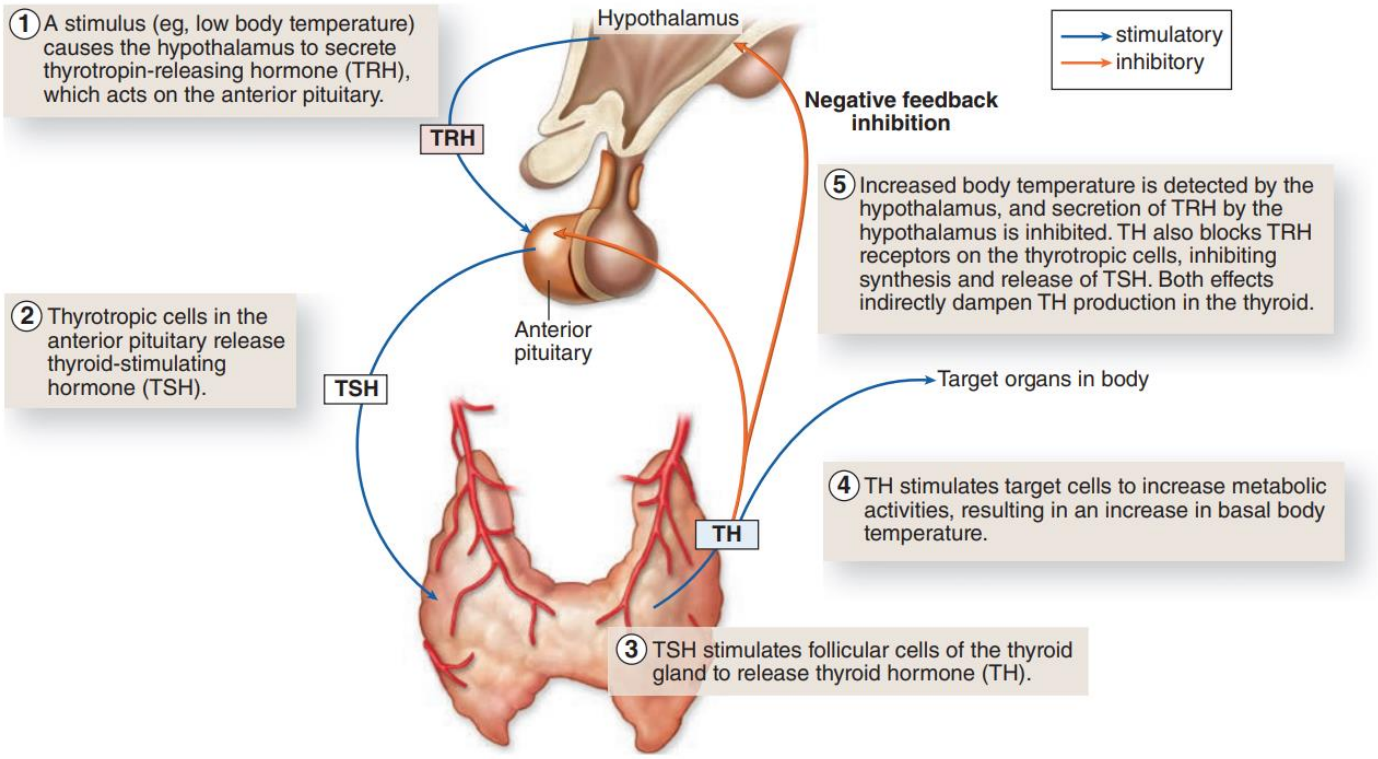

Figure 2. Negative feedback loops affecting anterior pituitary secretion

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 production of 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 granules with 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.

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 the 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 Ca^{2+} 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 hormone increases 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.

Parathyroid glands

These are four small ovoid masses—each 3 × 6 mm—with a total weight of about 0.4 g. They are located on the back of the thyroid gland, usually embedded in the larger gland's capsule. Each parathyroid gland is contained within a thin capsule from which septa extend into the gland. A sparse reticular stroma supports dense elongated clusters of secretory cells.

The endocrine cells of the parathyroid glands, called **principal (chief) cells**, are small polygonal cells with round nuclei and pale-staining, slightly acidophilic cytoplasm. Irregularly shaped cytoplasmic granules contain the polypeptide parathyroid hormone (PTH), an important regulator of blood calcium levels, PTH has three major targets:

- Osteoblasts respond to PTH by producing an osteoclast-stimulating factor, which increases the number and activity of osteoclasts. The resulting resorption of the calcified bone matrix and release of Ca^{2+} increase the concentration of circulating Ca^{2+}, which suppresses PTH production.
- In the distal convoluted tubules of the renal cortex, PTH stimulates Ca^{2+} reabsorption (and inhibits phosphate reabsorption in the proximal tubules).
- PTH also indirectly increases the Ca^{2+} absorption in the small intestine by stimulating vitamin D activation.

With increasing age, many secretory cells are replaced with adipocytes, which may constitute more than 50% of the gland in older people.

Much smaller populations of **oxyphil cells**, often clustered, are sometimes also present in parathyroid glands, more commonly in older individuals. These are much larger than the principal cells and are characterized by very acidophilic cytoplasm filled with abnormally shaped mitochondria.

Adrenal glands

The adrenal (or suprarenal) glands are paired organs lying near the superior poles of the kidneys, embedded in the pararenal adipose tissue and fascia. They are flattened structures with a half-moon shape, about 4-6-cm long, 1-2-cm wide, and 4-6-mm thick in adults. Together, they weigh about 8 g, but their weight and size vary with the age and physiologic condition of the individual.

Adrenal glands are each covered by a dense connective tissue capsule that sends thin trabeculae into the gland's parenchyma. The stroma consists mainly of reticular fibers supporting the secretory cells and microvasculature. Each gland has two concentric regions: a yellowish adrenal cortex and a reddish-brown central adrenal medulla.

The adrenal cortex and medulla can be considered two different organs with distinct embryonic origins, functions, and morphologic characteristics that become united during embryonic development. The cortex arises from mesoderm and the medulla from the neural crest.

The general histologic appearance of the adrenal gland is typical of an endocrine gland in which cells of both cortex and medulla are grouped in cords along wide capillaries.

Blood supply

The adrenal gland lacks a hilum, 3 adrenal arteries penetrate the capsule independently and branch immediately to form subcapsular arterial plexus. From this plexus 2 groups of arterioles arise; arterioles for the adrenal cortex and others for the medulla bypassing the cortex. Cortical capillaries irrigate endocrine cells of the cortex and then drain into the microvasculature of the medulla. The adrenal medulla has two a dual blood supply: arterial blood from the medullary arterioles and venous blood capillaries of the cortex. Venous drainage from the glands occurs via the suprarenal veins.

Adrenal cortex

Cells of the adrenal cortex have characteristic features of steroid-secreting cells: acidophilic cytoplasm rich in lipid droplets, with central nuclei. Ultrastructurally their cytoplasm shows an exceptionally profuse smooth ER (SER) of interconnected tubules, which contain the enzymes for cholesterol synthesis and conversion of the steroid prohormone pregnenolone into specific active steroid hormones. The mitochondria are often spherical, with tubular rather than shelflike cristae. These mitochondria not only synthesize ATP but also contain the enzymes for converting cholesterol to pregnenolone and for some steps in steroid synthesis. The function of steroid-producing cells involves close collaboration between SER and mitochondria.

The adrenal cortex has three concentric zones in which the cords of epithelial steroid-producing cells are arranged somewhat differently and which synthesize different classes of steroid hormones (summarized in below table 2):

table 2	Zona Glomerulosa	Zona Fasciculata	Zona Reticularis
% of the cortex	15%	65-80%	10%
Shape of cells	Columnar or pyramidal	Large polyhedral cells, with lipid droplets and appear vacuolated (**spongiocytes**)	Smaller cells, few lipid droplets & more lipofuscin pigment
Arrangement of cells	Rounded or arched cords	Long cords, one or two cells thick	Network or irregular cords
Hormones produced	Mineralocorticoids; **aldosterone**	Glucocorticoids; **cortisol**	Adrenal (weak) androgens **DHEA** > testosterone
ACTH control	Weak stimulation by ACTH	Yes, with feedback regulation	Yes, with feedback regulation
Other control	Angiotensin II (from RAAS) & high K level		
Action of hormone	Increase Na reabsorption & K & H excretion	Gluconeogenesis in many cells and glycogen synthesis in the liver, muscle proteolysis & fat mobilization, suppress immune system.	development of the male sex organs in childhood normal onset of female body hair following puberty

Addison disease or adrenal cortical insufficiency is a disorder, usually autoimmune in origin, which causes degeneration in any layer of adrenal cortex, with concomitant loss of glucocorticoids, mineralocorticoids, or androgen production. At the same there will be no negative feedback from cortical hormones resulting in elevated ACTH and MSH levels from the anterior pituitary consequently, results in skin darkening from the effect of high MSH.

Aldosterone-secreting tumors (of zona glomerulosa cells) causing a group of symptoms called Conn's syndrome.

Adrenal cortical adenoma that secretes cortisol resulting in Cushing syndrome.

Adrenal medulla

It can be considered a modified sympathetic postganglionic ganglion, lacking axons and dendrites and its ganglionic have specialized as secretory cells. The medulla is composed of large pale-staining polyhedral cells called **chromaffin cells** arranged in cords or clumps and supported by reticular fiber stroma intervened by profuse supply of fenestrated capillaries. Unlike cells of the adrenal cortex, chromaffin cells contain many electron-dense granules for the storage and secretion of catecholamines (epinephrine and norepinephrine). The granules of epinephrine-secreting cells are less electron-dense and generally smaller than those of norepinephrine-secreting cells. Both catecholamines, together with Ca2+ and ATP, are bound in granular storage complexes with proteins called **chromogranins** (catecholamine-binding protein). About 80% of the catecholamines secreted from the adrenal is epinephrine during fight-or-flight response.

Medullary chromaffin cells are innervated by preganglionic sympathetic neurons, which trigger epinephrine and norepinephrine release during stress and intense emotional reactions. Epinephrine increases heart rate, dilates bronchioles, and dilates arteries of cardiac and skeletal muscle. Norepinephrine constricts vessels of the digestive system and skin, increasing blood flow to the heart, muscles, and brain. Both hormones stimulate glycogen breakdown, elevating blood glucose levels.

In the adrenal medulla, benign pheochromocytomas periodically secrete high levels of catecholamines that cause swings in blood pressure between hypertension and hypotension.

Pancreatic islets (of Langerhans)

These are compact spherical or ovoid masses of endocrine cells embedded within the acinar exocrine tissue of the pancreas. Each of these islets contains several hundred cells, but some have only a few cells. The pancreas has more than 1 million islets, mostly in the gland's narrow tail region, but they only constitute 1%-2% of the organ's total volume.

A very thin reticular capsule surrounds each islet, separating it from the adjacent acinar tissue. Pancreatic islets have the same embryonic origin as the pancreatic acinar tissue. The cells of islets are polygonal or rounded, smaller & more lightly stained than the surrounding acinar cells arranged in cords that are separated by fenestrated capillaries.

The major islet cells are most easily identified and studied by immunohistochemistry:

- α or A cells secrete primarily glucagon and are usually located peripherally.
- β or B cells produce insulin (L. insula, island), are the most numerous, and are located centrally.
- δ or D cells, secreting somatostatin, are scattered and much less abundant.
- PP cells, produce pancreatic polypeptide, these cells are more common in the islets located within the head of pancreas.

Pineal gland

Also known as hypophysis cerebri, is a small pine cone-shaped gland, about 5-8 mm by 3-5 mm in the posterior wall of third ventricle attached to the brain by a stalk. It develops from neuroectoderm. The pineal gland is covered by connective tissue derived from pia mater, from which septa divide the parenchyma of the gland into lobules.

The main cells in the gland parenchyma are secretory cells called **pinealocytes**, they have lightly basophilic stained cytoplasm and irregular euchromatic nucleus. Pinealocytes appear to have long cytoplasmic processes extending to vascular connective tissue septa ending in dilatation near capillaries. Interstitial glial cells (modified astrocytes) can also be seen between cords of pinealocytes and around capillaries with elongated nuclei and more heavily stained than those of pinealocytes. The secretory cells of the pineal gland secret melatonin.

A characteristic feature of the pineal gland is the presence of variously sized concretions of calcium and magnesium salts called **corpora arenacea**, or brain sand. They gradually increase in number and size with age, with no apparent effect on the gland's function.

Melatonin release from pinealocytes is promoted by darkness and inhibited by daylight. The resulting diurnal fluctuation in blood melatonin levels induces rhythmic changes in the activity of the hypothalamus, pituitary gland, and other endocrine tissues that characterize the circadian (24 hours, day/night) rhythm of physiological functions and behaviors. the cycle of light and darkness is detected within the retinas and transmitted to the pineal via the retinohypothalamic tract, the suprachiasmatic nucleus, and the tracts of sympathetic fibers entering the pineal.