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ЭНДОКРИННЫЕ ЖЕЛЕЗЫ

ENDOCRINE GLANDS

Учебно-методическое пособие

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ЭНДОКРИННЫЕ ЖЕЛЕЗЫ
ENDOCRINE GLANDS

Учебно-методическое пособие
На английском языке

Ответственная за выпуск Н. А. Трушель
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LIST OF ABBREVIATIONS

GH — Growth hormone (syn. STH — somatotropin hormone)

GH — Growth hormone

ACTH — Adrenocorticotropin hormone

TSH — Thyroid-stimulating hormone

FSH — Follicle-stimulating hormone

LH — Luteinizing hormone

MSH — Melanocyte-stimulating hormone

GHRH — Growth hormone-releasing hormone

GHIH — Growth hormone-inhibiting hormone (somatostatin)

CRH — Corticotropin-releasing hormone

CRH — Corticotropin-releasing hormone

TRH — Thyrotropin-releasing hormone

GnRH — Gonadotropin-releasing hormone (syn. LHRH — Luteinizing hormone-releasing hormone

PRH — Prolactin-releasing hormone

PIH — Prolactin-inhibiting hormone

MOTIVATIONAL CHARACTERISTICS OF THE TOPIC

Topic of the lesson: Endocrine glands: topography, and structure.

Total time of classes: 3 (5) academic hours.

The endocrine system is one of the integrating systems of the body, consisting of functionally diverse and topographically unrelated organs and cells. Messenger molecules, hormones, secreted by endocrine cells, enter the bloodstream and are distributed throughout the body. This allows to control and integrate the functions of other organs, regulate all biological processes in the body, and maintain homeostasis. Disorders of the endocrine glands, which manifest themselves in hyper- or hypoproduction of hormones, can cause a wide range of serious disorders in the functioning of various organs and systems of the body.

Knowledge of the normal anatomy and basic functions of the endocrine glands, obtained in the anatomy course, is necessary for further in-depth study of their histology, physiology and pathology.

The aim: to provide the students with the knowledge of the anatomy, blood supply and innervation of the endocrine glands, as well as their basic functions.

Learning Objectives (to know):

1. Difference between exocrine and endocrine glands.
2. General functions of the endocrine system.

3. Topography, structure, and sources of development of the endocrine glands.

4. Anatomical and functional relationships between the hypothalamus and the pituitary gland.

5. The parts of the pituitary gland, their hormones and major functions.

6. Anatomical structure and endocrine functions of the pineal, thyroid, parathyroid, suprarenal glands, and paraganglia.

7. Structures of the pancreas and gonads, responsible for the hormone production.

8. Endocrine functions of nonendocrine organs.

Learning Objectives (to be able): to demonstration endocrine glands in the anatomical specimens and visual aids.

Control questions:

1. Name the main structural and functional differences between the exocrine and endocrine glands.

2. List the general functions of the endocrine glands.

3. Describe the topography, blood and nerve supply of the hypophysis.

4. Name the two structural parts of the pituitary gland and the embryonic sources from which they develop.

5. List hormones of the adenohypophysis and describe their main effects.

6. Name hormones released from the neurohypophysis and describe their principal functions.

7. Describe the anatomical and functional relationships between the hypothalamus and the anterior and posterior lobes of the pituitary gland.

8. Describe the location, structure, source of development, and effects of the hormone of the pineal gland.

9. What should you avoid doing in the middle of your sleep cycle that would lower melatonin?

10. Describe the location, anatomical structure, and development of the thyroid gland.

11. Name arteries and nerves supplying the thyroid gland.

12. Identify hormones, synthesized by the thyroid gland, and describe their major functions.

13. Name the conditions caused by over- and undersecretion of thyroid hormone in childhood and adulthood.

14. What is a goiter and why it can develop from over- and understimulation of the thyroid gland?

15. Describe the location, anatomical structure, and sources of development of the parathyroid glands.

16. Describe the sites of production and actions of hormones responsible for calcium balance.

17. Describe the location, structure, blood and nerve supply of the adrenal glands.

18. Identify the sources of embryonic development of the adrenal cortex and medulla, the hormones produced by these parts, and their main effects.

19. What are the three regions of the adrenal cortex and what hormones do they produce?

20. What hormone directly stimulates the secretion of the glucocorticoids from the adrenal cortex, and where is this hormone produced?

21. Why is the adrenal medulla referred to as a modified sympathetic ganglion?

22. Which hormones are involved in "fight or flight" response? Give examples of their effects.

23. Describe the location and function of the paraganglia.

24. What structures of the pancreas perform endocrine function? What hormones do they produce?

25. What are the main functions of the pancreatic hormones?

26. Name the main hormones produced by the testes and ovaries, indicate their functions and the sites of hormone production.

27. Describe the topography, anatomical structure, and role of the thymus as an immune and endocrine organ.

28. Name nonendocrine organs, which have endocrine function, state the function of their hormones.

29. Name the hormones produced by the placenta and state their functions.

OVERVIEW OF THE ENDOCRINE GLANDS

The **endocrine system** is one of the integrating systems that control and regulate body's physiological activities. It comprises endocrine glands, individual cells, or groups of cells that produce biologically active chemicals, called **hormones**. Together with the nervous system, the endocrine system monitors and adjusts activities of organs, systems of organs, and individual cells. The nervous system, through neurotransmitters released into the synaptic cleft, produces fast and short-term localized responses (muscle contraction and glands secretion) predominantly to environmental stimuli. The endocrine system via hormones, released into the bloodstream, causes slower but longer-lasting generalized effects on activities of various cells and tissues. Due to these the endocrine system is especially effective in regulating of development and growth, reproduction, metabolic processes and maintaining of homeostasis (fluid and electrolyte balance, acid-base balance, energy balance), and stress responses.

In some instances, the two systems, endocrine and nervous, are difficult to separate either anatomically or functionally. For example, the suprarenal medulla is an endocrine structure but functionally and developmentally it is a part of the nervous system, a modified sympathetic ganglion. On the other hand, the hypothalamus, which is a part of the brain, secretes a variety of hormones and therefore functionally is a part of the endocrine system. Besides, the two systems interact in regulating one another.

The **endocrine glands** are ductless (as oppose to exocrine glands) and secrete their products into the interstitial fluid (Fig. 1). The endocrine glands usually have extensive networks of permeable capillaries, through which hormones enter the bloodstream and are distributed throughout the body *(endocrine secretion)*. Hormones can reach any distant organ but act specifically only on their target cells or tissues. By binding to receptors of target cells, hormones alter cellular activity and cause a certain physiological effect. Hormones can also act locally, on neighboring cells *(paracrine secretion)*, or on the same cells that secreted the hormone *(autocrine secretion)*.

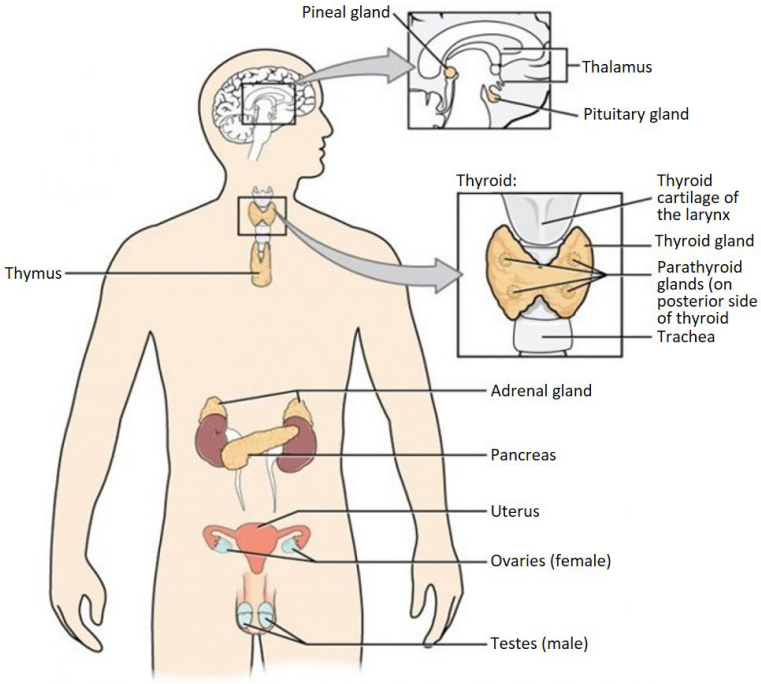

Fig. 1. Location of the endocrine glands in the human body [1]

By chemical structure hormones are divided into 3 main classes: amino acid-based molecules — amines (e.g., melatonin, thyroxine, epinephrine, norepinephrine), peptides and proteins (oxytocin, insulin, growth hormone), or steroid molecules derived from cholesterol (e.g., sex hormones, glucocorticoids and mineralocorticoids).

Endocrine activity is regulated in several ways:

1) by chemical changes, of the levels of ions or nutrients in the blood (e.g., a decline in the blood concentration of calcium ions causes the secretion of parathyroid hormone);

2) by neural stimuli (e.g., sympathetic regulation of the epinephrine release in the adrenal medulla;

3) by other hormones (e.g., some hormones of the hypothalamus regulate the release of hormones by the adenohypophysis, which, in turn, control the production of hormones by other endocrine glands).

In most cases, hormone secretion is controlled by negative feedback, i.e., as the level of a hormone in the circulation increases, its secretion by the gland slows down. Or vice versa, the low blood hormone level activates processes that increase its secretion.

The **hypothalamus** is a part of the brain, which at the same time plays an important role in endocrine regulation of body functions, and provides a link between the nervous and endocrine systems. The hypothalamus is the ventral part of the **diencephalon**. It makes up the cone-shaped floor of the third ventricle, which projects downward to forms the **tuber cinereum**. A small tubule, called the **infundibulum** (pituitary stalk), connects the tuber cinereum and the **hypophysis (pituitary gland)** (Fig. 2).

The hypothalamus controls the secretion of hormones from the adenohypophysis (anterior pituitary lobe). Nuclei of the hypothalamic **tuberal area**[1] produce releasing and inhibiting hormones ("liberins" and "statins") that are delivered to the hypophysis through the ***hypophyseal portal system*** (Fig. 2) (Table 1). The hormones are secreted into a *primary capillary plexus*, formed by the superior hypophyseal artery in the tuberal area. The **portal venules** arising from the primary capillary plexus surround the infundibulum and form a *secondary capillary plexus* in the adenohypophysis.

Besides, the hypothalamus secretes two hormones that act on distant target organs: **antidiuretic hormone (ADH)**, or **vasopressin**, and **oxytocin**. They are produced by neurosecretory cells of the **supraoptic nucleus** (both hormones), located above the optic chiasm, and **paraventricular nucleus** (mainly oxytocin), located in the wall of the 3rd ventricles. The hormones travel along the axons in the infundibulum and terminate in the neurohypophysis (posterior pituitary lobe) (Fig. 2).

[1] The tuberal area is the part of the third ventricle wall corresponding to the tuber cinereum on the base of the brain.

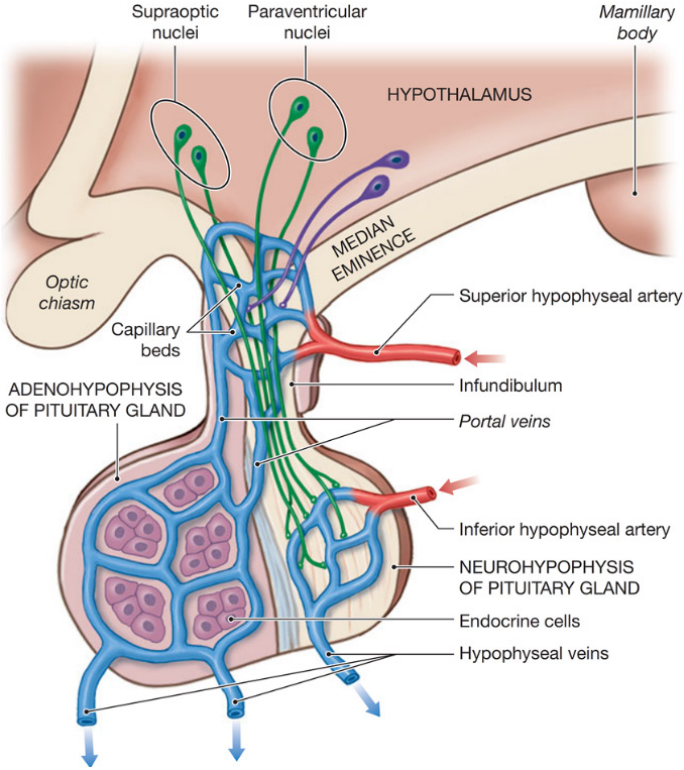

Fig. 2. Relationships of the pituitary gland and the hypothalamus. Hypophyseal portal system [5]

Table 1

Main regulating hormones of the hypothalamus and their effects on hormones of the pituitary system

Hypothalamic hormone	Pituitary hormone (stimulated or inhibited)	Effect of pituitary hormone
Growth hormone-releasing hormone (GHRH)	Growth hormone (GH) — somatotropin	Stimulates liver, muscle, cartilage, bone, and other tissues to secrete insulin-like growth factors (IGFs) that promote cells growth and division, protein synthesis, lipolysis, hepatic glycogenolysis and elevation of blood glucose level, bones mineralization, increase in muscle mass, etc.
Growth hormone-inhibiting hormone (GHIH) — somatostatin		

End of the Table 1

Hypothalamic hormone	Pituitary hormone (stimulated or inhibited)	Effect of pituitary hormone
Corticotropin-releasing hormone (CRH)	Adrenocorticotropin hormone (ACTH)	Stimulates synthesis of glucocorticoids (mainly cortisol) by adrenal cortex (regulate metabolism, stress and immune response)
Corticotropin-releasing hormone (CRH) excessive level	Melanocyte-stimulating hormone (MSH)	When present in excess, can cause darkening of skin
Thyrotropin-releasing hormone (TRH)	Thyroid-stimulating hormone (TSH)	Stimulates the release of thyroid hormones by thyroid gland (regulate development and growth, metabolism, energy balance)
Gonadotropin-releasing hormone (GnRH) or Luteinizing hormone-releasing hormone (LHRH)	Gonadotropins:	Stimulate functions of the gonads:
	1. Follicle-stimulating hormone (FSH)	Stimulates production of sperm and oocytes by gonads and estrogens in ovaries
	2. Luteinizing hormone (LH)	Stimulates production of sex hormones by gonads
Prolactin-releasing hormone (PRH)	Prolactin (PRL)	Promotes production of milk by mammary glands
Prolactin-inhibiting hormone (PIH)		

MAJOR ENDOCRINE GLANDS

Endocrine glands are the important part of the integrating systems of the body. They include the hypophysis (*syn.* pituitary gland), pineal gland (*syn.* epiphysis cerebri, pineal body), thyroid gland, parathyroid glands, suprarenal glands (*syn.* adrenal glands) and paraganglia (*syn.* sympathetic paraganglia) (Fig. 1). In addition, organs such as the pancreas and sex glands are often classified as endocrine glands.

Endocrine glands and endocrine cells have different embryonic origins. Sometimes, cells, derived from different sources and secreting different hormones, reside side by side within a single gland (e.g., the parafollicular cells located among the follicular cells within the thyroid gland).

Depending on the sources of development, endocrine glands can be divided into the following groups:

1. Glands of endodermal origin:

– derivatives of the pharyngeal (branchial) pouches: thyroid and parathyroid glands;

– derivatives of primitive gut epithelium: pancreatic islets (some cells of the islets are of neuroectodermal origin).

2. Glands of mesodermal origin: adrenal cortex and gonads.

3. Glands of ectodermal origin:

– originating from neuroectoderm: hypothalamus, neurohypophysis, epiphysis (pineal gland);

– originating from the neural crest: adrenal medulla, paraganglia, parafollicular cells of the thyroid gland;

– originating from the wall of the primitive oral cavity (Rathke's pouch): adenohypophysis.

Hypophysis (pituitary gland)

The **hypophysis**, or **pituitary gland** (Lat. ***glandula pituitaria***) is a pea-sized (≈ 1 × 1.2 cm), ovoid shaped structure. It lies in the sella turcica of the sphenoid bone, covered by a dural plate, the **diaphragma sellae**, with a small opening in the center. The funnel-shaped **infundibulum (pituitary stalk)** passes through the opening and connects the pituitary gland to the lying above tuber cinereum of the **hypothalamus**.

The pituitary gland consists of two lobes with the specific embryonic origin, structure and functions: the **anterior lobe** — **adenohypophysis**, and the **posterior lobe** — **neurohypophysis** (Fig. 2, 3).

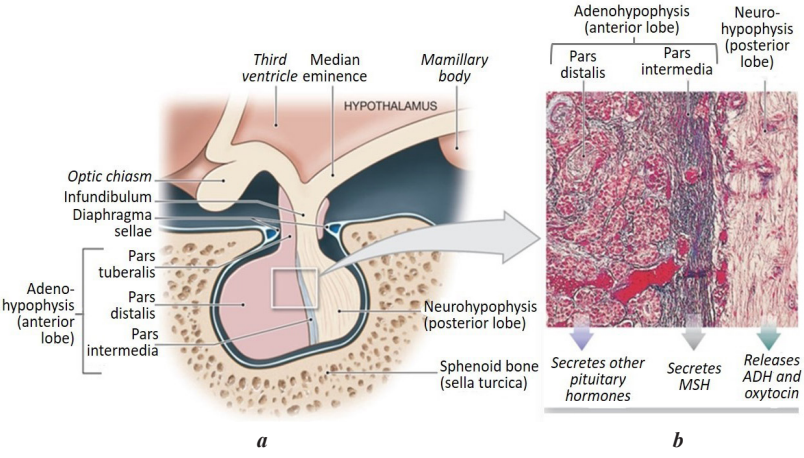

Fig. 3. Gross anatomy (a) and histological organization (b) of the hypophysis (pituitary gland) [5]

The **adenohypophysis** is subdivided into 3 regions: **pars distalis (anterior)** — the largest anterior portion of the gland; **pars tuberalis** — an extension around the lower end of the infundibulum; **pars intermedia** — a narrow zone adjacent to the neurohypophosis. The **neurohypophysis** consists of the **neural lobe** and the **pituitary stalk (infundibulum)** connected with the hypothalamus.

Functions:

1. The **adenohypophysis**, made of glandular tissue, consists of several types of epithelial cells producing different hormones. Most of them, called tropic hormones, stimulate the production of hormones by other endocrine glands and thus regulate many important physiological processes. In turn, the hormone production by the adenohypophysis is controlled by the hypothalamus, whose hormones enter through the portal vessels (Table 1) (Fig. 4).

The adenohypophysis secretes the following hormones:

– **adrenocorticotropin (ACTH)** stimulates cells of the adrenal cortex, producing glucocorticoids (mainly cortisol);

– **thyroid-stimulating hormone (TSH)** stimulates growth and secretion of hormones by the thyroid gland;

– **gonadotropins** regulate development, growth, and functions of male and female gonads, related to their hormone production and reproductive function. **Follicle-stimulating hormone (FSH)** stimulates the production and maturation of sex cells: in female — the development of oocytes and estrogens secretion in the follicles; in male — the production of sperm in the testis. **Luteinizing hormone (LH)** in female promotes ovulation and following development of the corpus luteum, production of estrogens and progesterone by the ovaries; in male it stimulates the interstitial cells of the testes to secrete testosterone;

– **prolactin (PRL)** together with other hormones, induces enlargement of glandular tissue of the mammary gland and stimulates milk production;

– **growth hormone (GH),** or **somatotropin**, is the most abundant anterior pituitary hormone. It stimulates protein synthesis and cell growth, especially development and growth of the skeleton and muscles. *Hyposecretion* of this hormone during childhood causes pituitary growth failure (pituitary dwarfism), as *hypersecretion* (before epiphyseal plates close) results in giantism. In adults it causes acromegaly, a disorder that results in the growth of bones in the face, hands, and feet;

– **melanocyte-stimulating hormone (MSH)** is produced by the **pars intermedia** of the adenohypophysis. MSH stimulates the melanocytes of the skin to increase melanin production in the fetal period, in young children and pregnant women, when its level is higher. Exact role of pituitary MSH in healthy adults is not clear (it may influence brain activity and suppress appetite).

2. The **neurohypophysis**, made of nervous tissue, stores **ADH** and **oxytocin** in axon terminals and releases them into the circulation. These hormones are

synthesized in the **supraoptic** and **paraventricular nuclei** of the hypothalamus and delivered to the neural lobe via axons running in the infundibulum (Fig. 2, 3, 4). **ADH (antidiuretic hormone, vasopressin)** increases reabsorption of water in the kidneys. In high concentrations, ADH can raise blood pressure by arterioles constriction. ADH deficiency due to dysfunction of the pituitary gland or hypothalamic supraoptic nucleus causes diabetes insipidus, which leads to rapid loss of water from the body through large volumes of urine (diabetes), which is hypotonic, dilute, and tasteless (insipid).

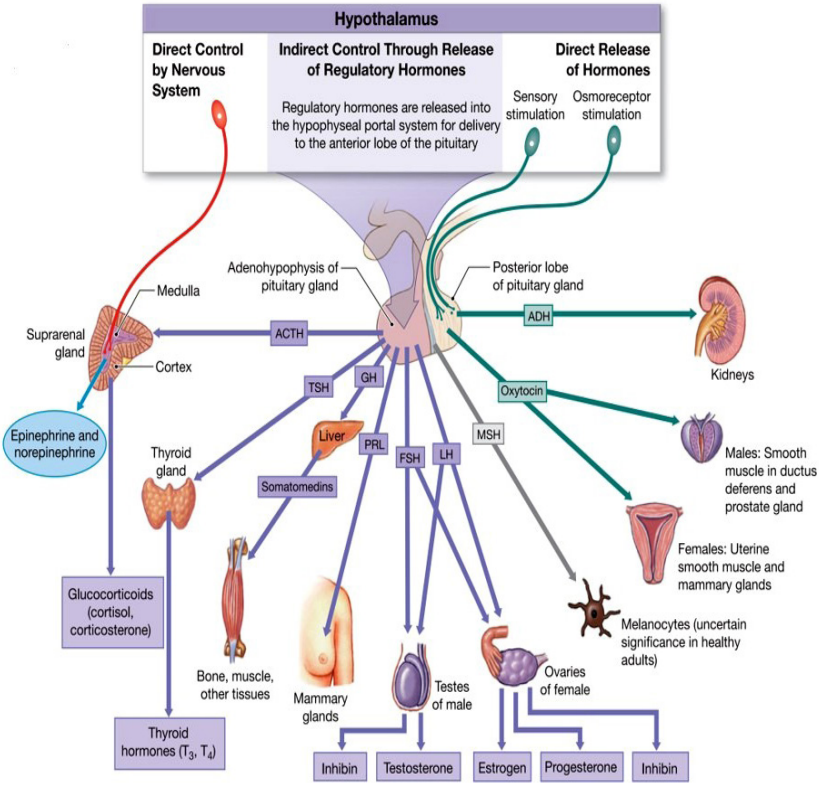

Fig. 4. Pituitary hormones and their targets:
ACTH — adrenocorticotropin hormone; TSH — thyroid-stimulating hormone; GH — growth hormone; PRL — prolactin; FSH — follicle-stimulating hormone; LH — luteinizing hormone; MSH — melanocyte-stimulating hormone; ADH — antidiuretic hormone [1]

Oxytocin[1] stimulates contraction of the uterine musculature and release of breast milk due contraction of myoepithelial cells of the breast ducts. It can also stimulate smooth muscle cells of the male reproductive tract, in addition to the locally produced hormone.

Development. The develops from two ectodermal pouches:

1) an outgrowth in the dorsal wall of the primitive oral cavity (Rathke's pouch), which extends upward in the direction of the neural ectoderm;

2) a ventral evagination from the *floor of the diencephalon* of the brain. The two pouches fuse, the first one gives rise to the anterior lobe, the second — to the posterior lobe of the pituitary gland.

Blood supply: branches of the internal carotid artery: the superior hypophyseal arteries to the adenohypophysis; the inferior hypophyseal arteries to the neurohypophysis. Venous drainage: via the hypophyseal veins to the cavernous and intercavernous sinuses.

Nerve supply: sympathetic innervation by the internal carotid plexus from the superior cervical ganglion; parasympathetic fibers from the pterygopalatine ganglion of the CN VII (autonomic innervation has little effect on hormones production by the hypophysis).

Pineal gland

The **pineal gland (pineal body, epiphysis cerebri)** (Lat. ***glandula pinealis***) is a small pinecone-shaped structure (5–7 mm length), reddish color due to rich vascularization. It is located in the midline between the superior colliculi of the midbrain at the posterior end of the third ventricle and is connected to the **epithalamus** of the diencephalon (Fig. 5).

Functions: the pineal gland is a neuroendocrine organ. It consists of clusters of secretory cells, pinealocytes, and neuroglia. Pinealocytes produce the hormone melatonin[2], which modulates the circadian rhythm of biological activities (appetite, body temperature, etc.) including the natural sleep-wake cycle. The melatonin production is dependent on light: it increases at night, inducing sleep, and decreases in the day time.

The main biological clock is located in the suprachiasmatic nucleus of the hypothalamus, which receives direct signals about the amount of light from the retina. This information is transmitted to the pineal gland via the sympathetic nervous system: the sympathetic center in the spinal cord, the superior cervical ganglion of the sympathetic trunk and its postganglionic fibers.

[1] Oxytocin released by the nuclei of the brain stem acts as a neurotransmitter on oxytocin receptors in different parts of the CNS and has the behavioral effects (plays role in social recognition, pair bonding, maternal behavior, etc.).

[2] Melatonin is a serotonin derivative; the source of serotonin is a dietary amino acid tryptophan.

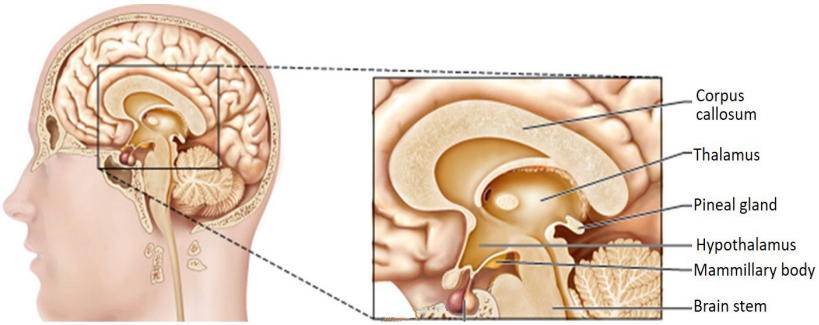

Fig. 5. Topography of the pituitary and pineal glands [6]

In childhood, the high level of melatonin delays reproductive development and gametes production (by suppressing release of hypothalamic GnRH and/or gonadotrophic hormones). Injury to the pineal gland in children accelerates skeletal development and puberty.

Melatonin also possesses antioxidant properties that are believed to increase immunity, prevent cardiovascular problems, and protect against neurodegeneration.

With age (after 40–45 years), melatonin secretion decreases due to degenerative processes in the pineal gland. It is accompanied by the deposition of calcium particles, called "pineal sand", which are clearly visible in radiographs.

Development: the pineal gland arises from neuroectoderm as a thickening of the ependymal layer in a diverticulum formed by the wall of the third ventricle.

Blood supply: from the choroid branch of the posterior cerebral artery. The pinealocytes are not isolated from the circulation by the blood-brain barrier.

Nerve supply: mainly sympathetic innervation from the superior cervical ganglion, which activates melatonin secretion; in addition, parasympathetic fibers from pterygopalatine (CN VII) and otic ganglia (CN IX) and sensory fibers from the trigeminal nerve.

Thyroid gland

The **thyroid gland** (Lat. ***glandula thyroidea***) is the largest endocrine gland in the body, located in the anterior region of the neck at the level from C5 to C7 vertebrae. It is highly vascularized organ of reddish-brown color, consisting of the **right** and **left lobes**, which are connected by the **isthmus** (Fig. 6). The lobes lie on the anterolateral surfaces of the larynx (reaching its midpoint) and trachea (up to the level of 4–6th tracheal rings), adjacent to the pharynx and esophagus posteriorly. The isthmus is located at the level of the 2nd to 3rd–4th tracheal rings. In some cases, a conical **pyramidal lobe** ascends from the isthmus towards

the hyoid bone. From outside the thyroid gland is covered by the infrahyoid muscles (sternothyroid, sternohyoid, superior belly of omohyoid) and the anterior border of the sternocleidomastoid muscle.

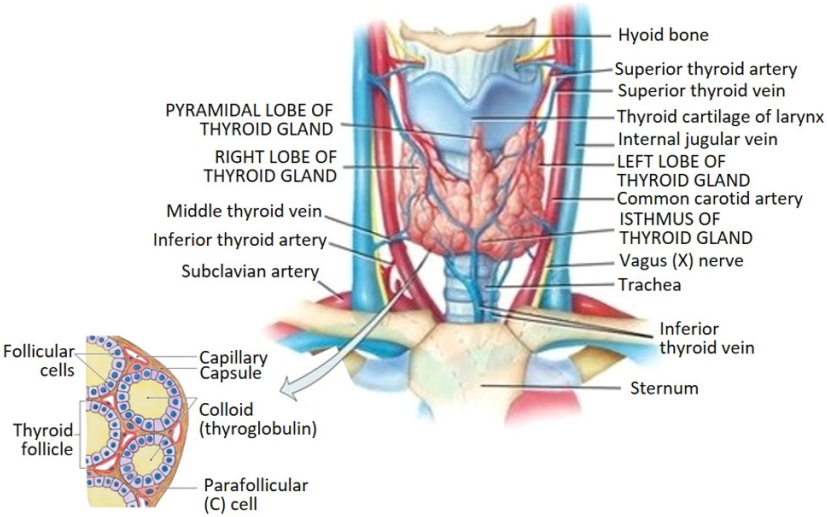

Fig. 6. Topography and structure of the thyroid gland [9]

The thyroid gland, together with the parathyroid glands lying on its posterior surface, is enclosed in the pretracheal fascia, which attaches the gland to the laryngeal cartilages. The **fibrous capsule** surrounds the thyroid gland deeper to the fascia. It continues with connective tissue partitions dividing the thyroid tissue into microscopic spherical acini, or **follicles**. The follicles are lined by a layer of epithelial cells, filled with protein-rich fluid, called **colloid**, and surrounded by a network of capillaries. The **follicular epithelium** absorbs iodine from the interstitial fluid and forms two thyroid hormones — *thyroxine (T4)* and *triiodothyronine (T3)*, containing the corresponding number of iodine atoms. The hormones are stored within the follicles until released into the capillaries due to influence of TSH from the pituitary gland.

Parafollicular cells, called **C-cells** because they secrete the hormone calcitonin, are small in number. They lie in the connective tissue adjacent to the follicles.

Functions of the thyroid hormones:

Thyroxine (T4) and **triiodothyronine (T3)** stimulate cellular metabolism. They increase protein synthesis, fat and carbohydrate metabolism, and energy use in most cells of the body. This, in turn, affects various organ systems — increases

tissue growth, body temperature, heart production, muscle tone, regulate functions of the nervous, cardiovascular, digestive, and reproductive systems.

During fetal life or early childhood, thyroid hormones play a role in growth and development of body tissues, including maturation of the nervous system. Hormonal deficiency during this period results in short and disproportionate body stature, mental retardation (cretinism), and other symptoms. In adults, thyroid dysfunction leads to hypo- or hyperthyroidism (Grave's disease).

Calcitonin reduces elevated blood calcium level by being an antagonist of parathyroid hormone. It promotes uptake of calcium into bone tissue, inhibits osteoclasts, and stimulates Ca excretion by the kidneys. In childhood it stimulates bone growth and calcification of the skeleton.

Development: the thyroid gland develops from the ventral wall of the primitive pharynx (Fig. 7). An endodermal outgrow — the *thyroglossal duct*, arises between the germs of the developing tongue; the foramen cecum is its rudiment. The duct becomes a cord and its distal end, the thyroid gland, descends down the neck. Parafollicular cells derive from the ultimopharyngeal body, which is formed by the ventral swelling of the 4th pharyngeal pouch and gets integrated into the thyroid gland.

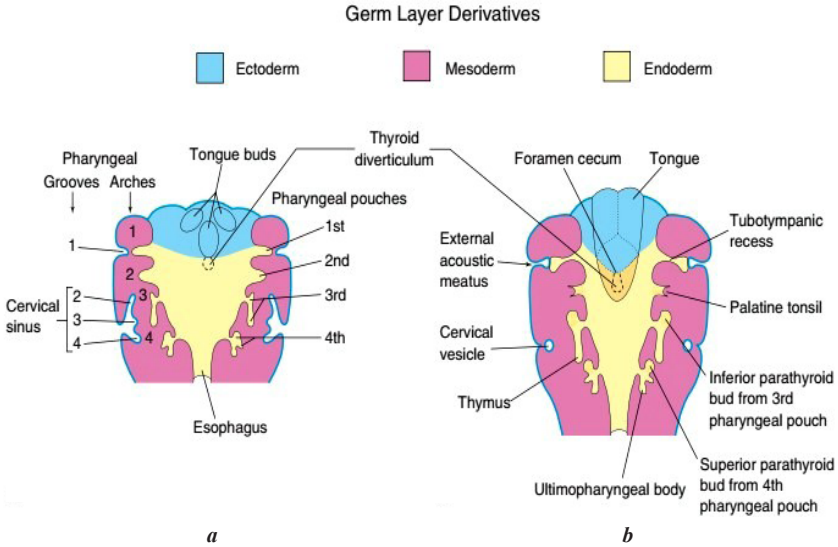

Fig. 7. The sources of development of the thyroid gland, parathyroid glands, and the thymus at 5th (a) and 6th (b) weeks of prenatal life (schematic sections through the pharyngeal pouches) [8]

Due to *incomplete descent*, the thyroid gland tissue, **accessory thyroid glands**, can be found at any point between the base of the tongue and the trachea. The lingual location, beneath the foramen cecum, is the most common. The *persistent duct* can result in the *cysts* that may occur along the thyroglossal duct, commonly below the hyoid bone. The epithelial cyst secretes mucus and may become infected and produce a *sinus*, or *fistula*, in the soft tissue of the neck.

Disorders. Hyperthyroidism (hypersecretion of hormones, Grave's disease) is characterized by increased metabolism and weight loss, excess body heat, nervousness, insomnia, fast heartbeat, diarrhea, muscle weakness, and other symptoms. Exophthalmos (caused by edema of the retrobulbar tissue) and goiter, i.e. enlargement of the gland, may occur.

Hypothyroidism (hyposecretion of hormones) in adults is characterized by reduced metabolism, weight gain, low tolerance to cold, low blood pressure and heart rate, reduced mental and physical activity, accumulation of subcutaneous fluids (myxedema), etc. Hypothyroidism caused by a lack of iodine in the diet also leads to goiter.

Blood supply: from the paired superior thyroid artery (branch of the external carotid artery) and the inferior thyroid artery arising from the thyrocervical trunk of the subclavian artery, and the unpaired thyroid ima artery (if exists). Venous drainage: via the superior, middle and inferior thyroid veins into the internal jugular and brachiocephalic veins.

Lymph drainage: into the deep lateral cervical nodes, some into the paratracheal nodes.

Nerve supply: sympathetic innervation from the superior, middle and inferior cervical ganglia of the sympathetic trunk; parasympathetic and sensory fibers from the vagus nerve through the paired superior and recurrent laryngeal nerves.

Parathyroid glands

The **parathyroid glands** (Lat. ***glandula parathyroidea***) are small yellowish oval structures, the size of a grain of rice, typically 4 in number (more than 4 in 5–10 % of cases). They are located on the posterior aspect of the thyroid gland or imbedded into it, separated from the thyroid tissue by the fibrous capsule of the thyroid gland (Fig. 8). The paired **superior parathyroid glands** lie at the upper poles of the thyroid lobes. The paired **inferior parathyroid glands** usually lie near the lower poles of the lobes, but their location is more variable. The parathyroid glands consist of cords of the epithelial cells that produce parathyroid hormone (parathormone — PTH). Together with thyroid calcitonin, PTH maintains blood concentration of Ca, which is an important in bone strength, as well as transmission of signals between the nerve cells and at neuromuscular junctions.

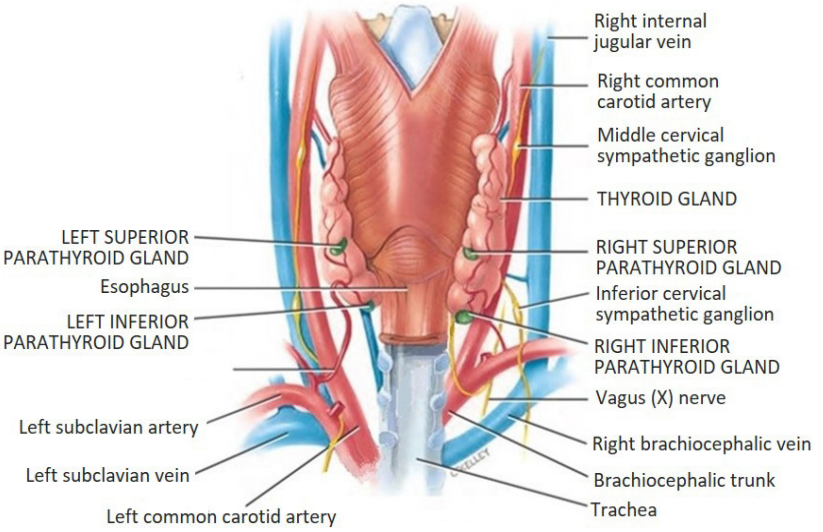

Fig. 8. Position of the parathyroid glands and their related structures (posterior view) [9]

Function of parathyroid hormone: PTH stimulates release of Ca from the bones, its reabsorption (together with Mg) in the kidney, and production of calcitriol (active form of vitamin D_3) in the kidneys helping Ca absorption from the intestine.

Development and anomalies: the superior parathyroid glands originate from the endoderm of the 4th pharyngeal pouches. The inferior parathyroid glands, together with the thymus, are derived from the 3rd pharyngeal pouches and during embryonic life descend together and appear below the superior glands (Fig. 7). The longer process of descent of the inferior glands explains the variability in their position. Ectopic parathyroid tissues can be found at any level between the mandible and the pericardium. The inferior parathyroid glands may be located within the thymus, in the tissues of the neck posterior to the pretracheal fascia, or in the mediastinum along the trachea.

Disorders. *Hypersecretion* of PTH causes excessive calcium reabsorption from the bones, resulting in decreased bone density — osteoporosis and spontaneous bone fractures, hypercalcemia and high concentration of Ca in the tissues. Calcium phosphate deposits impair functions of organs — cause kidney stones formation, bone and joint pain, abdominal pain and other symptoms. This condition usually occurs due to adenoma or hyperplasia of the glands or other conditions, e.g. severe calcium or vitamin D deficiency.

Hyposecretion of PTH and hypocalcemia may result in muscle twitching, spasms (cramping) and tetany (cramps of the entire body). This is very rare condition, which may occur because of damage or occasional surgical removal of the parathyroid glands.

Blood supply: is similar to that of the thyroid gland: mainly from the inferior thyroid artery, additionally, from the superior thyroid artery and thyroid ima artery (if exists). Venous drainage: via the parathyroid veins, which subsequently drain into the thyroid venous plexus and the internal jugular vein.

Lymph drainage: into the deep lateral cervical nodes, some into the paratracheal nodes.

Nerve supply: sympathetic (vasomotor) innervation from the cervical ganglia of the sympathetic trunk; parasympathetic and sensory fibers from the vagus nerve similar to the thyroid gland. Regulation of hormone secretion occurs by the blood calcium level.

Suprarenal glands (adrenal glands)

The paired **suprarenal (adrenal) glands** (Lat. ***glandula suprarenalis***) are yellowish pyramidal shape glands located in the retroperitoneal space at the superomedial aspects of the kidneys. Their length is about 5 cm, width — 3 cm, thickness — 1 cm. Each suprarenal gland has **surfaces: anterior, posterior** and **renal**. The anterior surface has the **hilum** corresponding to the exit point of the central vein.

The suprarenal glands together with the kidneys are surrounded by the perirenal fat and the renal fascia, by which their posterior surfaces are fixed to the crura of the diaphragm. The syntopy of the two glands differs. The right suprarenal gland lies posterior to the right lobe of the liver, medially it is adjacent to the inferior vena cava. The left suprarenal gland lies behind the stomach and above the pancreas (Fig. 9).

Structure and function. The suprarenal glands are divided into two distinct regions: the **cortex** externally and the **medulla** internally (Fig. 10).

The **adrenal cortex** comprises about 90 % of the adrenal gland in adult humans. It consists of glandular tissue, formed by layers of epithelial cells, producing vital steroid hormones, collectively called *corticosteroids*. Depending on the structure and the main hormones produced, the adrenal cortex is divided into **3 regions**:

1. *Zona glomerulosa* (peripheral): contains cells arranged in spherical clusters; produces the mineralocorticoids, mainly *aldosterone*, which controls electrolyte and water balance and thus regulates blood volume and blood pressure. Aldosterone acts on the kidneys, increasing sodium and water reabsorption and

potassium excretion. (Aldosterone secretion is regulated primarily by the renin-angiotensin system).

2. *Zona fasciculata* (middle): the largest zone with cells arranged in parallel cords; produces *glucocorticoids*, mainly cortisol, under the control of pituitary ACTH. Cortisol helps the body cope with stress by increasing blood glucose levels. It stimulates gluconeogenesis in the liver, i.e. synthesis of glucose from the breakdown products of proteins (mainly from skeletal muscles) and fats. In larger quantities, cortisol raises blood pressure, reduces inflammation, and suppresses reactions of the immune system. In fetus it regulates development of brain, lungs and surfactant formation.

3. *Zona reticularis* (internal): a narrow layer whose cells form a branching network; produces week androgens (dehydroepiandrosterone, DHEA) that serve as precursors to testosterone and estrogens in the peripheral tissues. The suprarenal androgens may contribute to growth and development of the male reproductive system and maintaining muscle mass and libido in female.

The **adrenal medulla** has reddish-brown color. It consists of neuroendocrine chromaffin cells that are modified postganglionic sympathetic neurons. Upon sympathetic stimulation they secrete amine hormones, adrenaline (epinephrine) and noradrenaline (norepinephrine), to stimulate the fight-or-flight response: increase heart rate, blood flow to the brain and muscles, elevate blood pressure, blood glucose levels, suppresses digestion, etc.

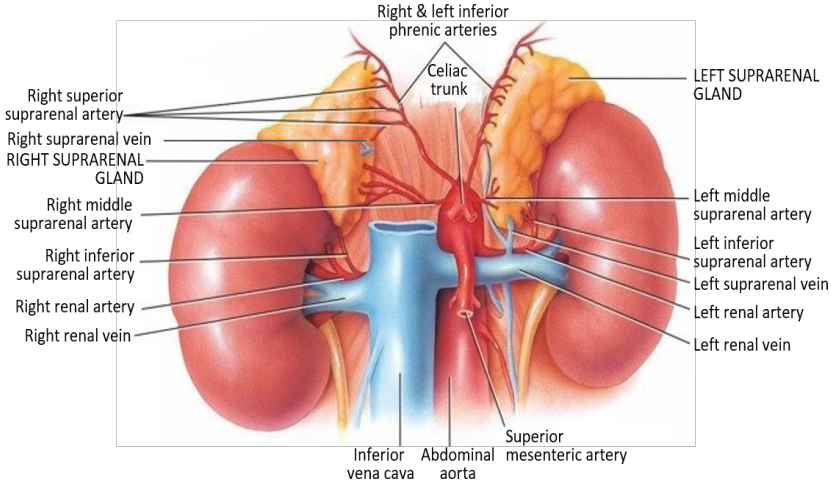

Fig. 9. Suprarenal glands: topography and related vessels [9]

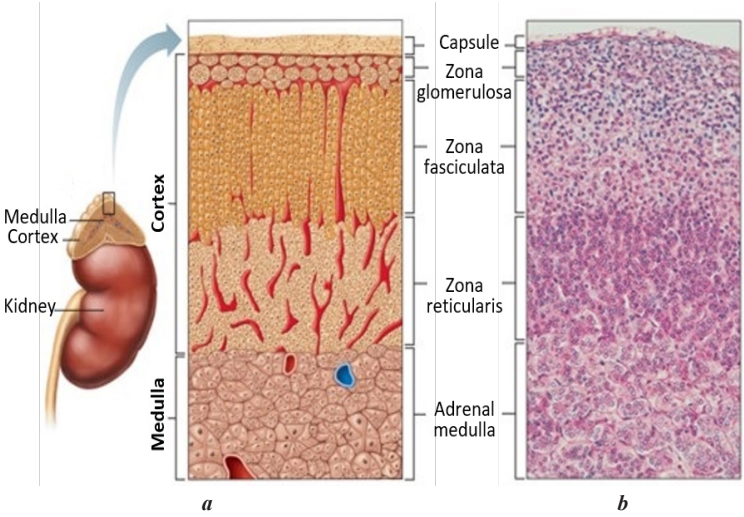

Fig. 10. Structure of the suprarenal gland:
a — drawing of the adrenal histology; *b* — photomicrograph (140×) [6]

Development: the adrenal glands are composed of two heterogeneous types of tissue of different embryonic sources. The adrenal cortex originates from the intermediate mesoderm near the root of the dorsal mesentery, while the adrenal medulla develops from the neuroectoderm, particularly neural crest cells. These cells migrate to the mesodermal primordium via the developing sympathetic trunk.

The adrenal glands in a newborn are much larger in relation to the body size than in an adult. For example, at the age of 3 months, the glands are four times the size of the kidneys. Then the size of the glands decreases relatively, mainly due to shrinkage of the cortex, which almost completely disappears by the age of 1 year. However, from 4–5 years the cortex develops again.

Disorders:

1. Disorders of the adrenal cortex:

Congenital hyperfunction, known as *adrenogenital syndrome*, is an inherited defect in one of the enzymes needed for the cortisol production. This is accompanied by hyperplasia of both adrenal glands, insufficient production of cortisol and excess adrenal androgens. It leads to masculinization and pseudohermaphroditism in girls, and to premature sexual development in boys.

Acquired hyperfunction of the adrenal cortex may be due to either an adrenal tumors or hyperplasia. It is manifested by either an excess of glucocorticoid hormones (Cushing syndrome), androgen excess, or aldosterone excess (primary aldosteronism).

Hypersecretion of glucocorticoid hormones, Cushing's disease (Cushing's syndrome), is caused by a tumor of the adrenal cortex or, more commonly, an ACTH-secreting pituitary tumor. This condition is characterized by high blood glucose levels, rapid weight gain, loss of protein from muscles and muscle weakness, depression, high blood pressure, accumulation of lipid deposits on the face (a moon-shaped face) and neck ("buffalo hump" on the posterior neck). In addition, elevated glucocorticoids depress immunity and resistance to infection,

Androgen excess in women is characterized by excessive hair growth on the face and other regions and amenorrhea; in men, androgen excess has few effects.

Primary aldosteronism is characterized by increased retention of salt and water by the kidneys, and low serum potassium concentrations due to its excessed excretion in the urine. It leads to high blood pressure, muscle weakness and cramps, increased thirst and urination.

The major *hyposecretory disorder* of the adrenal cortex, *Addison's disease*, involves deficiencies of both glucocorticoids and mineralocorticoids. This causes low blood glucose and sodium levels and may lead to severe dehydration and low blood pressure. Hyperpigmentation of the skin appears due to stimulation of melanocytes by ACTH, which is structurally similar to MSH. Other symptoms may include fatigue, abdominal pain, nausea, weight loss, loss of appetite, craving for salty food.

2. A disorder of the adrenal medulla, pheochromocytoma, is a tumor of chromaffin cells secreting excessive quantities of epinephrine and norepinephrine. It leads to periodic episodes of hypertension or persistent high blood pressure, palpitations of the heart, sweating, headaches, and anxiety.

Blood supply: 3 suprarenal arteries: 1) superior — from the inferior phrenic artery, 2) middle — from the aorta, 3) inferior — from the renal artery. Venous drainage: right suprarenal vein into the inferior vena cava directly, left vein — via the left renal vein.

Nerve supply: to the medulla — preganglionic sympathetic fibers from the splanchnic nerves of the sympathetic trunk (stimulate hormone secretion); to the cortex — postganglionic sympathetic fibers from the celiac plexus (can stimulate glucocorticoid secretion) and parasympathetic fibers of the vagus nerve.

Lymph drainage: into the lumbar nodes.

Paraganglia

Paraganglia (sympathetic paraganglia) are aggregations of chromaffin cells of the neural crest origin, similar to the chromaffin cells of the suprarenal medulla. They are dispersed throughout the body, often found along the blood vessels, connected with the ganglia of the sympathetic trunk or sympathetic plexuses.

Paraganglia are highly variable in number and location. According to Anatomical Terminology [3], the most constant are the following:

– **carotid body** (at the bifurcation of the common carotid artery) (Fig. 11);

– **jugular body** (along the cervical vagus nerve, between the internal carotid artery and internal jugular vein);

– **aorticopulmonary paraganglion** (between the pulmonary trunk and the aortic arch);

– **paraaortic paraganglia** (along the abdominal aorta);

– **coccygeal body** (at the end of the median sacral artery and apex of the coccyx).

Each paraganglion is surrounded by a connective tissue capsule and consists of neuroendocrine cells, which essentially function the same way as the adrenal medulla. The paraganglia, associated with the branches of the parasympathetic nerves, glossopharyngeal and vagus (e.g., carotid and jugular bodies), contain chemoreceptors sensitive to changes in carbon dioxide and oxygen levels, thereby aiding in the regulation of respiration and circulation.

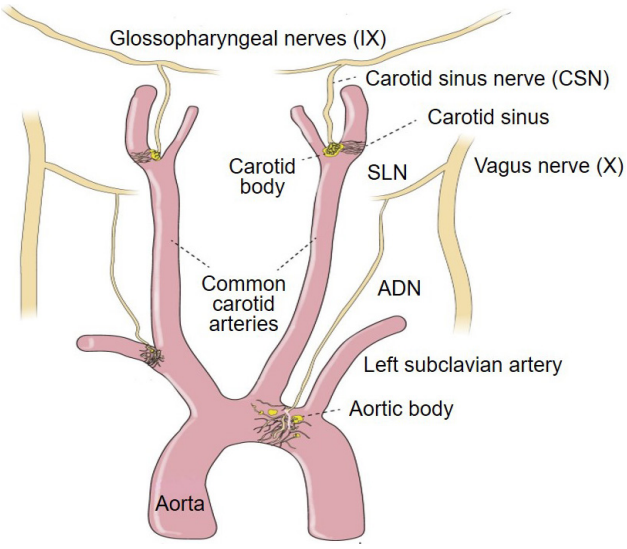

Fig. 11. Location of the carotid and aortic bodies:
SLN — superior laryngeal nerve; AND — aortic depressor nerve [10]
(https://www.cell.com/neuron/fulltext/S0896-6273%2821%2901037-0#fig3)

Pancreas

The pancreas is an organ with both exocrine and endocrine functions, located retroperitoneally in the posterior wall of the abdominal cavity behind the stomach. Most of the organ is formed by exocrine acinar cells that secrete digestive enzymes into the duodenum to digest food. The endocrine part makes up about 1–2 % of the pancreas (Fig. 12). It consists of spherical clusters of endocrine cells, scattered among the exocrine acini, called **pancreatic islets (islets of Langerhans)**. A capillary network surrounding the islets carries their hormones into the hepatic portal vein.

The main hormones produced in the islets of the pancreas are **glucagon** (produced by α-cells) and **insulin** (produced by β-cells) that are responsible for glucose metabolism and maintaining blood glucose levels:

Glucagon raises blood glucose levels: stimulates both release of glucose from the liver glycogen stores and gluconeogenesis (i.e., glucose formation from amino acids and products of fat breakdown).

Insulin lowers blood glucose levels: it stimulates the uptake of glucose from the blood and its utilization by most cells of the body (mainly skeletal muscle and adipose cells) and by the liver, which stores it as glycogen.

The pancreatic islets contain 4 types of cells:

– alpha cells (α-cells) secrete glucagon; most of them lie at the periphery of the pancreatic islets;

– beta cells (β-cells) secrete insulin; they are more numerous and occupy the central part of the islets;

Minor cell types scattered throughout the islets:

– delta cells (δ-cells) secrete somatostatin (growth hormone inhibiting hormone) that inhibits the secretion of glucagon and insulin in the pancreas, as well as hormones and enzymes in the digestive tract;

– F-cells secrete pancreatic polypeptide (PP), which suppresses exocrine pancreatic function and gallbladder contraction and control absorption of nutrients by the digestive tract.

Development: the pancreas is formed during the 5th weeks of embryogenesis by fusion of the ventral and dorsal buds, which derive from the endodermal lining of the duodenum. The cells of the pancreatic islet arise at different time points in development and are thought to be of heterogeneous origin, both endodermal and neuroectodermal.

Disorders. Diabetes mellitus is a condition caused by insufficient secretion of insulin by beta cells (type 1 diabetes) or insulin resistance of body's cells, i.e., inability to absorb glucose (type 2 diabetes). This results in abnormally high blood glucose levels (hyperglycemia) and inability to reabsorb all glucose by kidney. Glucose appears in the urine and urine production increases. Diabetes mellitus can be caused by genetic abnormalities, injuries, immune disorders or other conditions.

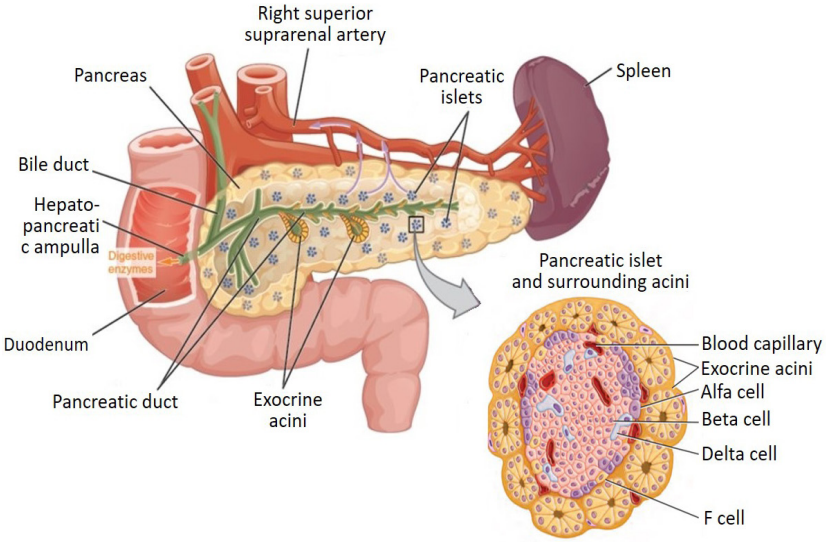

Fig. 12. Structure of the pancreas [1]

Gonads

The gonads, testes and ovaries, are organs of the reproductive system and at the same time are the main sources of the steroid sex hormones: androgens in male and estrogens and progesterone in female.

Testes. The main androgen of the testes is **testosterone**. It is formed by the interstitial (Leydig) cells located between the seminiferous tubules and enters both the tubules and the blood. In the tubules, testosterone promotes spermatogenesis (paracrine effect). Testosterone stimulates the development of the male reproductive system and male secondary sex characteristics, maintains the functioning of the genitals, and stimulates an increase in muscle mass.

Ovaries. Cells of growing ovarian follicles produce **estrogens** (mostly estradiol), which regulate many physiological processes: the development of female genital organs and secondary sex characteristics, such as an increase in adipose tissue and mammary glands growth, maturation of ovarian follicles, regulation of the menstrual cycle, maintaining pregnancy, and contraction of the uterine muscles (Fig. 13). Androgens secreted in the ovaries are directly converted into estrogens by ovarian follicle cells.

The corpus luteum, which forms after ovulation from the ruptured follicle, secretes another ovarian hormone, **progesterone,** along with estrogens.

Progesterone contributes regulation of the menstrual cycle. It prepares the uterine wall for implantation of the egg by stimulating secretion in the endometrium and is important for maintaining pregnancy. The corpus luteum persists for 2 weeks, during the second half (luteal phase) of each ovarian cycle. If fertilization occurs, the corpus luteum lasts for about 12 weeks until the **placenta** begins to secrete most hormones.

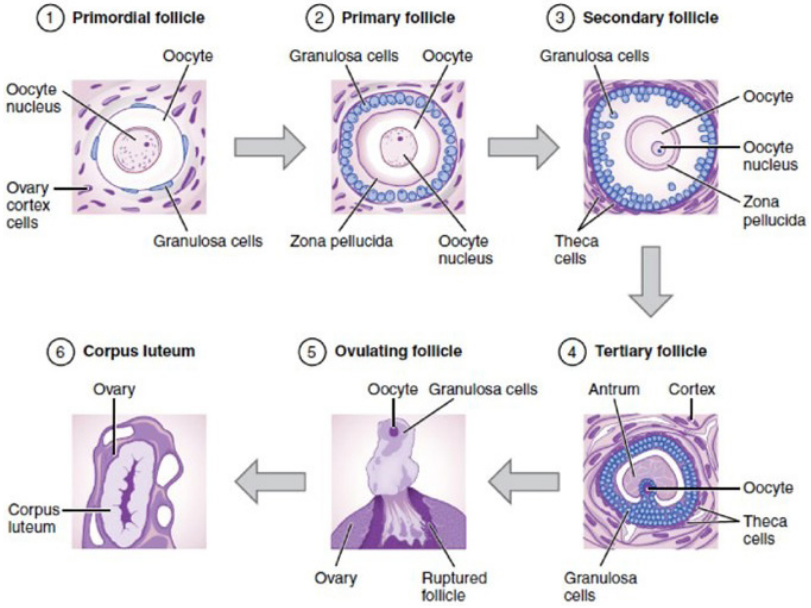

Fig. 13. The maturation of a follicle in the ovary (shown in a clockwise direction): the granulosa and theca cells produce estrogens; the corpus luteum produces progesterone [1]

ORGANS WITH SECONDARY ENDOCRINE FUNCTIONS. DIFFUSE NEUROENDOCRINE SYSTEM

In addition to endocrine glands, various organs of the body, such as the thymus, kidneys, heart, epithelium of the digestive tract, placenta, etc., have secondary endocrine functions. They contain endocrine cells that secrete amine and peptide hormones, or other signaling molecules, some of which are chemically identical to neurotransmitters. These hormones can act not only distantly but also locally regulating various bodily functions, including digestion, metabolism, inflammation, and the nervous system functioning. Collectively, all these

specialized cells scattered throughout the body make up the diffuse neuroendocrine system (DNES), which interacts with the nervous system and the immune system, influencing their activities.

Placenta

The human placenta develops within the uterus during the early stages of pregnancy. It supplies the fetus with oxygen and nutrients, removes waste products, and synthesizes several protein and steroid hormones that influence the course of pregnancy.

Protein hormones are similar by structure to those of the anterior lobe of the pituitary gland, e.g., **human chorionic gonadotropin (hCG),** human chorionic thyrotropin, human chorionic corticotropin. The first hormone secreted by the placenta is hCG (tested for in pregnancy tests). It appears in the maternal blood and urine in the second embryonic week as the fertilized egg implants into the uterus. Its concentration reaches a maximum by the eighth week and then declines. HCG maintains the corpus luteum of the ovaries, which produces progesterone, preventing the onset of menstruation, and inhibits immune response against the fetus. Another protein hormone, human placental lactogen (hPL) plays a role in preparing the breasts for lactation.

The steroid hormones synthesized by the placenta are **progesterone** and **estrogens**. After the 12th week, the placenta is the main source of progesterone, which is necessary for maintaining pregnancy.

Kidneys

The kidneys contain cells that produce certain hormones. **Renin** is secreted by specialized muscle cells of the juxtaglomerular (JG) apparatus — the JG cells (granular cells), located in the walls of the afferent arterioles of the nephrons. Renin has a crucial role in regulating blood pressure and fluid balance. It triggers the renin-angiotensin-aldosterone system (RAAS), which causes the adrenal cortex to secrete aldosterone and stimulate the reabsorption of sodium and water[1].

Other kidney hormone, **erythropoietin,** stimulates the production of red blood cells (erythrocytes) in the bone marrow. It is produces by interstitial fibroblast-like cells, located in the connective tissue of the cortex and outer medulla between the renal tubules and peritubular capillaries.

The kidneys also produce hormone **calcitriol**, the active form of vitamin D, released in response to the secretion of parathyroid hormone. Calcitriol elevates

[1] Renin catalyzes conversion of angiotensinogen (produced in the liver) to angiotensin I in the kidneys; in the lungs, angiotensin I is converted into angiotensin II, which causes aldosterone secretion by the adrenal glands.

blood calcium levels (increase absorption of dietary calcium and phosphate from the gastrointestinal tract and reabsorption of calcium in the kidneys, stimulates the release of calcium from the bones).

Heart

The atria of the heart contain specialized cardiac muscle cells that secrete hormone **atrial natriuretic peptide (ANP)** in response to stretching of the heart's atrial wall. ANP decreases excess blood volume, high blood pressure, and blood sodium concentration. ANP signals the kidneys to reduce sodium reabsorption, thereby decreasing the amount of water reabsorbed from the urine filtrate and reducing blood volume. In addition, ANP inhibits renin secretion by the kidneys.

Gastrointestinal tract and its derivatives

Enteroendocrine cells are hormone-secreting cells scattered within the epithelial lining of the gastrointestinal tract and gut-derived organs, including the pancreas, liver, and the respiratory tube. Collectively, these cells belong to the diffuse neuroendocrine system (DNES). They secrete hormones that regulate digestion, controlling secretion of digestive enzymes, local blood flow and motility of the digestive tube. Some of these hormones act on nearby target cells without first entering the bloodstream.

An example of a hormone secreted by the stomach cells is **gastrin**, that stimulates the release of hydrochloric acid and pepsin and contraction of the pyloric region of the stomach in response to stomach distention. **Secretin** is secreted by the small intestine as acidic chyme moves from the stomach. It stimulates the release of water and bicarbonate from the pancreas to buffer the acidic chyme, inhibits secretion of gastrin in the stomach, delaying gastric emptying. **Cholecystokinin** produced in the small intestine promotes the secretion of pancreatic enzymes and the release of bile from the gallbladder into the intestine.

The liver is responsible for some important hormones or hormone precursors. **Insulin-like growth factor-1** stimulates growth by mediating secretion of growth hormone from the pituitary gland. **Angiotensinogen** is the precursor to angiotensin, which increases blood pressure. **Thrombopoetin** stimulates the production of the blood's platelets. **Hepcidins** block the release of iron from the body's cells, helping to regulate iron homeostasis in body fluids.

THYMUS

The thymus does not belong to endocrine glands but has endocrine functions as well. The thymus is a primary lymphoid organ. Its main function is to produce immunocompetent T lymphocytes, which are able to attack foreign antigens and pathogens without harming the cells of the body. The mature T cells are released into the bloodstream and lymph and populate the peripheral lymphoid organs providing adaptive immune response.

The endocrine function of the thymus is the production by epithelial reticular cells a group of peptide hormones called thymosins. **Thymosins** regulate the development and differentiation of T lymphocytes, their migration to the T-dependent zones of the secondary lymphoid organs, and contribute to immune responses.

The thymus is located in the superior mediastinum, behind the sternum and anterior to the pericardium, aortic arch, left brachiocephalic vein, and trachea (Fig. 14). During the period of maximum activity, superiorly it may reach the thyroid gland, inferiorly — the level of the 4th costal cartilage. The thymus consists of **two lobes,** surrounded by the fibrous capsule. The capsule forms thin septa dividing the thymus into small **lobules**. Each lobule consists of the outer **cortex** with densely packed cells and the central **medulla** containing fewer cells and thymic (Hassall's) corpuscles composed of clusters of epithelial cells. Within the lobules, lymphoid stem cells proliferate and become mature T-cells.

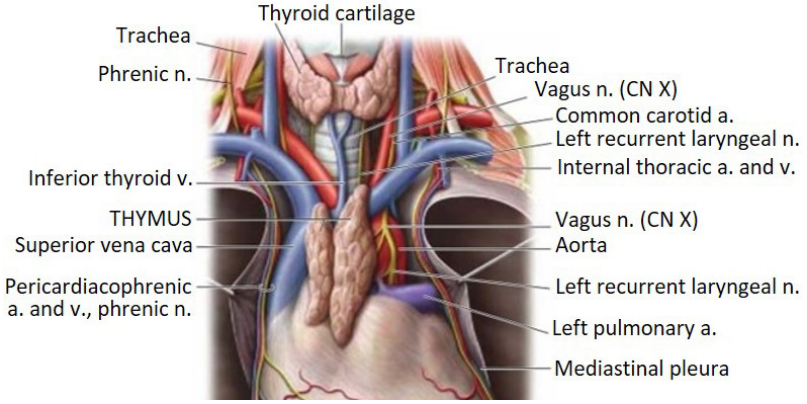

Fig. 14. Topography of the thymus [4]

The thymus develops from the third pharyngeal pouches and clefts that give rise to the epithelial stroma of the organ (Fig. 7). In the 9th gestational week, hematopoietic cells migrate from the bone marrow into the thymus anlage. After the 12th week, the thymus descends into the thoracic cavity and gains its definitive shape and structure. The thymus starts functioning in early fetal life, grows throughout fetal period, infancy and childhood when it is most active. It reaches its maximum relative size in the first – second years after birth and its absolute size — by puberty. After puberty, the thymus undergoes involution that is decrease in size and decline in function due to gradual replacement of functional tissue with fibrous and fatty tissue.

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