GOMEL STATE MEDICAL UNIVERSITY
Normal and Pathological Physiology Department

HUMORAL REGULATION OF PHYSIOLOGICAL FUNCTIONS

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Lecture plan:

1. Properties of hormones.

2. The mechanism of hormone action on target cells.

3. Study methods of the activity of the endocrine glands.

4. Incretion of the hypophysis:

- **Anterior lobe of the hypophysis**
- **Intermediate lobe of the hypophysis**
- **Posterior lobe of the hypophysis.**

5. Regulation of incretion of the hypophysis.

1. *Properties of hormones*

Endocrinology is the science which studies the development, structure, and functions of the endocrine glands (EG) and endocrine cells.

Hormones (from the Greek word *«horman»* — *to excite*) are biologically active substances which are secreted by EG in the blood or lymph and regulate human metabolism and body physiological functions.

The **pituitary body, thyroid gland, parathyroids, insular apparatus of the pancreas, cortical and medullary layers of the adrenal glands, sex glands, placenta, and epiphysis** are related to EG (Figure). These glands release their secret directly into the bloodstream or the lymphatic system, therefore they are called EG. Besides, some hormones are secreted by organs and tissues performing in the body apart from endocrine other specific functions (kidneys, gastrointestinal tract, etc.).

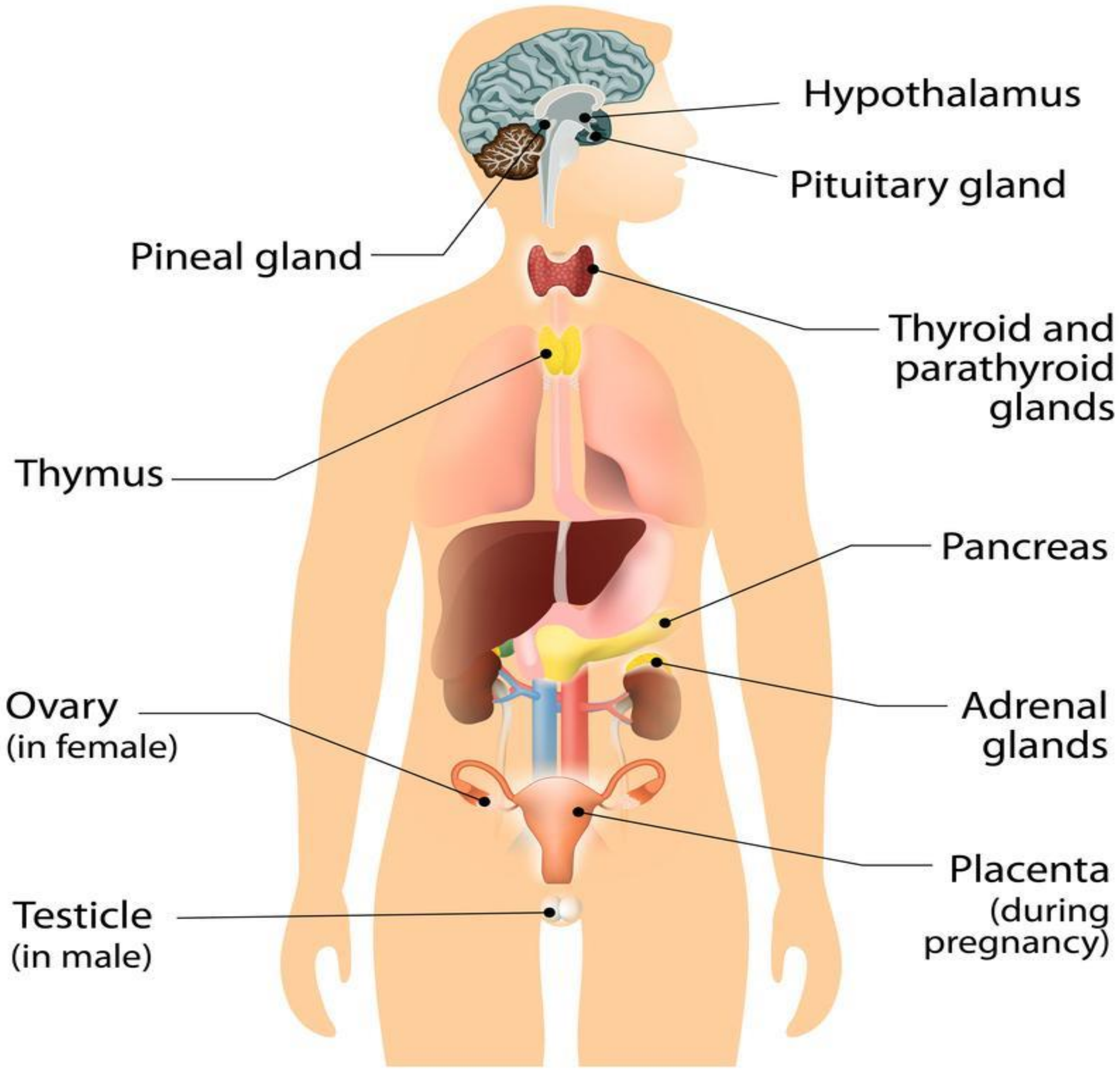

Figure — Endocrine glands

Hormones have some properties:

1. Distant character of their action, i. e. coming into the blood vessels, they can influence organs and tissues located distantly from the glands where they are formed.

2. Specificity of hormones, i. e. each hormone carries out a certain function and cannot be replaced with other biologically active substances. For example, growth hormone.

3. High biological activity of hormones. Hormones are active at low doses. For example, 1 gram of adrenaline can increase the heart rate of 10 million frogs, 1 gram of insulin can decrease the blood glucose level of 125 thousand rabbits.

4. The small size of the hormone molecules facilitates the transit of some hormones through the cell membranes.

5. Hormones are quickly destroyed. For example, the half-life of thyroxin is 4 days, aldosterone — 30 minutes, adrenaline — 2.5 minutes.

6. Some hormones are not species-specific, i.e. some animal hormones can influence the human body as well. For example, thyroid hormones, adrenaline.

There are five types of the influence of hormones on the body:

1. Metabolic (impact on metabolism).

2. Morphogenetic (stimulation of form-building processes, differentiation, body growth, metamorphosis).

3. Kinetic (including certain activity of organs).

4. Correcting (changing of the intensity of organ and tissue functions).

5. Permissive (the presence of one hormone is required to allow a second hormone to exert its full effects on the target cell. For example, thyroid hormones increase the number of receptors available for adrenaline in the target cell, thereby increasing the effect of adrenaline on that cell).

By their chemical structure, hormones can be divided into three basic classes:

1) steroids:

— corticosteroids (cortisol, aldosterone);

— sex glands hormones (androgens, estrogens, progesterone);

2) derivatives of amino acids:

— thyroxin, adrenaline, melatonin;

3) protein-peptide compounds:

— **polipeptides** (vasopressin, releasing hormones);

— **proteins** (insulin, somatotropin, prolactin);

— **glycoproteins** (thyrotropin, corticotropin).

Steroid hormones and hormone derivatives of amino acids have no species specificity and usually render the same action on representatives of different species.

Protein-peptide hormones, as a rule, are species-specific.

2. The mechanism of hormone action on target cells

Hormones influence the target cell by changing the cell activity: they decrease or increase the rates of cellular processes.

The influence of hormones on the cell is performed basically by:

1) redistribution of substances in the cell;

2) chemical modification of cell proteins;

3) induction or suppression of the processes of protein synthesis.

These primary effects lead to changes of the number and activity of regulatory cell proteins and rate of catalytic processes and, as a result, cause the physiological response of tissues to the hormone signal.

The main two mechanisms of the action of hormones are as follows:

— **formation of intracellular second messengers, which mediate the target-cell response to the hormone;**

— **direct gene (DNA) activation by the hormone.**

The regulatory influence of protein-peptide hormones, catecholamines, and some others is performed through the system of ***second messengers*** (*cyclic AMP, GMP and others)*. The mechanism of the action of second messengers can be demonstrated on the example of cyclic AMP. When the hormone binds to the receptors coupled to the membrane bound enzyme adenylate cyclase, adenylate cyclase is activated and catalyses the conversion of intracellular ATP to cyclic AMP (cyclic adenosine 3', 5'-monophosphate). Cyclic AMP then diffuses throughout the cell and initiates a cascade of chemical reactions, as a result of which proteinkinases phosphorylate different proteins, many of which are enzymes. The process of phosphorylation activates some of these proteins and inhibits others, which causes various reactions.

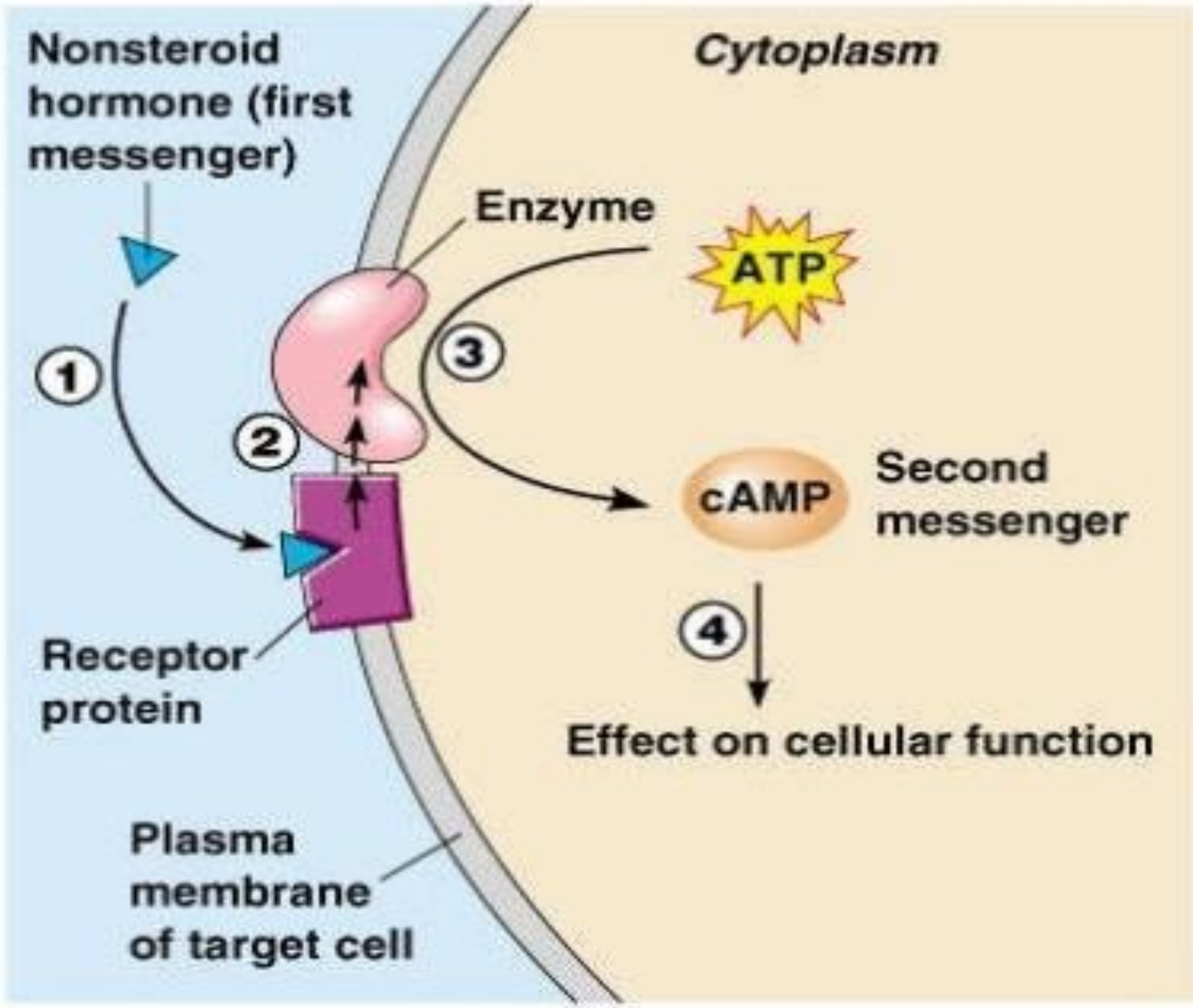

Figure — Mechanism of the action of nonsteroid hormones

Steroid, thyroid hormones after getting into the cell bind to the receptors in the cytoplasm and nucleus (Figure). Then the hormone-receptor complex is connected with the DNA and proteins of chromatin, which stimulates transcription of certain genes and, as a result, synthesis of new proteins in the cell. These proteins include enzymes which influence the metabolic activity and in some cases the synthesis of structural proteins.

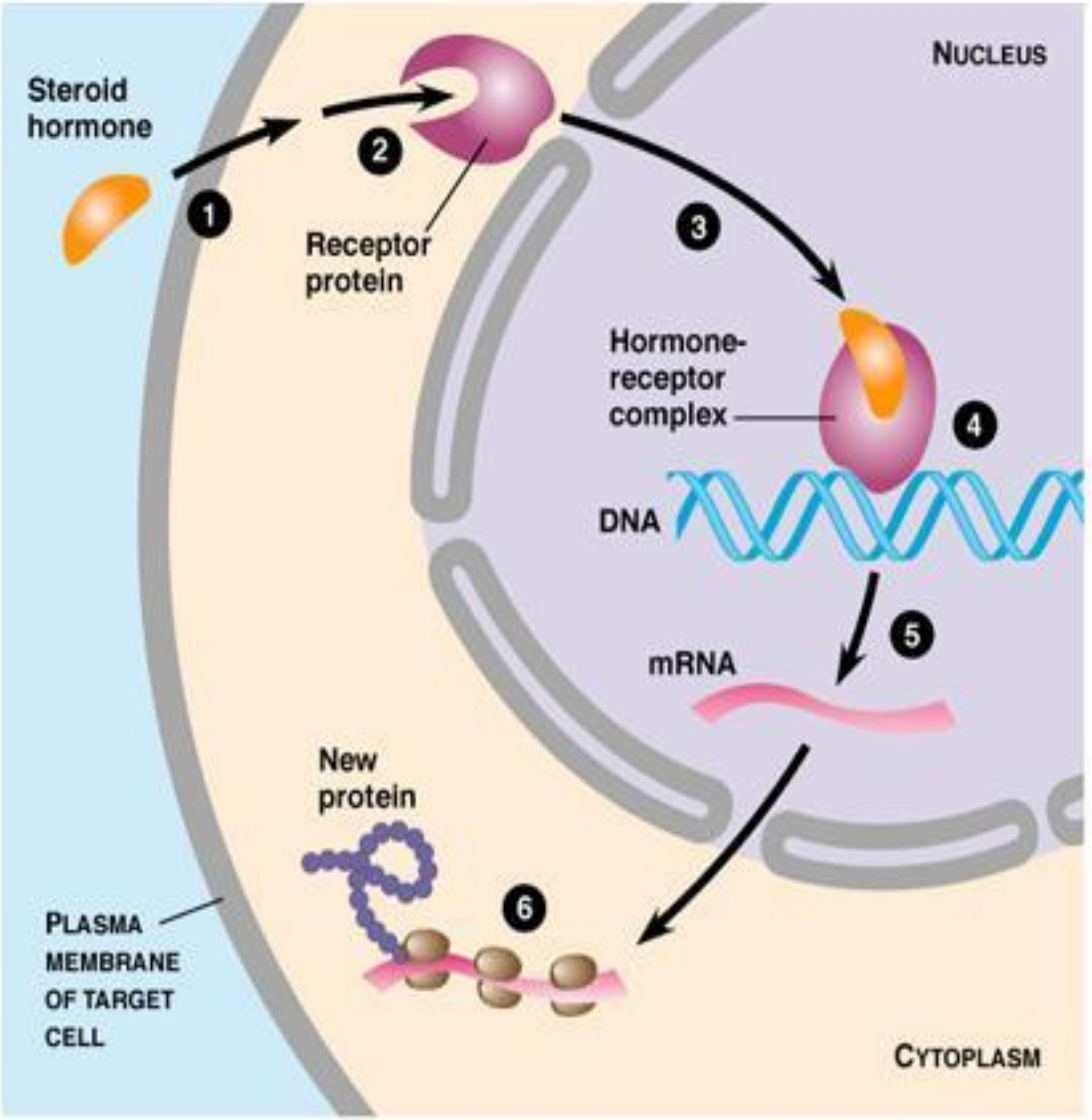

Figure — Mechanism of the action of steroid hormones

3. Study methods of the activity of the endocrine glands

The following methods are usually applied to study the EG functions:

1. **Removal** (complete or partial) of the glands and observation over the body functions.
2. **Administration of extracts** received from a particular gland, to a healthy animal or an animal after the removal of the glands or transplantation of the tissue of this gland into the body.
3. **Formation of common blood circulation of the two organisms**, one of which has affected or removed EG.
4. **Comparison of the physiological activity of the blood flowing into and out of EG**.

5. Biological or chemical determination of the concentration of a certain hormone in the blood and urine.

6. Examination of the mechanisms of hormone biosynthesis (more often with the help of the method of radioactive atoms, i. e. radioactive isotopes).

7. Determination of the chemical structure and artificial synthesis of the hormone.

8. Examination of patients with hypo- or hyperfunction of a particular EG and outcomes of surgical operations performed in these patients for medical purposes.

4. Incretion of the hypophysis

The hypophysis (pituitary gland) consists of three lobes – anterior, intermediate, and posterior, each of them being EG. The posterior lobe, which is connected with the hypothalamus, is called neurohypophysis, and the anterior – adenohypophysis.

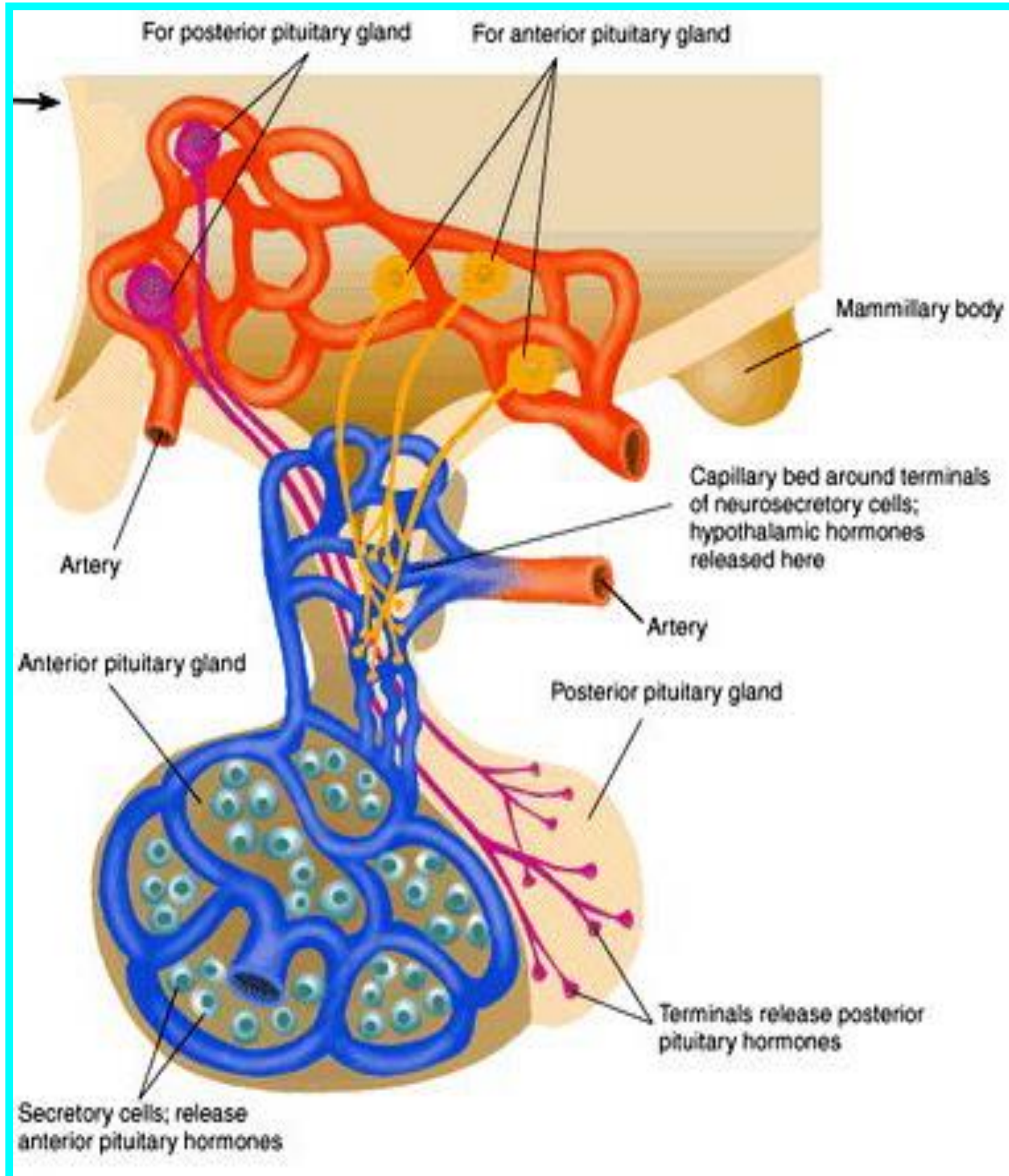

Figure — Hypophysis

Anterior lobe of the hypophysis

The anterior lobe, or adenohypophysis, consists of the **main, or chromophobic cells** (55–60 % of all cells) **and chromophilic cells**: *acidophilic* (30–35 %) and *basophilic* (5–10 %). Chromophobic cells, apparently, do not produce hormones and are precursors of chromophilic cells. Acidophilic cells produce somatotropic hormone (STH, growth hormone) and prolactin. All the hormones of the anterior lobe are protein substances. The production of these hormones is regulated by the release and inhibition of the hormones of the hypothalamus.

Basophilic cells produce adrenocorticotropic hormone (ACTH), thyrotropic and gonadotropic (follicle-stimulating and luteinizing) hormones.

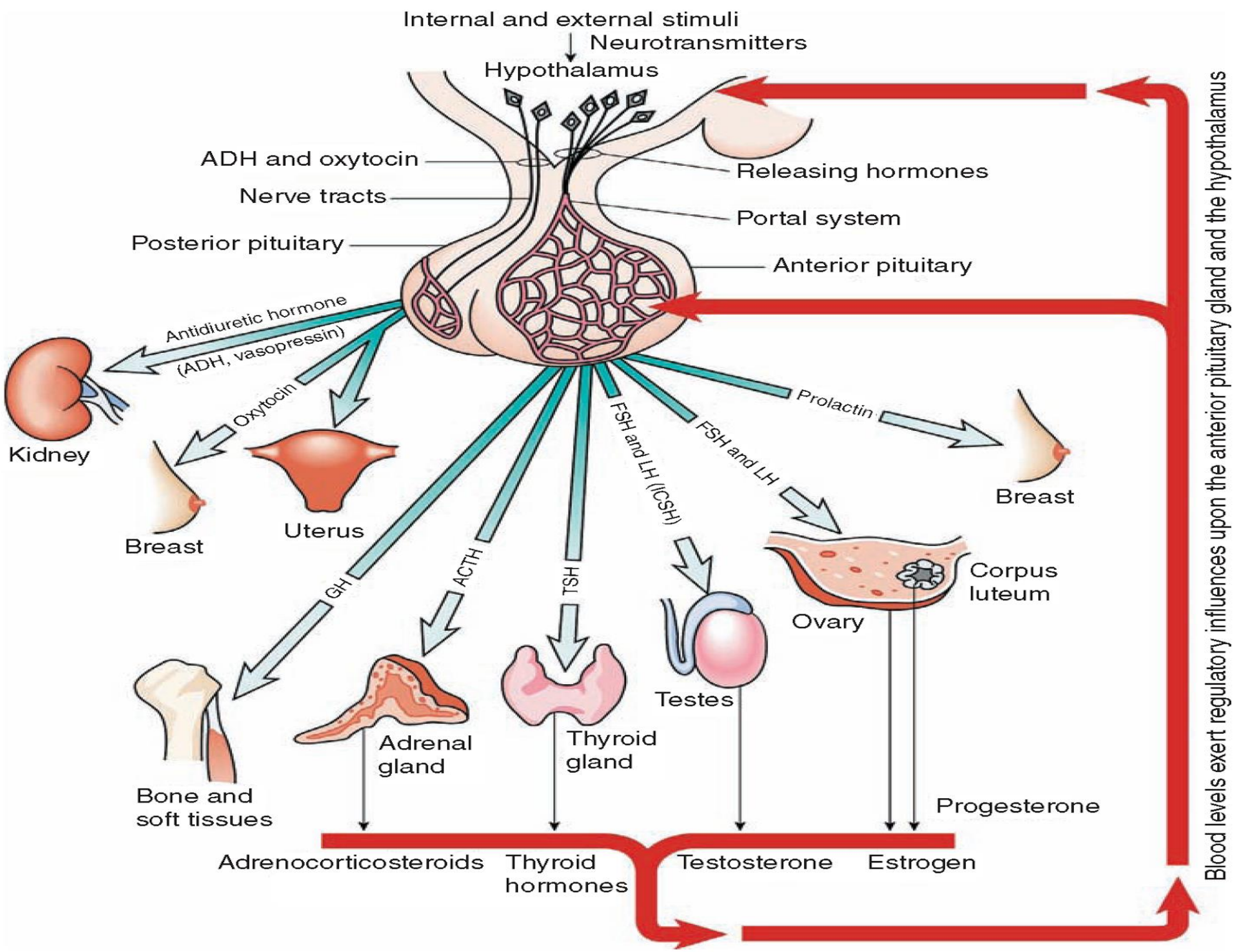

Figure — Hypophysis (pituitary) hormones

Notes: GH — growth hormone; FSH — follicle-stimulating hormone; LH — luteinizing hormone; TSH — thyroid-stimulating hormone; ACTH — adrenocorticotropic hormone.

Somatotropic hormone (STH, somatotropin, growth hormone) stimulates the synthesis of proteins in organs and tissues and promotes body growth of young organisms.

Somatotropin increases the biosynthesis of ribonucleic acid necessary for protein synthesis. It strengthens amino acid transport from the blood into cells. There is retention of nitrogen (nitrogen balance becomes positive), phosphorus, calcium, sodium in the body.

For the somatotropin effect which intensifies protein synthesis in the cell, the presence of carbohydrates and insulin is necessary. After the removal of the pancreas in animals, and also if carbohydrates are excluded from diet, the action of growth hormone is inhibited. The administration of growth hormone increases fat mobilization from the depot and its use in energy metabolism. It leads to increased fat metabolism, and also to the increased level of ketone bodies in the blood and their excretion with urine.

Growth hormone deficiency causes a sharp growth delay in children. A lack of this hormone in early childhood leads to ***pituitary dwarfism,*** and the person remains a dwarf for the whole life. The body constitution in these individuals is rather proportional, however, their wrists, feet are little, fingers are thin, the ossification of the skeleton is delayed, their genitals and secondary sex characteristics are underdeveloped, their hair differs in terms of softness and silkiness typical of healthy children. These people bear infectious diseases and other illnesses badly and frequently die at a young age. Sexual development is often delayed or impaired into adulthood. Males with this disease often suffer from impotence, i.e. the inability to copulate or get an erection, and females suffer from sterility, i. e. the disability to procreate.

Overproduction of growth hormone in children causes ***gigantism***; the body height of such an individual can reach 240–250 cm, and body weight — 150 kg and more.

Figure — Gigantism

If overproduction of growth hormone develops in an adult whose bone growth has stopped, the body height does not increase on the whole, but some body parts are capable to keep growing: fingers and toes, hands and feet, nose, lower jaw, tongue, organs of the thoracic and abdominal cavities. This disease is called ***acromegaly*****.** In acromegaly insulin insufficiency in the tissues of the pancreas results in diabetes and other serious health effects. The cause of acromegaly is usually tumors of the anterior lobe of the hypophysis.

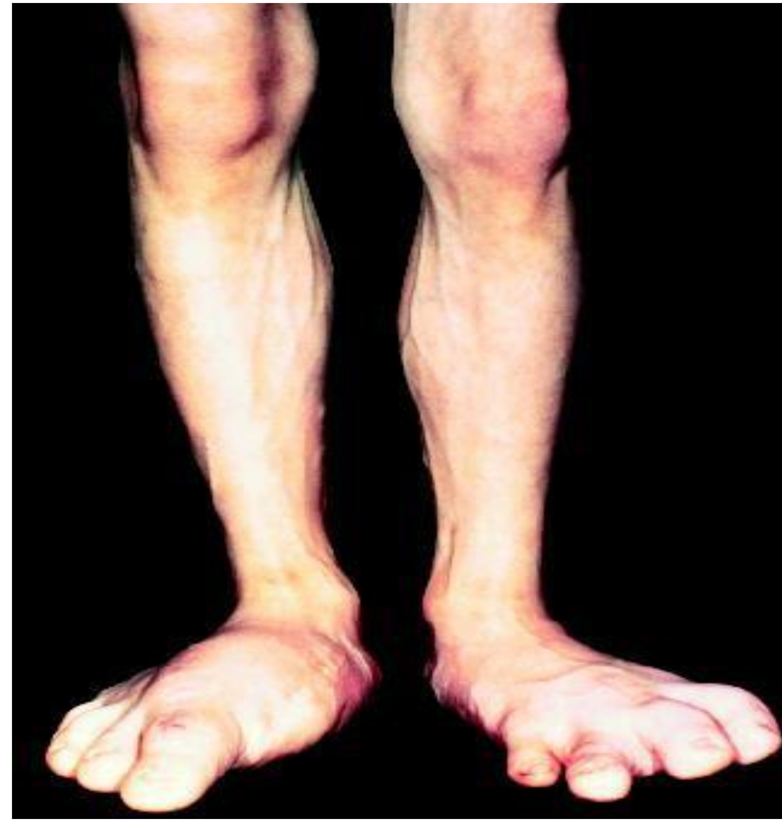

Figure — Acromegaly

Gonadotropic hormones (gonadotropins)

Gonadotropic hormones are **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)**.

The physiological effects produced by **FSH** and **LH** are caused by their action on male and female genitals, stimulation of the development of the pubertal gland and follicles (formation of sexual hormones).

The administration of gonadotropic hormones to castrates causes no typical physiological effects.

The immediate cause of puberty is the action of the hormones formed by the genitals but not of the gonadotropines of the hypophysis.

The secretion of **FSH** and **LH** by the hypophysis is stimulated by the action of hypothalamic neurosecretion (**gonadotropin-releasing hormone).** Increased androgen level (in males) or estrogen level (in females) in the blood inhibits the secretion of the above hormone, and also the secretion of the gonadotropins by the adenohypophysis. This negative feedback regulates the normal level of the sex hormones in the body.

The production of gonadotropic hormones in humans is influenced by emotional experience. Thus, during World War II the fear caused by bomb attacks sharply affected the secretion of gonadotropic hormones in women and led to the arrest of menstruation.

Prolactin (luteotropic hormone) released by the acidophilic cells of the anterior lobe of the hypophysis strengthens the production of milk in the mammary glands, and also stimulates the development of the yellow body.

If to remove the hypophysis in nursing rats, lactation, or the secretion of milk decreases. The administration of prolactin does not only stimulate milk secretion in nursing rats but also produces its low secretion in non-nursing ones if they have reached puberty and even if they are castrated. Prolactin injections may also cause lactation in males. However, for this purpose estrogens and progesterone should be administered to them for some time as males have rudimentary mammary glands and thus cannot lactate. The administration of prolactin before puberty produces the development of the maternal instinct.

Prolactin decreases the consumption of glucose by tissues, which causes an increase of its amount in the blood, i. e. its effect is similar to somatotropin but is much weaker.

Prolactin secretion is stimulated by the reflex of the centers of the hypothalamic region. The reflex arises during the stimulation of the receptors of the nipples (during suction). This results in excitation of the hypothalamic nuclei, which influences the function of the hypophysis in the humoral way.

The reflex stimulation of prolactin secretion is carried out by the decreased production of prolactin-inhibiting factor.

Thyroid-stimulating hormone (TSH), or thyrotropin stimulates the thyroid function. The mechanisms of this stimulation are numerous. TSH intensifies the secretion of thyroxine and triiodothyronine into the blood, promotes iodine accumulation in the thyroid gland; besides, it increases the activity of its secretory cells and increases their number.

TSH administration produces the growth of the thyroid gland, and the removal of the hypophysis in young animals leads to their underdevelopment. In animals after the removal of the hypophysis, basal and protein metabolism reduce. It can be once again increased by the administration of thyroxine, transplantation of the hypophysis or administration of thyrotropin. Thyroxine administration normalizes basal and protein metabolism. This is the way insufficient production of thyroxine in the atrophied thyroid gland of the animal is compensated, and the transplantation of the hypophysis or administration of TSH normalizes metabolism, ensuring growth of the thyroid gland exposed to atrophy in the absence of this hormone.

If an excessive amount of TSH is daily administered to animals for a long time, they acquire the symptoms of ***Basedow's disease (Graves' disease).***

Thyrotropin is constantly secreted in small amounts. The stimulation of thyrotropin secretion is carried out by the hypothalamus whose nervous cells produce ***thyrotropin-releasing hormone*** stimulating the formation of thyrotropin in the adenohypophysis. The level of thyrotropin secretion depends on the amount of the thyroid hormones in the blood. If the amount is sufficient, thyrotropin secretion is inhibited, and vice versa.

If the body is cooled down, thyrotropin secretion intensifies and increases the formation of the thyroid hormones thus increasing heat production (thermogenesis). The cortex of cerebrum can influence the secretion of TSH.

Corticotropin, or adrenocorticotropic hormone (ACTH) produces the growth of the fascicular and reticular regions of the adrenal cortex and intensifies the synthesis of their hormones but does not influence the glomerular zone of the cortex and adrenal medulla. ACTH impacts the adrenals and increases the production of glucocorticoids (which promote higher body resistance to unfavorable factors), and, to some extent, androgens.

The ACTH release by the hypophysis is increased under the influence of all extreme stimuli producing strains (stress) in the body. These stimuli by the reflexes influence the nuclei of the hypothalamus in which the formation of adrenocorticotropin-releasing factor increases. This substance reaches the cells of the anterior lobe of the hypophysis and stimulates ACTH secretion

Intermediate lobe of the hypophysis

The intermediate lobe of the hypophysis in the majority of animals and humans is separated from the anterior lobe and is adherent with the posterior one. The hormone of the intermediate lobe is **intermedin, or melanocyte-stimulating hormone.**

Intermedin is reported to cause skin dimness in amphibians (frogs, in particular) and in some fishes due to expansion of its pigment cells — melanophores — and wider distribution of pigments in their protoplasm. The value of intermedin consists of the adjustment of body integuments to the color of the environment.

In humans having skin spots which do not possess any pigment, the subcutaneous administration of intermedin on the appropriate spots results in gradual normalization of their color.

In pregnancy and adrenal cortical deficiency (changes in skin pigmentation are often observed in both the cases), the amount of intermedin in the hypophysis increases. Apparently, in humans intermedin is a regulator of dermal pigmentation as well.

Intermedin secretion is regulated by the action of light on the eye retina. In mammals and humans, intermedin is essential for the regulation of the movements of the black pigmented layer cells in the eye. Under the action of bright light, the cells of the pigmented layer release pseudopodia, due to which the excess of light rays is absorbed by the pigment, and the retina is not exposed to intensive stimulation.

Posterior lobe of the hypophysis

The posterior lobe of the hypophysis (neurohypophysis) consists of cells similar to those of glia, — so-called *pituicytes.* These cells are regulated by the nerve fibers which pass to the peduncle of the hypophysis and are processes of the neurons of the hypothalamus.

From the posterior lobe of the hypophysis two preparations are obtained: one sharply decreases urinary excretion and increases blood pressure, and the other one stimulates the muscle contractions of the uterus. The former is called **antidiuretic hormone, or vasopressin**, the latter is **oxytocin**.

The ***antidiuretic effect of vasopressin*** is based on accelerated re-absorption of water in the renal tubules. That is why the administration of this hormone to animals and humans not only leads to decreased diuresis, but also to increased relative density of urine.

Overproduction of the antidiuretic hormone is a cause of ***non-sugar diabetes (diabetes insipidus)***. In this disorder excretion of too much sugar-free urine (sometimes dozens of liters daily) and excessive thirst are observed. Damage to the posterior lobe of the hypophysis is usually revealed. The subcutaneous administration of the preparation of the posterior lobe of the hypophysis to these patients normalizes their daily urinary excretion.

Vasopressin produces contractions of smooth muscles of the blood vessels (especially of arterioles) and leads to increased blood pressure. However, the pressor effect is observed only after artificial administration of big doses of the hormone; the amount of vasopressin secreted in norm gives only the antidiuretic effect and practically does not influence the smooth musculation of the blood vessels.

Oxytocin stimulates contractions of the smooth muscles of the uterus, especially at the end of pregnancy. This hormone is essential for normal delivery. After the removal of the hypophysis in pregnant females delivery becomes more complicated. Oxytocin also influences milk secretion.

Regulation of incretion of the hypophysis

The incretion of the hypophysis, regulating functions of some other glands (sex, adrenal, thyroid glands), depends on the functioning of these glands. Thus, the deficiency of androgens, estrogens, glucocorticoids, and thyroxine in the blood stimulates the production of gonadotropins, ACTH and TSH of the hypophysis respectively, and vice versa. Thus, the hypophysis is included into the system of neurohumoral regulation working by the principle of negative feedback, automatically supporting the production of hormones of the corresponding glands at the necessary level.

In the hypothalamus, substances are formed and then transferred to the adenohypophysis. They are called ***releasing factors (hormones)***: ***corticotropin-releasing factor***, ***thyrotropin-releasing factor, gonadotropin-releasing factor, somatotropin-releasing factor.*** They promote the formation and secretion of ACTH, gonadotropins, thyrotropin, somatotropin.

The substances inhibiting the secretion of some hormones by the adenohypophysis are formed in the hypothalamus. In particular, these substances are the factor inhibiting the formation of prolactin (prolactostatin) and growth hormone-inhibitory factor (somatostatin).

The evidence that the products of hypothalamic neurosecretion influence the function of the hypophysis plays an important role and is proved by the fact that the hypophysis transplanted to the neck stops secreting ACTH, gonadotropin, thyrotropin, and somatotropin.

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