HORMONES

Hormones are characterized by high specificity, high biological activity, thst they are synthesys in special endocrine glands and carried to the tissues by blood. But there are some species like hormones synthesized not in endocrine gland, or synthesized in various cells. They are called hormonoids. For instance, erythropoietin is synthesized in the kidneys and stimulates erythropoiesis in the bone marrow. Atrial peptide, or sodium urethic factor is synthesized in the atria and removes Na^+ from the kidneys. Prostaglandins are also hormone-like substances because they are synthesized in various cells. Hormones can be classified in different ways: depending on option of action, structure, mechanism of action, physico-chemical properties and function.

Classification of hormones depending on options of hormonal action.

Hormones differ depending on the site of action and the distance of the target cells. So, the action of hormones can occur in the following forms:

1. Hormonal (distant): hormone affects the organ that is localized far away from the organ in which the hormone is synthesized.

2. Isocrinic: hormone affects cells that are in close contact with the producer cell.

3. Paracrine: hormone affects on nearby cells.

4. Autocrine: hormone affects on the cell itself producing.

5. Neurocrine or neuroendocrine: through nerve endings. The secreted substance is called a neurotransmitter or neuro-transmodulator, the substances that change the effect of the neurotransmitter. These include endorphins and enkephalins.

By structure, hormones are divided into 3 groups:

1.Hormones of polypeptide and protein nature. These are hormones of the pancreas, pituitary, calcitonin, etc. (Fig.1.);

2. Derivatives of amino acids: catecholamines, i.e. adrenaline, norepinephrine, thyroxin, melatonin, serotonin);

3. Steroid hormones: androgens, estrogens, gestagens, corticosteroids, calcitriol - an active form of vitamin D.

Some hormones are represented by natural peptides, as endorphins and enkephalins. β-endorphin is a powerful pain killer, while enkephalins are neutrotransmitters.

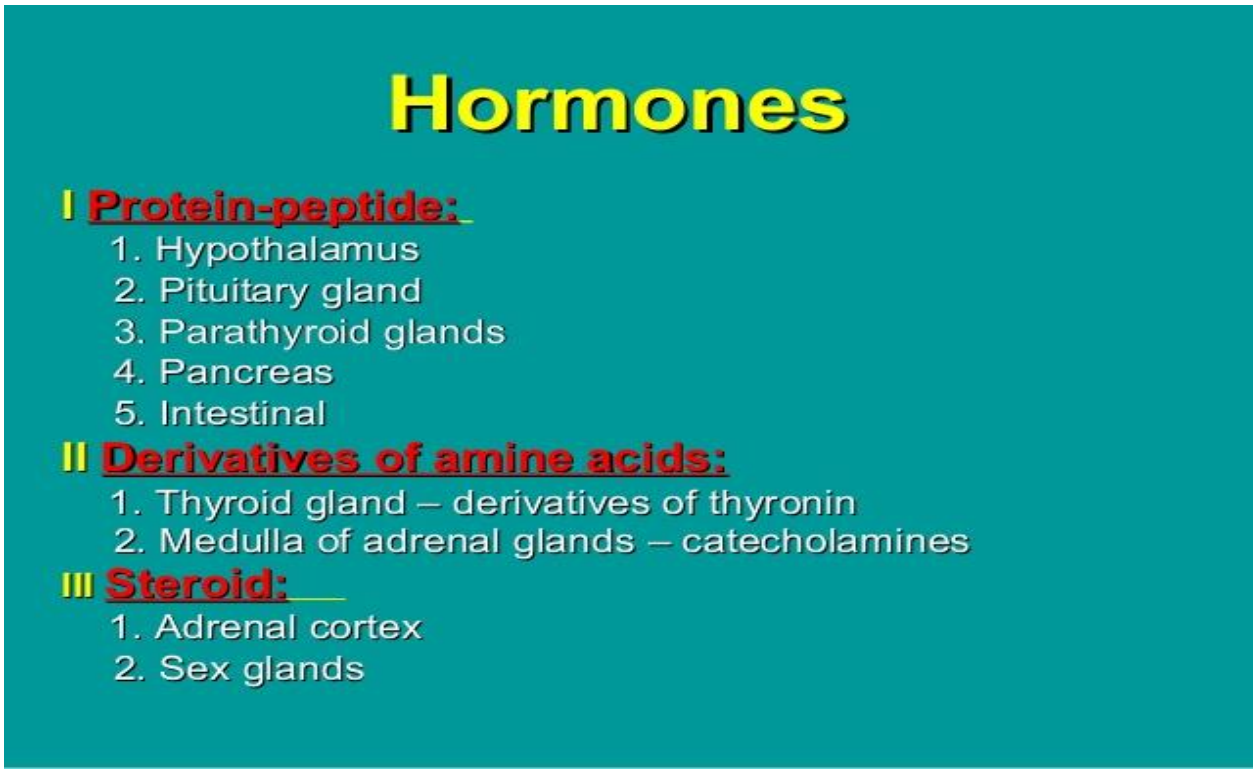


Fig.1. Classification of hormones according to their structure

According to the **physico-chemical properties** hormones are divided into 2 groups:

1. Hydrophilic, as proteins and catecholamines;

2. Lipophilic, which are the hormones of steroid nature (calcitriol, corticoids) and thyroxin.

• According to the mechanism of action, hormones are divided into:

1) membrane action, as insulin,

2) membrane-intracellular. Protein hormones, catecholamines, prostaglandins, serotonin, neurotensin hormones exhibit this kind of action. They affect the plasma membrane.

3) cytosolic. Steroid hormones and thyroxin show this activity. They act with the help of the intracellular receptor.

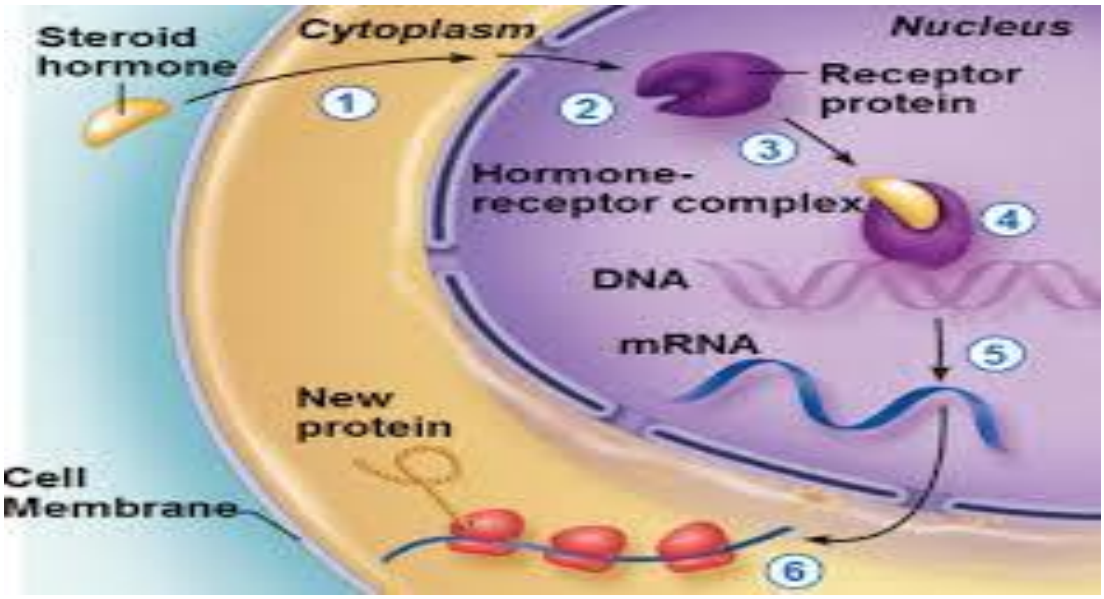


Fig.2. Classification of hormones according to their mechanism of action

From **a functional** point of view, hormones are sort as following:

1. Effector: directly to the target organ, causing an effect.

2. Tropic: regulate the peripheral gland (glandotropic).

3. Hypothalamic, as liberins and statins.

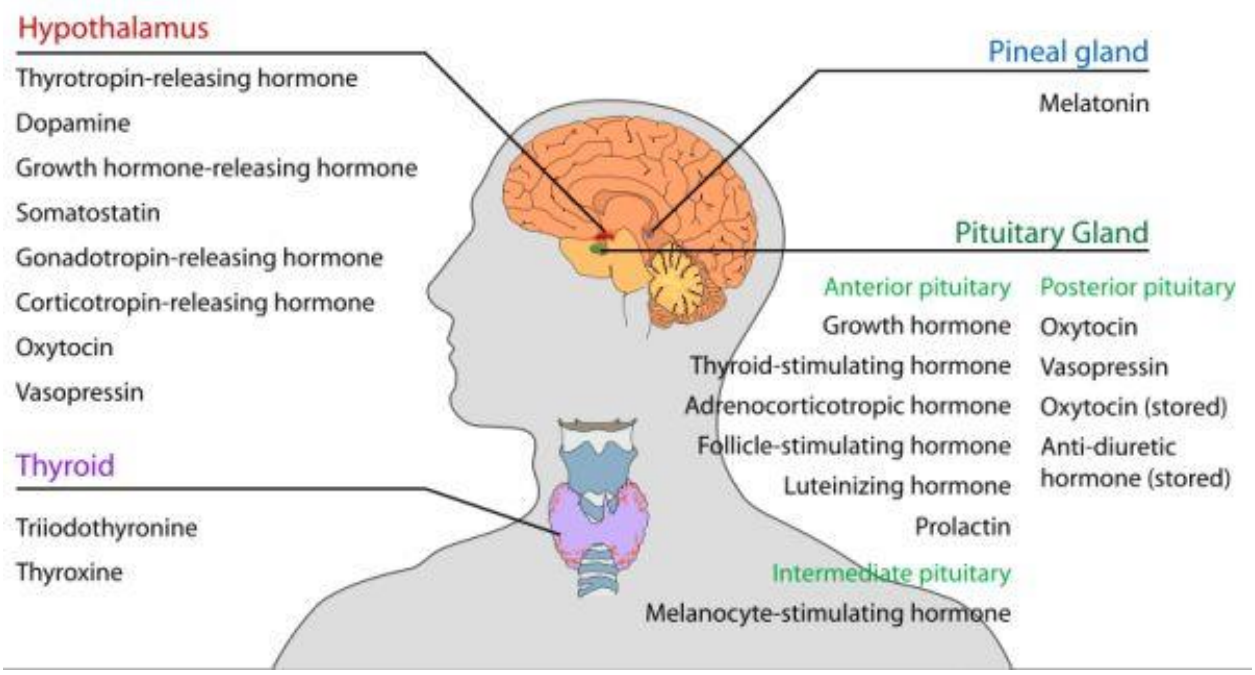


Fig.3. Classification of hormones according to their function and site of synthesis

Depending on the pathological process location, **3 types of endocrinopathies are distinquished**. Primary endocrinopathy is a disorder of peripheral gland. Secondary endocrinopathy is a disorder in the pituitary gland.Tertiary endocrinopathy means a disorder in the hypothalamus.

Hormones mechanism of action & regulation

Hormones are regulated by the central nervous system through the pituitary and outside the pituitary (para-pituitary). Their ssecretion is regulated via feedback mechanism.

The main types of connections between the glands:

1. Feedback. This mechanism can be positive and negative;

2. Synergism, as between glucagon and adrenaline: both these hormones break down glycogen in the liver;

3. Antagonism, as between insulin and glucagon, or insulin and adrenaline; estrogens and progesterone.

Agonists are corticosterone and aldosterone for cortisol, as they facilitate the binding of cortisol to the receptor.

4. Permissive action show glucocorticoids for catecholamines.

Hydrophilic hormones are transported in the blood in a free form, act through the plasma membrane receptor.

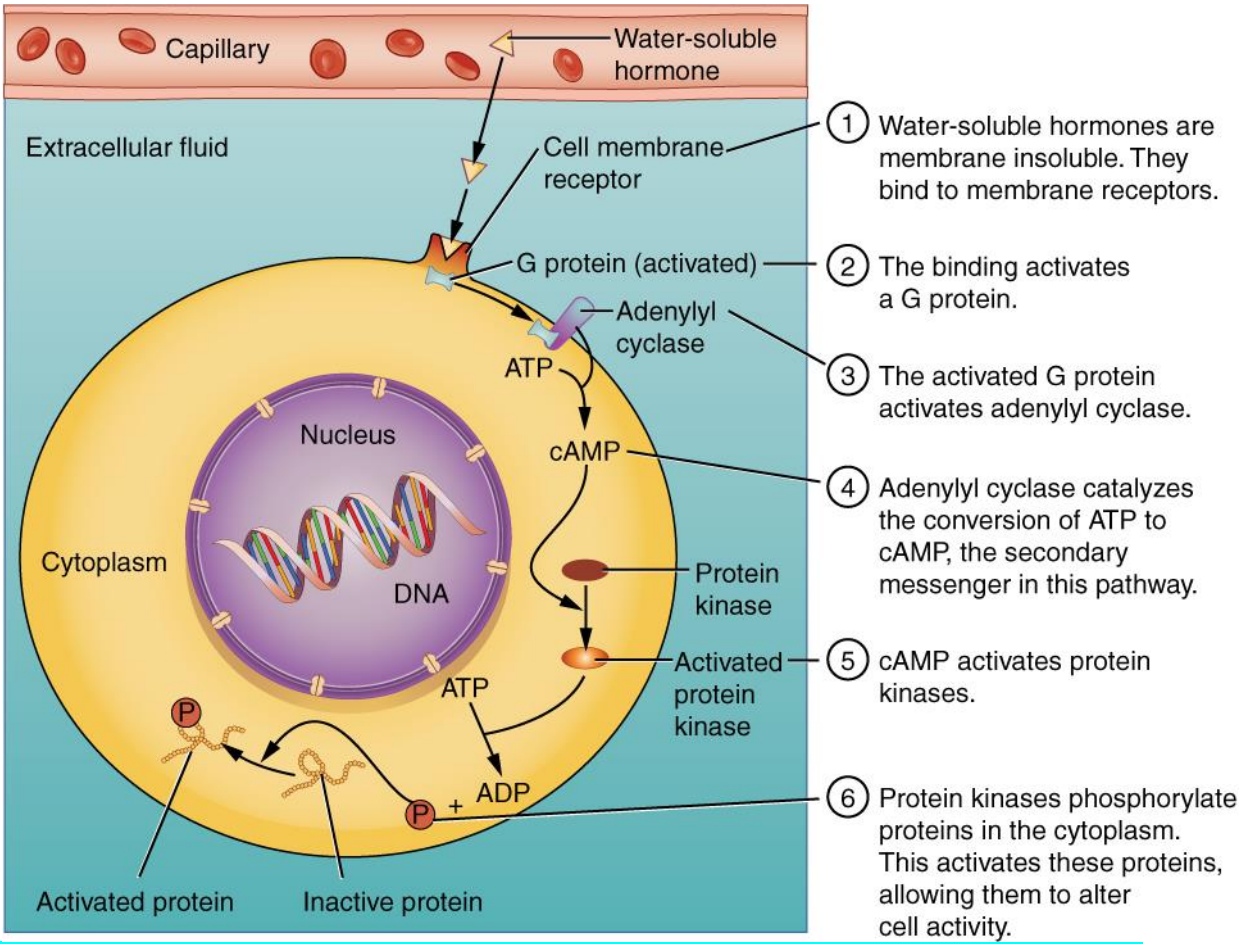


Fig.4. Action of water-soluble hormones responsible on target cell metabolism (all the following drawings are shifted +1)

90-95% of lipophilic hormones are found in the blood in protein-bound form and only 5% - in free form.They affect through the cytoplasmic and nuclear receptor.They bind in the nucleus to a specific region of DNA and stimulate the synthesis of a new protein-enzyme. But hydrophilic hormones act quickly and for a

short time. After binding of such hormone to its receptor the secondary messenger is formed. They are: c-AMP, c-GMP, Ca^{2+} (calmodulin), inositol phosphate, diacyl-glycerol.

ADENILYL-CYCLASE SYSTEM

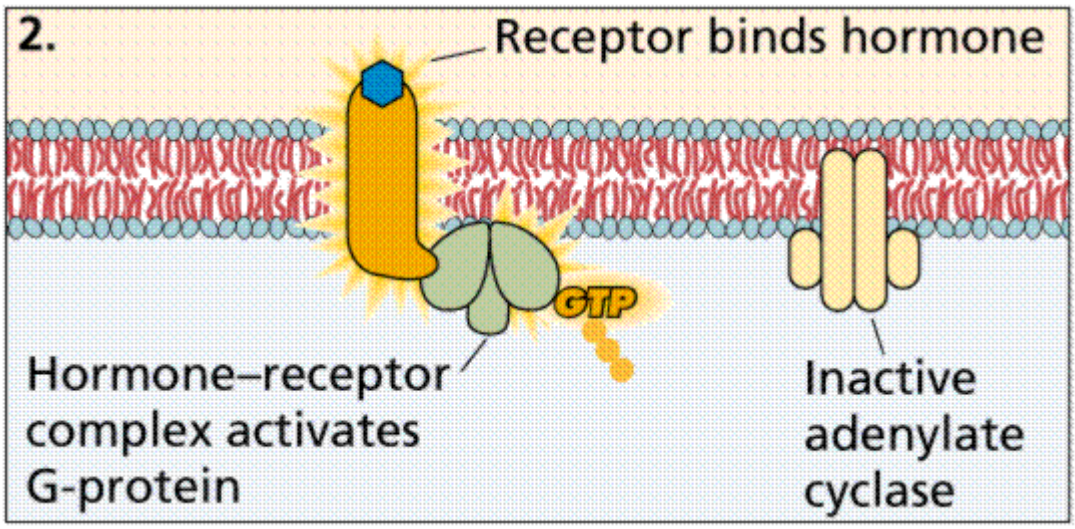


Fig.5. Diagram of the adenylyl; cyclase system

Through c-AMP act: ACTH, catecholamines, calcitonin, parathyroid hormone, vasopressin, secretin, glucagon. Adenylate cyclase consists of 3 parts:

1. Enzyme adenylate cyclase that forms cAMP from ATP,

2. cAMP dependent protein kinase A,

3. Phospho-diesterase, which cleaves cAMP to 5'-AMP and stops action of hormone.

Adenylate cyclase in turn consists of 3 proteins:1. Receptor (extracellular domain that attaches the hormone), 2. Regulatory (G-protein), 3. Catalytic part, that converts ATP to cAMP. First. hormone molecules associates with the receptor (for example, adrenergic receptor). After hormone attachement to receptor, G protein becomes activated. Activated G-protein activates the membrane- bound enzyme adenylyl cyclase, after which the hormonal signal transduction cascade

begins. Adenylyl cyclase creates multiple (hundreds) cyclic AMP molecules, which activate protein kinases leading to change in metabolism.

GUANYLATE-CYCLASE SYSTEM.

Atrial peptide and the vasodilating factor NO act through the cGMP system, reducing aldosterone in the blood. As a result increases emission of NaCl, increasing diuresis. Soluble guanylate cyclase stimulators increase its activity, after which the enzyme in the cardio-pulmonary system relaxes smooth muscle of vessels resulting in pulmonary vasodilation and improved cardiac output.

Like an adenylate cyclase system, guanylate cyclase system has 3 parts:

1. Receptor (extracellular domain), 2. Intramembrane domain, 3. Catalytic domain (Fig.6).

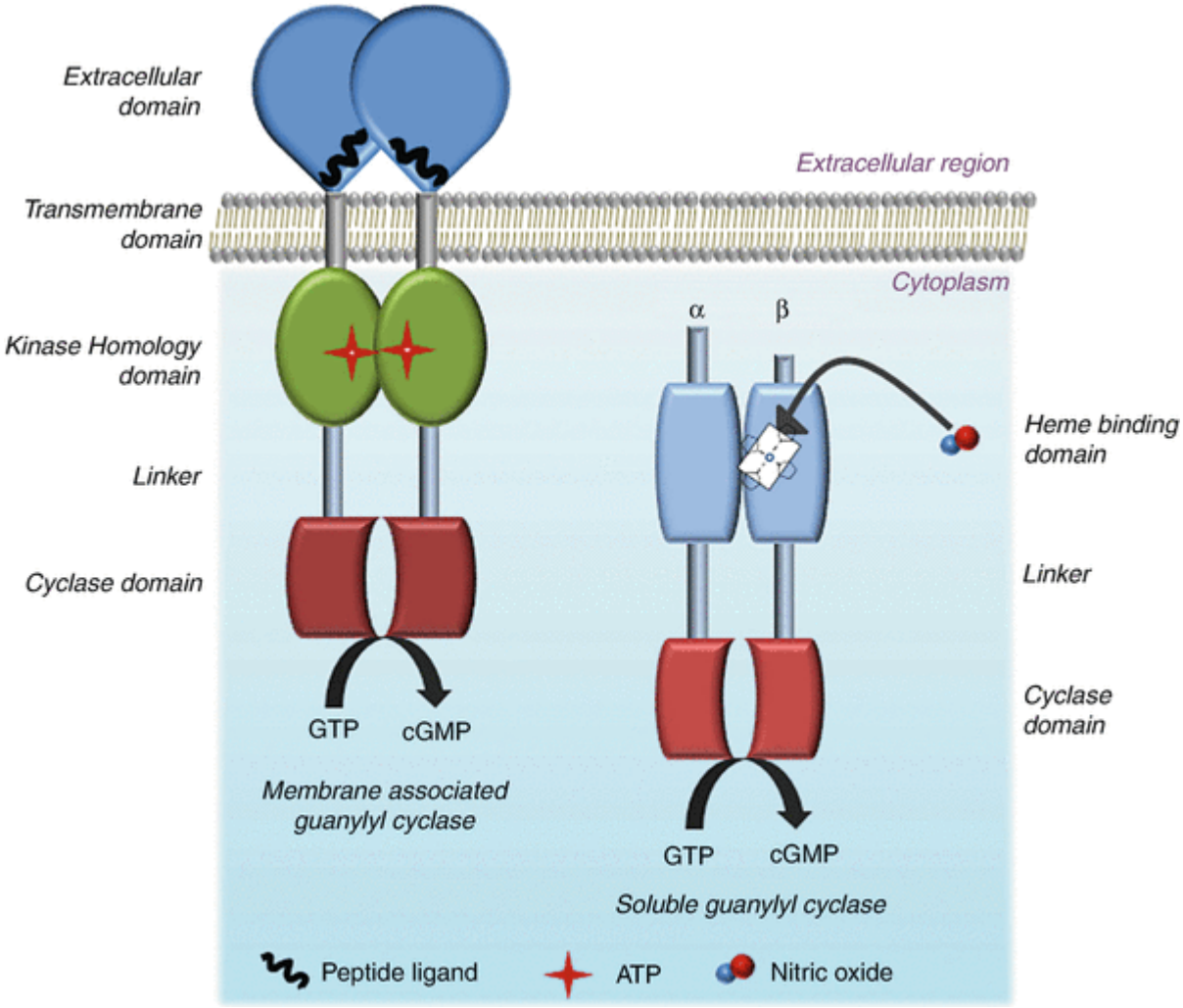


Fig.6. Diagram of the guanylate cyclase system

Guanylate cyclase is also found in the retina, where it modulates visual phototransduction in rods and cones.

Calcium calmodulin system

There are also hormones whose second messenger is calcium ions. Hormones, the secondary messenger of which is Ca^{2+} - polyphosphoinositol are: oxytocin, gastrin, cholecystokinin, angiotensin. Such hormones are mainly responsible for the contraction of smooth muscles. Calmodulin is a calcium-binding messenger protein actin via Ca ions. İnitially, hormone causes the release of calcium ions from the endoplasmic reticulum to cytopasm. Binding of Ca2+ to calmodulin in cytopasm of smooth muscle

activates myosin light chain kinase, which catalyzes myosin phosphorylation. This reaction leads to smooth muscle contraction. The result of this interaction is a physiological effect, for example, contraction of the smooth muscles of uterus. Removal of Ca^{2+} from the cytosol or myosin phosphatase action initiate the process of smooth muscle relaxation.

Hypothalamus

The hypothalamus is the central gland that controls the entire hormonal system. It releases hormones to the pituitary gland, which controls the peripheral organs. In hypothalamus are formed statins (inhibiting factors) and liberins (releasing factors) controlling pituitary gland. The following hormones are produced in the hypothalamus: corticotropin-releasing hormone (corticoliberin), somatotropin-releasing hormone (somatoliberin), somatostatin, gonadotropin-releasing hormones (gonadoliberins), thyrotropin-releasing hormone (thyroliberin), prolactoliberin, prolactostatin, melanoliberin and melanostatin. Gonadotropin-releasing hormones are represented by folliberin and luliberin. There is still no cure for hypothalamic injury. If the hypothalamus is damaged (for example, with a traumatic brain injury), treatment is based on the replacement of hormones lost. Hypothalamic disorder with hyposecretion of gonadotropic hormones is called adipose-genital dystrophy, or Babinski-Frehlich syndrome.

Hypophysis

The adult pituitary gland consists of two lobes: anterior and posterior. The anterior lobe is also termed the adenohypophysis, and the posterior lobe is also called the neurohypophysis.

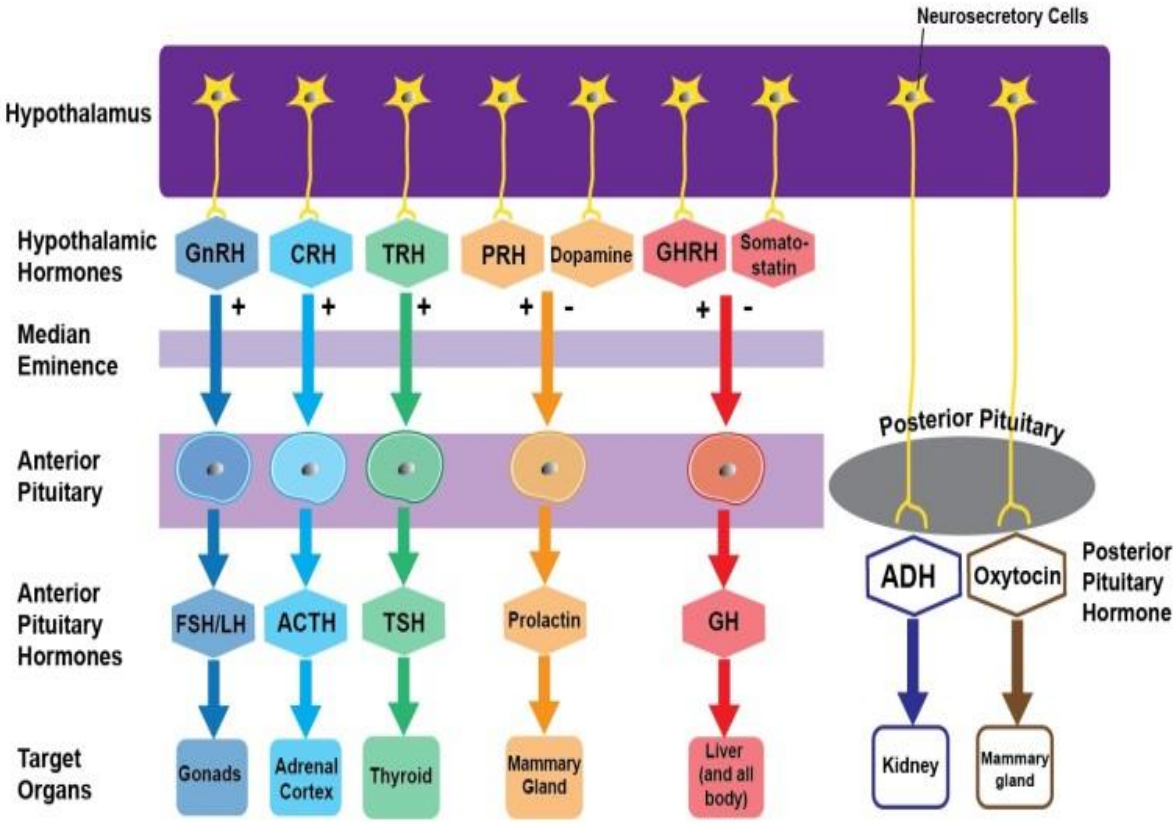


Fig.7. Hypophyseal hormones and their target cells

Neurohypophysis

The posterior pituitary gland does not produce but stores two hormones: oxytocin and vasopressin. They are formed in the hypothalamus and are transported with neurophysins to the neurohypophysis. With neurophysins, oxytocin and vasopressin accumulate in the granules.These hormones are short peptides with 9 amino acids, in which cysteine molecules are bound via disulfide bonds. Oxytocin plays a role in reproduction, childbirth and the postpartum period. Oxytocin is released into the bloodstream during childbirth. Oxytocin stimulates uterus contractions during childbirth. It helps to create mother-child communication and milk production. The production and secretion of oxytocin is controlled by a positive feedback mechanism, where its initial release stimulates the further production and release. In pregnant women, oxytocinase present in the blood inhibits the action of oxytocin.

Vasopressin is an antidiuretic hormone (ADH), that increases the reabsorption of water in the kidneys distal tubules. İn high (not physiological) doses, it has a vasoconstrictive effect.

Vasopressin hypersecretion leads to hyperhydropexic syndrome , or Parhon syndrome. Edema, decrease in electrolytes in the blood, loss of feeling of thirst develope. Osmolality and urine density increase, urine becomes thick. Diabetes insipidus is result of vasopressin hyposecretion. The urine density falls below 1,008 - to 1,001. Diuresis increases: hypostenuric polyuria occurs. An increase in the osmotic pressure of the blood leads to thirst and polydipsia.

Anterior pituitary (Adenohypophysis)

In **adenohypophysis** are formed following hormones:

* Somatotropin, or somatotrop hormone STH (teeermed also growth stimulating hormone - GH),

*TSH,

*Adrenocorticotropin, or adrenocorticotrop hormone (ACTH),

* Gonadotropins: follitropin/follicle stimulating hormone (FSH) and lutropin, or luteinising hormone (LH),

*prolactin,

*Pro-opio-melano-cortin (POMC).

POMC, or pro-opio-melanocortin being hydrolysed forms ACTH, melanocyte stiulating hormone (MSH), lipotropin, endorphins, enkephalins.

Growth hormone stimulates the growth and development of cells, tissues.

TSH is a glycoprotein. It acts, like all peptides, through cAMP, stimulating the thyroid gland.

• Gonadotrop hormones (GH), namely FSH and LH are also glycoproteins. Inhibitor of FSH in men is inhibin, in women - folliculostatin.
Prolactin is responsible for the development of the mammary glands, lactation. During pregnancy, prolactin protects the corpus luteum.

• ACTH acts on the adrenal cortex and stimulates synthesis and secretion of adrenal hormones through cAMP. It increases protein synthesis in the adrenal glands, resulting in corticosteroid formation. ACTH in turn, stimulates lipolysis (breakdown of lipids) in extremities and lipogenesis (synthesis of lipids) in body torso.

•There are 2 types of melanocyte stiulating hormones (MSH): α-MSH and β-MSH. MSH is responsible for the production of melanin in melanocytes and causes darkening of the skin. MSH raises in humans during pregnancy and stress.

• Lipotropic hormone, β-Lipotropin, activates TAG-lipase via cAMP. After hydrolysis of β-lipotropin, endorphins and enkephalins are formed. They bind to opiate receptors and have an analgesic effect and cause euphoria, which is stronger than the action of morphine.

In the total form of pituitary deficiency called panhypopituitarism, STH and GH (sometimes along with TTH) are not secreted into the blood. There are 2 syndromes panhypopituitarism disease: Sheehan syndrome and Symmonds syndrome. They are also called pituitary-cerebral cachexia syndromes, as they are hypothalamic-pituitary disorders. Hypopituitarism is more common in women and develops as postpartum Sheehan syndrome. The rest forms of total pituitary disorders are known as Simmonds disease. The onset of Simmonds disease usually occurs during post-puberty.

Gigantism is an increase of the growth hormone before the reproductive period, since childhood. STH stimulates lipolysis, which is why in hypersecretion of STH free fatty acids increase in the blood. Liver uses them in the β-oxidation and ketogenesis. Patients with gigantism are abnormally tall (more than 2 meters in height).They have abnormal but proportional growth of the face, arms and legs and

ehickened facial features. Due to the weakness of muscle tissue, they sweat excessively with little activity. They often have the vision and hearing problems, such as double vision and deafness.

Acromegaly is an increase of growth hormone after completion of skeletal growth. Patients have enlarged hands and feet, fatigue and sleep problems. They usually visit the doctor due to gradual coarsening of facial features, such as an increase in the superciliary arches, lower jaw and nose, or an increase in the distance between the teeth (the appearance of a diastema);

Nanism, or dwarfism is a result of the congenital growth hormone hyposecretion. This condition is characterized by abnormally small, but proportional growth (less than 1.5 meters in height); These patients have constant hypoglycemia, because the effect of STH on insulinase drops out.

Itsenko-Cushing disease is result of ACTH hypersecretion. Gluconeogenesis is enhanced, which is why hyperglycemia and glycosuria appear. ACTH stimulates lipolysis in extremities, which is why in hypersecretion of ACTH, as in hypersecretion of STH free fatty acids increase in the blood, and liver gain auses them in the β-oxidation and ketogenesis. But the synthesis of lipids of the body increases, and android-type obesity appear. Melanocyte-stimulating effect of ACTH appears in hyperpigmentation such as acanthosis nigricans in the armpit. Darkening of the skin is also due to the fact, that MSH and ACTH share POMC as a common precursor. Hyperpigmentation is also observed in Addison's disease caused by primary damage to the adrenal glands. Darkening of the skin in areas not exposed to the sun is characteristic for them: skin folds in the hands, the nipple, and inside the cheek. İn these patients, new scars become hyperpigmented, while old ones do not darken.

In case of Addison *syndrome* there is no hyperpigmentation due to ACTH hyposecretion.

Hyperthyrosis occurs in hypersecretion of TSH. When endemic goiter TSH also increases, which causes hypertrophy of the thyroid gland. Hypothyroidism occurs during hyposecretion of TSH.

The hypersecretion of FSH and LH from childhood leads to early maturation. Hyposecretion of these hormones leads to infantilism.

Hyperprolactinemia leads to galactorrhea and amenorrhea. In men, it causes gynecomastia.

Epiphysis

From 5 years of age, the epiphysis is exposed to involution, from 8 years – to calcification.

Epiphysis regulates circadian, daily biological rhythms and adapts the body to the intensity of light. In the epiphysis are produced: serotonin, melatonin, adrenoglomerotropin, antihypothalamic peptide.

Serotonin, 5-hydroxytryptamine, is a prodct of tryptophan decarboxylation. It is considered a hormone of happiness & satisfaction. In large doses, serotonin constricts arterioles and increases blood pressure. It Increases sensitivity to kinin-dependent pain. It increases vasopressin in the blood, which causes an antidiuretic effect.

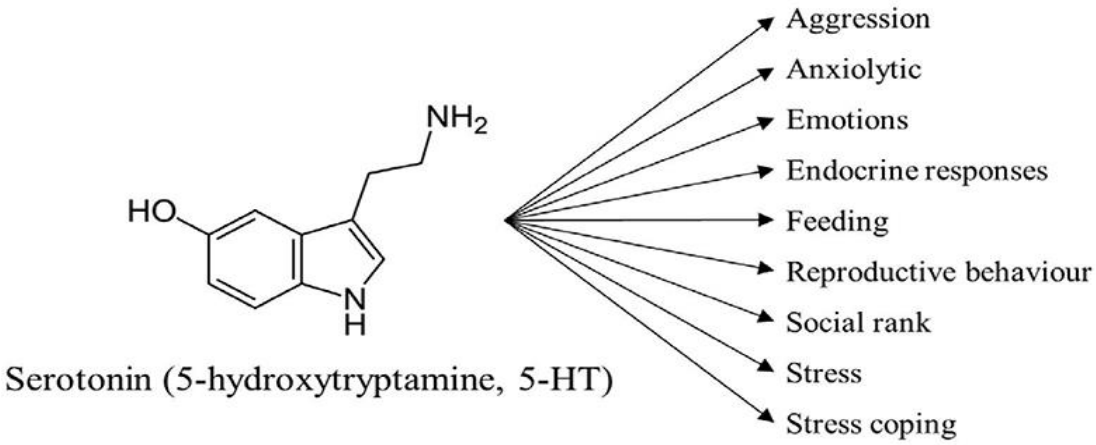


Fig.8. Serotonine, 5-hydroxy triptamine area of effect

Melatonin is made from serotonin and is an antagonist of pituitary hormones. Darkness increases melatonin synthesis, while light reduces.

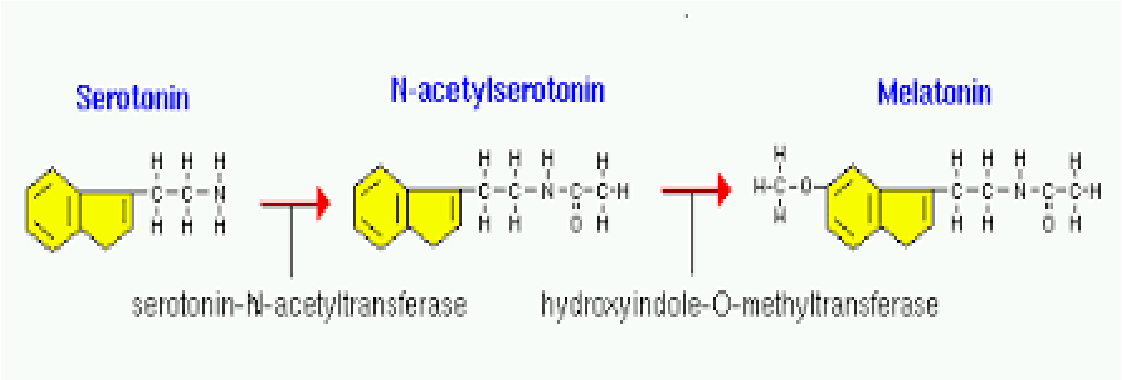


Fig.9. Conversion of triptophan to melatonin

Adrenoglomerotropin stimulates the secretion of aldosterone. In this regard, it reduces the lumen of blood vessels & increases blood pressure, heart rate and contractions. enlarges the lumen of the bronchi.

Hyperpinealism causes a temporary inhibitory effect on the pituitary and hypothalamus. Hypopinealism in children causes early maturation. Thei mental development of patients is lagging behind, macrogenitomy developes. The muscles of patients witn hypopinealism are overdeveloped. Their limbs are short, while the body is relatively long.

The thymus

The thymus is the primary lymphoid organ of the immune system.

Fig. 10. Location of thymus

After puberty, thymus undergoes involution. The thymus produces lymphocytes called thymic T cells and some hormones affecting immune system. Here are formed:

1. Cells of the immune system, or T-lymphocytes. Differentiation and clonal selection of T-lymphocytes occurs in the thymus.

2. Hormones that affect the growth and activity of cells of the immune system.Timosterol is formed in thymus steroid hormone. The rest thymus

hormones are polypeptides: timopoietin, timosins (α_1, α_2, α_3 ..... β - they are insulin-like hormones); α-protimosin, which is a precursor of α-thymosins, thymulin (the only hormone with metal, Zn), homeostatic thymic factor (synergist of STH), hormonal thymic factor.

There are several types of thymus insufficiency. One of them is congenital aplasia of the thymus is called Di-George syndrome. When complete DiGeorge syndrome, the absence or hypoplasia (underdevelopment) of the thymus occur. Disease is characterized by very low amount of T cells. Absence or hypoplasia of the thymus results in an increased susceptibility to viral, fungal and bacterial infections termed immunodeficiency.

Hypoplasia with disrupted cellular immunity is called Nezelof syndrome. Nezelof syndrome is the atrophy or hypoplasia of the thymus appeared in severe combined immunodeficiency. The reason of disease is the defect of purine ***Nucleoside phosphorylase***. Deficiency of phosphorylase results in an accumulation of deoxy-GTP that inhibits ribonucleotide reductase.

A Glanzman-Riniker syndrome (Swedish type of a-ɣ-globulinemia) and ataxia-telangiectasia are also types of thymic hypoplasia, but with impaired both cellular and humoral immunity. Glanzmann–Riniker syndrome, or a severe mixed immunodeficiency syndrome is alymphocytosis due to thymic alymphoplasia. It is a rare genetic disorder with disturbed development of T cells and B cells. Symptoms include the production of defective antibodies due to malfunction of antibody-producing B lymphocytes, or due to improper activation of B lymphocytes due to non-functional T helper cells. Consequently, both B cells and T cells of the adaptive immune system are impaired.

Ataxia-telangiectasia, or Louis–Bar syndrome is a rare hereditary disease that mainly affects the immune and nervous systems. Disease is characterized by the diminished muscle coordination usually noticed when a child begins to walk.

When poisoning with cytostatics due to the use of drugs that inhibit cell growth, and in hypercortisolism acquired hypoplasia of thymus occurs. [Biton S, Barzilai A, Shiloh Y. The neurological phenotype of ataxia-telangiectasia: solving a persistent puzzle. DNA

Repair (Amst). 2008 Jul 1;7(7):1028-38. doi: 10.1016/j.dnarep.2008.03.006. Epub 2008 May 5. PMID: 18456574]

Thyroid hormones

Thyroid gland is located at the base of the neck just beyond larinx and is regulated by TSH (TTH). TSH increases iodine penetration into thyrocytes, tyrosine iodization, and hormone secretion.

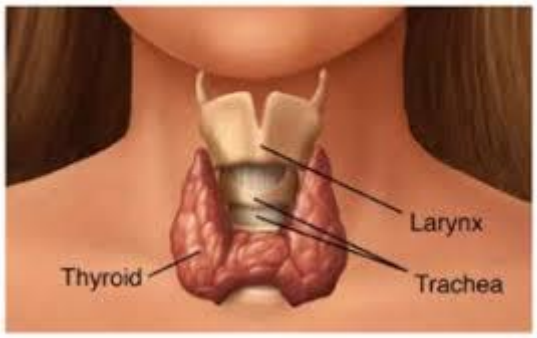


Fig. 11. Thyroid gland location

The synthesis of thyroid hormones occurs on the basis of thyroglobulin containing 120 tyrosine residues. Thyroglobulin is a 660kDa glycoprotein secreted into the lumen of follicles. Its tyrosine units are iodinated for hormone formation. Synthesis of triiodothyronine (T_3) and tetraiodothyronine (thyroxin, T_4) takes place in 4 stages:

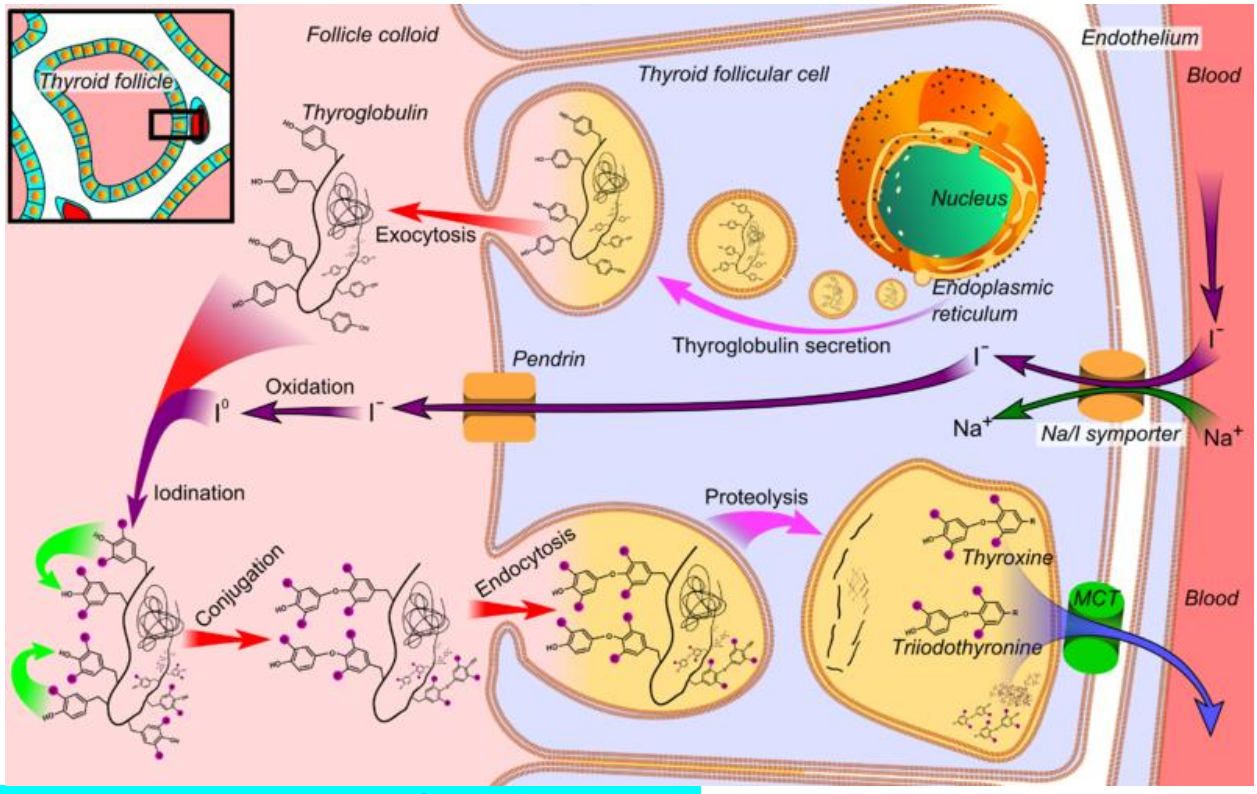


Fig. 12. Synthesis and secretion of thyroid hormones

1) First, iodine is activated by iodine peroxidase. Iodine peroxidase sits at the apical plasma membrane, where it reduces H_2O_2 oxidizing iodide to active state I^+.

2) Then thyroglobulin is synthesized, containing 120 units of tyrosine. Iodine peroxidase attaches the active iodine to tyrosine units on thyroglobulin. Active iodine (I^+) attachment results in 3-monoiodotyrosine (MIT) and 3,5-diiodotyrosine (DIT) formation.

3) T_3 and thyroxin are produced by coupling of one DIT with one MIT or two DITs respectively:

MIT+DIT → T_3 (triiodothyronine);

DIT+DIT → T_4 (thyroxin or tetraiodothyronine).

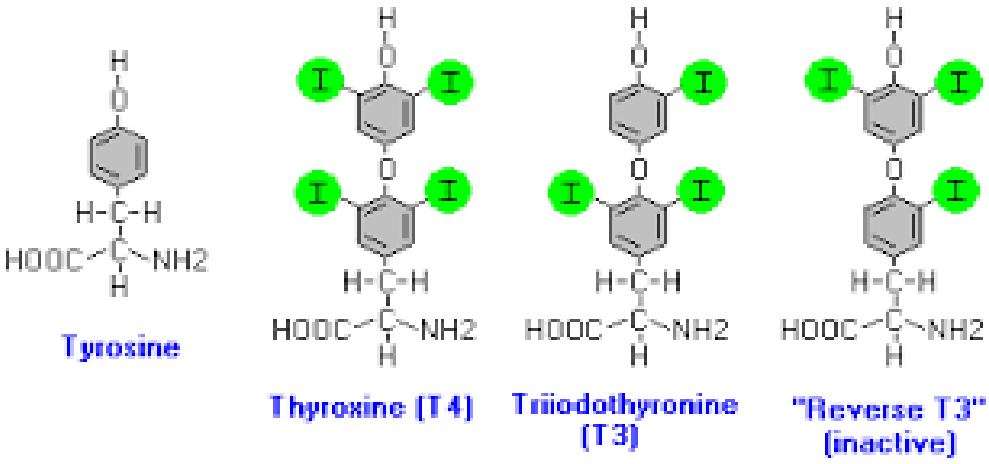


Fig.13. Thyroid hormones secreted into the blood

4) Secretion: hormones T_3 and T_4 are separated from thyroglobulin protein and secreted into the blood. For this, follicular cells hydrolyze thyroglobulin, releasing free T_3 and thyroxin. [Rousset B, Dupuy C, Miot F, et al. Chapter 2 Thyroid Hormone Synthesis And Secretion. [Updated 2015 Sep 2]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK285550/]

Thyrocyte membrane does not distinguish iodine ions from monovalent anions (CNS^-, ClO_4^-). For this reason, with a high concentration of fluorides contained in toothpastes, the thyroid gland binds them from the bloodstream instead of iodides, which leads to a decrease in the concentration of active gland hormones in the bloodstream and thereafter hypothyroidism.

T_3 activity is 5-10 times higher than that of thyroxin. To have an effect on the cell, T4 must first turn into T_3, this process occurs in the liver. There are receptors for thyroid hormones on the plasma membrane, in the cytosol, and in mitochondria. Part of the diiodothyrosins seeps into the blood. Diiodotyrosine reduces the secretion of TSH, but does not exhibit a hormonal effect.

İn the blood, T_3 and T_4 are transported in bound form with globulin, pre-albumin and albumin, but mainly with thyroxin-binding globulin. Receptors for thyroid hormones present in all cells of the body. They are located on the cell membrane, in the cytoplasm and mitochondria. The introduction of low doses of the hormone

gives an anabolic effect, while the administration of high doses gives a catabolic effect. Because in physiological concentration T_3 increases the synthesis of RNA, ATP and protein. But in large doses, in hyperthyrosis called ***thyrotoxicosis,*** it uncouples oxidation and phosphorylation in mitochondria. Thus, in hyperthyroidism, the formation of ATP from $FADH_2$ and $NADH_2$ decreases, and the energy of substrate oxidation in the ETC dissipates resulting in subfebrile temperature and heat intolerance. There are 3 main signs of overproduction of thyroid hormone, namely thyrotoxicosis, or Grave's disease: goiter (enlargement of the thyroid gland), exophthalmos, palpitation (tachycardia). In this state, oxygen consumption increases and basal metabolism is enhanced. This can lead to heart failure and anxiety if prolonged.The catabolism of carbohydrates, proteins, fats is elevated. Outwardly, this manifests itself in the consumption of large quantities of food (polyphagia), but the loss of fat and weight. Hexokinase is activated, so glucose uptake is also activated. Glycogen phosphorylase is activated, therefore glycogenolysis in the liver and muscles increases, leading to hyperglycemia. Insulinase is activated too, leading to secondary diabetes. Fatty acids are β-oxidized, what leads to the formation of a large amount of acetyl-CoA. Due to the lack of adequate oxaloacetate, excess acetyl-CoA enters ketogenesis pathway. Finally, ketonemia and ketonuria occur. Acetyl CoA is also used for cholesterol synthesis, which is why

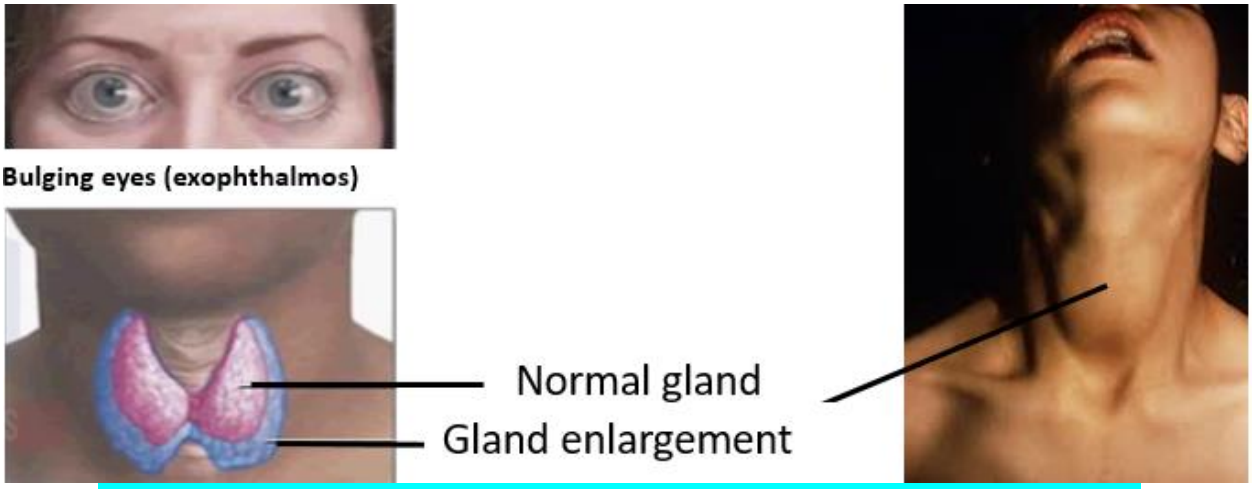


Fig.14. Thyroid gland hypertrophy and exophtalmos in thyrotoxicosis

hypercholesterolemia occurs. Goiter is a common symptom of both hypo- and hyperthyrosis. In hyperthyroidism, the enlargement of the thyroid gland occurs due to an increase in the hormone-producing part of the gland, while in hypothyroidism the hypertrophy is secondary, that is, compensatory in nature. It does not lead to additional secretion of thyroid hormones, since in hypothyroidism only connective tissue grows in the gland.

Myxedema is hypothyroidism in adults. Outwardly, it manifests itself in dry skin, coarse and sparse hair, periorbital edema, puffy face. Their temperature is reduced, bradycardia occur, subcutaneous adipose tissue accrues. Temperature decreases as a result of basal metabolism decrease. Oxidation processes, glycogen phosphorylase activity are weakened. Activity of hexokinase also drops, and as a result, glucose is poorly absorbed from the intestine, so hypoglycemia occurs. The catabolism of amino acids is increased, as they supply energy instead of glucose.

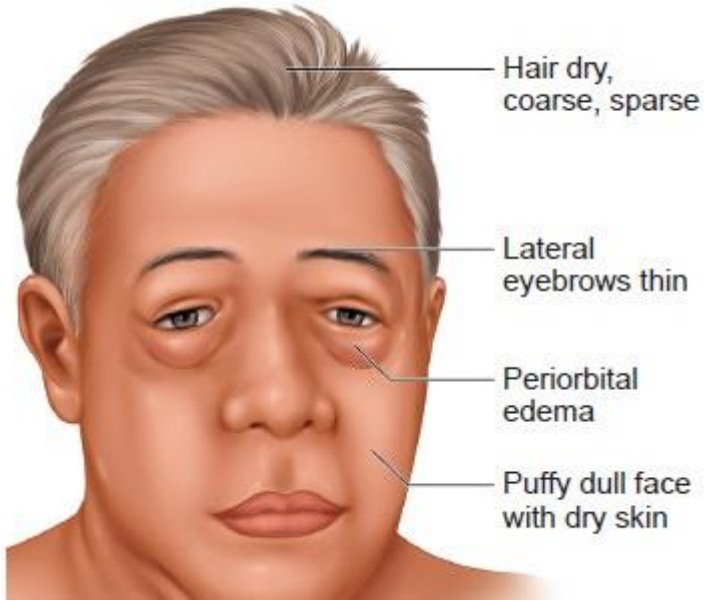


Fig.15. Thyroid insufficiency (myxedema)

Cretinism is a congenital hypothyroidism. Mental retardation, short stature, big head, small and slanting eyes are characteristic for them. The body looks longer than the limbs.

Hashimoto thyroiditis is an autoimmune (autoallergic) disease. It is a chronic

lymphocytic thyroiditis in which the thyroid gland is gradually destroyed. Over time, the thyroid gland may enlarge, but this is a painless goiter

Endemic goiter is associated with the absence of iodine in water and food. Therefore thyroid hormones are reduced, compensatory TSH increases and hypertrophy of the thyroid gland develops. This goiter can be treated with iodine administration.

Calcitonin is formed from preprocalcitonin in para-follicular cells of the thyroid gland. Calcitonin reduces Ca^{2+} and P in the blood because it increases the number of osteoblasts, weakens and reduces the number of osteoclasts in the bones. It also reduces the reabsorption of Ca and phosphorus in the kidneys, increasing their excretion. As a result, calciuria and phosphaturia (excess excretion of posphates in the urine) occur. Hypocalcemia (a drop in calcium concentration) and hypophosphatemia (a decrease in phosphate concentration) in the blood are observed.

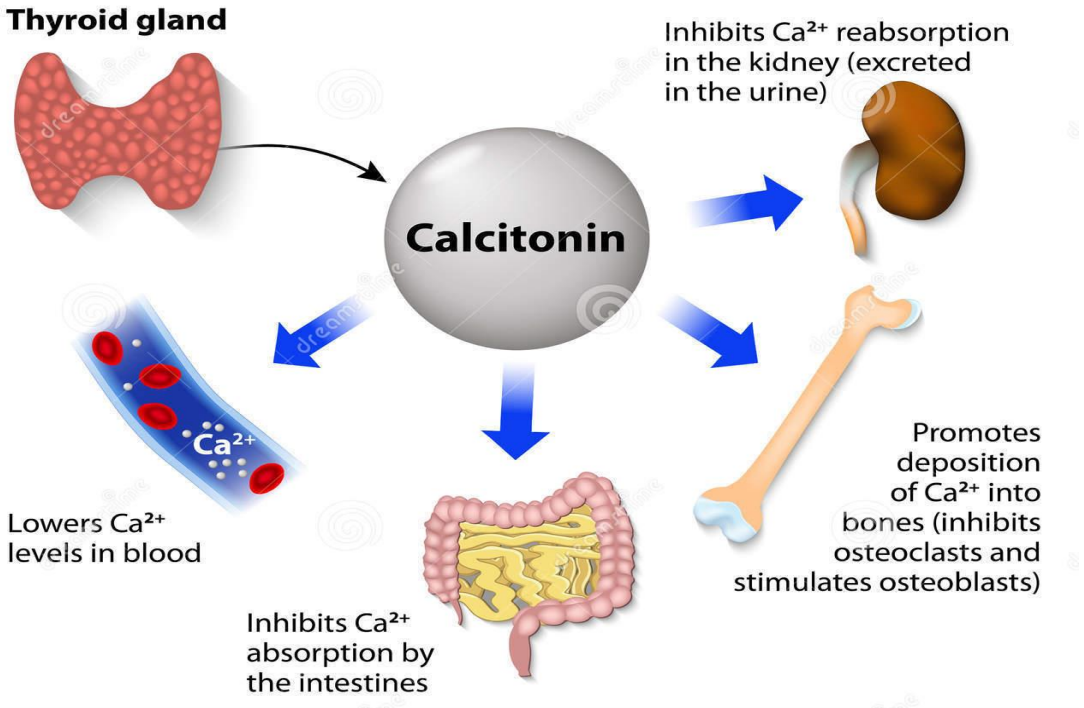


Fig.16. Calcitonin mechanism of action

Parathyroid glands

Parathyroid glands produce peptide, a parathyroid hormone, from a pre-pro-parathyroid hormone.

This hormone increases Ca^{2+} in the blood. For this, it increases the Ca^{2+} ions absorption in intestine and reduces Ca^{2+} excretion in urine. It activates and increases the number of osteoclasts. Since under the action of parathyroid hormone the number of osteoblasts decreases, it causes demineralization of the bones. Simultaneously, the bone collagen undergoes proteolysis resulting in increase of hydroxyproline in blood and urine. Since parathormone is responsible for increasing calcium to normal values when it decreases in the blood, when Ca^{2+} ions increase in in the blood, parathyroid hormone secretion decreases.

But parathyroid hormone decreases phosphorus in the blood by reducing its reabsorption from the kidneys and causing phosphaturia (phosphate excretion in the urine).

In the kidneys, parathyroid hormone converts 25 (OH) calciferol to 1.25 dihydroxy calciferol, called calcitriol which is an active form of vitamin D. Parathormone through calcitriol activates Ca^{2+} ions suction in kidneys.

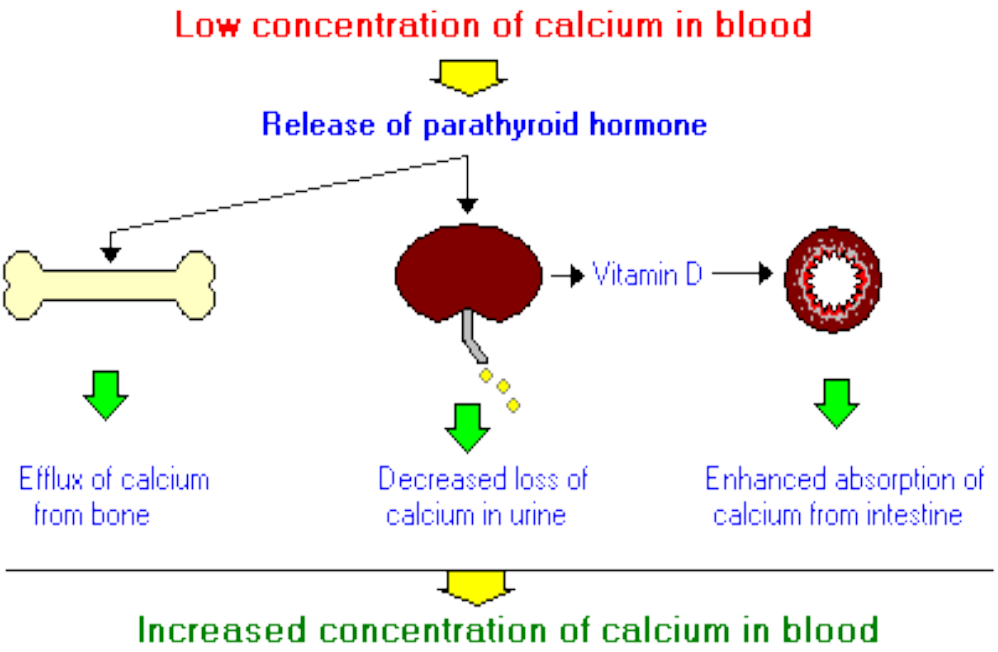


Fig.17. Impact of low Ca^{2+} ion levels on the parathyroid hormone and calcitriol (vitamin D) action

Hyperparathyroidism appear due to a genetic disorder resulting in fibrous osteochondrodystrophy called Von Recklinghausen's disease. Disease is characterized by the tumor of the nerves and bone deformities.

At ***hypoparathyroidism*** Ca^{2+} in the blood decreases, but phosphate increases resulting in stunted growth. Tonic convulsions appear, because Ca^{2+} decrease in the blood, which leads to the excitation of neuromuscular impulses. The disease is characterized by retarded mental development in children. In this disease, calcium deposits in the brain can cause balance problems and seizures, blurred vision due to cataracts.

Hypoparathyroidism in children leads to spasmophilia (laryngism, asphyxia), treated with activated vitamin D and calcium supplements. The treatment for hypoparathyroidism may also need magnesium supplementation.

PANCREAS

The pancreas is located in front of the spine behind the stomach. The pancreas is surrounded by the gallbladder, liver, and spleen. The head of the pancreas is directed towards the right side of the body and is located along the duodenum.

In α-cells of the islets of Langerhans, glucagon is formed; in β-cells - insulin; in δ-cells - somatostatin; in G-cells - gastrin; in F, or PP cells - pancreatic peptide, which is an antagonist of cholecystokinin.

Insulin is formed from preproinsulin. It consists of 51 amino acids. Insulin contains 2 chains: A and B connected via disulfide bonds. Insulinase tears these linkages separating A and B chains. In pro-insulin, the C-peptide called linking chain binds peptides A and B. Carboxypeptidase activates insulin by splitting off C-peptide from proinsulin.

Insulin secretion depends on the level of glucose, amino acids, fatty acids and ketone bodies in the blood, i.e. the levels of energy substrates.

Insulin is a universal regulator: it facilitates the penetration of glucose, amino acid, K^+, Ca^{2+} through cell membranes into the cell. Insulin enhances glycolysis by activating key enzymes of glycolysis: hexokinase or glucokinase, phosphofructruokinase and pyruvate kinase. By this way insulin enhances ATP synthesis. Simultaneously insulin inhibits gluconeogenesis, because it inhibits the synthesis of key enzymes of process, namely phosphoenol pyruvate carboxykinase

and fructose-1,6-diphosphatase. Insulin activates glycogen synthase and inhibits phosphorylase. Thus, enhancing synthesis of glycogen (glycogenesis), insulin causes hypoglycemia. Under the influence of insulin synthesis of lipids (lipogenesis) is enhanced too, because glycerol phosphate required for process is made up from glyceraldehyde phosphate formed in glycolysis. Acetyl-CoA, a product of glucose catabolism, donates carbon atoms for the assembly of fatty acids. Insulin activates pentose phosphate pathway to provide NADPH for lipogenesis. Insulin is the only hormone inhibiting lipolysis. Lipolysis is weakened by inactivation of the triacyl glycerol lipase (TAG- lipase).

Insuloma is a tumor of the islets. Insulinoma is a β cell tumor and leads to hypoglycemia, which is characterized by decrease of blood glucose to 2.2 mmol / l leading to faint.

Diabetes mellitus can be of pancreatic and extrapancreatic origin. Non-pancreatic causes of diabetes include an increase in the level of hormones which are insulin antagonists. Thus, an elevated level of ACTH, adrenaline and glucocorticoids, growth hormone and glucagon increases the level of glucose in the blood and creates the conditions for diabetes. The main signs of diabetes are hyperglycemia, glycosuria and thirst. In diabetes mellitus, the synthesis of amino sugars such as glycosaminoglycans is disrupted, which leads to a delay in skin regeneration. Glycolysis is inhibited, so the amount of pyruvate decreases, and then the amount of oxaloacetate drops, which inhibits the Krebs cycle. Acetyl CoA accumulation increases the ketone bodies and cholesterol synthesis resulting in ketonemia and hypercholesterolemia.

Since insulin is reduced in diabetes, glucose-6-phosphatase is activated leading to release of free glucose into the blood. This free glucose washed out of the cells can not be involved in the synthesis of glycogen. At hyperglycemia, the hexokinase in the kidneys is inhibited, which is followed by disture of glucose reabsorption in the tubules resulting in glucosuria. Glycosuria causes osmotic diuresis followed by thirst.

Lipids are compensatory mobilized from fat depots, resulting in hyperlipidemia, which leads to fatty infiltration of the liver. Three factors stimulate ketonemia:

1. Mobilization of fatty acids and their β-oxidation in the liver;
2. Inhibition of Krebs cycle.
3. İmpaired fatty acid resynthesis due to the decrease of $NADPH_2$.

Inhibition of glycolysis and Krebs cycle in diabetes results in drop of ATP production followed by delay of protein synthesis. Instead, amino acids are catabolized and involved in gluconeogenesis. As a result, the products of amino acid catabolism, namely ammonia and urea increase in the blood.

Coma is a complication of diabetes.The reason of coma is ketonemia and acidosis. Single hyperglycemia without acidosis does not lead to coma.

Glucagon is formed from inactive prohormone, namely proglucagon. It exhibits the opposite effect of insulin, in this regard, glucagon is antagonist of insulin. Glucagon increases glucose in the blood and by this way stimulates insulin secretion. It enhances breakdown of glycogen (glycogenolysis) because it activates glycogen phosphorylase and inhibits glycogen synthase. Receptors for glucagon are present only on the surface of liver cells and adipose tissue. Therefore, unlike adrenaline, glucagon breaks down only hepatic glycogen, causing hyperglycemia and does not affect muscle glycogen. Unlike adrenaline, glucagon does not affect heart rate and vascular tone. Like adrenaline, glucocorticoids and ACTH glucagon stimulates gluconeogenesis. Glucagon enhances lipolysis.

Somatostatin is formed in delta cells of pancreas and in hypothalamus as well. It reduces the secretion of insulin and glucagon. It is secreted in the first minutes of the food uptake and creates the conditions for the regulation of glucose by mechanisms bypassing insulin and glucagon. Somatostatin is stimulated by digestive hormones, but somatostatin itself inhibits the hormones of digestion. With food intake, somatostatin and pancreatic polypeptide increase in the blood. *Pancreatic polypeptide* (PP) is formed in F- or PP- cells of pancreas. PP increases

the secretion of gastric juice, but inhibits pancreatic stimulation with cholecystokinin (formerly called pancreozymin). PP is an analytical marker of endocrine neoplasia.

Leptin, adiponectin & ghrelin

These three hormones are key molecules in the regulation of lipid metabolism. By this way they plays a role in body weight.

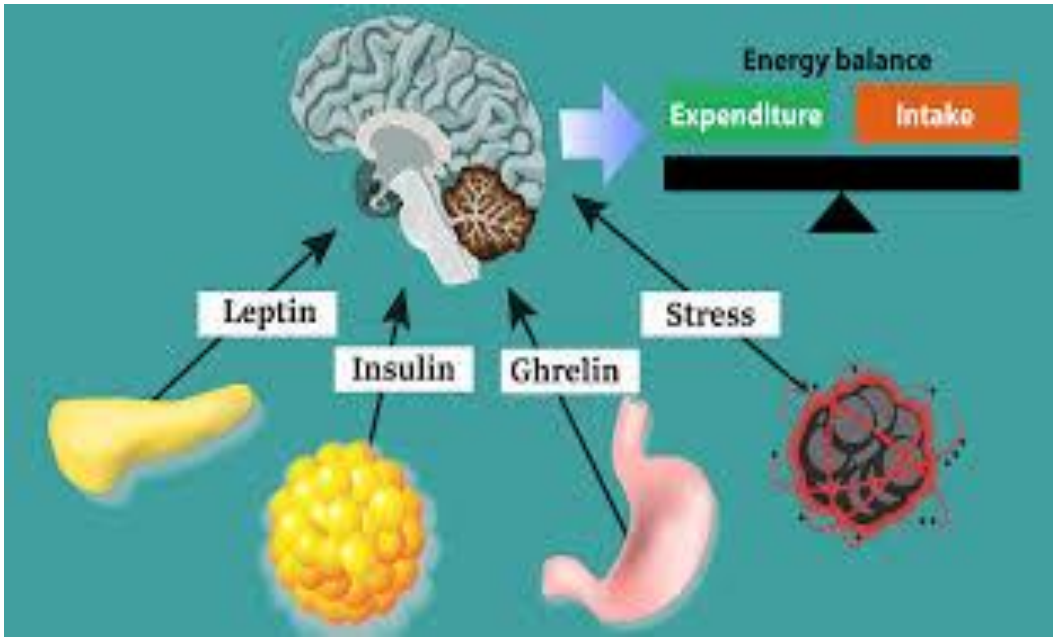


Fig.18. Leptin, ghrelin and insulin balance the food intake and energy expenditure.

Leptin and insulin share common effects in the control of food intake and energy metabolism. Leptin and adiponectin are cytokines produced excessively by adipocytes, hence their name is "adipokines". Leptin is also produced in the peripheral system as well as in the brain. Leptin regulates lipid metabolism independently of food intake. Independent of the anorexic effect, leptin regulates glucose and lipid metabolism in peripheral tissues. Leptin reduces appetite and inhibits food intake. Levels of this appetite suppressor are lower when the body is thin. When a person gains weight, leptin levels rise (to lower appetite). Leptin increases energy expenditure and reduces body fat.

The action of adiponectin on appetite is controversial. Insulin and leptin are secreted in direct proportion, while adiponectin in negative proportion to the size of the adipose mass. In contrast to most other adipocyte-derived hormones, leptin & adiponectin increase insulin sensitivity. Leptin and insulin directly regulate each other. In leptin sensitive individuals, leptin inhibits insulin biosynthesis and secretion from pancreatic β-cells. By contrast, insulin stimulates leptin secretion from adipose tissue.

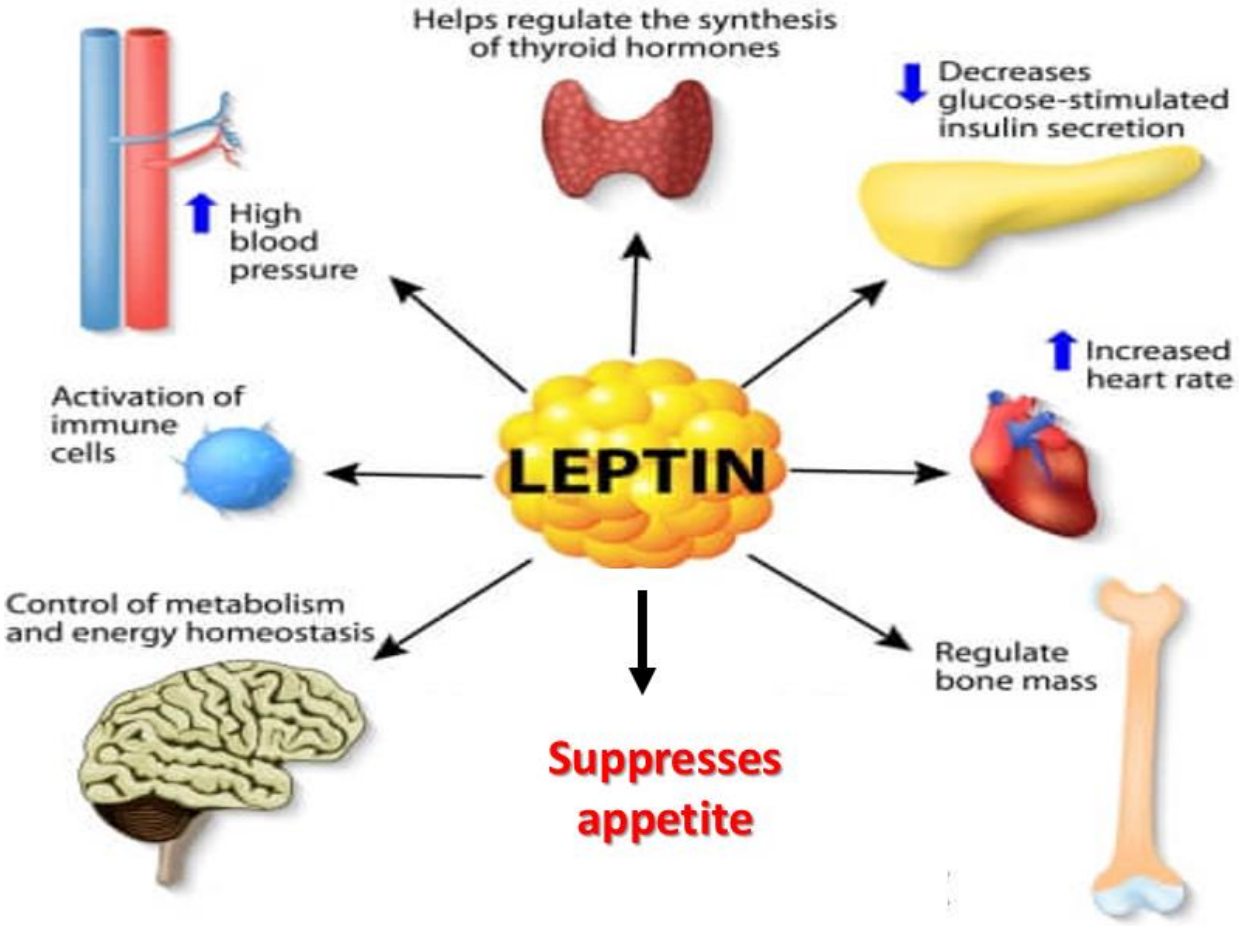


Fig. 19. Effects of leptin on body functions

Leptin administration inhibits *de novo* lipogenesis and stimulates lipolysis in adipose tissue and liver via activation of the sympathetic nervous system. This effect of leptin is opposite to insulin. Leptin stimulates hepatic gluconeogenesis and hepatic insulin sensitivity via the hepatic branch of the vagus nerve. In parallel with its activation of AMP-activated protein kinase, leptin suppresses the activity of Acetyl-CoA carboxylase, thereby

stimulating the oxidation of fatty acids in muscle. Leptin is thought to be responsible for several cardiovascular diseases associated with obesity. The next fat-derived hormone, adiponectin appears to play a crucial role in protecting against insulin resistance/diabetes and atherosclerosis. Decreased adiponectin levels are thought to play a central role in the development of type 2 diabetes, obesity and cardiovascular disease in humans. Ergo, adiponectin is considered to be cardioprotective. Ghrelin is a gastric peptide that increases appetite. Leptin and adiponectin also regulate inflammation. Ghrelin possesses anti-inflammatory properties. [Toussirot E, Streit G, Nguyen NU, Dumoulin G, Le Huédé G, Saas P, Wendling D. Adipose tissue, serum adipokines, and ghrelin in patients with ankylosing spondylitis. Metabolism. 2007 Oct;56(10):1383-9. doi: 10.1016/j.metabol.2007.05.009. PMID: 17884449]

Fig. 20. Ghrelin and leptin regulate appetite and metabolism

HORMONES OF ADRENAL MEDULLA, CATECHOLAMINS

The hormones of the adrenal medulla, catecholamines, are neurotransmitters, so they are a kind of continuation of the sympathetic nervous system.

Synthesis of adrenaline (epinephrine), norepinephrine (norepinephrine), dopamine takes place in the granules. Adrenaline makes up 83% of the hormones synthesized here. Catecholamines circulate in the blood in a free state. They are very quickly eliminated from the blood, in some minutes. They are catabolized by enzymes monoamine oxidase (MAO) and catecholamine-O-methyltransferase (COMT), mainly by MAO. They are excreted in the urine in a form of vanillyl almond acid.

During catabolism, adrenaline turns into hydroxy-adrenochrome, or oxyadrenochrome, which reduces heart rate and dilates blood vessels, so it exhibits effect opposite to adrenaline.

Catecholamine are secreted into the blood during hypoglycemia, decrease of fatty acids in the blood (hypolipidemia), i.e. in response to decrease of energy substrates in the blood.

There are different adrenergic receptors such as α_1, α_2, β_1, β_2 and so on. Adrenaline enhances the heart rate and contraction, narrows blood vessels resulting in increases of blood pressure. Adrenaline enhances the breakdoün of energy substrates, i.e. glycogenolysis, lipolysis, protein catabolism. It stimulates the penetration Na^+, K^+, Ca^{2+} into the cell and sharply increases blood glucose.

* By stimulating liver and muscle phosphorylase, adrenaline breaks down glycogen in the liver and muscles.

* Adrenaline stimulates gluconeogenesis.

The hyperglycemic effect of norepinephrine is 5% of adrenaline. Although epinephrine increases blood glucose levels, it reduces the entry of glucose into cells, thereby inhibiting glycolysis. In adipose tissue, adrenaline activates lipase, resulting in increased lipolysis, and it increases the level of fatty acids released into the blood from adipocytes.

Chromaffinoma, or pheochromocytoma is an adrenal medulla tumor. With this disease, hypermetabolism, hyperglycemia, arterial hypertension appear. Adrenal

chromaffinoma increases adrenaline and norepinephrine in the blood, while chromaffinoma of other sites of body increases only norepinephrine in the blood. With chromaffinoma, glycogenolysis is enhanced, causing hyperglycemia, and lipolysis is enhanced. Vision is disturbed, sweating, anxiety, fear, palpitations, belching, vomiting occur.

The hyposecretion of catecholamines causes only arterial hypotension.

Hormones of the adrenal gland cortex

Mineralocorticoids (MC), glucocorticoids (GC), and nonspecific sex hormones produced in the adrenal cortex are called "corticosteroids" because they have a steroidal structure. Their structure is based on cyclopentane-perhydrophenanthrene, i.e. steran structure. Sterane is formed by the condensation of three 6-carbon and one 5-carbon cyclic compounds.

In general, all steroid hormones are formed from 4 steroids:

1. estran (C_{18}); 2. Androstan (C_{19}); 3. pregnan (C_{21}); 4. Cholestan (C_{27}). Cholesterol is derivative of cholestan. Corticosteroids are derivatives of pregnan.

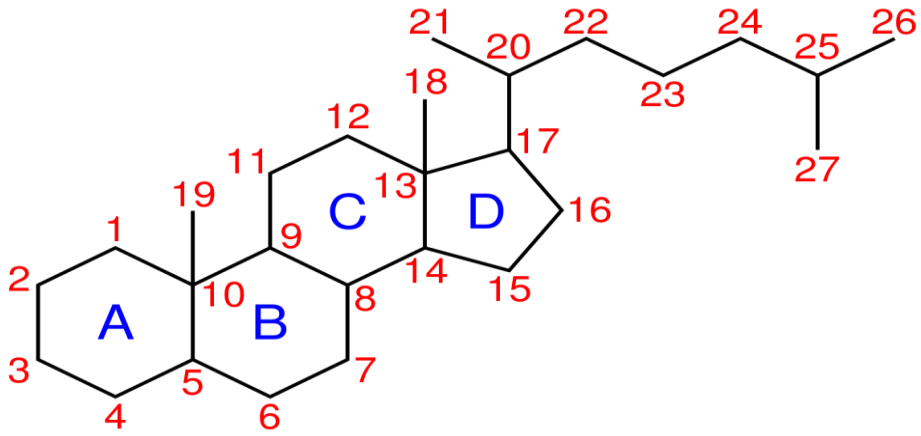


Fig.21. Steran structure and atomic numbering

All steroids are lipophilic compounds that easily pass across the membranes. The adrenal glands contain up to 50 types of steroids. GCs

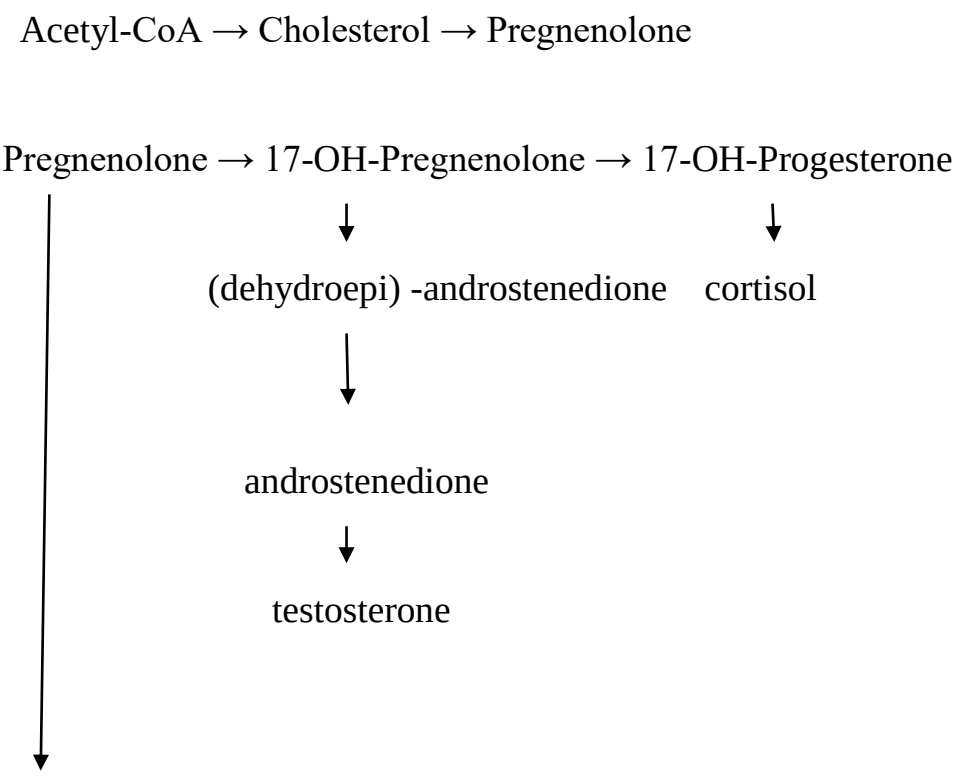
affect carbohydrate, protein, fat and nucleic acid methabolism. MC affect water-salt metabolism.

Glucocorticoids are represented by 3 main hormones: corticosterone, cortisone, and cortisol or hydrocortisone which reaches maximum level in the blood at 6-8 o'clock in the morning.

Cortisol and corticosterone are more active. Cortisone first turns into cortisol, and only then becomes active. All GCs, especially corticosterone, show a weak mineralocorticoid effect.

Steroid hormones are synthesized from cholesterol. Cholesterol enters the adrenal cortex from the blood or is synthesized internally from acetyl-CoA. Cholesterol accumulates in the membrane, and its esters (cholesterides) - in lipid granules. ACTH stimulates the synthesis of steroid hormones from cholesterol in following steps:

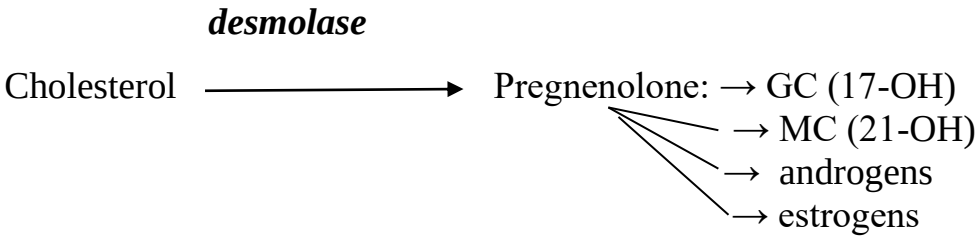
SYNTHESIS OF STEROID HORMONES



The conversion of progesterone to 11-deoxy-corticosterone is catalyzed by 21-

hydroxylase.

Cholesterol is first converted to pregnenolone. In this step, with the help of desmolase, the 6-carbon component is cleaved from the side chain. A hereditary defect in desmolase disrupts this process, and such newborns die in the first days of life. From pregnenolone, GC, MC, androgens and a small amount of estrogens are formed:



11-deoxy-corticosterone and aldosterone are mineralocorticoids, the most active of which is aldosterone. Aldosterone secretion depends on:

- renin-angiotensin system
- kallikrein-kinin system.
- ACTH,
- prostaglandins,
- Na^+, K^+ ions concentration in the blood, because aldosterone reduces K+ and increases the concentration of Na+ ions in the blood. When K+ rises in the blood, aldosterone is secreted to decrease it. But when blood Na+ rises, aldosterone decreases. Renin of the kidneys activates blood angiotensin, and angiotensin II increases the secretion of aldosterone. ACTH stimulates aldosterone 20 times less than GC, but the circadian rhythm of aldosterone depends on ACTH.

Corticosteroids are transported in the blood in a free and bound state. They are associated with specific protein transcortin and non-specific blood proteins. Aldosterone is not transported by a specific protein, but by albumin. Other types of MCs are associated with trancortin.

Target organs for *GCs* are liver, kidneys, muscle, lymphoid and connective tissues (adipose, bone, subcutaneous tissue). There are cytosolic receptors for GC. In the liver and kidneys, GCs increase synthesis of proteins, namely enzymes of gluconeogenesis. As a result, the synthesis of NA and protein in the liver is enhanced. In other tissues under the action of GC, the breakdown of proteins is enhanced, which leads to an increase in the level of amino acids in the blood. These free amino acids are taken up by the liver and kidneys and used both for the synthesis of enzymes of gluconeogenesis and glucose formation. Therefore, hyperglycemia occurs. Hyperglycemia is maintained by three mechanisms:

1. gluconeogenesis in the liver;

2. the inclusion of amino acids formed during protein catabolism into gluconeogenesis;

3. permissive effect of GC on adrenaline, which enhances glycogenolysis. For the purpose of gluconeogenesis, the synthesis of enzymes of this process is enhanced:

1. pyruvate carboxylase

2. PEP-carboxykinase

3. Fructose diphosphatase

4. Glucose-6-phosphatase

To activate the gluconeogenesis, ALAT and other enzymes convert amino acids into pyruvate, which enters the process of glucose synthesis. GC, as well as adrenaline, by stimulating glycogen synthase, store glycogen.

Since glycolysis is reduced in fat cells, the amount of glycerol in them decreases. Thus, the synthesis of TAG becomes impossible. As a result, lipolysis in the limbs increases resulting in increase the concentration of fatty acids in the blood. Intense lypogenesis in the trunk leads to android obesity. Android obesity is the result of activated lipolysis in the extremities and increased lipogenesis in the face and trunk. As GC enhance the action of adrenaline, TAG-lipase is also activated. This additionally increases the fatty acid concentration in the blood. The fatty acids are captured by the liver, where they undergo β-oxidation and are

involved in ketogenesis. As a result, ketonemia and ketonuria occurs.
In very high doses, GC, as aldosterone affect mineral metabolism. Due to this, with hypercortisolism, Na^+ rises in the blood, and it retains water, which leads to edema. In hypercortisolism, Ca^{2+} and phosphorus are washed out of the bones and lost through the kidneys. Unlike vasopressin, GCs enhance filtration in the kidneys increasing diuresis.

GCs secretion is elevated in the stress. GCs hypersecretion (hypercortisolism) results in atrophy of the thymus and lymphoid glands followed by a decrease in immunity during stress.
17-ketosteroids are the products of androgen inactivation. In men, 2/3 of 17-ketosteroids is formed from the adrenal glands. In women, all 17-ketosteroids are made up from adrenal androgens.

To diagnose Cushing's syndrome, cortisol is measured at 11:00 pm when it is at its lowest, whereas iin norm t is measured at 9:00 am. Keep in mind that stress raises cortisol levels. Therefore, the patient must be restrained before cortisol analysis. Aldosterone is also measured in the morning, but the patient must lie all night before.

Hypercorticosteroidism can be central, peripheral and ectopic. The central, secondary form is called ***Cushing's disease***. With this disease, the level of ACTH increases resulting in hypercortisolism accompanied by hyperpigmentation. A peripheral tumor causes primary hypercortisolism, termed ***Itsenko-Cushing's syndrome***. In Cushing's syndrome, hyperpigmentation is not observed. An extraendocrine tumor causes ectopic hypercortisolism.

In Cushing's syndrome, gluconeogenesis is increased, leading to hyperglycemia. Hyperglycemia promotes the release of insulin. The constant need for high secretion of insulin causes the pancreas to overwork, resulting in functional failure of the pancreas with a subsequent disease called ***steroid diabetes.***
In the body, lipolysis is weakened and the synthesis of TAG is enhanced. Fat accumulates on the face, neck, chest and abdomen. The limbs look thin compared to the torso. TAGs are synthesized in the liver and are packed into particles termed

very low density lipoproteins (VLDL). VLDL are converted to low density lipoproteins (LDL) in the blood. Finally, increase of VLDL and LDL in the blood increases the risk of atherosclerosis.

Hypercortisolism also causes the following changes:

- Accumulation of Na^+ and water in the body resulting in raise of blood volume inside the vessels. Blood pressure rises, due to which the sensitivity of the vascular walls to adrenaline increases. Since protein catabolism increases, ammonia builds up in the body. Ammonia further increases blood pressure and vascular tone.

Hypercortisolism is accompanied by an increased secretion of K^+ in the urine.

- Ca^{2+} and inorganic phosphates (Pi) are removed from the bones and excreted by the kidneys, which leads to drop of Ca^{2+}. Drop of Ca^{2+} results in secondary hyperparathyroidism. Parathyroid hormone removes Ca^{2+} from the bones leading to spontaneous fractures.

The action of *aldosterone* is that it enhances the reabsorption of Na^+ and Cl^- in the kidneys, and increases the excretion of K^+, H^+ and NH_3 in the urine.

At primary aldosteronism called Conn syndrome, excess K^+ is excreted by the kidneys resulting in drop of K^+ in the blood. Due to hypokalemia, the sensitivity of the kidneys to vasopressin decreases, which causes polyuria. Due to polyuria, there is no edema in Conn's syndrome. Conn syndrome is treated with an aldosterone antagonist, verospiron (spironolactone).

The following changes in metabolism can lead to secondary aldosteronism:

1. Reduced aldosterone inactivation in the liver at liver diseases,
2. Raise of renin in blood due to kidney diseases.
3. Dehydration at heart diseases.

This is the cause of edema of hepatic, renal and cardiac origin. With any form of aldosteronism, there is a retention of Na^+ ions in the blood and a loss of K^+ ions through the kidneys. Hypernatremia and hypokalemia occur. An increase in

Na^+ increases the sensitivity of vascular cells to adrenaline: vascular tone and blood pressure increase. A decrease in K^+ in cells reduces muscle contractility: paresis and paralysis occur.

Hypoaldosteronism can be central (secondary) or peripheral (primary). ***Addison's disease*** is a primary endocrinopathy, which is also called chronic total hypo-aldosteronism. Due to a compensatory increase in ACTH, hyperpigmentation occurs.

Addison's syndrome is central hypoaldosteronism due to a lack of ACTH. Therefore, hyperpigmentation is not observed in Addison's syndrome.

With the Waterhouse-Friderichsen syndrome in newborns and pregnant women, hemorrhages in the adrenal cortex are manifested in adrenal failure folloüed by a sharp decrease in pressure (hypotension). Hypotension leads to collapse, weakness, abdominal pain, fever, chills, and convulsions. Adynamia appears as a result of hyponatremia and hyperkalemia. In muscles, protein synthesis is also reduced, so adynamia occurs due to a decrease in muscle contractile proteins. Reduction of heart rate, arrhythmia, hypoglycemia appear.

Aldosteron secretion is regulated by *renin-angiotensin system.*

The renin-angiotensin system serves to restore blood flow in the glomeruli of the kidneys to ensure the renal filtration process. As soon as the pressure in the arterioles decreases leading to poor filtration, renin is secreted from the kidneys into the blood. Renin converts a protein, blood angiotensinogen, into angiotensin I. Then carboxypeptidase cleaves 2 amino acids from the C-end of the formed angiotensin I. As a result of these transformations, a powerful vasoconstrictor, angiotensin II is formed. Angiotensin 2 not only constricts blood vessels, but also stimulates the secretion of aldosterone from the adrenal glands, leading to NaCl and water retention, thereby helping to restore pressure in the vessels. Angiotensin II is the strongest vasopressor in the body that enhances the synthesis of aldosterone.

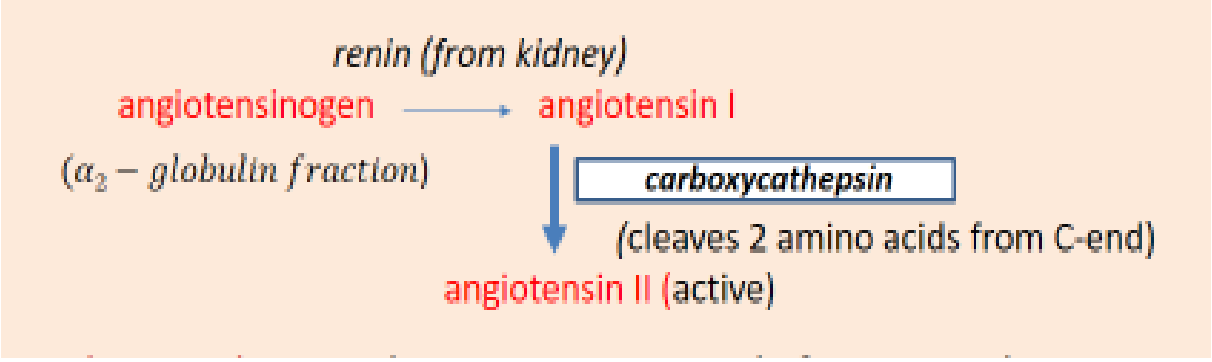


Fig. 22. renin-angiotensin system: carboxycathepsin cleaves 2 amino acids from C-end of angiotensin I converting it to angiotensin II.

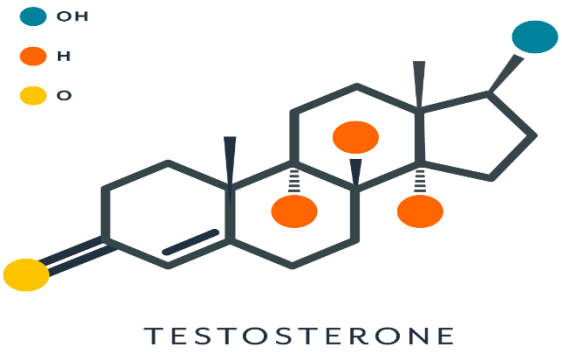
Androgens

Androgens (from the Greek andr-, means "male") are steroids that regulate the development of male characteristics. Androgens help initiate puberty and play a role in the reproductive development. Both men and women produce androgens, but men have 20-25 times more. *Testosterone* is the most powerful androgen.

During adolescence, androgens thicken the vocal cords, resulting in a coarsening of the voice. They enhance bone growth and increase the number of muscle fibers. Androgens also create feelings of well-being. Androgens increase fructose in germ cells. These hormones enhance the synthesis of DNA, RNA, protein on the body. The anabolic effect of testosterone is stronger than any other hormone.

Testosterone synthesıs:

Pregnenolone → 17hydroxy-pregnenolone → dehydroepi adrostenedione → androstenedione → testosterone.



TESTOSTERONE

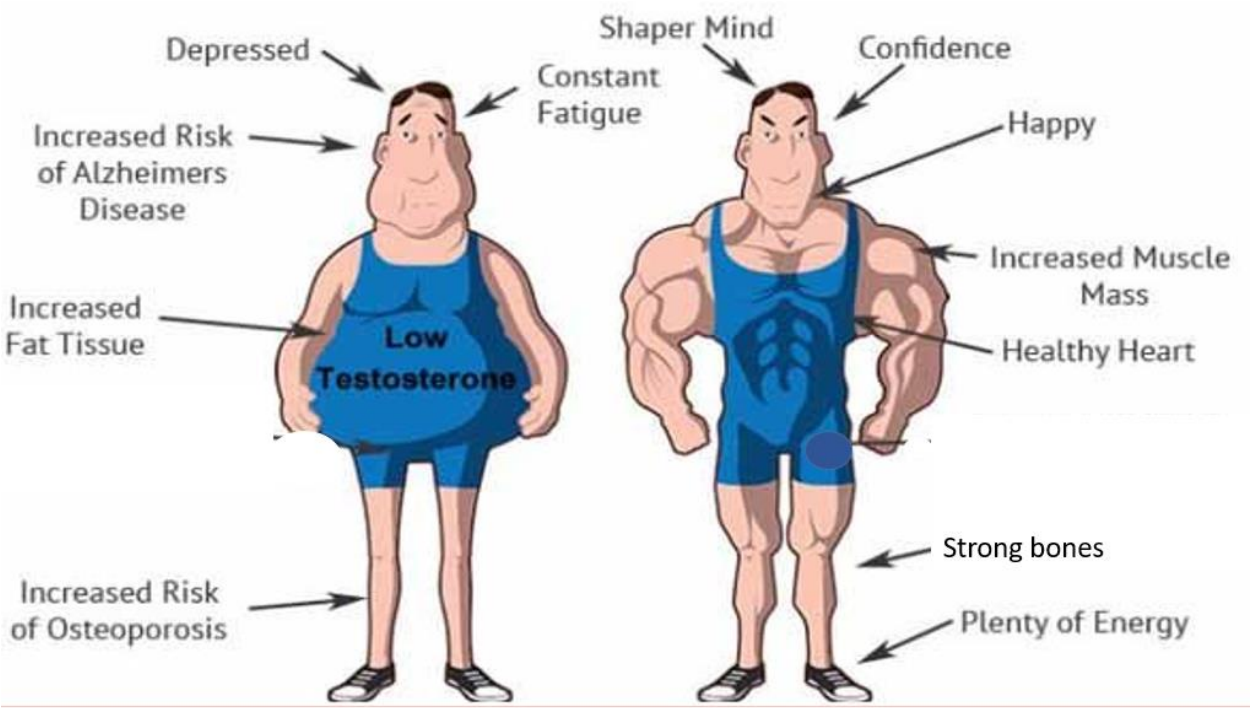
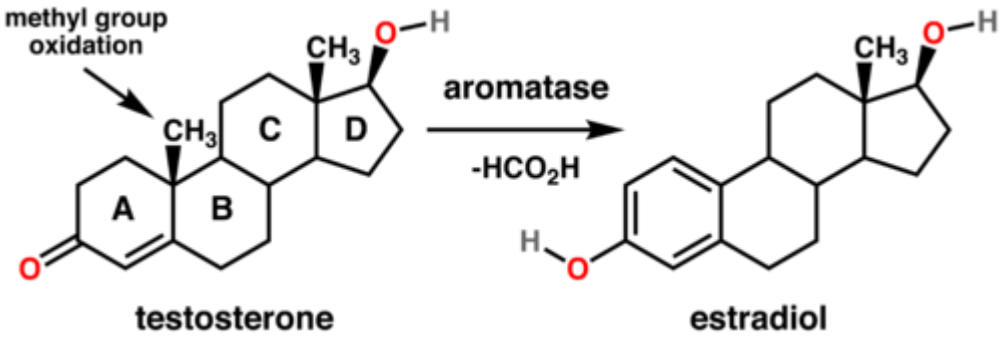


Fig. 23. Benefits of optimal testosteron

Estrogens

Estrogens are produced mainly in women. They ensure the normal maturation of the development of women and ensure fertility.

Androgens are precursors of estrogen and play a key role in the maturation of ovarian follicles. In healthy women, the ovaries and adrenal glands produce between 40% and 50% of testosterone in the body. Androgens are converted to estrogens by the action of aromatase. Aromatase deficiency leads to a decrease in estrogen and an increase in testosterone. Aromatase, or estrogen synthase, is a CYP19A1 member of the cytochrome P450 monooxygenase superfamily:



In women, elevated androgen levels due to aromatase deficiency can lead to facial hair growth and difficulty getting pregnant. Excessive production of androgens is observed in polycystic ovary syndrome.

In addition to estrogens, in women are synthesized progesterone and relaxin. They are produced in the corpus luteum. Progesterone helps the uterus grow during pregnancy and also prevents it from contracting. Comparison between estrogen and progesterone effects is given in the table below.

Table 1. Comparison between estrogens and progesteron

Estrogen action	Progesteron action
Increase body fat	Encourages fat burning
Depression, headache/migraine	Anti-depressant
Interferes with thyroid hormone	Facilitates thyroid hormone action
Increases blood clotting	Normalizes blood clotting

During late pregnancy, progesterone prepares the breasts for milk production. Relaxin is especially important during pregnancy: it relaxes and softens the ligaments of the pelvis during childbirth. Relaxin is similar to insulin: it contains 2 polypeptide chains linked via disulfide bonds.

Pregnancy changes the body's hormones background. In the last months of pregnancy, 90% of estrogens are represented by estriol. The rest pregnancy time estriol is less than other estrogens. During the pregnancy, a new hormone-producing tissue appears in the mother's body: the placenta. Main placenta hormones are followings:

- chorionic gonadotropin is only made during pregnancy, and almost exclusively in the placenta. It increases the synthesis of progesterone in the corpus luteum, progesterone supports pregnancy. It appears in the mother's blood and urine during the first trimester, and may play a part in the nausea and vomiting often linked to pregnancy.

- chorionic mammotropin, which enhances the penetration of glucose from maternal blood to the fetus

-thyrotropic and steroid hormones.

Eicosanoids

Eicosanoids are signaling molecules made by the oxidation of arachidonic acid or of other similar to arachidonic acid. When imunoglobulin (Ig) binds with Ag, phospholipase A_2 is activated. It cleaves arachidonic acid from the membrane p hospholipid. From arachidonic acid, in turn, are formed prostanoids.

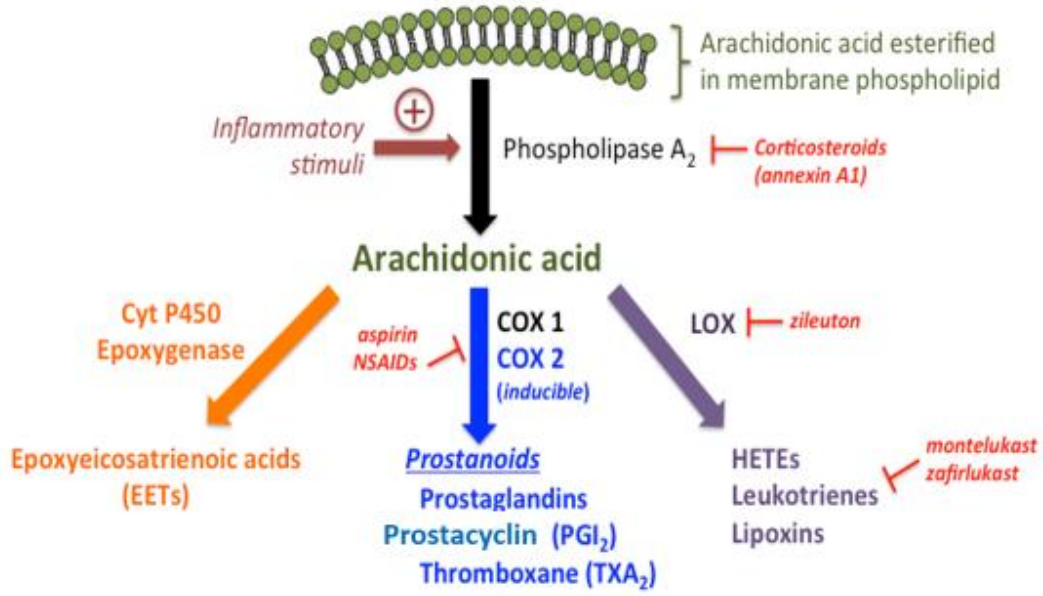


Fig. 24. Formation of eucosanoids. COX – cyclooxygenase, LOX-Lipoxygenase, CytP450 – cytochrome P450, NSAIDs- non-steroidal anti-inflammatory drugs.

Prostaglandins (Pg) are found in all tissues. Prostaglandins can be considered as derivatives of prostanoic acid. Prostanoic acid is not natural, it is synthesized artificially. Pg act on the cells that produce them (autocrine effect) or on neighboring cells.

In general, prostaglandins are divided into two groups: soluble in ether PgE, and soluble in phosphate buffer PgF. The body produces four main bioactive prostaglandins: PgE2, PgD2, PgF2α and prostacyclin PgI2. PgI2 is both an inhibitor of platelet aggregation and a potent vasodilator (reduces blood pressure). It inhibits atherosclerosis and the thrombosis. PgE1 protects the stomach and intestines from ulcers. PgE2 is used against bronchial asthma, ulcers and hypertension.

In leukocytes, lipoxygenase forms leukotrienes (LT). LT A, LT B, LT C, LT D, LT E are distinquished. Leukotrienes are formed not only in leukocytes, but also in

platelets and lungs. Leukotrienes are involved in inflammatory, anaphylactic, allergic, immune reactions.

Thromboxanes (Tx) are sort into Tx A and TxB.

TxA_2 increases platelet aggregation and adhesion. TxA_2 is formed not only in platelets, but also in the kidneys, liver, brain, spleen.

When atherosclerosis, the TxA2 / PcI2 ratio, increases which raises a risk of thrombosis.

Inclusion of eicosapentaenoic acid in food helps the formation of TxA_3 and PcI_3, which reduce the risk of atherosclerosis and thrombosis.

Cytokines

Cytokines are low molecular weight proteins, formed mainly in lymphocytes. Depending on the type of cells in which they are formed, cytokines are classified as interleukins (IL), monokines, chemokines, interferons, colony-stimulating factors.

According to the biological effect, cytokines are sort into:

1. Pro-inflammatory: IL2, IL6, IL8, interferon, α-tumor necrosis factor (α-TNF).

2. Anti-inflammatory: IL4, IL10.

3. Regulators of cellular and humoral immunity.

IL2 is formed in T-lymphocytes after activation with antigen. IL2 is stimulated by IL2 itself, and IL6. IL3 is formed in variety of cells colony-stimulating factor (CSF). This is a growth factor that stimulates erythropoiesis and the formation of neutrophils. It increases proliferation and differentiation of stem cells.

Depending on the type of cells, the growth of which they stimulate, CSFs are sort into: granulocyte CSF, monocytic CSF, granulocyte-monocytic CSF, erythropoietin, thrombopoietin. Granulocyte CFS stimulates the growth and development of granulocytes, mainly neutrophils. Monocytic CSF stimulates the growth and development of macrophages. Granulocyte-monocytic CSF stimulates the growth and development of both granulocytes and monocytes.

Interferon is a non-specific antiviral factor. There are α-, β-, γ- interferons. The most effective amid them is an α-interferon.

The cytokine TNF plays an important role in cell survival, proliferation and differentiation, and cell death as well. This pro-inflammatory cytokine is secreted by inflammatory cells, and may be involved in inflammation-related carcinogenesis. There are 2 types of TNF: α-TNF and β-TNF.

αTNF is formed in macrophages and T-lymphocytes and is also termed cachexin. In low concentration it enhances the synthesis of adhesive molecules on the endothelial cells of the inflammation site. This facilitates adhesion of neutrophils to the endothelium and starts the promotes the inflammation. In order to cleanse the tissue of microorganisms, it enhances tissue respiration in neutrophils. In high concentration αTNF enhances the shocking effect of endotoxins and inhibits lipoprotein-lipase activity. This reduces the flow of fatty acids into adipose tissue and causes cachexia.

β TNF, called lymphotoxin, is formed only in activated T-lymphocytes. It exhibits all the effects of αTNF.

Methods for obtaining hormonal drugs

Hormones are used in replacement therapy with a lack of production of endogenous hormones. For example, insulin - in diabetes mellitus, L-thyroxine - in hypothyrosis, somatotropic hormone - in dwarfism, vasopressin - in diabetes insipidus and so on. For this purpose, hormones have to be obtained in various ways. For example, insulin is obtained by synthesis from amino acids (sequencing), genetic engineering or from natural raw materials (pigs). İn general, all methods for obtaining hormones are sort into the followings:

1. Purification from biological material;
2. Chemical synthesis;
3. Genetic engineering. Insulin, somatostatin, STH are obtained by this way.