

# Neuroendocrine system

## Hypophysis

## Pineal gland

### Adenohypophysis

### Neurohypophysis

Interstitial cells  
Pinealocytes  
|  
Melatonin

Pars tuberalis

Pars distalis

Infundibulum

Pars nervosa

Acidophils

Basophils

Pituicytes

Unmyelinated axons

Growth hormone

Prolactin

Gonadotropins

Thyroid-stimulating hormone

Adrenocorticotropic hormone

Follicle-stimulating hormone

Lutenizing hormone

Oxytocin

Antidiuretic hormone

Paraventricular nucleus

Supraoptic nucleus

Hypothalamus

Neurophysin (carrier)  
Oxytocin or antidiuretic hormone

Arteriole  
Collecting tubule (kidneys)

Myometrium (labor)  
Myoepithelial cell (lactation)

Hormonal targets

Hormonal targets

Liver  
|  
Insulin-like growth factor-1  
|  
Bone

Lactating mammary gland

Granulosa cells (ovaries)

Sertoli cells (testes)

Corpus luteum (ovaries)

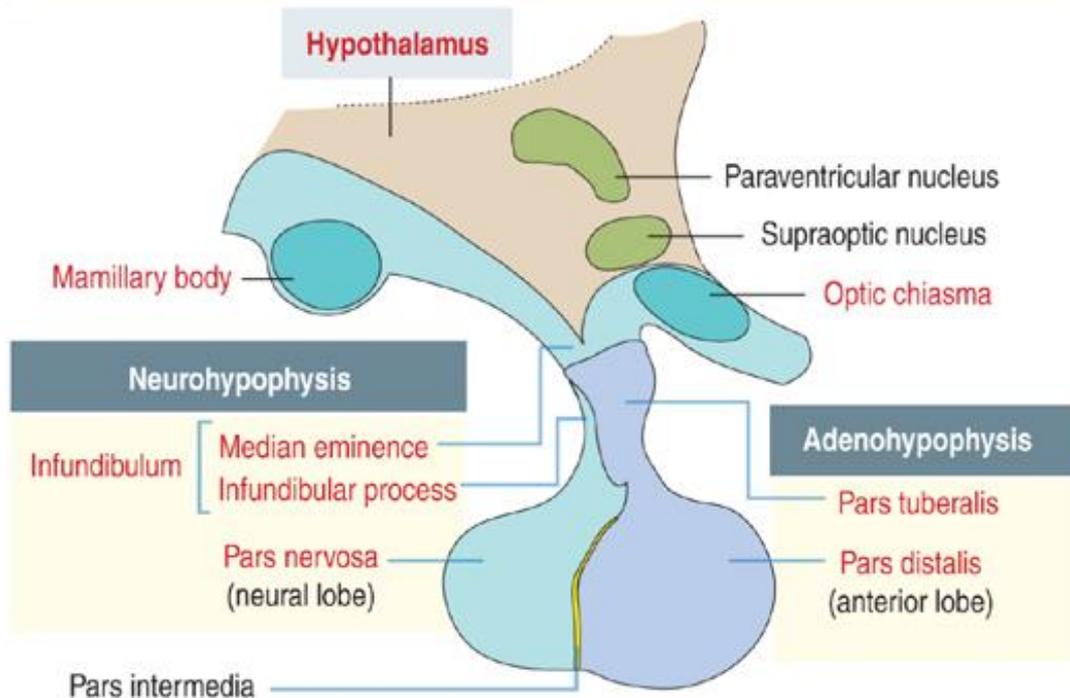
Leydig cells (testes)

Follicular cells (thyroid)

Zona fasciculata

Zona reticularis

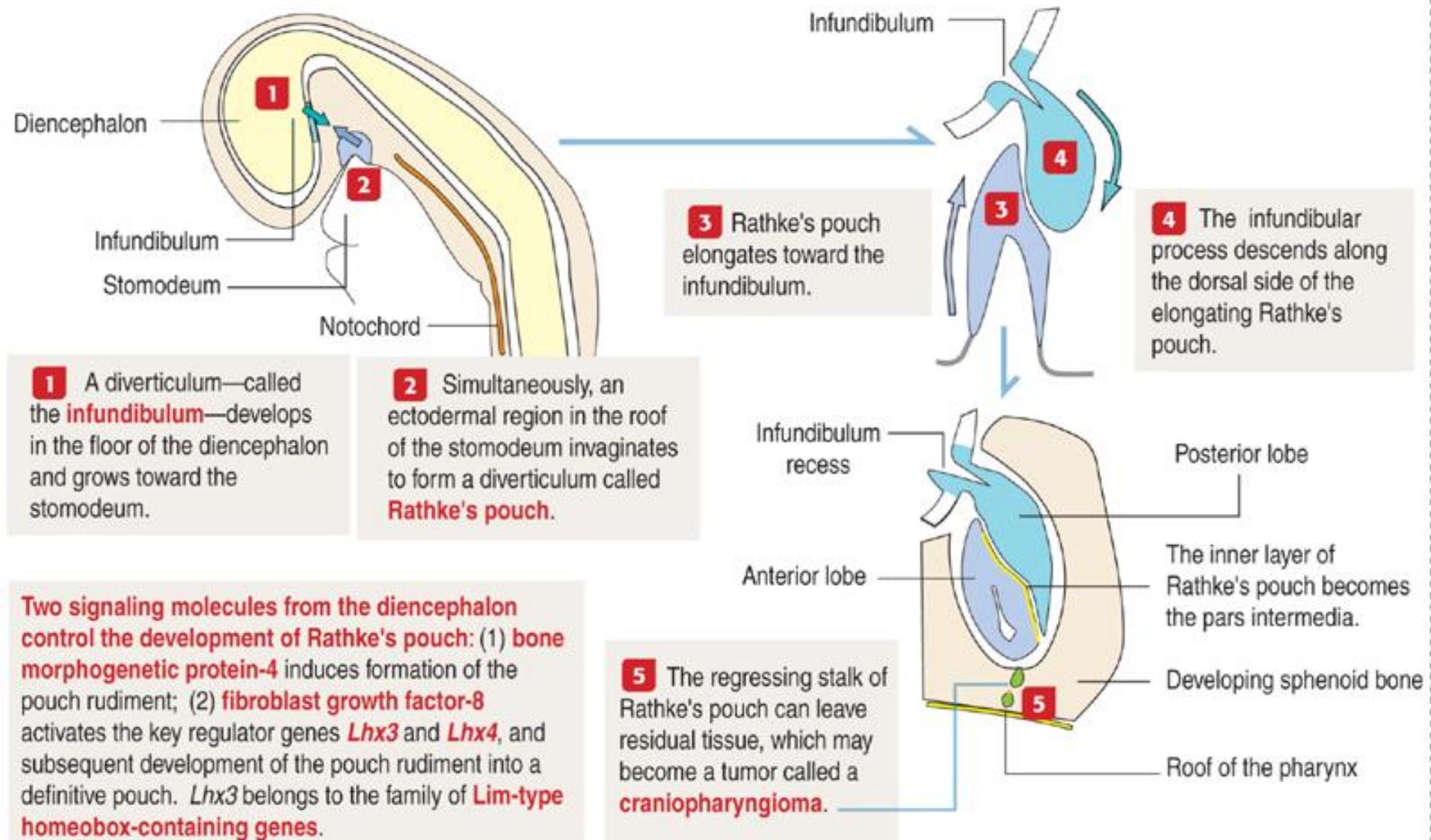
The **hypothalamus** is divided into two symmetric halves by the third ventricle. It is limited rostrally by the **optic chiasma**, caudally by the **mamillary bodies**, laterally by the **optic tracts**, and dorsolaterally by the **thalamus**.

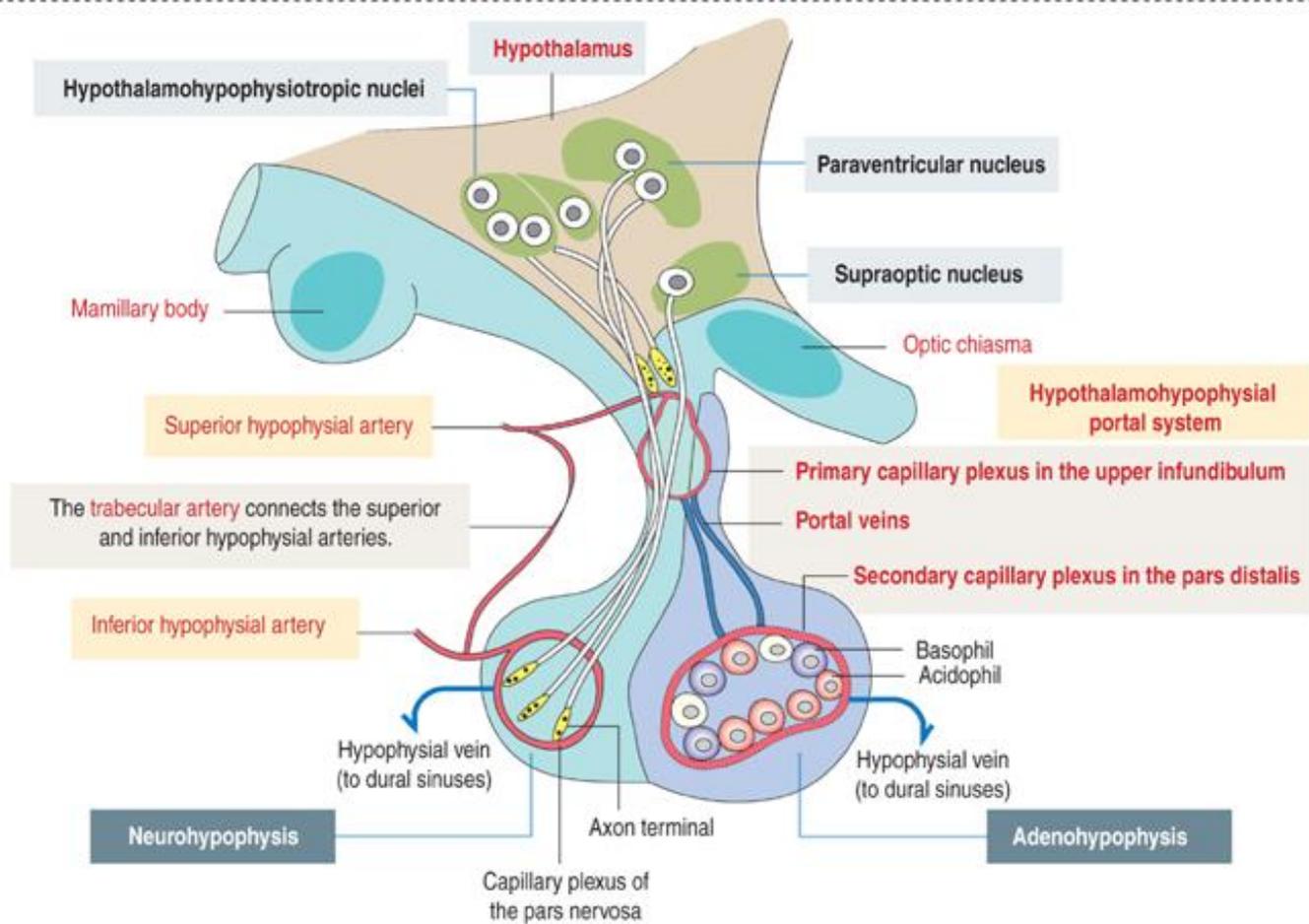


### Major subdivisions of the hypophysis

The **adenohypophysis** is formed by three major subdivisions: (1) the **pars distalis**, or **anterior lobe**, the main glandular epithelial component; (2) the **pars tuberalis**, a collar-like nonsecretory tissue enveloping the infundibulum of the neurohypophysis; and (3) the **pars intermedia**, a narrow wedge forming a cap around the pars nervosa (neural lobe).

The **neurohypophysis** consists of two parts: the **pars nervosa**, or neural lobe, and the **infundibulum**. The infundibulum is formed by two structures: (1) the **median eminence**, a funnel-shaped extension of the hypothalamus; and (2) the **infundibular process**.





### Blood supply to the hypophysis

The **superior hypophysial artery** forms a **primary capillary plexus** in the infundibulum (formed by the median eminence and infundibular stem). The primary capillary plexus receives releasing and inhibitory hormones from the neuroendocrine **hypothalamohypophysiotropic nuclei**.

The primary capillary plexus is drained by **portal veins**.

Portal veins supply blood to the **secondary capillary plexus**, with which basophils and acidophils are associated.

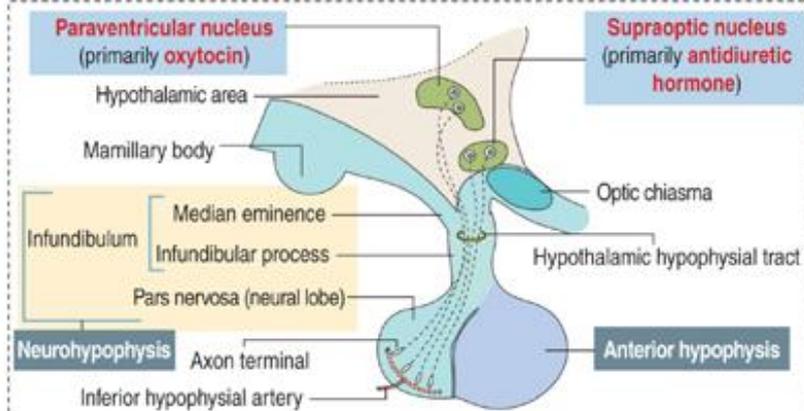
By this mechanism, hypothalamic releasing and inhibitory factors act directly on cells of the pars distalis (anterior

hypophysis) to regulate their endocrine function.

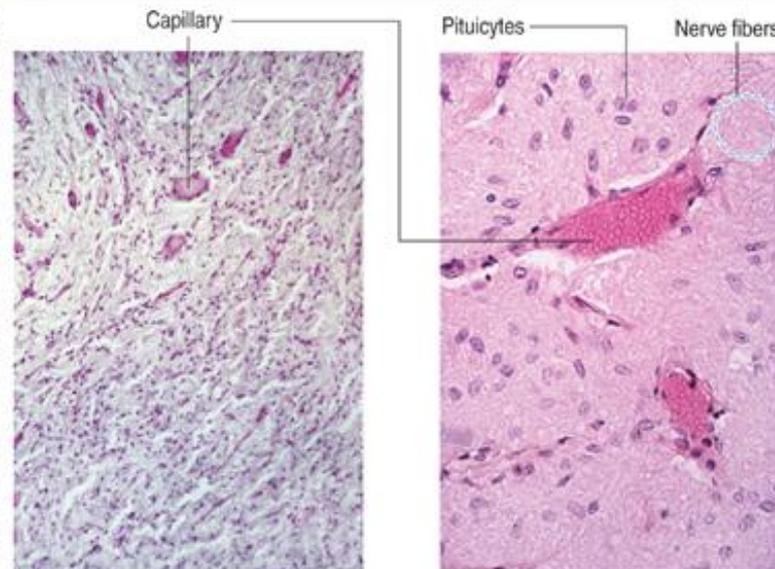
The primary and secondary capillary plexuses linked by the portal veins form the **hypothalamohypophysial portal system**.

The **inferior hypophysial artery** supplies the pars nervosa, forming a capillary plexus, which collects vasopressin (antidiuretic hormone) and oxytocin produced by neuroendocrine cells of the supraoptic and paraventricular nuclei, respectively.

The superior and inferior hypophysial arteries are connected by the **trabecular artery**.



The hormones **antidiuretic hormone** (or **arginine vasopressin**) and **oxytocin** are synthesized in the neurons of the **supraoptic** and **paraventricular nuclei**, respectively. The hormones are transported along the axons forming the **hypothalamic hypophysial tract**, together with the carrier protein **neurophysin**, and are released at the axon terminals. The hormones enter **fenestrated capillaries** derived from the inferior hypophysial artery.

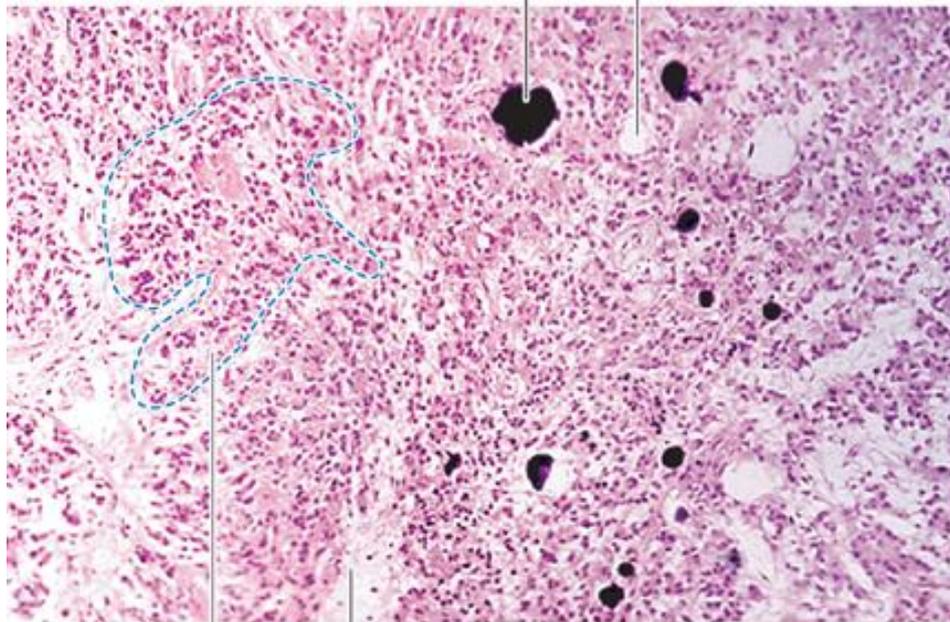
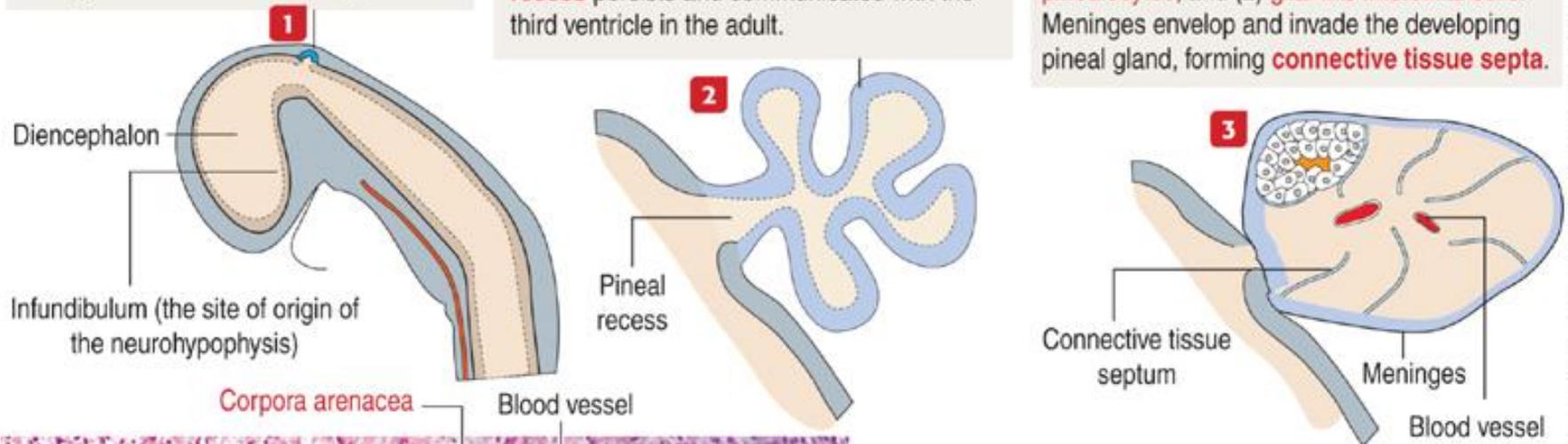


The neurohypophysis is formed by supporting neuroglial cells—the **pituicytes**—whose cytoplasmic processes surround the **unmyelinated nerve fibers** arising from neurons of the paraventricular and supraoptic nuclei. Abundant capillaries are visualized. Antidiuretic hormone and oxytocin accumulate temporarily in axon dilations, forming the **Herring bodies** (not seen in these photomicrographs).

**1** A dorsal diverticulum, an outpocketing of the diencephalon, initiates the formation of the pineal gland during the 10th week of development.

**2** The wall of the vesicular evagination thickens. The lumen is occluded, except at the base of the outpocketing, where the **pineal recess** persists and communicates with the third ventricle in the adult.

**3** The pineal gland becomes a compact structure containing two cell types derived from the primordial neuroepithelial cells: (1) **pinealocytes**; and (2) **glial-like interstitial cells**. Meninges envelop and invade the developing pineal gland, forming **connective tissue septa**.



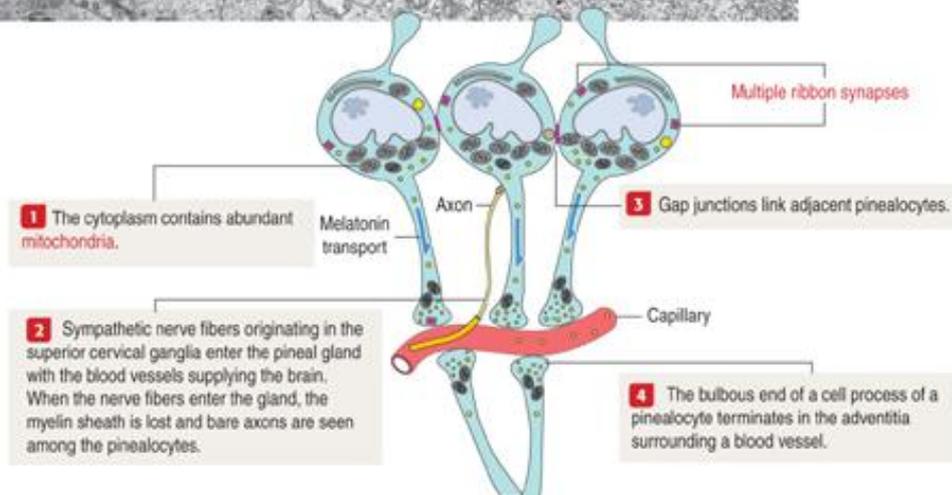
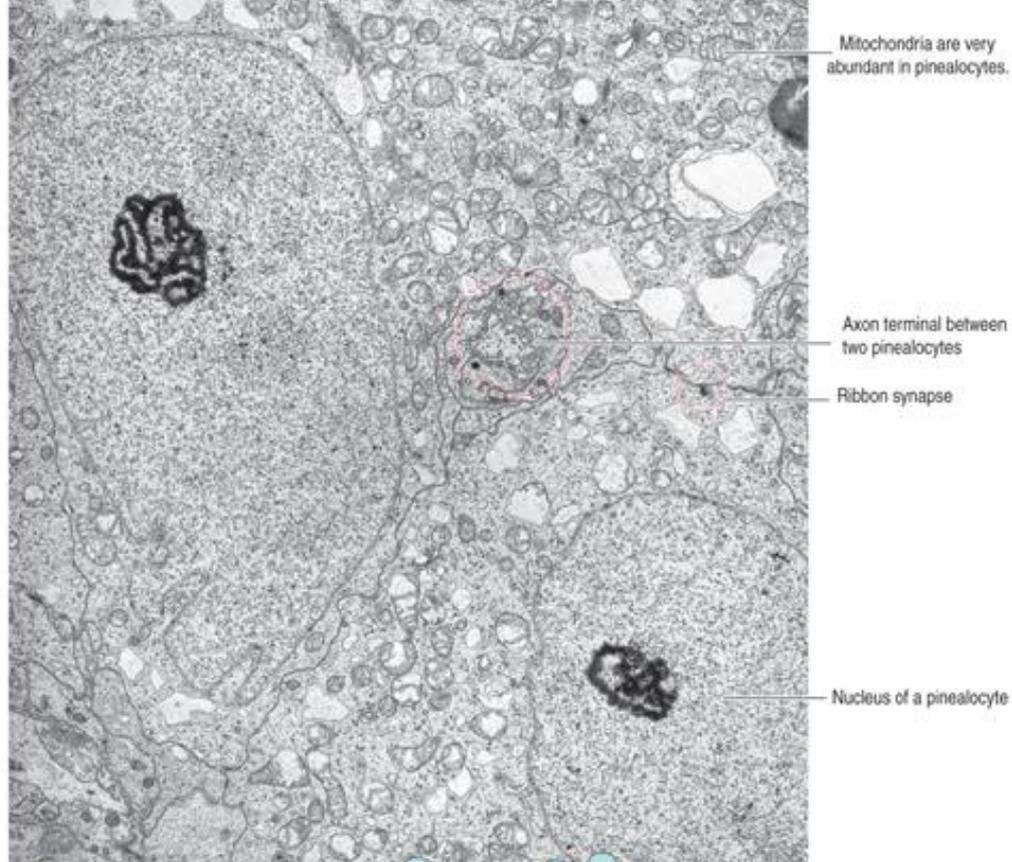
Cluster of pinealocytes      Connective tissue septum

### The pineal gland

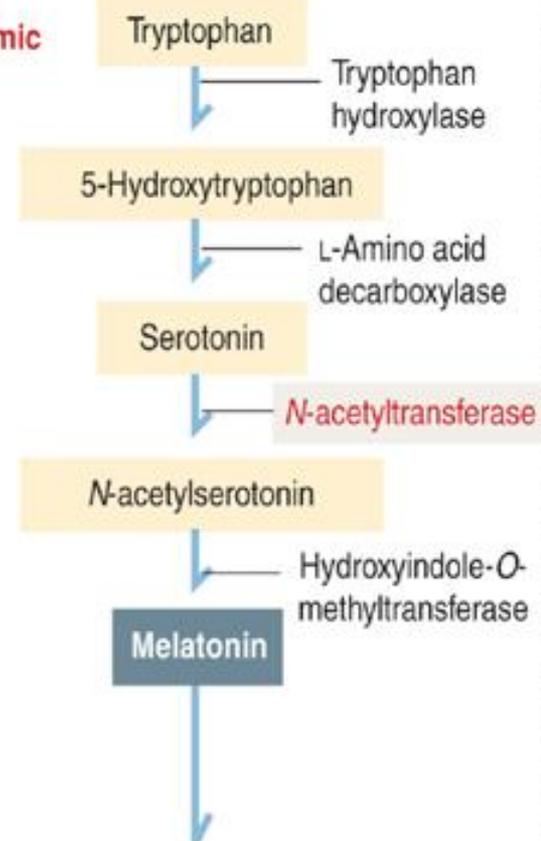
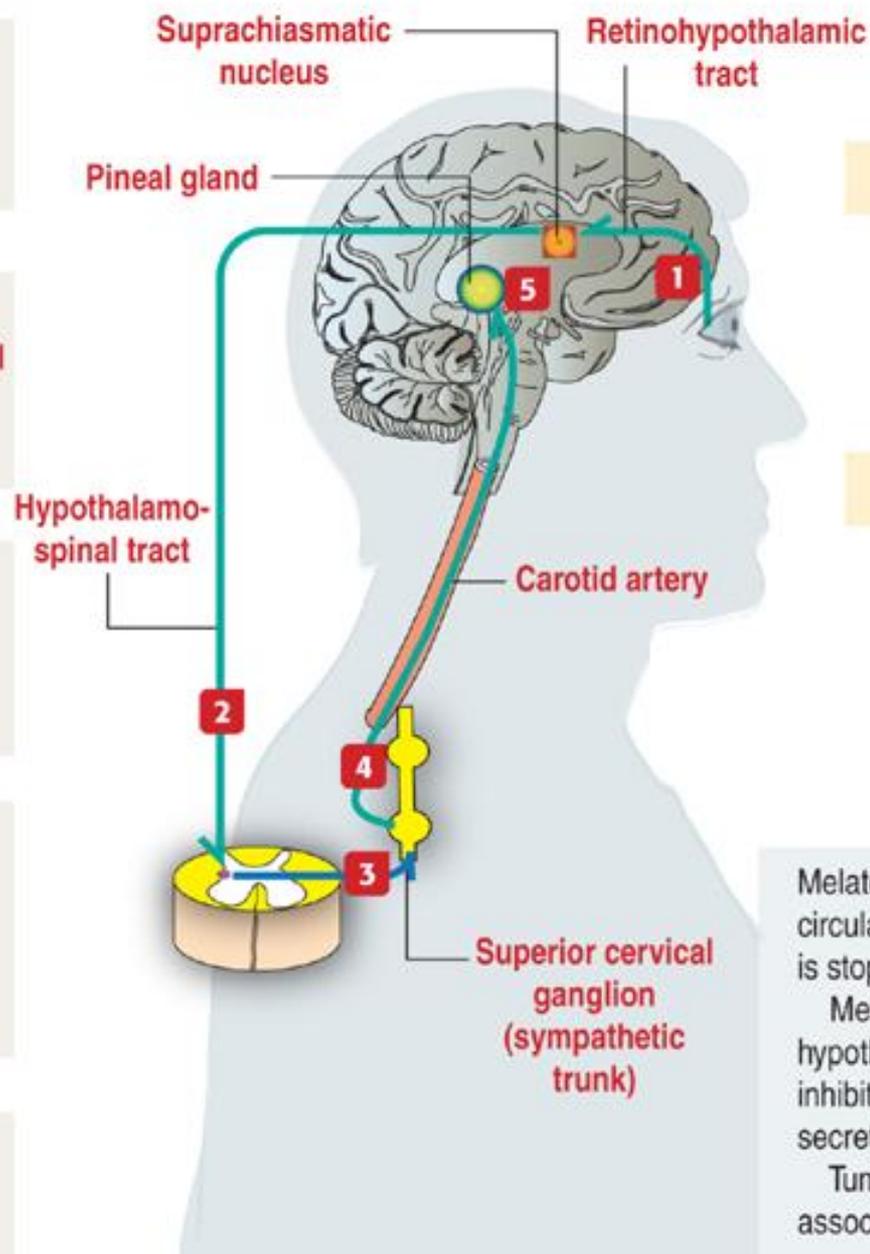
The pineal gland (so-called because it resembles a pine cone) consists of **melatonin-secreting pinealocytes** arranged in solid cords enclosed by processes derived from the **glial-like interstitial cells**. Cell processes projecting from the pinealocytes surround the blood vessels.

A typical feature of the histology of the pineal gland is the presence of calcium deposits, called **corpora arenacea** ("brain sand"), found in the extracellular space.

The nerve input to the pineal gland is from the **postganglionic sympathetic nerve fibers** derived from the **superior cervical ganglion**.



- 1** Light signals are conducted to the **suprachiasmatic nucleus** in the hypothalamus by the **retinohypothalamic tract**.
- 2** Information from the hypothalamus is delivered to the **intermediolateral cell column of the thoracic spinal cord** by the **hypothalamospinal tract**.
- 3** Information from the spinal cord is transmitted to the **superior cervical ganglion (preganglionic sympathetic fibers)**.
- 4** Information from the superior cervical ganglion is conducted by **postganglionic sympathetic fibers** traveling in association with blood vessels entering the pineal gland.
- 5** **Darkness stimulates the production of melatonin**. Light rapidly suppresses production of melatonin.



Melatonin is secreted into the general circulation after exposure to darkness and is stopped upon exposure to light.

Melatonin acts on both the hypothalamus and anterior hypophysis to inhibit gonadotropin and growth hormone secretion.

Tumors of the pineal gland are associated with **precocious puberty**.

## **General organization of the neuroendocrine system.**

The hypothalamus and the hypophysis (pituitary gland) form an integrated system known as the hypothalamohypophysial system consisting of two components: (1) the hypothalamic adenohypophysial system (linking the hypothalamus to the anterior hypophysis), and (2) the hypothalamic neurohypophysial system (connecting the hypothalamus to the neurohypophysis).

## **Functional aspects of the neuroendocrine system.**

The hypothalamus contains clusters of neurons called nuclei. Some of the neurons are neuroendocrine cells exerting positive and negative effects on the two components of the hypophysis. These effects are mediated by releasing and inhibitory hormones or factors.

The transport of signaling molecules is mediated by the hypothalamohypophysial portal circulation consisting of a primary capillary plexus in the lower hypothalamus connected by portal veins to a secondary capillary plexus in the anterior lobe of the hypophysis. A third capillary plexus supplies the neurohypophysis.

The primary capillary plexus is supplied by the superior hypophysial artery; the third capillary plexus is supplied by the inferior hypophysial artery. The two arteries are connected by the trabecular artery. There is no connection between the secondary and third capillary plexuses. The hypophysial vein drains the second and third capillary plexuses to the dural sinuses.

The hypophysis consists of two embryologically distinct portions: (1) the adenohypophysis or glandular component, derived from Rathke's pouch, an invagination of the roof of the future oral cavity, and (2) the neurohypophysis or neural component, an infundibular downgrowth from the floor of the diencephalon.

**The adenohypophysis** consists of three subdivisions: (1) the pars distalis (anterior lobe), (2) the pars tuberalis, surrounding the neural infundibular stem or stalk, and (3) the pars intermedia (the rudimentary intermediate lobe). The neurohypophysis consists of two subdivisions: (1) the pars nervosa and (2) the median eminence.

The anterior lobe contains three components: (1) epithelial cell cords, (2) a connective tissue stroma, and (3) fenestrated capillaries (sinusoids) of the secondary capillary plexus.

There are three distinct cell populations: (1) acidophil cells (stain with an acidic dye), (2) basophil cells (stain with a basic dye), and (3) chromophobe cells (lacking cytoplasmic staining). Acidophil cells secrete peptide hormones (growth hormone and prolactin); basophils secrete glycoprotein hormones (gonadotropins FSH and LH, TSH, and ACTH). Chromophobe cells are cells that have depleted their cytoplasmic hormonal content.

**Growth hormone** (also called somatotropin). It is secreted in a pulsatile pattern with peak secretion occurring during the first 2 hours of sleep. Growth hormone exerts its actions through insulin-like growth factor-1 (IGF-1) produced in hepatocytes after stimulation by growth hormone. The release of growth hormone is stimulated by growth hormone-releasing hormone produced in the hypothalamus and by high blood levels of IGF-1. Inhibition of growth hormone release is mediated by somatostatin (also produced in the hypothalamus and in the islets of Langerhans in the pancreas) and high blood levels of glucose.

**Gigantism** during childhood and puberty is caused by excessive secretion of growth hormone (usually produced by a benign tumor of the hypophysis called adenoma). **Acromegaly** (enlargement of hands, feet, jaw, and soft tissues) is seen in adults when growth hormone production is high.

**Prolactin** has a main function: to stimulate the initiation and maintenance of lactation postpartum. Lactation involves (1) mammogenesis, the growth and development of the mammary glands, (2) lactogenesis, the initiation of lactation; and (3) galactopoiesis, the maintenance of milk production. A secondary function is to facilitate the steroidogenic action of LH in Leydig cells by up-regulating the expression of the luteinizing hormone (LH) receptor. The pulsatile secretion of prolactin is regulated primarily by an inhibitory mechanism rather than by stimulation. The main inhibitor is dopamine. Prolactin-releasing hormone and thyrotropin-releasing hormone, both originating in the hypothalamus, stimulate prolactin release.

*Excessive secretion of prolactin (hyperprolactinemia) by a benign tumor of the hypophysis in both genders causes gonadotropin deficiency. In women, hyperprolactinemia is associated with infertility, anovulation, and oligomenorrhea or amenorrhea (dysfunctional uterine bleeding). A decrease in fertility and libido is seen in males. Galactorrhea (non-puerperal milk secretion) caused by hyperprolactinemia is common in both genders.*

**Gonadotropins: FSH and LH.** The release of gonadotropins is stimulated by gonadotropin-releasing hormone (GnRH; also called luteinizing hormone-releasing hormone or LHRH). GnRH is secreted in pulses at 60- to 90-minute intervals. A single basophil can produce both FSH and LH.

In the female, FSH stimulates folliculogenesis (the development of the ovarian follicle). In the male, FSH targets Sertoli cells in the testes to convert testosterone into estrogen (by aromatization) and produce androgen-binding protein (ABP).

In the female, LH stimulates steroidogenesis in the ovarian follicle and corpus luteum. In the male, LH controls the production of testosterone by Leydig cells.

The release of FSH and GnRH is inhibited by inhibin (an  $\alpha\beta$  heterodimer) produced by the target cells (follicular cells and Sertoli cells), and estradiol. The release of FSH is enhanced by activin (a  $\beta\beta$  homodimer).

*A drop in the secretion of GnRH (caused by anorexia nervosa, a tumor of the hypophysis, or a condition known as **hypogonadotropic hypogonadism** in males) can abolish the secretion of FSH and LH. Castration (ovariectomy or orchidectomy) causes a significant increase in the synthesis of FSH and LH and the vacuolization of gonadotropin-secreting cells (castration cells).*

**Thyroid-stimulating hormone (TSH;** or thyrotropin) regulates thyroid function. Thyrotropin-releasing hormone stimulates the release of TSH (and prolactin). Thyroid hormones triiodothyronine (T3) and thyroxine (T4) inhibit the release of TSH.

***Hypothyroidism**, characterized by reduced cell metabolism and temperature, is caused by deficient secretion of TSH and by the autoimmune disorder **Hashimoto's disease**. **Hyperthyroidism** is usually determined by an autoantibody directed against the TSH receptor in thyroid follicular cells (Graves' disease).*

**Adrenocorticotrophic hormone (ACTH;** or corticotropin) stimulates growth and steroid synthesis in the zona fasciculata and zona reticularis of the adrenal cortex.

ACTH derives from the large precursor pro-opiomelanocortin (POMC) processed in the anterior hypophysis. Corticotropin-releasing hormone (CRH) derived from neuroendocrine neurons of the paraventricular nuclei (which also produce antidiuretic hormone [ADH]), stimulates the release of ACTH. This CRH stimulatory effect is potentiated by ADH and angiotensin II. High levels of cortisol prevent the release of CRH or ACTH.

***Cushing's disease**, caused by an ACTH-producing adenoma of the hypophysis, results in the overproduction of cortisol by cells of the zona fasciculata of the adrenal cortex, obesity, osteoporosis, and muscle wasting.*

# Neurohypophysis

Three histologic components are found in the neurohypophysis: (1) pituicytes, astrocyte-like cells containing the intermediate filament protein glial fibrillary acidic protein and providing support to axons; (2) unmyelinated axons derived from neuroendocrine cells of the hypothalamic supraoptic and paraventricular nuclei forming the hypothalamic hypophysial tract; and (3) fenestrated capillaries.

Axons display intermittent bulging segments called Herring bodies containing neuroendocrine secretory granules. Each secretory granule consists of two components: the carrier protein neurophysin and the associated hormone ADH (also called arginine vasopressin) or oxytocin.

Oxytocin participates in the contraction of uterine smooth muscle during labor, and of myoepithelial cells in the lactating mammary alveoli to facilitate milk ejection. ADH regulates water excretion in the kidneys and, at a higher concentration, is also a potent vasoconstrictor.

**Neurogenic diabetes insipidus** occurs when the secretion of ADH is reduced. It is caused by severe head injury, an invasive tumor disrupting the hypothalamic hypophysial tract, or the autoimmune destruction of ADH-producing neurons. Polyuria is a common clinical finding. **Nephrogenic diabetes insipidus** occurs in certain chronic renal diseases that are not responsive to ADH.

**Pineal gland.** The pineal gland is an endocrine organ containing cells with a neurosecretory function and without direct nerve connection with the brain. The pineal gland is supplied by postganglionic sympathetic nerve fibers derived from the superior cervical ganglia (SCG). Preganglionic fibers to the SCG derive from the lateral column of the spinal cord.

## The pineal gland

•develops from a saccular outpocketing of the posterior diencephalic roof in the midline of the third ventricle. It contains cells called pinealocytes, arranged in cords and clusters, and **supporting glial-like interstitial** cells. The pinealocyte displays cytoplasmic extensions with bulbar endings. These cell processes end close to a capillary. **Pinealocytes** contain abundant mitochondria and characteristic multiple ribbon synapses. Remember that ribbon synapses are also seen in photoreceptor cells of the retina and in hair cells of the inner ear. An important landmark of the pineal gland are calcified deposits called corpora arenacea ("brain sand").

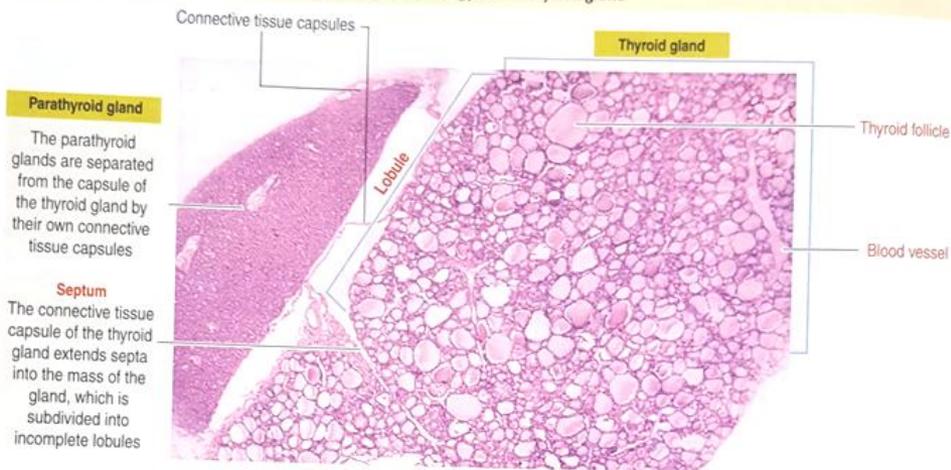
The major secretory product of the pineal gland is **melatonin**, synthesized from tryptophan by pinealocytes and immediately secreted. The concentration of melatonin in the pineal gland is high during the night.

**The 24-hour circadian clock** is an endogenous oscillator controlling circadian rhythms, including sleep and feeding patterns. The retinohypothalamic tract conducts light signals from the retina (in particular from melanopsin-producing ganglion cells that function as luminance detectors) to the hypothalamic suprachiasmatic nucleus (regarded as the circadian "clock"). This is the first regulatory step of melatonin synthesis and secretion.

**Jet lag**, a condition associated with fatigue, insomnia, and disorientation experienced by many travelers, is caused by a disruption of the circadian rhythm. Bipolar disorder and sleep disorder are also linked to the abnormal functioning of the circadian rhythms.

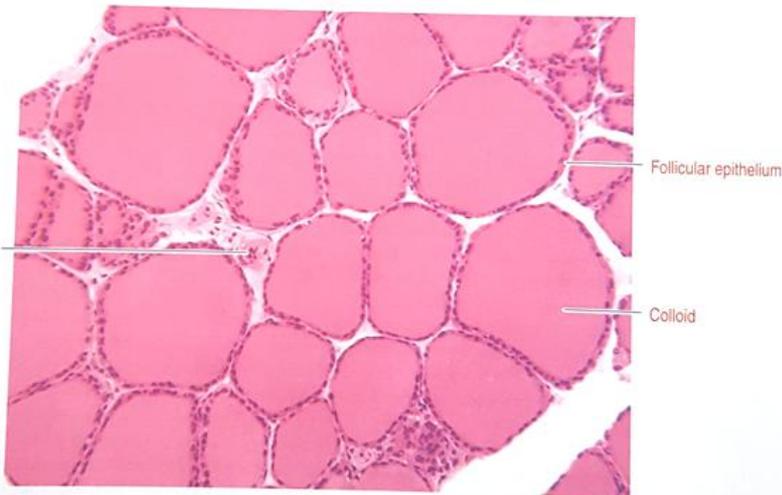
A tumor of the pineal gland (called **pinealoma**) is associated with **precocious puberty (pubertas precox)** and with a neurologic disorder known as **Parinaud's syndrome** (paralysis of upward gaze, looking steadily in one direction, pupillary areflexia to light, paralysis of convergence, and wide-based gait).

Figure 19-1. Histology of the thyroid gland



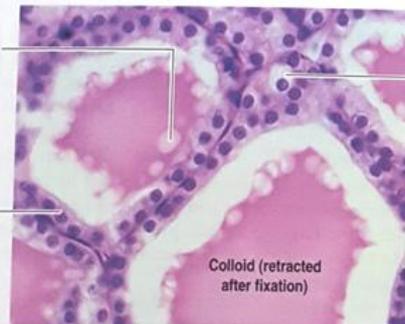
The variable diameter of the thyroid follicles reflects the level of the section and the content of colloid

Blood vessel in the connective tissue stroma



Area of colloid resorption

**Follicular epithelium**  
In the resting follicle, the follicular epithelium is simple low cuboidal, or squamous. During their active secretory phase, the cells become columnar



A **C cell** can be distinguished from surrounding follicular cells by its pale cytoplasm.

Two more effective identification approaches are:  
1. Immunocytochemistry, using an antibody to calcitonin.  
2. Electron microscopy, to visualize calcitonin-containing cytoplasmic granules.

### C cells (thyroid follicle)

C cells derive from neural crest cells and are associated with thyroid follicles. C cells:

1. Represent about 0.1% of the mass of thyroid tissue.

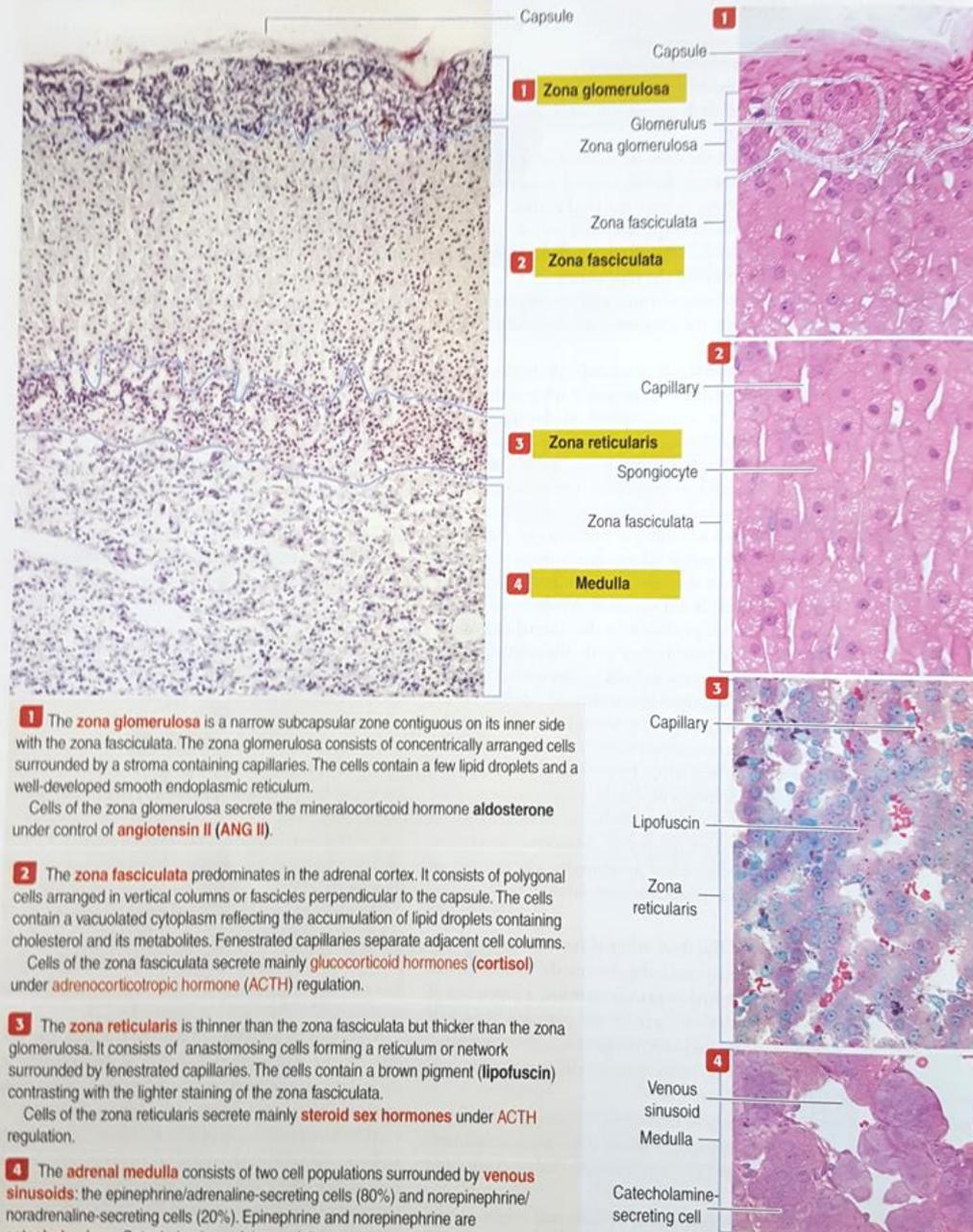
2. May be present within (or outside) the thyroid follicle but are not in contact with the colloid.

3. Produce **calcitonin**, encoded by a gene located on the short arm of chromosome 11 (Figure 19-6).

Calcitonin is a 32-amino-acid peptide derived from a 136-amino-acid precursor. It is stored in secretory granules. The calcitonin gene is also expressed in other tissues (hypothalamus and hypophysis), giving rise to a **calcitonin gene-related peptide (CGRP)** consisting of 37 amino acids. CGRP has neurotransmitter and vasodilator properties.

The main function of calcitonin is to antagonize the effects of PTH. Calcitonin suppresses the mobilization of calcium from bone by osteoclasts triggered by an increase in cAMP. Calcitonin secretion is stimulated by an increase in blood levels of calcium (hypercalcemia).

Figure 19-6. Histologic organization of the adrenal gland



**1** The **zona glomerulosa** is a narrow subcapsular zone contiguous on its inner side with the zona fasciculata. The zona glomerulosa consists of concentrically arranged cells surrounded by a stroma containing capillaries. The cells contain a few lipid droplets and a well-developed smooth endoplasmic reticulum.

Cells of the zona glomerulosa secrete the mineralocorticoid hormone **aldosterone** under control of **angiotensin II (ANG II)**.

**2** The **zona fasciculata** predominates in the adrenal cortex. It consists of polygonal cells arranged in vertical columns or fascicles perpendicular to the capsule. The cells contain a vacuolated cytoplasm reflecting the accumulation of lipid droplets containing cholesterol and its metabolites. Fenestrated capillaries separate adjacent cell columns.

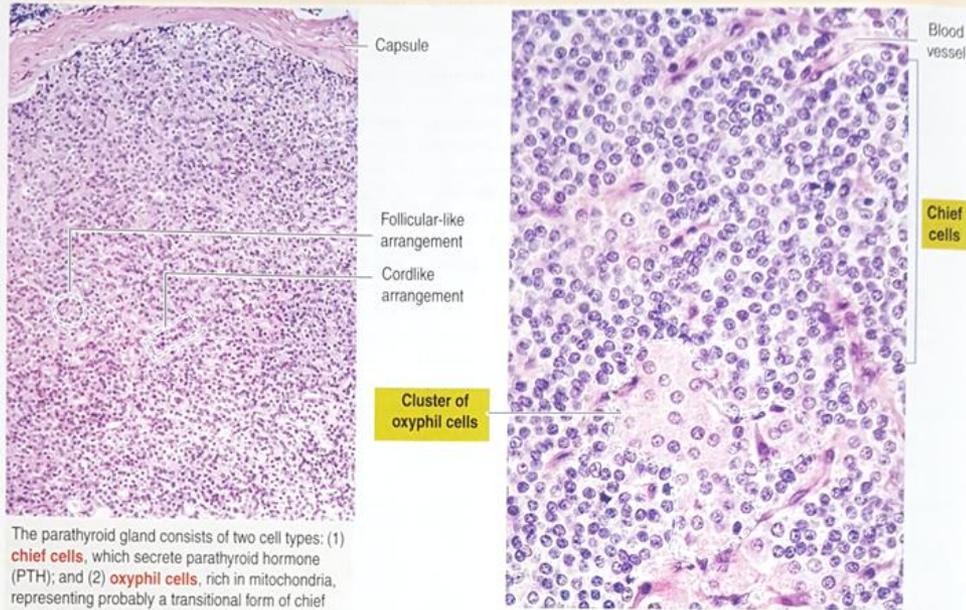
Cells of the zona fasciculata secrete mainly **glucocorticoid hormones (cortisol)** under **adrenocorticotropic hormone (ACTH)** regulation.

**3** The **zona reticularis** is thinner than the zona fasciculata but thicker than the zona glomerulosa. It consists of anastomosing cells forming a reticulum or network surrounded by fenestrated capillaries. The cells contain a brown pigment (**lipofuscin**) contrasting with the lighter staining of the zona fasciculata.

Cells of the zona reticularis secrete mainly **steroid sex hormones** under **ACTH** regulation.

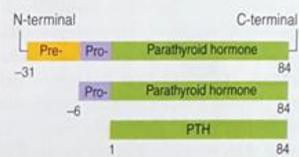
**4** The **adrenal medulla** consists of two cell populations surrounded by **venous sinusoids**: the epinephrine/adrenaline-secreting cells (80%) and norepinephrine/noradrenaline-secreting cells (20%). Epinephrine and norepinephrine are **catecholamines**. Catecholamines of the medulla generate a brown color when exposed to air or the oxidizing agent potassium dichromate (**chromaffin reaction**).

Figure 19-5. Structure and function of the parathyroid gland

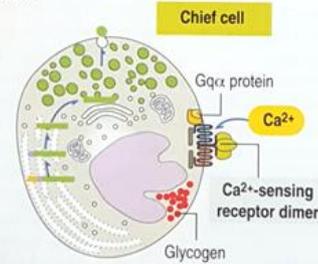


The parathyroid gland consists of two cell types: (1) **chief cells**, which secrete parathyroid hormone (PTH); and (2) **oxyphil cells**, rich in mitochondria, representing probably a transitional form of chief cells. Cells are arranged in a **cordlike** arrangement, but a **follicular-like** arrangement can also be observed.

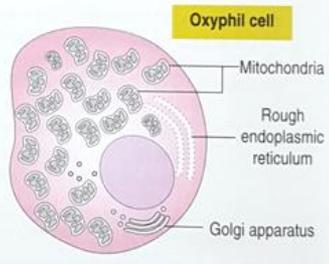
**Processing of parathyroid hormone**



**Preparathyroid hormone** precursor is synthesized in the rough endoplasmic reticulum and processed to **parathyroid hormone** to **PTH**.



**Chief cells synthesize and secrete PTH.** **Ca<sup>2+</sup>-sensing receptor (CaSR)** is a seven-transmembrane-spanning receptor dimer coupled to Gqα protein on the plasma membrane of the parathyroid chief cell. A **reduction** in serum calcium levels activates CaSR and **increases PTH secretion**, leading to an **increase** in serum calcium.



**Oxyphil cells** appear after puberty and increase in number with age. They contain abundant **mitochondria**, which give this cell type an acidophilic staining in hematoxylin-eosin preparations. The rough endoplasmic reticulum and Golgi apparatus are not prominent. Oxyphil cells do not secrete PTH.

**Calcium regulation**

Ca<sup>2+</sup> is found inside and outside cells, is a major component of the skeleton, is required for muscle contraction, blood clotting, nerve impulse transmission, and enzymatic activities. Ca<sup>2+</sup> is an essential mediator in cell signaling (for example, through **calcium-binding calmodulin**).

Ca<sup>2+</sup> homeostasis is regulated by:

1. **Parathyroid hormone (PTH)**, secreted from the parathyroid glands. PTH acts on **bone** and the **kidneys** to **raise Ca<sup>2+</sup> levels in blood**.
2. **Calcitonin**, produced by C cells lodged in the thyroid gland, **lowers Ca<sup>2+</sup> levels in blood**.
3. **Vitamin D** (calcitriol, or 1,25-dihydroxycholecalciferol) enhances the uptake of Ca<sup>2+</sup> by the small intestine by stimulating the synthesis of Ca<sup>2+</sup>-

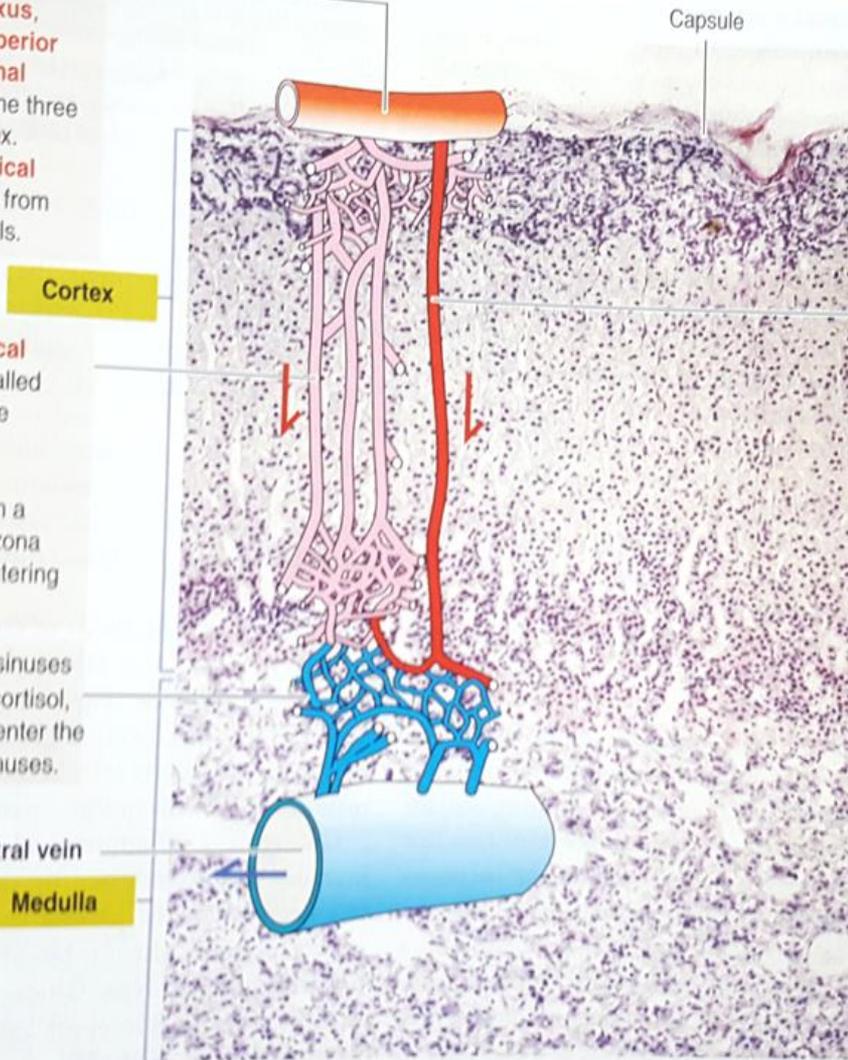
Figure 19-14. Blood supply to the adrenal gland

Blood vessels derived from the **capsular plexus**, formed by the **superior and middle adrenal arteries**, supply the three zones of the cortex. **Fenestrated cortical capillaries** derive from these blood vessels.

**Fenestrated cortical capillaries** (also called sinusoids) percolate through the zonae glomerulosa and fasciculata and form a network within the zona reticularis before entering the medulla.

Medullary venous sinuses  
Mineralocorticoids, cortisol, and sexual steroids enter the medullary venous sinuses.

Central vein  
Medulla



The **medullary artery**, derived from the **inferior adrenal artery**, enters the cortex within a connective tissue trabecula and supplies blood directly to the adrenal medulla.

#### Medullary artery

The **medullary artery bypasses the cortex without branching**. In the medulla, the artery joins with branches from the cortical capillaries to form **medullary venous sinuses**. Thus, **the medulla has two blood supplies**: one from cortical capillaries and the other from the medullary artery.

The conversion of norepinephrine to epinephrine by chromaffin cells is dependent on **phenylethanolamine N-methyltransferase (PNMT)**, an enzyme activated by cortisol transported by the cortical capillaries to the medullary venous sinuses.



# Concept mapping | Endocrine System

## Endocrine system

### Glands regulated by the hypophysis

Thyroid-stimulating hormone (TSH)

#### Thyroid gland

Thyroid follicle

Thyroid follicle cell

Exocrine phase

Thyroglobulin

Iodothyroglobulin

$T_3, T_4$

Endocrine phase

Adrenocorticotropic hormone (ACTH)

#### Adrenal gland (cortex)

Angiotensin II → Zona glomerulosa → Aldosterone

Zona fasciculata → Cortisol

Zona reticularis → Sex hormones

#### Adrenal gland (medulla)

Norepinephrine (20%)

Epinephrine (80%)

Acetylcholine

Gland regulated by calcium

#### Parathyroid gland

Chief cells → Calcium-sensing receptor

Parathyroid hormone

Osteoblast

Osteoclastogenesis

Bone resorption

Oxyphil cells

Cell regulated by calcium

#### C cell

Calcitonin

Osteoclast

Glandular structure regulated by glucose

#### Islet of Langerhans

A cells → Glucagon

B cells → Insulin

D cells → Gastrin/somatostatin

F cells → Pancreatic polypeptide